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Original Article

The Impact of COVID-19 on Patients with IBD in a Prospective European Cohort Study

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Abstract

Background and Aims: There are concerns regarding the potential impact of the COVID-19 outbreak on patients with inflammatory bowel disease [IBD]. We report on the impact of the COVID-19 outbreak in a European prospective cohort study of patients with IBD

Patients and Methods: We prospectively collected data from 5457 patients with IBD nested in the ongoing I-CARE project and still followed up in April 2020, with monthly online monitoring of clinical activity, treatment, imaging and endoscopy. Investigators were also contacted to report incidental cases.

Results: In total, 233 [4.3%] reported COVID-19 and 12 [0.2%] severe COVID-19, with no COVID-19 deaths. The risk of COVID-19 in patients with IBD was not increased compared to the general population (standardized incidence ratio [SIR]: 1.18, 95% confidence interval [CI] [1.03–1.34], $p = 0.009$), as well as the risk of severe COVID-19 (SIR: 0.69, 95% CI [0.35–1.20], $p = 0.93$). We did not observe any negative impact of the different IBD-related medication on the risk of either COVID-19 or severe COVID-19. In 2020, the COVID-19 outbreak resulted in a drastic decrease in endoscopic and imaging procedures from March to May 2020 compared to 2018 and 2019. No impacts on clinical IBD disease activity as well as ongoing treatment were noted.

Conclusion: No increases in either COVID-19 or severe COVID-19 incidences were observed in patients with IBD. There was no impact of COVID-19 on IBD-related medication and clinical activity. Access to endoscopy and imaging was restricted during the first months of the first COVID-19 outbreak.

Key Words: Crohn's disease; ulcerative colitis; inflammatory bowel disease; patient experience

1. Introduction

Novel coronavirus disease [COVID-19] is a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], first identified in Wuhan, China.[1] SARS-CoV-2 has spread from human to human and is now responsible for a massive outbreak affecting more than 430 million individuals.[2] The viral infection causes a series of respiratory illnesses, including acute respiratory distress syndrome, and has accounted for almost 6 million deaths. The risk of COVID-19 or COVID-19-related mortality in patients with inflammatory bowel disease [IBD] is uncertain, especially for those currently treated with an immunomodulator [IMM] and/or biologics. It has been presumed that patients who are immunosuppressed are at higher risk for infection with SARS-CoV-2 and higher risk of COVID-19-related mortality.[3] However, whether aminosalicylates, IMM and/or biologics increase the risk of COVID-19 or COVID-19-related mortality remains to be established.

I-CARE is a prospective observational cohort study that has enrolled 13 469 adult patients with IBD followed for at least 3 years in 15 European countries.[4] At inclusion, investigators collect patients' and disease characteristics, history of cancer, previous medications and vaccination status. Clinical disease activity, surgical procedures, all hospitalization reports, IBD-related medications, serious infections and dysplasia/cancers are reported monthly by the patient and yearly confirmed by the investigator who also reports endoscopy and radiology findings.[5]

In the present study, we aimed to assess the impact of the COVID-19 outbreak in patients with IBD, in a cross-sectional cohort study nested in the I-CARE cohort study which allows prospective follow-up and an exact denominator of patients to assess incidence rates.

2. Patients and Methods

2.1. Study population

We conducted a cross-sectional cohort study nested in a European prospective longitudinal multicentre cohort study [the I-CARE cohort study]. The primary objective of the I-CARE study is to assess prospectively risks and associated predictors of serious infection and malignancies in patients with IBD. Patients with IBD were recruited in the I-CARE cohort study from March 2016 to April 2019 by 500 investigators in 15 countries [for details on the I-CARE cohort study, see https://www.icare-ibd.com and https://www.clinicaltrials.gov/ct2/show/NCT02435550]. The trial protocol was approved by the I-CARE executive committee and by the institutional review board or ethics committee at each trial site. All the patients provided written signed informed consent. Patients included in the I-CARE cohort study had to complete a monthly online questionnaire [e-PRO] related to ongoing treatment, imaging and endoscopy, follow-up and hospitalization, incidental adverse events and IBD activity.

2.2. Patients

Patients were 18 years and older with an established diagnosis of Crohn's disease [CD], ulcerative colitis [UC] or IBD unclassified made at least 3 months earlier based on usual radiological, endoscopic or histological criteria.[6,7] Patients also accepted to sign the informed participating consent form, stating that he or she accepts to provide personal details [mobile and home phone number, e-mail address], to complete the e-PRO as required and to be contacted by a Study Coordinator and his/her gastroenterologist for the purpose of the study during the entire study [3 years with a potential additional 2-year period] period and during follow up if required.

2.3. I-CARE monthly e-PRO questionnaire

From the date of inclusion to the date of completion of the 3-year study period or the date of discontinuation of the study, patients included in the I-CARE cohort study were asked to complete the e-PRO questionnaire reporting clinical activity based on the Harvey–Bradshaw index for patients with CD and simple clinical colitis activity index [SCCAI] for patients with UC and IBD unclassified, ongoing treatment, endoscopic procedure [colonoscopy, flexible sigmoidoscopy, upper gastrointestinal endoscopy and other endoscopic procedures], morphological examination [magentic resonance imaging enterography, ultrasonography, computed tomography scan, barium contrast and other morphological examination], hospitalization, pregnancy and occurrence of any adverse events.[8,9] In case of reported hospitalization, serious infection, pregnancy and/or malignancy, dedicated reports were retrieved by the I-CARE study team.

2.4. Additional COVID-19 e-PRO questionnaire

From April to December 2020, patients included in the I-CARE cohort study were asked to respond to a four-questions survey added to the monthly e-PRO assessment asking [1] whether they have been tested for SARS-CoV-2 [Yes or No] and if yes with which test (polymerase chain reaction [PCR] test for SARS-CoV-2 on nasopharyngeal swab, or specific serological test). [2] If yes, why have they been tested? [Screening or symptoms]. [3] If yes, was the test positive? [Yes or no]. [4] If positive, were they hospitalized due to COVDI-19? [Yes or No]. We included in the present study all consecutive patients who were previously included in the I-CARE cohort study and who responded to at least one e-PRO COVID-19 questionnaire. Monthly follow-up in the I-CARE cohort study and e-PRO COVID-19 questionnaire was maintained from April to December 2020, whether they had previously responded and/or reported COVID-19. Additionally, the gastroenterologists were asked to report all cases of COVID-19, either symptomatic or not, in patients included in the I-CARE cohort study.

2.5. Outcomes and definition of COVID-19 infection

The main outcome measure was the rate of incidental COVID-19, defined as a positive PCR test for SARS-CoV-2 on nasopharyngeal swab and/or a positive serological test for SARS-Cov-2 without prior vaccination. Secondary outcomes included the risk of severe COVID-19, defined as any COVID-19 requiring hospitalization, intensive care unit stay or death, and the impact of ongoing treatment on the risk of COVID-19 and severe COVID-19 adjusted for age and body mass index [BMI]. Furthermore, we assessed the impact of COVID-19 on IBD activity and the frequency of endoscopic procedures and imaging during 2020 compared to the years 2018 and 2019.

2.6. Covariates

Data were collected in an electronic case report form. Relevant covariates were extracted from the I-CARE electronic database on January 7, 2021 and included: age, gender, type of IBD [CD, UC or IBD unclassified], BMI, occupational status, smoking habit, past and current medication exposure, medical and surgical history of IBD, IBD phenotype according to the Montreal classification, familial history of IBD and cancer, baseline serological [for HIV, HBV, HCV and EBV] and vaccination [for VZV, HBV, Bacille Calmette-Guerin and pneumococcal vaccines] status, history of symptomatic mononucleosis, and disease activity reported monthly by the patients according to the Harvey–Bradshaw index for patients with CD and SCCAI for patients with UC and IBD unclassified.

2.7. Statistical analysis

The data are expressed as numbers [%] for qualitative data and as means ± standard deviation [SD] or medians [interquartile ranges] for quantitative data. Qualitative variables were compared using the Chi^2 test or Fisher's exact test, and

Table 1. Demographic and baseline disease characteristics and ongoing treatment of 5457 patients with inflammatory bowel disease in the I-CARE cohort study who have responded to at least one e-PRO COVID-19 questionnaire from March to December 2020.

	Patients with COVID-19 [*n* = 233]	Patients with absence of COVID-19 [*n* = 5224]	p	Overall study population [*n* = 5457]	Missing values [%]
Age, years	43.7 ± 12.4	44.4 ± 13.2	0.45	44.3 ± 13.2	0
Age > 50 years	1707 [32.7%]	73 [31.3%]	0.72	1780 [32.6%]	
Male gender, no. [%]	100 [42.9%]	2451 [46.9%]	0.25	2551 [46.7%]	0
Body mass index, kg/m^2	24.9 ± 5.2	24.7 ± 4.8	0.59	24.7 ± 4.8	589 [10.8%]
Body mass index > 30 kg/m^2	892 [12.7%]	29 [14.4%]	0.45	621 [12.8%]	
Smoking habits, no. [%]					522 [9.6%]
Current smoker	23 [11.2%]	741 [15.7%]	0.09	764 [15.5%]	
Past smoker	66 [32.0%]	1460 [30.9%]	0.76	1526 [30.9%]	
Never smoked	117 [56.8%]	2528 [53.5%]	0.36	2645 [53.6%]	
Occupational status, no. [%]					103 [1.9%]
Student	21 [9.0%]	418 [8.0%]	0.54	439 [8.0%]	
Active worker	191 [82.0%]	3963 [75.9%]	0.03	4154 [76.1%]	
Jobless	13 [5.6%]	407 [7.8%]	0.26	420 [7.7%]	
Retired	8 [3.4%]	436 [8.3%]	0.005	444 [8.1%]	
History of intestinal resection	53 [52.6%]	1378 [29.2%]	0.28	1431 [29.1%]	2 [<0.1%]
Familial history of inflammatory bowel disease	26 [13.1%]	539 [11.9%]	0.58	565 [11.9%]	42 [0.8%]
Age at diagnosis					
A1: ≤16 years	27 [11.6%]	567 [10.9%]	0.75	594 [10.9%]	0
A2: 17–40 years	163 [70.0%]	3675 [70.3%]	0.88	3838 [70.3%]	0
A3: > 40 years	43 [18.5%]	982 [18.28]	0.99	1025 [18.8%]	0
Crohn's disease, no. [%]	142 [60.9%]	3192 [61.1%]	0.99	3334 [61.1%]	0
Disease location, no. [%]					
L1: Ileal	43 [35.5%]	1097 [38.5%]	0.57	1140 [38.3%]	330 [6.6%]
L2: Colonic	27 [22.3%]	557 [19.5%]	0.48	584 [19.6%]	
L3: Ileocolonic	51 [42.1%]	1199 [42.0%]	0.99	1250 [42.0%]	
L4: Upper GI tract	10 [8.3%]	233 [8.3%]	0.99	243 [8.3%]	
Disease phenotype, no. [%]					
B1: non-structuring – non-penetrating	64 [54.7%]	1436 [50.7%]	0.4	1500 [50.8%]	
B2: Stricturing	26 [22.2%]	825 [29.1%]	0.12	851 [28.8%]	383 [7.0%]
B3: Penetrating	27 [23.1%]	573 [20.2%]	0.48	600 [20.3%]	
Perianal disease, no. [%]	39 [32.0%]	788 [27.6%]	0.3	827 [27.7%]	1180 [21.6%]
Ulcerative colitis, no. [%]	85 [36.5%]	1935 [37.0%]	0.89	2020 [37.0%]	0
Proctitis	12 [14.3%]	297 [16.1%]	0.76	309 [16.0%]	
Left-sided colitis	37 [44.0%]	718 [38.8%]	0.36	755 [39.0%]	86 [1.6%]
Pancolitis	35 [41.7%]	835 [45.1%]	0.58	870 [45.0%]	
Indeterminate colitis, no. [%]	6 [2.6%]	97 [1.9%]	0.45	103 [1.9%]	0
Treatment history					
Aminosalicylates monotherapy	83 [40.7%]	1746 [37.8%]	0.42	1829 [37.9%]	628 [11.5%]
Oral steroids	126 [61.2%]	3084 [65.7%]	0.18	3210 [65.5%]	557 [10.2%]
Thiopurines	81 [39.1%]	1701 [35.3%]	0.27	1782 [35.5%]	437 [8.0%]
Methotrexate	13 [6.3%]	324 [6.7%]	0.99	337 [6.7%]	445 [8.2%]
Anti-TNF	64 [21.0%]	1254 [18.4%]	0.11	115 [18.5%]	466 [8.5%]
Vedolizumab	5 [2.4%]	93 [1.9%]	0.6	98 [2.0%]	456 [8.4%]
Ustekinumab	0	16 [0.3%]	0.99	16 [0.3%]	447 [8.2%]
Current treatment					
None	38 [16.3%]	905 [17.3%]	0.79	943 [17.3%]	0
Aminosalicylates monotherapy	30 [12.9%]	835 [16.0%]	0.23	865 [15.9%]	0
Oral steroids	18 [7.7%]	277 [5.3%]	0.14	295 [5.4%]	0
Immunosuppresant monotherapy	17 [7.3%]	742 [14.2%]	0.002	756 [13.9%]	0
Thiopurines	17 [7.3%]	701 [13.4%]	0.005	716 [13.4%]	0
Methotrexate	0	40 [0.8%]	0.42	40 [0.7%]	0

Table 1. Continued

	Patients with COVID-19 [*n* = 233]	Patients with absence of COVID-19 [*n* = 5224]	p	Overall study population [*n* = 5457]	Missing values [%]
Anti-TNF	100 [42.9%]	1801 [34.5%]	0.009	1901 [34.8%]	0
Monotherapy	74 [31.8%]	1371 [26.2%]	0.07	1445 [26.5%]	0
Combotherapy	26 [11.2%]	432 [8.3%]	0.12	456 [8.4%]	0
Vedolizumab	20 [8.6%]	425 [8.1%]	0.81	445 [8.2%]	0
Ustekinumab	18 [7.7%]	407 [7.8%]	0.99	445 [8.2%]	0
Tofacitinib	4 [1.7%]	44 [0.8%]	0.15	48 [0.9%]	
Clinical activity*					
Harvey–Bradshaw Index [HBI]	3.0 ± 3.6	3.2 ± 3.4	0.67	3.1 ± 3.5	0
SCCAI	1.4 ± 2.0	1.6 ± 2.1	0.61	1.5 ± 2.1	0
Clinical remission	168 [72.1%]	3612 [69.1%]	0.28	3780 [69.3%]	0
Mild activity	44 [18.9%]	1210 [23.2%]		1254 [23.0%]	
Severe activity	21 [9.0%]	402 [7.7%]		423 [7.8%]	

SCCAI: Simple Clinical Colitis Activity Index; TNF: tumour necrosis factor α.
*According to HBI and SCCAI.
Clinical remission was defined as HBI ≤ 4 for Crohn's disease patients and SCCAI ≤ 2 for ulcerative colitis patients. Mild activity was defined as HBI 4–8 for Crohn's disease patients and SCCAI 3–4 for ulcerative colitis patients. Severe activity was defined as HBI > 8 for Crohn's disease patients and SCCAI > 4 for ulcerative colitis patients.
Variables are presented as *n* [%]. Mean ± SD.
The *p* values are based on a two-sided chi-square test for all categorical variables and Mann–Whitney test for all quantitative variables.

quantitative variables using the Mann–Whitney test. The expected number of cases of COVID-19 and severe COVID-19 in the general population of each country was obtained by multiplying the number of patients by the corresponding specific national incidence rate calculated with data from the European Centre for Disease Prevention and Control on January 7, 2021 [https://www.ecdc.europa.eu/en/covid-19/data].[10] The standardized incidence ratio [SIR] was obtained by dividing the observed and the expected number of cases of COVID-19 and severe COVID-19 in each country. Confidence intervals [CIs] for SIR were calculated with an exact method based on the Poisson distribution. We used stratified binary logistic regression models to quantify the strength of associations between each treatment exposure and COVID-19 and severe COVID-19. For the multivariable models, we used forced-entry methods to include age and BMI. Disease activity, endoscopic procedures and imaging were compared monthly between 2018, 2019 and 2020 using Wilcoxon's matched-pairs signed-rank test. A result was considered significant at $p < 0.05$. All the statistics were analysed using SPSS Statistics v23 software.

3. Results

3.1. Study population

A total of 13 469 patients were included in the I-CARE cohort study between March 2016 and April 2019. Of those, 6679 chose to discontinue the study before the end of the follow-up period, 439 completed the 3-year follow-up period before April 2020, and 894 did not fill any COVID-19 e-PRO questionnaire and were excluded from this study. In total, 5457 patients were included in the present study [Supplementary Figure 1]. Patient demographic data, occupational status, vaccine and serological data, disease characteristics and activity, medication history and current treatment are presented in Table 1 and in Supplementary Table 1.

3.2. Incidental COVID-19 and severe COVID-19

A total of 233 patients [4.3%] reported COVID-19 infection, including 158 [67.8%] with symptomatic COVID-19, accounting for 3.2 per 100 patient-years. Of these, 12 [0.2%] reported severe COVID-19. The monthly incidence rates, from April to December 2020, are presented in Figure 1. A diagnosis of COVID-19 was made using PCR for SARS-CoV-2 alone in 67.1%, a serological test alone in 12.9%, and a combination of PCR and serological test in 19.7%. Comparative characteristics of patients with COVID-19 and controls are presented in Table 1 and those of patients with severe COVID-19 and non-severe COVID-19 in Table 2. Table 3 shows SIRs in each country and in the whole cohort. We observed a 18% increase in COVID-19 incidence in patients with IBD compared to the general population (SIR: 1.18, 95% CI [1.03–1.34], $p = 0.009$). However, the SIR of COVID-19 varied among countries and was increased only in France, Hungary, Ireland and Italy. We observed no increase in severe COVID-19 (SIR: 0.69, 95% CI [0.35–1.20], $p = 0.93$).

The results of the multivariate analysis regarding the impact of ongoing treatment to the risk of COVID-19 and severe COVID-19 are presented in Table 3 including crude results and after adjustment for age and BMI. We observed a decreased risk of COVID-19 in patients treated with thiopurine monotherapy while there was non-significant trend for an increase of COVID-19 in patients treated with steroids, tofacitinib and anti-tumour necrosis factor [anti-TNF]. Additionally, we observed no effect of medication exposure on the risk of severe COVID-19 infection in patients with IBD.

3.3. Impact of the COVID-19 outbreak on clinical activity and ongoing treatment

Considering ongoing treatment, we did not observe any changes in therapy during 2020 with the exception of a mild decrease in steroid use in patients with CD between April and March 2020 [5.9% vs 5.5%, $p = 0.05$] [Figure 2A and D].

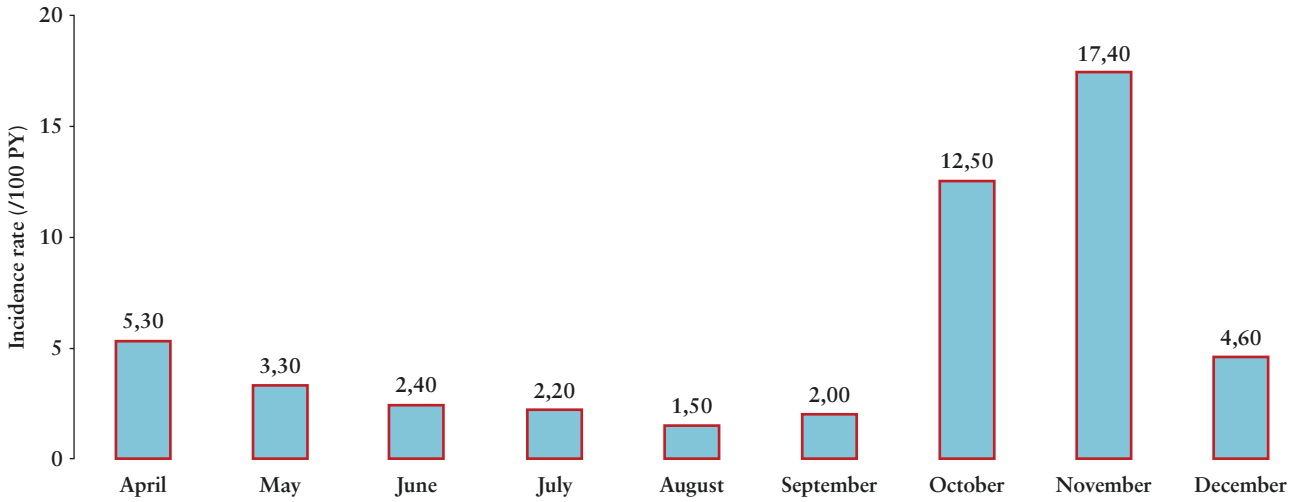

Figure 1. Monthly incidence rates, from April to December 2020, in 5457 patients with inflammatory bowel disease in the I-CARE cohort study who have responded to at least one e-PRO COVID-19 questionnaire from March to December 2020.

Considering disease activity, we did not observe any changes in Harvey–Bradshaw index and SCCAI during 2020 with the exception of a mild decrease between February and March 2020 for both Harvey–Bradshaw index [3.2 ± 3.4 vs 3.1 ± 3.4; $p = 0.007$] and SCCAI [1.56 ± 2.04 vs 1.49 ± 1,99; $p = 0.04$] with subsequent mild increase between May and June 2020 [3.1 ± 3.4 vs 3.2 ± 3.5; $p = 0.02$] for Harvey–Bradshaw index and between September and October 2020 for SCCAI [1.46 ± 1.97 vs 1.53 ± 2.01; $p = 0.05$] [Figure 2B and E]. We did not observe any changes in Harvey–Bradshaw index and SCCAI in patients with COVID-19 compared to patients who did not developed infection [Figure 2C and F].

3.4. Impact of the COVID-19 outbreak on endoscopic imaging procedures and disease activity

The COVID-19 outbreak resulted in a drastic decrease in endoscopic procedures [Figure 3A] and morphologic examination [Figure 3B] during the first lockdown period from March to May 2020, compared to in 2019 and 2018 [$p < 0.05$]. We did not observe any decrease in the rate of endoscopic procedures or morphological examinations during the rest of 2020, not even during the last trimester when the second lockdown occurred in European countries at various points.

4. Discussion

We investigated the prevalence of COVID-19, as well as of severe COVID-19, in a prospective, pan-European cohort of more than 5000 IBD patients. The pooled incidence of COVID-19 was 18% higher than that of the general population, although incidence rates varied across countries. Treatment with thiopurine monotherapy was associated with a decreased risk of COVID-19, while no association with treatment with anti-TNF or 5-aminosalicylic acid [5-ASA] was observed. While the number of endoscopic procedures decreased significantly during the initial months of the pandemic from March to May 2020, no increase in clinical disease activity scores of the cohort were observed during that period and rates of endoscopic procedures normalized to June 2020.

There have been concerns among healthcare providers and patients about whether patients with IBD may be more susceptible to COVID-19 infection or more prone to severe disease than others. This is partly related to IBD management, which involves immunosuppression and hence resulting in IBD patients being at increased risk of opportunistic infections and respiratory illnesses.[11,12] Several studies have investigated the occurrence of COVID-19 in IBD populations, but methodological heterogeneity make comparisons difficult.[13] Furthermore, differences in the severity of the pandemic, as well as how test strategies and preventive measures such as lockdowns have been implemented across countries, probably influence findings.

However, the findings of the present study are somewhat in accordance with previous reports.[14,15] The incidence of COVID-19 overall in the IBD patients was slightly higher than that of the general population, but incidence rates differed significantly between countries. This increased incidence rate was driven by findings from countries such as France, Italy and Hungary which have seen high number of COVID-19 cases. Our findings from Denmark are in accordance with two recent population-based studies demonstrating that IBD patients were not at increased risk of COVID-19.[16,17] Similarly, a Dutch study observed a comparable risk of COVID-19 between IBD patients and the general population.[18]

We found that patients receiving monotherapy with thiopurines were at a decreased risk of COVID-19. Despite the limited number of patients at risk, this is in contrast to a recent report from the international Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease [SECURE- IBD] database, where thiopurine as monotherapy or in combination with anti-TNF was associated with an increased risk of severe COVID-19.[19] However, findings from the SECURE-IBD registry probably suffer from reporting bias, which make them not fully representative of the general IBD patient population. Also, these findings have not been replicated in population-based cohorts.[16,18] Furthermore, we did not observe that the use of 5-ASA or biological therapies influenced the risk of COVID-19, which is in accordance with other cohorts. A recent meta-analysis found a pooled increased risk in patients exposed to 5-ASA and corticosteroids,[13,15,20] but this meta-analysis included

Table 2. Standardized incidence ratio [SIRs] of COVID-19 and severe COVID-19 according to country recruitment in 5457 patients with inflammatory bowel disease in the I-CARE cohort study who have responded to at least one e-PRO COVID-19 questionnaire from March to December 2020.

	Cases	COVID–19						Severe COVID–19					
		Control incidence*	Expected cases	Reported cases	Cases incidence*	SIR [95% CI]	*p* value	Control incidence*	Expected cases	Reported cases	Cases incidence*	SIR [95% CI]	*p* value
Belgium [BE]	279	56.88	15.9	20	71.7	1.26 [0.77–1.95]	0.18	4.35	1.2	0	–	–	–
Germany [DE]	141	21.39	3.0	4	28.4	1.33 [0.36–3.40]	0.35	1.06	0.1	1	7.09	6.69 [0.09–37.22]	0.14
Denmark [DK]	128	29.06	3.7	3	23.4	0.81 [0.16–2.36]	0.72	1.45	0.2	1	7.81	5.40 [0.07–30.06]	0.17
Spain [ES]	302	41.73	12.6	8	26.5	0.63 [0.27–1.25]	0.93	4.76	1.4	2	6.62	1.39 [0.16–5.03]	0.42
France [FR]	2189	39.63	86.8	125	57.1	1.44 [1.20–1.72]	<0.001	3.77	8.2	3	1.37	0.36 [0.07–1.06]	0.99
Greece [GR]	607	13.06	7.9	7	11.5	0.88 [0.35–1.82]	0.68	0.28	0.2	0	–	–	–
Hungary [HU]	140	33.65	4.7	11	78.6	2.33 [1.16–4.18]	0.009	NA	–	2	14.29	1.09 [0.12–3.93]	0.55
Ireland [IR]	89	20.78	1.8	2	22.5	1.08 [1.22–3.91]	0.55	0.73	0.1	0	–	–	–
Israel [IL]	47	51.09	2.4	0	–	–	–	3.20	0.2	0	–	–	–
Italy [IT]	471	35.71	16.8	29	61.6	1.72 [1.15–2.48]	0.004	3.90	1.8	2	4.25	4.25 [0.12–3.93]	0.98
Netherlands [NL]	40	47.45	1.9	0	–	–	–	1.32	0.1	0	–	–	–
Poland [PL]	57	34.84	2.0	1	17.5	0.50 [0.01–2.80]	0.86	0.51	0.0	0	–	–	–
Portugal [PT]	77	42.00	3.2	2	26.0	0.62 [0.07–2.23]	0.83	1.16	0.1	0	–	–	–
United Kingdom [UK]	890	39.83	35.5	21	23.6	0.59 [0.37–0.91]	0.99	4.34	3.9	1	1.12	0.26 [0.01–1.44]	0.98
Overall	5457	–	198.24	233	42.7	1.18 [1.03–1.34]	0.009	2.37	17.49	12	3.04	0.69 [0.35–1.20]	0.93

*Per 1000 patient-years. NA: not available.

Table 3. Unadjusted and adjusted analyses comparing the impact of ongoing treatment on the risk of COVID-19 and severe COVID-19 in 5457 patients with inflammatory bowel disease in the I-CARE cohort study who have responded to at least one e-PRO COVID-19 questionnaire from March to December 2020.

	COVID–19						Severe COVID–19					
	Unadjusted odds ratio	*p*–value	Adjusted odds ratio*	*p*–value	Number of patients at risk	Number of cases	Unadjusted odds ratio	*p*–value	Adjusted odds ratio*	*p*–value	Number of patients at risk	Number of cases
No treatment	0.93 [0.65–1.33]	0.69	0.90 [0.61–1.33]	0.59	943	38	0.45 [0.06–3.57]	0.45	0.85 [0.10–7.69]	0.89	38	1
Aminosalicylates monotherapy	0.78 [0.53–1.15]	0.21	0.86 [0.58–1.30]	0.48	865	30	0.60 [0.07–4.76]	0.63	∞	0.99	30	1
Steroids	1.49 [0.91–2.46]	0.11	1.59 [0.94–2.70]	0.08	295	18	2.56 [0.52–12.50]	0.25	2.70 [0.47–16.67]	0.27	18	2
Thiopurine monotherapy	0.51 [0.31–0.84]	0.008	0.51 [0.30–0.88]	0.01	716	16	5.00 [1.19–20.00]	0.03	3.45 [0.55–20.00]	0.19	17	3
Anti-TNF	1.43 [1.10–1.86]	0.008	1.32 [0.99–1.76]	0.06	1901	100	0.43 [0.11–1.61]	0.21	0.83 [0.18–3.70]	0.81	100	3
Anti-TNF monotherapy	1.31 [0.99–1.75]	0.06	1.23 [0.901.67]	0.20	1445	74	0.18 [0.02–1.45]	0.11	0.37 [0.04–3.13]	0.36	74	1
Anti-TNF combination therapy	1.40 [0.92–2.13]	0.20	1.32 [0.83–2.08]	0.24	456	26	1.64 [0.34–7.69]	0.54	2.27 [0.37–14.29]	0.38	26	2
Vedolizumab	1.06 [0.66–1.69]	0.81	1.19 [0.73–1.93]	0.48	445	20	1.02 [0.12–7.69]	0.98	∞	0.99	20	1
Ustekinumab	1.03 [0.61–1.62]	0.97	0.99 [0.58–1.70]	0.98	425	18	1.09 [0.13–9.09]	0.94	3.33 [0.32–33.33]	0.32	18	1
Tofacitinib	2.06 [0.53–5.78]	0.17	2.33 [0.83–6.58]	0.11	48	4	∞	NS	∞	0.99	4	0

*Adjusted for age and body mass index.

Figure 2. Impact of the COVID-19 outbreak on clinical activity and treatment of 5457 patients with inflammatory bowel disease in the I-CARE cohort study who have responded to at least one e-PRO COVID-19 questionnaire from March to December 2020. Ongoing treatment during 2020 of patients with [A] Crohn's disease and [B] ulcerative colitis and inflammatory bowel disease unclassified. Disease activity during 2020 [C] according to Harvey–Bradshaw index in patients with Crohn's disease and [D] according to Simple Clinical Colitis Activity Index in patients with ulcerative colitis and inflammatory bowel disease unclassified and [E and F] according to COVID-19.

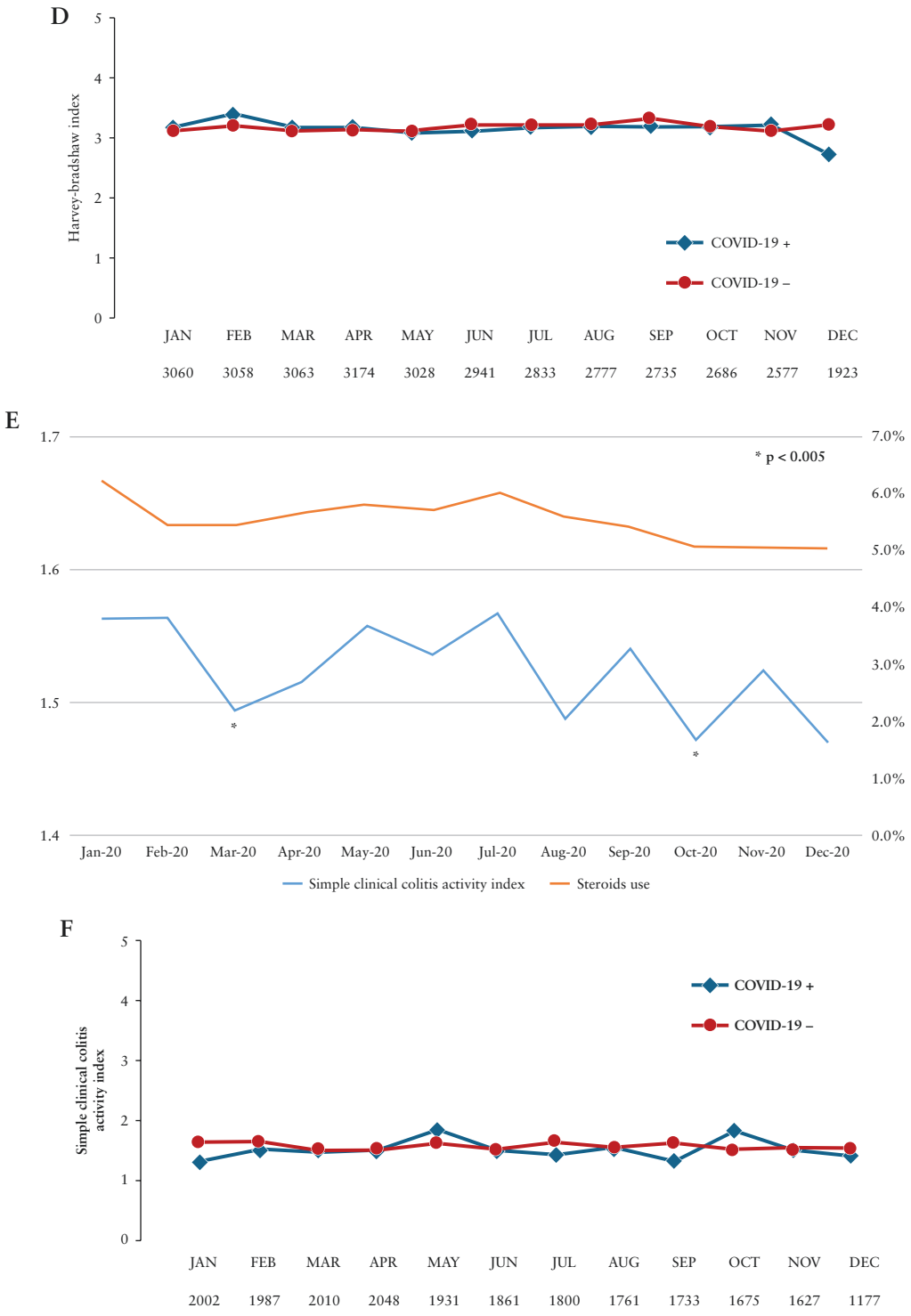

Figure 2. Continued

mostly cohorts who were prone to selection bias and hence limited generalizability. Thus, our findings are reassuring for both patients and healthcare providers.

Finally, we observed that the number of endoscopic procedures decreased markedly during the initial months of the pandemic. While we did not collect data on indications for diagnostic procedures in the cohort, our finding is not surprising given the dramatic and significant reductions in staffing levels seen during the pandemic, which has affected routine care for people with IBD, including disease and treatment monitoring.[21,22] Physicians have opted to cancel elective endoscopic procedures and to reserve endoscopy for acute situations in accordance with international recommendations.[23–26] As the situation stabilized in many countries during mid-2020, the rate of endoscopy in our cohort returned to that of the previous two years. While we were unable to assess the impact of this reduction in investigations on the disease course of our cohort, it is comforting that no change in clinical disease activity was observed during that period.

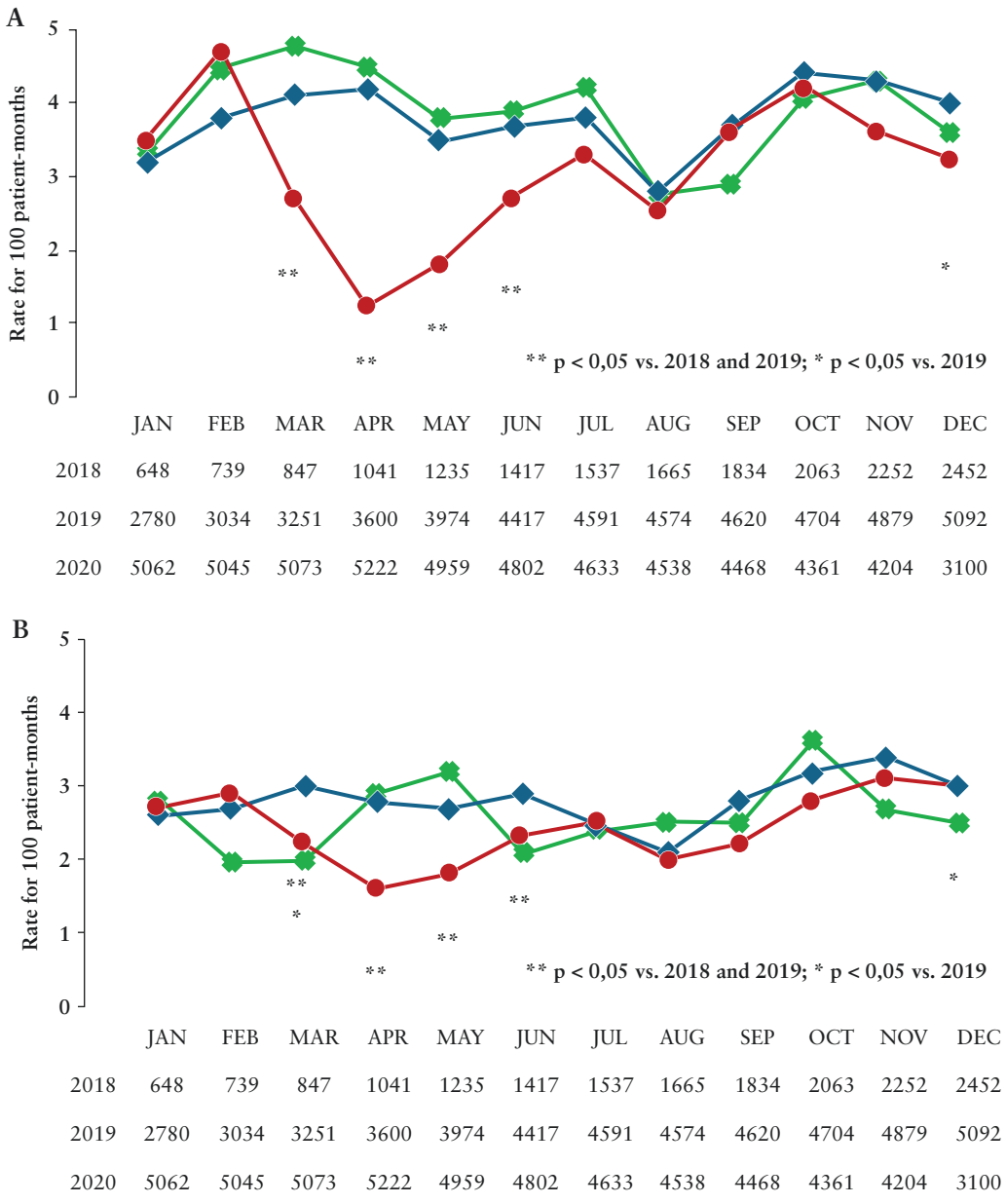

Figure 3. Impact of the COVID-19 outbreak on endoscopic imaging of 5457 patients with inflammatory bowel disease in the I-CARE cohort study who have responded to at least one e-PRO COVID-19 questionnaire from March to December 2020. [A] Monthly rate of endoscopic procedures [colonoscopy, flexible sigmoidoscopy, upper gastrointestinal endoscopy and other endoscopic procedures] in 2020, 2019 and 2018. [B] Monthly rate of morphological examination [magnetic resonance imaging enterography, ultrasonography, compted tomography scan, barium contrast and other morphological examination] in 2020, 2019 and 2018.

The strengths of the present study include its prospective design and the simultaneous inclusion of patients in several European countries. Furthermore, we were able to compare the incidence rates of COVID-19 within the I-CARE cohort with those of the receptive background populations.[4] Finally, with more than 5000 IBD patients, the present study is among the largest investigating COVID-19 in IBD. However, several limitations need to be taken into consideration. Data on COVID-19 were self-reported by patients, which might introduce inaccuracy. Additionally, the diagnosis of COVID-19 was performed using either serological or PCR tests in the I-CARE cohort whereas the European Centre for Disease Prevention and Control only reported COVID-19 cases with a positive PCR test. Indeed, the diagnosis of COVID-19 was performed using a serological test alone in 12.9% in the I-CARE cohort. However, the I-CARE study is designed to rely on prospectively reported information by patients and subsequent investigator confirmation. We collected hospitalization reports of patients who reported severe COVID-19 without any discrepancy. Furthermore, patients were selected by their physicians for inclusion in the I-CARE study and therefore might not be fully representative of the general IBD population of their respective country. Finally, we acknowledge limitations of the epidemiological data on COVID-19 incidence and prevalence extracted from the European Centre for Disease Prevention and Control.[10] Indeed, heterogeneity in the diagnostic process and its access to the general population was high at the beginning of the COVID-19 outbreak. Furthermore, age-specific data were not available for all European countries involved in the I-CARE study, which did not allow us to performed age-adjusted analysis.

In conclusion, we have provided pan-European and prospective data on the risk of COVID-19 and severe COVID-19 in patients with IBD compared to the general population, showing no increase in either COVID-19 or severe COVID-19 rates. We did not find any association between use of aminosalicylates, steroids, and immunosuppressant and/or biological agents and the risk of COVID-19 and severe COVID-19. Meanwhile, access to endoscopy and imaging was significantly restricted during the first months of the European COVID-19 outbreak, fortunately without any increase in clinical disease activity scores within the cohort. Those results should allow us to reassure our patients with respect to their treatment.

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Conflict of Interest

Aurelien Amiot has received consulting fees from Abbvie, Tillotts pharma, Janssen, Hospira, Takeda, Fresenius Kabi, Pfizer and Gilead as well as lecture fees and travel accommodations from Abbvie, Janssen, Biocodex, Hospira, Ferring, Biogen, Tillotts pharma, Fresenius Kabi, Takeda and MSD. Filip Baert has received grant/research support from AbbVie, Amgen, Janssen and Takeda; honoraria from AbbVie, Amgen, Arena, Celgene, Ferring, Fresenius Kabi, Janssen, Merck Sharp & Dohme, Pfizr, and Takeda; and was on speaker bureaus for AbbVie, Ferring, Janssen, Merck Sharp & Dohme, Pfize, and Takeda. Jean-François Rahier reports: speaker fees from Abbvie, MSD, Takeda, Pfizer, Ferring, Falk, Biogen, Amgen, Celltrion. Consultancy: Abbvie, Takeda, Hospira, Mundipharma, MSD, Pfizer, GlaxoSK and Janssen; research grant from Takeda and Abbvie. Livia Biancone received lecture fees and travel accommodations from Janssen, Zambon, Takeda, Vifor Pharma and Ferring. Eugeni Domènech has served as a speaker, or has received research or education funding or advisory fees from AbbVie, Adacyte Therapeutics, Biogen, Celltrion, Gilead, Janssen, Kern Pharma, MSD, Pfizer, Roche, Samsung, Takeda and Tillots. Catherine Reenaers has served as a speaker and advisory board member for Abbvie, Janssen, Pfizer, Takeda and Celltrion. Ailsa Hart has served as consultant, advisory board member or speaker for AbbVie, Arena, Atlantic, Bristol-Myers Squibb, Celgene, Celltrion, Falk, Ferring, Galapogos, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. She also serves on the Global Steering Committee for Genentech. Laurent Peyrin-Biroulet received consulting fees from Merck, Abbvie, Janssen, Genentech, Ferring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pilège, BMS, UCB-Pharma, Hospira, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, Pfize, and HAC-Pharma; and received lecture fees from Merck, Abbvie, Takeda, Janssen Cilag, Ferring, Norgine, Tillots, Vifor, Therakos, HAC-Pharma and Mitsubishi. The remaining authors have no conflicts of interest to report.

Author Contributions

Conception and design of the study: AAm, LBe, FB, JFR, LPB, JB. Generation, collection, assembly, analysis and/or interpretation of data: AAm, JB. Drafting or revision of the manuscript: AAm, JFR, FB, SN, AH, NV, LBi, ED, CR, LPB, LBe, JB LB, FB, JFR, LPB, JB. Approval of the final version of the manuscript: AAm, JFR, FB, SN, AH, NV, LBi, ED, CR, LPB, LBe, JB LB, FB, JFR, LPB, JB.

Data Availability

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

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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