ORIGINAL ARTICLE

Inflammatory bowel disease is associated with higher seroprevalence rates of antibodies against SARS-CoV-2

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KEY WORDS

antibody, COVID-19, inflammatory bowel disease

EDITORIAL

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ABSTRACT

INTRODUCTION According to the current data, there has been no increase in the incidence of COVID-19 in patients with inflammatory bowel disease (IBD).

OBJECTIVES The available data are based on symptomatic cases and do not include the asymptomatic ones. To measure the exact infection rate, we initiated a study that aimed to assess the seroprevalence of anti–SARS-CoV-2 antibodies in IBD.

PATIENTS AND METHODS A total of 864 individuals were enrolled in the study, including 432 patients with IBD (290 with Crohn disease and 142 with ulcerative colitis) and 432 controls without IBD (healthcare professionals) matched for age and sex. Serum samples were prospectively collected, and the presence of anti–SARS-CoV-2 immunoglobulin (Ig) G and IgM + IgA antibodies were measured using the enzyme-linked immunoassay method (Vircell Microbiologists).

RESULTS A significantly higher percentage of positive results for anti–SARS-CoV-2 antibodies, both in the IgG and IgM + IgA class, was found in patients with IBD (4.6% and 6%, respectively, compared with 1.6% and 1.1%, respectively, in controls; both P values <0.05). No patient had symptomatic COVID-19. There was no association among patients' age, sex, drugs used for IBD, or disease activity and the occurrence of IgG antibodies.

CONCLUSIONS Patients with IBD may be at higher risk of developing SARS-CoV-2 infection, defined as the presence of elevated levels of anti–SARS-CoV-2 IgG antibodies, but not of having a symptomatic and/or severe course of COVID-19 compared with healthcare professionals without IBD.

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INTRODUCTION The COVID-19 pandemic, caused by SARS-CoV-2, has significantly impacted the whole world in recent months. Much effort is being made to introduce an effective strategy to protect people from SARS-CoV-2 infection or find a medical cure for it. Up till now, however, neither a vaccine nor a targeted antiviral therapy has been successfully developed and approved to be used in clinical pr tice.[1-3] Thus, it seems that following the rules of social distancing, especially in the high-risk groups, remains the most reasonable strategy to limit the spread of the disease.[4-7]

WHAT'S NEW?

This study aimed to measure the exact rate of SARS-CoV-2 infection in patients with inflammatory bowel disease (IBD), based on the assessment of the seroprevalence of anti–SARS-CoV-2 antibodies. Hyperinflammation plays a crucial role in the pathogenesis of severe COVID-19, as well as in inflammatory bowel disease. This makes the group of patients with IBD particularly interesting in the context of epidemiology and the course of COVID-19. Our study shows that patients with IBD are more likely to develop SARS-CoV-2 infections, but these are mainly asymptomatic. Inflammatory bowel disease, or the drugs used to treat it, may have a protective effect on severe COVID-19.

Although COVID-19 is mainly associated with the respiratory tract, it is also of interest to gastroenterologists.[8-11] Patients with inflammatory bowel disease (IBD), including Crohn disease (CD) and ulcerative colitis (UC), constitute a group of gastroenterological patients who require special care during the pandemic. Since the dysregulation of immune response plays a fundamental role in the pathogenesis of IBD and the vast majority of drugs used in the IBD therapy suppress immune system function, it was speculated that patients with IBD are at high risk of both SARS-CoV-2 infection and severe disease course.[12] That hypothesis was additionally supported by the fact that infectious diseases are one of the most common complications of both CD and UC and treatment.[13,14] Therefore, numerous scientific societies issued guidelines for the management of patients with IBD during the pandemic.[15-19] However, the data available so far do not support concerns about the safety of patients with IBD. Moreover, there have been reports suggesting the protective effect of these diseases on infection risk and severity.[20,21] This could be explained by the fact that hyperinflammation, which plays a crucial role in the pathogenesis of severe COVID-19, can be dampened by drugs interfering with immune response and used in IBD or by IBD itself.[20,22]

The current data on the impact of IBD on the course of COVID-19 are based mainly on symptomatic cases confirmed by a positive nasopharyngeal swab test result.[8,20,21] However, a growing body of evidence suggests that the percentage of asymptomatic cases of SARS-CoV-2 infection is very high.[23-25] That is why, to measure the exact infection rate and to monitor the epidemic spread of COVID-19 in IBD, we initiated a study aimed at estimating the seroprevalence of anti–SARS-CoV-2 antibodies among Polish patients with CD and UC.

PATIENTS AND METHODS This study is a multicenter, prospective, observational study assessing the seroprevalence of anti–SARS-CoV-2 antibodies in Polish patients with IBD. Three tertiary centers, recruiting patients from 3 different geographical areas in Poland: east-central (Warsaw), western (Poznań), and south-central (Łódź), participated in the study. All consecutive patients with IBD who visited hospitals between May 1 and June 15, 2020 were included in the analysis. The visits were either due to the continuation of biologic treatment or disease exacerbation.

Patient characteristics Upon admission, each patient filled out a dedicated questionnaire on the presence of any symptoms suggestive of respiratory tract infectious disease in the past 7 days. Moreover, a detailed assessment of gastrointestinal symptoms was performed, together with the evaluation of IBD activity using either the Crohn Disease Activity Index or partial Mayo score.

Control group The control group consisted of healthcare professionals without IBD, employees of the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland (n = 1036). To reliably compare patients with IBD and those without IBD, a propensity matching method was applied using a logistic regression model (n = 432).

Laboratory analysis Serum samples were prospectively collected from non-IBD healthcare professionals and all patients with IBD on admission and immediately stored at –80 °C. The concentrations of anti–SARS-CoV-2 immunoglobulin (Ig) G and IgM + IgA antibodies were measured using the enzyme-linked immunoassay method, targeting viral spike (S) and nucleocapsid (N) antigens (Vircell Microbiologists, Granada, Spain). All tests were performed in the Coronavirus Laboratory Diagnostic Unit of the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland. According to the manufacturer's recommendations, the results were considered positive if the antibody index (defined as sample optical density / cutoff mean serum optical density × 10) was above 6 in the case of IgG and above 8 in the case of IgM + IgA.

Data assessment After all clinical data and serum samples were prospectively collected, seroprevalence was assessed and the results were retrospectively analyzed. All patients who had test results positive for IgG were asked about any suspicious symptoms suggestive of symptomatic COVID-19 (fever, cough, loss of smell and / or taste, chills, and dyspnea) in the previous 4 months. For epidemiological reasons, in the case of patients with results positive for IgM + IgA, nasopharyngeal swabs were taken post-hoc for the detection of SARS-CoV-2 infection using the polymerase chain reaction (PCR) technique (FIGURE 1).

Statistical analysis The comparison of seroprevalence between the IBD and control groups was performed using the χ^2 test of independence. The Mann–Whitney test was used to compare the levels of immunoglobulins between the study groups.

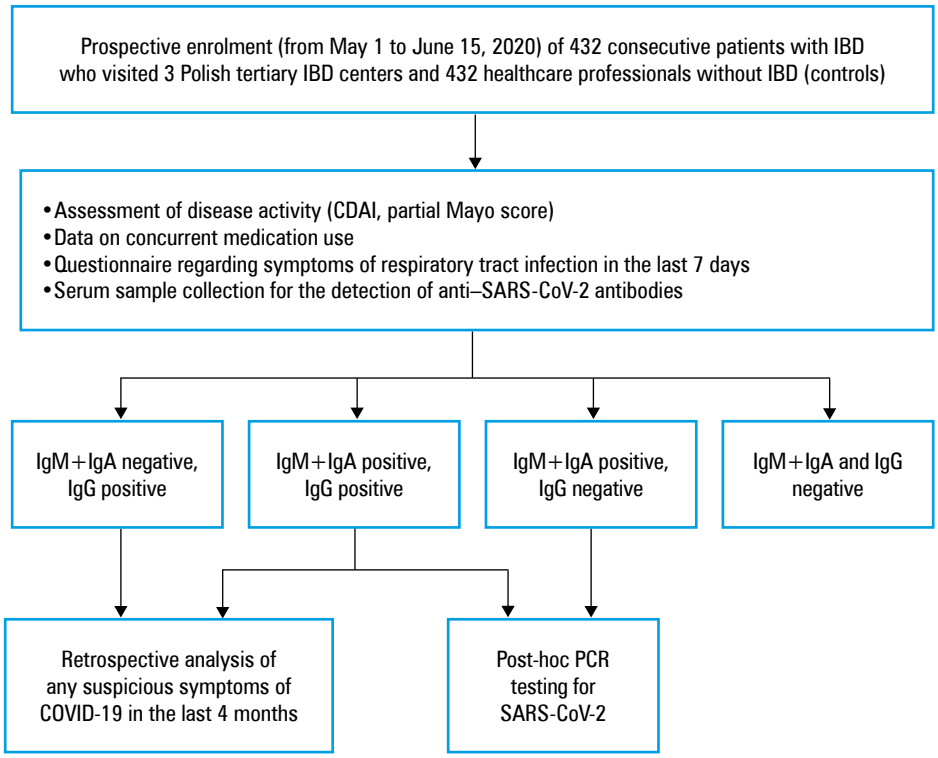

FIGURE 1 Study flowchart
Abbreviations: CDAI, Crohn Disease Activity Index; IBD, inflammatory bowel disease; Ig, immunoglobulin; PCR, polymerase chain reaction

TABLE 1 Characteristics of the study and control groups, including the immunoglobulin (Ig) G and IgM + IgA anti–SARS-CoV-2 seroprevalence

Variable		Patients with IBD (n = 432)	Control group (n = 432)	*P* value
Age, y, mean (SD)		35.7 (12.4)	35.7 (12.3)	–
Sex, n (%)	Female	173 (40)	173 (40)	–
	Male	259 (60)	259 (60)	
Positive anti–SARS-CoV-2 IgG results, n (%)		20 (4.6)	7 (1.6)	0.01
Positive anti–SARS-CoV-2 IgM + IgA results, n (%)		26 (6)	5 (1.1)	<0.001
Anti–SARS-CoV-2 IgG index, mean (min–max)		2 (0.5–27.5)	1.9 (0–33.8)	<0.001
Anti–SARS-CoV-2 IgM + IgA index, mean (min–max)		2.8 (0–38.3)	1.8 (0–16.8)	<0.001

Abbreviations: see FIGURE 1

To estimate factors that might have caused the risk of seropositive status in patients with IBD, we used a Bayesian logistic regression model, accounting for numerous covariates of the patient population. The analysis was performed with the use of the STATA 16 statistical package (StataCorp LCC, College Station, Texas, United States). We used noninformative normal (0.1) priors for logistic regression β coefficients. Using the Metropolis–Hastings sampling, we ran Markov chain Monte Carlo with 12 500 iterations with the first 2500 for burn-in and assessed convergence visually. The results were presented as odds ratios (ORs) of being seropositive for each subset using the posterior draws for each logistic regression coefficient and their 95% CIs. A *P* value less than 0.05 was considered significant.

Ethics approval This study was approved by the Ethics and Supervision Committee for Human and Animal Research at the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland (No. 66/2020) and the Bioethics Committee at Poznan University of Medical Sciences (No. 364/20). All patients provided written informed consent to participate in the study.

RESULTS

A total of 864 individuals were enrolled in the study: 432 patients with IBD (290 with CD and 142 with UC) and 432 healthcare professionals without IBD who were matched for age and sex and constituted the control group. The baseline characteristics of the study groups along with data on anti–SARS-CoV-2 seroprevalence and levels of IgG and IgM + IgA are presented in TABLES 1 and 2. The associations between IgG or IgM + IgA seropositivity against SARS-CoV-2 and clinical variables, as well as IBD treatment, are shown in FIGURES 2 and 3.

A significantly higher percentage of positive results of anti–SARS-CoV-2 antibodies, both in the IgG and IgM + IgA classes, was found in patients with IBD compared with controls (4.6% vs 1.6%; $P = 0.01$ and 6% vs 1.1%; $P < 0.001$, respectively). Positive IgG antibody results were more frequent among younger male patients (especially below 30 years of age). No differences were noted when the study patients were stratified by the type of IBD (UC vs CD) or by the type of treatment used.

Regarding IgM + IgA antibodies, no difference in terms of sex and age was observed. On the other hand, there was a strong association between

TABLE 2 Characteristics of the study group, including disease activity and inflammatory bowel disease treatment

Variable		Patients with IBD (n = 432)
Clinical activity of IBD, mean (min–max)	Crohn disease, CDAI	138 (12–636)
	Ulcerative colitis, partial Mayo score	2 (0–8)
Treatment received	5-ASA	370 (86.1)
	Thiopurines	243 (56.3)
	Methotrexate	8 (1.9)
	Anti–TNF-α antibodies	214 (49.8)
	Infliximab	165 (38.4)
	Adalimumab	49 (11.4)
	Vedolizumab	102 (23.7)
	Ustekinumab	14 (3.3)
	Systemic steroids	58 (13.5)
	Budesonide	29 (6.7)

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: ASA, acetylsalicylic acid; TNF, tumor necrosis factor; others, see **FIGURE 1**

the use of mesalazine and the presence of elevated levels of IgM + IgA antibodies (OR, 22.75; 95% CI, 1.07–146.1). No effect of other drugs on the occurrence of IgM + IgA antibodies was observed.

None of the IgG-seropositive patients with IBD reported any symptoms suggestive of COVID-19 in the 4 months preceding enrolment in our study. In the post-hoc analysis, none of the IgM + IgA–seropositive patients with IBD had positive PCR test results for SARS-CoV-2 infection from nasopharyngeal swabs.

DISCUSSION Despite extensive research in the field, the diagnosis of SARS-CoV-2 infection is not easy. Polymerase chain reaction testing of nasopharyngeal swabs remains the gold standard. However, this method has some significant limitations. These include the fluctuating nature of virus replication in the nasopharynx, the risk of incorrect material collection, as well as the methodology of the determination itself, requiring the use of specialized equipment, which is time-consuming and expensive.[26,27]

A high percentage of asymptomatic infections, together with the above-mentioned limitations of PCR testing, compelled us to look for alternative methods to diagnose COVID-19, or at least to identify individuals at increased risk of infection, in order to narrow down the group of people tested with the reference method. Serological methods seem appropriate for these purposes. They are easy to perform, cheaper, and suitable for screening. Therefore, from the beginning of the pandemic, a lot of tests based on the detection of antibodies against SARS-CoV-2 have appeared. These tests differ in many respects, which translates into their reliability and, hence, clinical usefulness. These differences are related to the method of antibody detection used, the type of detected antibodies, and their class. Other limitations of serological methods result from the delayed appearance of antibodies at detectable concentrations (on average, 5.5 days from the onset of symptoms for IgM antibodies and 14 days for IgG antibodies), the presence of cross-reacting antibodies (eg, with other viruses or in autoimmune diseases), and a reduced ability to produce antibodies in some patient groups (eg, patients receiving immunosuppressive therapy).

Serological tests using IgM antibodies are still not recommended in the diagnosis of active infection. Therefore, to increase their sensitivity, a parallel assessment of anti–SARS-CoV-2 IgA antibodies has been proposed. Despite the increase in sensitivity, the usefulness of tests based on those antibodies is still controversial. The production of antibodies in the IgM and IgA classes can differ individually and is time-dependent. A few studies assessing the usefulness of determining antibodies in these classes in addition to using the standard method (PCR testing of nasopharyngeal swabs) have been published. These were, however, inconclusive.[28] The sensitivity of the test used in the study was assessed by the manufacturer as 88% (5 days after a positive PCR test result), and specificity, 99%.[29-32]

In contrast, the high diagnostic accuracy of serological tests in identifying patients who recovered from SARS-CoV-2 infection is recognized. The most reliable tests are those using the enzyme-linked immunoassay method, assessing IgG antibodies against viral spike (S) and nucleocapsid (N) antigens. Such a test was used in this study. The sensitivity of the test was assessed by the manufacturer as 85% (10 to 19 days after a positive PCR test result), and specificity, 98%.[29-32]

The presented results indicate a significantly increased percentage of patients with SARS-CoV-2 infection among patients with IBD in the Polish population (IgG antibodies) compared with healthcare professionals without IBD. At the same time, not a single case of symptomatic infection was observed.

Of note, the control group consisted of healthcare professionals without IBD—the employees of a hospital that was completely transformed during the pandemic into a multiprofile infectious disease center. It was the biggest hospital in Poland, providing comprehensive, multispecialist care for patients with COVID-19. Since all Polish citizens were recommended to limit contact with healthcare institutions to the necessary minimum, serological population studies have not been initiated in Poland so far during the COVID-19 pandemic. As a consequence, no studies have been conducted to compare hospital workers and the general population in terms of the presence of anti–SARS-CoV-2 antibodies. Nevertheless, our control group allowed us to obtain conclusive results regarding the seroprevalence of anti–SARS-CoV-2 antibodies among patients with IBD. All individuals without IBD were

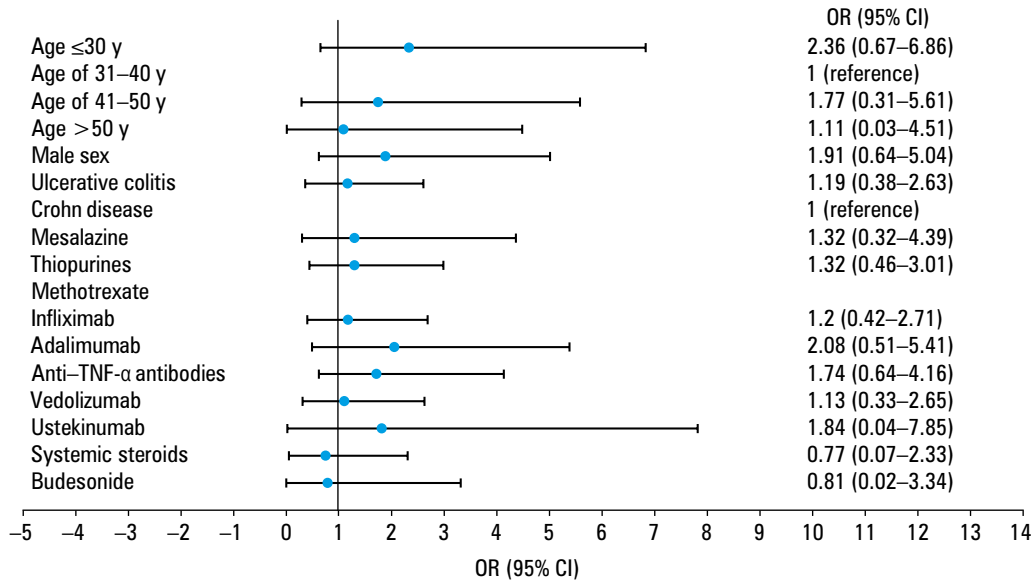

FIGURE 2 Associations between immunoglobulin G seropositivity against SARS-CoV-2 and clinical variables, as well as inflammatory bowel disease treatment
Abbreviations: OR, odds ratio; others, see **TABLE 2**

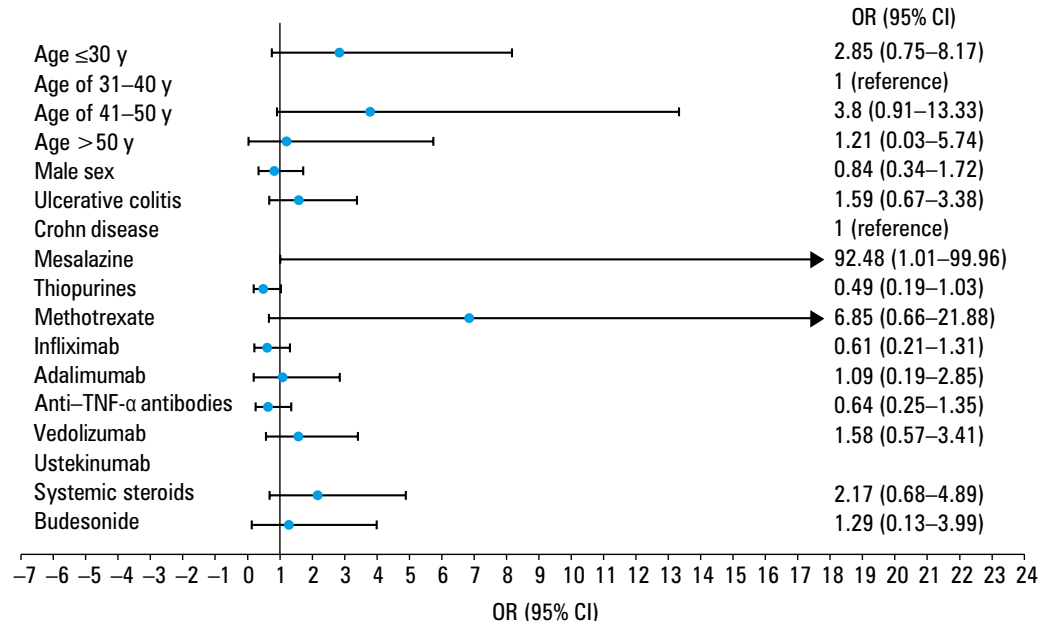

FIGURE 3 Associations between immunoglobulin M + immunoglobulin A seropositivity against SARS-CoV-2 and clinical variables, as well as inflammatory bowel disease treatment
Abbreviations: see **FIGURE 2** and **TABLE 2**

very precisely selected in terms of sex and age using the propensity matching method. Despite the use of the recommended personal protective equipment by the hospital employees, staying for a long time in an environment in which the presence of SARS-CoV-2 is confirmed can be a risk factor for anti–SARS-CoV-2 seropositivity. Therefore, the finding of an increased frequency of positive IgG antibody results among patients with IBD, as compared with the control group, seems to be of utmost importance.

The possible explanations for this phenomenon are probably complex. Patients with IBD are young, professionally and socially active people. They are also characterized by more frequent personal contact with healthcare facilities, which, despite numerous efforts, represent the major sources of spreading the virus.[15,16] Of note, there was a high percentage of patients on biologic treatment in our study group. Despite recommended social isolation, those patients had to come to the center to have another dose of the drug administered, since it has been suggested not to discontinue treatment if it ensures the patient's clinical remission.[15] Moreover, reaching the center often entails breaking the rules of social distancing. Thus, despite the high awareness of the disease and related risks, strict adherence to the rules of social distancing can be difficult for patients with IBD. Since the median Crohn Disease Activity Index and Mayo score indicated IBD remission in the majority of patients in our study group, disease severity was not a limitation to the patients' everyday activity.

Another hypothetical explanation for higher rates of seropositivity against SARS-CoV-2 among patients with UC and CD could be the IBD therapy used. Indeed, patients undergoing immunosuppressive therapy, especially biologic treatment, were initially believed to be at higher risk of SARS-CoV-2 infection.[16-18] In our study, however, no effect of the IBD treatment on the occurrence of IgG antibodies was observed. Interestingly, a significant association was found between the use of mesalazine and the presence of elevated levels of IgM + IgA antibodies. This

was not confirmed in the case of IgG antibodies. The complex and not entirely understood mechanism of mesalazine action[33,34] makes, however, these findings difficult to interpret in the context of the risk of coronavirus infection. A very high percentage of the study patients taking mesalazine may additionally influence the obtained findings. Nevertheless, it seems to be an interesting starting point for further research.

None of the patients with confirmed SARS--CoV-2 infection (based on the presence of IgG antibodies) developed symptomatic COVID-19. As mentioned above, this could result from the dysregulation of immune system function due to IBD itself or due to its treatment. Consequently, the inadequate, enhanced immune response, which plays a crucial role in the pathogenesis of symptomatic, severe COVID-19, can be hypothetically inhibited.[20-22,35] The underlying mechanism remains unclear, but autoantibodies may play a role here. New data have shown increased autoantibody production (including autoantibodies targeting cytokines or chemokines with a potential immunomodulatory role) in patients with COVID-19.[36] The effect of IBD and the drugs used for its treatment on the humoral response is well established.

As there were no symptomatic cases in our study population, no conclusions can be drawn regarding the risk factors of poor prognosis in IBD patients infected with SARS-CoV-2. However, one can hypothesize that the suppression of immune response in patients with IBD may play a protective role, thus hindering the development of symptomatic COVID-19. This is especially true of anti-TNF drugs, for which increasing evidence has shown a protective effect against severe COVID-19, in contrast to thiopurine and high-dose steroids.[37]

Limitations Our study had several limitations. In patients with positive IgM + IgA antibodies, we could not confirm viral replication in nasopharyngeal swabs by using the PCR technique. This was, however, to be expected, since PCR tests were performed post-hoc only due to epidemiological reasons, a couple of weeks after serum sample collection, and after obtaining all serological test results. Moreover, the exact time of the viral exposure of seropositive patients could not be estimated, as serum samples were only taken from each individual once, upon the first admission to the hospital. We expect more data from the analysis of samples collected repeatedly during the follow-up of patients, which is ongoing.

Conclusions To conclude, this is one of the first studies assessing the seroprevalence of anti–SARS-CoV-2 antibodies in a large cohort of patients with IBD. We showed that the risk of coronavirus infection was higher as compared with healthcare professionals without IBD. At the same time, the prognosis of patients with IBD was good, irrespectively of the treatment used, since there were no cases of symptomatic COVID-19 in our study cohort. Thus, it supports the hypothesis that patients with CD and UC are not at higher risk of the severe course of COVID-19.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT MŁ, KM, and PE designed the original clinical study, research, and its conceptualization, curated the data, interpreted the results, and wrote the manuscript. MŁ, KM, PE, KW, KS-E, and MW-J participated in sample and data collection. MM and PE performed statistical analyses. MC performed sample analyses. AD, AG, WW, and GR supervised the study and critically reviewed the manuscript. All authors read, critically revised, approved, and take responsibility for the final version of the paper.

CONFLICT OF INTEREST None declared.

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REFERENCES

1 Zhai P, Ding Y, Wu X, et al. The epidemiology, diagnosis and treatment of COVID-19. Int J Antimicrob Agents. 2020; 55: 105955.

2 Vijayvargiya P, Esquer Garrigos Z, Castillo Almeida NE, et al. Treatment considerations for COVID-19: a critical review of the evidence (or lack thereof). Mayo Clin Proc. 2020; 95: 1454-1466.

3 Pascarella G, Strumia A, Piliego C, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med. 2020; 288: 192-206.

4 Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382: 1708-1720.

5 Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020; 579: 270-275.

6 Zhou F, Ting Y, Ronghui D, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054-1062.

7 Bielecki M, Züst R, Siegrist D, et al. Social distancing alters the clinical course of COVID-19 in young adults: a comparative cohort study. Clin Infect Dis. 2021; 72: 598-603.

8 Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin Gastroenterol Hepatol. 2020; 18: 1636-1637.

9 Cheung KS, Hung IF, Chan PP, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from the Hong Kong cohort and systematic review and meta-analysis. Gastroenterology. 2020; 159: 81-95.

10 Du M, Cai G, Chen F, et al. Multiomics evaluation of gastrointestinal and other clinical characteristics of SARS-CoV-2 and COVID-19. Gastroenterology. 2020; 158: 2298-2301.

11 Eder P, Łodyga M, Dorowolska A, et al. Addressing multiple gastroenterological aspects of coronavirus disease 2019. Pol Arch Intern Med. 2020; 130: 420-430.

12 Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. Gastroenterology. 2020; 159: 481-491.

13 Bonovas S, Fiorino G, Allocca M, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. Clin Gastroenterol Hepatol. 2016; 14: 1385-1397.

14 Kirchgesner J, Lemaitre M, Carrat F, et al. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. Gastroenterology. 2018; 155: 337-346.

15 Kennedy NA, Jones GR, Lamb CA, et al. British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic. Gut. 2020; 69: 984-990.

16 Ferreira de Abreu CM. 1st Interview COVID-19 ECCO Taskforce, published March 13, 2020. European Crohn's and Colitis Organisation. https://www.ecco-ibd.eu/images/6_Publication/6_8_Surveys/1st_interview_COVID-19%20ECCOTaskforce_published.pdf. Accessed August 3, 2020.

17 Zhu LR, Mao R, Fiorino G, Schneider T. 2nd Interview COVID-19 ECCO Taskforce, published March 20, 2020. European Crohn's and Colitis Organisation. https://www.ecco-ibd.eu/

images/6_Publication/6_8_Surveys/2nd_Interview_COVID-19_ECCO_Taskforce_published.pdf. Accessed August 3, 2020.

18 Kappelman MD, Ungaro R. 3rd Interview COVID-19 ECCO Taskforce, published March 27, 2020. European Crohn's and Colitis Organisation. https://www.ecco-ibd.eu/images/6_Publication/6_8_Surveys/3rd_Interview_COVID-19_ECCO_Taskforce_published.pdf. Accessed August 3, 2020.

19 Łodyga M, Eder P, Dobrowolska A, et al. The position statement of the Polish Society of Gastroenterology and the Polish National Consultant in Gastroenterology regarding the management of patients with inflammatory bowel disease during the COVID-19 pandemic. Prz Gastroenterol. 2020; 15: 85-88.

20 Monteleone G, Ardizzone S. Are patients with inflammatory bowel disease at increased risk for Covid-19 infection? J Crohns Colitis. 2020; 14: 1334-1336.

21 Norsa L, Indriolo A, Sansotta N, et al. Uneventful course in IBD patients during SARS-CoV-2 outbreak in northern Italy. Gastroenterology. 2020; 159: 371-372.

22 Neurath MF. COVID-19 and immunomodulation in IBD. Gut. 2020; 69: 1335-1342.

23 Gao Z, Xu Y, Sun C, et al. A systematic review of asymptomatic infections with COVID-19. J Microbiol Immunol Infect. 2021; 54: 12-16.

24 Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status. Mil Med Res. 2020; 7: 11.

25 Meo SA, Alhowikan AM, Al-Khlaiwi T, et al. Novel coronavirus 2019-nCoV: prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV. Eur Rev Med Pharmacol Sci. 2020; 24: 2012-2019.

26 Zhu, N. Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382: 727-733.

27 Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020; 581: 465-469.

28 Xiang F, Wang X, He X, et al. Antibody detection and dynamic characteristics in patients with COVID-19. Clin Infect Dis. 2020; 71: 1930-1934.

29 Guo L, Ren L, Yang S, et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). Clin Infect Dis. 2020; 71: 778-785.

30 Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection. J Med Virol. 2020; 92: 1518-1524.

31 Liu W, Liu L, Kou G, et al. Evaluation of nucleocapsid and spike protein-based enzyme-linked immunosorbent assays for detecting antibodies against SARS-CoV-2. J Clin Microbiol. 2020; 58: e00461-20.

32 To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020; 20: 565-574.

33 Iacucci M, de Silva S, Ghosh S. Mesalazine in inflammatory bowel disease: a trendy topic once again? Can J Gastroenterol. 2010; 24: 127-133.

34 Rousseaux C, Lefebvre B, Dubuquoy L, et al. Intestinal antiinflammatory effect of 5-aminosalicylic acid is dependent on peroxisome proliferator-activated receptor-gamma. J Exp Med. 2005; 201: 1205-1215.

35 Antonio T, Vetrone L, Papa A. Anti-TNF-α agents in inflammatory bowel disease and course of COVID-19. Inflamm Bowel Dis. 2020; 26: e73.

36 Wang EY, Mao T, Klein J, et al. Diverse functional autoantibodies in patients with COVID-19. medRxiv. 2020 Dec 12. [Epub ahead of print].

37 Ungaro RC, Brenner EJ, Gearry RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. Gut. 2020 Oct 20. [Epub adead of print].