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

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Conflicts of interest
The authors disclose no conflicts.

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What Is the Incidence of COVID-19 in Patients With IBD in Western Countries?

Dear Editors:

We read with interest the article by Gubatan et al[1] reporting that, among 168 patients with inflammatory bowel disease (IBD) tested in Northern California (Stanford University School of Medicine), the prevalence of coronavirus disease 2019 (COVID-19) was 3.0%, comparable with the population-weighted prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–positive serology in Santa Clara County at 2.8%. The authors concluded that their results provided much-needed epidemiologic data and reassurance that COVID-19 rates in patients IBD may be comparable with that in the general population.

Data on COVID-19 incidence in IBD have been contradictory. Initial evidence from China suggested that patients with IBD even had a decreased risk of COVID-19 compared with the general population, because no patients with IBD were reported to be infected with SARS-CoV-2 in the IBD Elite Union, which covers the 7 largest IBD referral centers in China, or in the 3 largest tertiary IBD centers in Wuhan.[2] Subsequently, a study reported that, among 522 patients with IBD followed in a tertiary center at Bergamo, the Italian province with one of the highest rates of infection anywhere in the world, no case of COVID-19 was diagnosed.[3]

We recently evaluated the risk of COVID-19 and associated mortality among 1918 patients followed at an IBD Unit in the Madrid region (Hospital Clínico San Carlos), one of the most affected regions in Spain, and compared it with the general population.[4] Through April 8, 2020, we detected 12 COVID-19 cases, giving a crude cumulative incidence of 6.2 cases per 1000 patients with IBD. Because we do not follow pediatric patients in our unit, the mean age of 50 years in our patients with IBD (0.15% of patients <20 years) was significantly higher than the mean age of 42 years in the general population in Madrid (20.2% of individuals under 20 years; $P < .001$, unpublished data, May 10, 2020). After adjusting for age we obtained an age-standardized rate of 4.9 COVID-19 cases per 1000 patients with IBD, which was slightly lower than the rate in the general population. Given the low number of COVID-19 cases in our series, any missed diagnoses would, however, have a high impact on the reported incidence rate. We also reported an age-adjusted COVID-19 associated mortality rate of 0.82 per 1000 patients with IBD, similar to that of the general population.

A third study assessed the incidence of COVID-19 among a cohort of patients with IBD from France (Nancy University Hospital; 2000 patients) and Italy (Humanitas, Milan; 4000 patients).[5] They identified 15 COVID-19 cases, corresponding with a crude cumulative incidence of 2.5 cases per 1000 patients with IBD, which was considered broadly similar to that observed in the general population (the cumulative incidence in France and Italy was 1.7 cases per 1000 at the time of the study). The incidence was not adjusted by age, and we do not know if the mean age of the IBD cohort was higher than that of the general population. If this were so, it would be expected that the age-standardized rate of COVID-19 in IBD would be less than that reported. We believe this study could also be affected by underreporting of COVID-19 among the IBD population, while all positive viral reverse transcriptase polymerase chain reaction were counted for the general population.

Although available evidence is limited, it seems that patients with IBD are not at a greater risk of acquiring COVID-19. This finding is noteworthy because approximately 37% of patients with IBD in the Northern California cohort and our cohort in Madrid were receiving immunosuppressants and/or biologics.[1,5] The impact of these drugs on SARS-CoV-2 infection acquisition or progression needs to be further investigated. Although thiopurines[6] and anti–tumor necrosis factor agents[7] have been associated with serious viral infections, some authors believe that patients with IBD might be protected against severe disease because the viral-induced "cytokine release storm" sometimes reported in COVID-19 could potentially be attenuated by the potent anti-inflammatory drugs commonly used to treat IBD. As a result, COVID-19 may be milder in these patients and so infection may not be confirmed by testing. In agreement, a recent study of patients included in the SECURE-IBD registry reported that tumor necrosis factor antagonist monotherapy was not associated with and even may have a protective effect against severe COVID-19.[8] We also believe that rigorous adherence of patients with IBD to protective measures, encouraged by routine advice from IBD nurses and IBD staff, may further help contain SARS-CoV-2 dissemination in this population.

In conclusion, we agree with Gubatan et al[1] that the available data indicate that COVID-19 is not more prevalent in patients with IBD than in the general population.

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Conflicts of interest

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Reply. We appreciate the positive response from Dr Carlos Taxonera and colleagues[1] regarding our epidemiological study on rates of Coronavirus Disease 2019 (COVID-19) among patients with inflammatory bowel disease (IBD).[2] Our results, based on our experience in Northern California during the early days of the COVID-19 pandemic (March 4, 2020, to April 14, 2020), suggested that the prevalence of COVID-19 among patients with IBD was comparable with the general population.[2] Since our study, much data have rapidly accumulated to overcome sample size limitations and enabled us to expand and refine our understanding of the risks of COVID-19 among patients with IBD both at the national level and on a global scale.

In a retrospective, multicenter research network study (data collected from January 20, 2020, and May 26, 2020) in the United States involving more than 40 million patients from multiple health care organizations, Singh et al[3] reported COVID-19 in 232 patients with IBD and 19,776 patients without IBD. In unadjusted analysis, there was no difference in the risk of severe COVID-19 between the IBD and non-IBD groups (risk ratio [RR], 1.15; 95% CI, 0.92–1.45; $P = .23$). After propensity score matching, the risk of severe COVID-19 was similar (RR 0.93; 95% CI, 0.68–1.27; $P = .66$) between both groups.[3] In the same study, immune-mediated therapy in the preceding year was not associated with a higher risk of severe COVID-19 compared with patients with IBD not on immune-mediated therapy. However, preceding corticosteroid use was associated with an increased risk of severe COVID-19 compared with patients with IBD without corticosteroids.

In a systematic review (up to July 29, 2020) and meta-analysis of 23 studies including 243,760 patients with IBD, D'Amico et al[4] reported COVID-19 in 1028 patients with IBD (49.5% with Crohn's disease, 41.6% with ulcerative colitis) resulting in a cumulative prevalence of 0.4%. Increasing age and the presence of comorbidities were recognized as risk factors for COVID-19 and negative clinical outcomes. In another systematic review and meta-analysis (December 2019 to July 2020) by Singh et al[5] including 24 studies (patient cohorts from the United States, Spain, Iran, Italy, France, Germany, Greece, China, South Korea, Hong Kong, Taiwan, and the international registry SECURE-IBD), the pooled incidence rate of COVID-19 in patients with IBD was 4.02 (95% CI, 1.44–11.17; $I^2 = 98\%$) per 1000, whereas the pooled rate of COVID-19 in the general population was 6.59 (95% CI, 3.25–13.35; $I^2 = 100\%$) per 1000. The pooled relative risk of COVID-19 in patients with IBD was not different from the general population (relative risk 0.47; 95% CI, 0.18–1.26; $I^2 = 89$).

We agree with Taxonera et al[1] that the impact of IBD therapies on risks of COVID-19 infection acquisition and progression warrants further investigation, as immunosuppressive drugs have been linked with risk of infection in IBD.[6] In the meta-analysis by Singh et al,[5] only 5-aminosalicylic acid (5-ASA) use was associated with increased risk of COVID-19 (relative risk 1.89; 95% CI, 1.23–2.93; $I^2 = 37\%$). Furthermore, 5-ASA and steroid use were associated with increased risk of COVID-19 inpatient hospitalizations, intensive care unit admissions, and mortality, whereas there were no significant associations with immunomodulators and biologic therapies.[5] In an analysis of the SECURE-IBD registry (1439 cases from 47 countries), Ungaro et al[7] demonstrated that mesalamine (5-ASA) use was associated with severe COVID-19 compared with no 5-ASA use or anti–tumor necrosis factor monotherapy as reference groups. The authors also demonstrated that thiopurine monotherapy and the combination thiopurines with anti–tumor necrosis factor agents were associated with significantly increased risk of severe COVID-19.[6] Further studies will be needed to understand the mechanisms of how 5-ASA and steroids may confer risk of COVID-19 infection and how thiopurines may modulate COVID-19 severity in patients with IBD. Although biologic therapies have not been linked to COVID-19 susceptibility and severity in IBD, a recent study demonstrated that patients with immune-mediated inflammatory diseases receiving cytokine inhibitors have low prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seroconversion.[8] Future studies investigating the ability of patients with IBD on immunosuppressive drugs to develop robust, longstanding immunity against SARS-COV-2 after natural infection or vaccination are warranted.

In conclusion, cumulative evidence to date support our original finding that the risk of COVID-19 in patients with IBD is comparable with the general population.[2] Future shift in focus toward understanding the incidence of protective SARS-CoV-2 antibodies in patients with IBD on different therapies in light of the increasing number of patients recovering from COVID-19 and the expanding availability of COVID-19 vaccines would be highly valuable.