

Prevalence and predictive factors associated with positivity of SARS-COV-2 serological markers in patients with inflammatory bowel disease at an IBD referral center

Sandro da Costa FERREIRA¹, Rogério Serafim PARRA², Marley Ribeiro FEITOSA², Omar FERES², Rodrigo de Carvalho SANTANA¹ and Luiz Ernesto de Almeida TRONCON¹

Received: 17 August 2021
Accepted: 13 April 2022

ABSTRACT – Background – Data related to SARS-CoV-2 exposure rates in patients with inflammatory bowel diseases (IBD) are scarce. **Objective** – Our aim was to determine the prevalence of serological markers of SARS-Cov-2 and the predictive factors for positivity in patients with IBD. **Methods** – This is a cross-sectional, observational study carried out from May to September 2020. SARS-CoV-2 serological markers were determined using chemiluminescence immunoassay in 233 IBD patients without evidence of COVID-19 symptoms. Patient age was 36.6 ± 11.1 years, 118 patients were male (50.6%), and 63.1% had Crohn's disease. Patient clinical data were extracted from individual electronic medical records and complemented by a structured interview. **Results** – Twenty-six out of the 233 patients with IBD had positive serum markers for SARS-CoV-2 (11.2%). Female sex ($P < 0.003$), extra-intestinal manifestations ($P = 0.004$), use of corticosteroids ($P = 0.049$), and previous contact with individuals with flu-like symptoms ($P < 0.001$) or confirmed diagnosis of COVID-19 ($P < 0.001$), were associated with a significant increased rate of positive SARS-Cov-2 serological markers. No significant difference was observed regarding to adherence to protection measures and positivity of SARS-Cov-2 serological markers ($P > 0.05$). **Conclusion** – SARS-CoV-2 previous infection in IBD patients was not that uncommon, and its prevalence was 11.2% in our series. Positivity to SARS-CoV-2 serological markers was associated with female sex, extra-intestinal manifestations, use of corticosteroids, and contact with individuals with suspected or confirmed COVID-19. Studies with longer follow-up periods are needed to confirm these findings.

Keywords – Inflammatory bowel diseases; COVID-19; serological markers.

INTRODUCTION

The first cases of 2019 novel coronavirus disease (COVID-19) infection were reported in December 2019, in Wuhan, capital of Hubei province, China, and spread rapidly worldwide through air travel⁽¹⁻⁶⁾. On March 11, 2020, the World Health Organization (WHO) declared the outbreak of COVID-19 a pandemic due to widespread infectivity and high rates of contagion^(7,8). Currently, Brazil has one of the highest numbers of confirmed COVID-19 cases worldwide, with the São Paulo State being the most affected region.

Previous studies have shown that COVID-19 may have implications for the management of patients with preexisting digestive diseases, including inflammatory bowel diseases (IBD)^(9,10). Usually patients with IBD, including both Crohn's disease (CD) and ulcerative colitis (UC), need to regularly attend health facilities, whether for medical appointments and tests or for treatment⁽¹¹⁾. A significant number of these patients use immunosuppressors and immunobiological and corticosteroid agents during their disease, and the potential risk of infectious complications due to these therapies in the context of IBDs is well known^(12,13). Therefore,

it is reasonable to consider that patients with IBDs are at higher risk of developing COVID-19, perhaps with an increased risk of progressing to a more severe clinical course or even to death, when compared to the general population^(9,14).

Restrictive measures, such as reducing or canceling face-to-face visits and elective operations or exams, and guidance through telemedicine were some strategies adopted to reduce the risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) infection in patients with IBD⁽¹⁵⁾. However, these measures can have a negative impact on the treatment of these patients⁽¹⁶⁾. A recent study published by our group showed that most patients missed medical appointments for IBD and almost one third of the patients discontinued medical therapy, which may have implications for disease control in the near future⁽¹⁷⁾.

Despite the postulated increased risk of SARS-Cov-2 in IBD patients and the possibility of progression to more severe forms of this infection, previous studies are reassuring, as they have not confirmed this possibility, nor progression to more severe forms, in comparison with the general population⁽¹⁸⁻²¹⁾. However, these studies did not report the prevalence of exposure to SARS-CoV-2 and COVID-19 in patients with IBD.

Declared conflict of interest of all authors: none

Disclosure of funding This research was supported by the *Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas* da Faculdade de Medicina de Ribeirão Preto (FAEPA).

¹ Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Departamento de Clínica Médica, Ribeirão Preto, SP, Brasil. ² Faculdade de Medicina da Universidade de São Paulo, Departamento de Cirurgia e Anatomia, Ribeirão Preto, SP, Brasil.

Corresponding author: Sandro da Costa Ferreira. E-mail: sandrocferrera1705@gmail.com

Therefore, the present study aimed to determine the prevalence of serological markers (IgG and IgM) of SARS-Cov-2 and the predictive factors for positivity in patients with IBD in a Brazilian tertiary referral center.

METHODS

Patients

Out of the 685 patients who were being followed up at our IBD unit (University Hospital, Ribeirão Preto Medical School, University of São Paulo, Brazil), the study included 233 patients who, for a diversity of reasons, kept follow-up despite the pandemic. There were 147 CD and 86 UC patients, 118 (50.6%) were male, and the mean age was 36.6 ± 11.1 years. The diagnosis of CD or UC was established based on clinical, endoscopic, histopathological, and radiological aspects, and patients were classified according to the Montreal criteria⁽²²⁾. Patients who had a confirmed COVID-19 diagnosis prior to the study were excluded.

All patients were using their regular medications, whether conventional or biological, at the time serological testing was performed concomitantly with obtaining their responses to an exploratory questionnaire.

Study design and data collection

This was a cross-sectional study carried out from May 26 to September 30, 2020. This coincided with the main phase of the local epidemic in 2020, in which there was a significant increase in cases of COVID-19 in Southeast Brazil (State of São Paulo). Blood samples for serological markers for SARS-Cov-2 were obtained from all patients and the blood collection was performed during the routine outpatient consultation.

All patients specifically denied symptoms suggestive of COVID-19, such as fever, cough, sore throat, runny nose, nasal congestion, dyspnea, anosmia, headache, and dysgeusia. Patients with previous polymerase chain reaction by reverse transcriptase (RT-PCR) positivity were excluded from the study.

Patients were also subjected to a structured questionnaire administered by the research team as a structured interview. The questionnaire comprised items that addressed: i) factors related to COVID-19 risk (travel, contact with individuals with flu-like symptoms or previous diagnosis of COVID-19, occurrence of flu-like symptoms prior to blood collection and hospital admissions); and ii) preventive measures against COVID-19 (masks use, adherence to social distance and personal hygiene measures) in IBD patients. We also performed a review of clinical and demographic information from the electronic medical records of patients with IBD.

Serological markers of SARS-Cov-2

The presence of SARS-Cov-2 serological markers was determined using the chemiluminescence methodology with a cridine ester (COV2T assay, Siemens Healthineers nr. 11206711, Munich, Germany). The COV2T test is an automated 1-step antigen chemiluminescent sandwich immunoassay for total antibodies against the SARS-CoV-2 virus. The COV2T assay is designed as a qualitative assay and detects the presence of total antibodies against SARS-Cov-2, not differentiating between IgM and IgG. The performance of this assay was assessed on a Atellica IM1300 analyzer (Siemens Healthineers, Erlangen, Germany).

For the method comparison, the anti-SARS-CoV-2 ELISA was

used. The sensitivity of the COV2T assay increased gradually with disease progression, reaching 100% (95%CI, 89.7–100.0%) 14 days after PCR positivity. After validation by testing serum samples from patients with current or previous diagnosis of COVID-19, this method demonstrated greater sensitivity and clinical specificity when compared to tests that detect IgM and IgG alone, with 99.8% specificity and 100% sensitivity^(23,24), after 14 days of positivity with RT-PCR.

Ethical aspects

Both the local Institutional Review Board and the Ethics Committee (nr. 34260620.7.0000.5440) approved this study. All patients agreed to participate in the study and signed a structured consent form. All procedures were in accordance with the ethical standards of the national committee on human experimentation and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical analysis

Statistical analyses were performed using SPSS version 20.0 software (SPSS, Chicago, IL, USA). Categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as mean \pm standard deviation (SD). Categorical variables were compared with the chi-squared test and Fisher's exact test. The Kolmogorov-Smirnov test was used to check for normality of variables. Univariate Cox regression was used to identify candidate predictors for inclusion in a multivariate analysis model, which was performed using binary logistic regression. A *P*-value < 0.05 was considered statistically significant.

RESULTS

Characteristics of IBD patients with positive SARS-Cov-2 serological markers

Out of the 233 IBD patients included in the study, 26 presented positive results, thus demonstrating a rate of 11.2% SARS-CoV-2 seroprevalence.

The majority of IBD patients with positive serology were female (76.9%). Fourteen patients (53.8%) had Crohn's disease and 12 (46.2%) had ulcerative colitis. Regarding the location and behavior of CD, ileocolic location and fistulizing phenotype were more commonly associated with positive serology for SARS-CoV-2, being present in 9 (64.2%) and 6 (42.8%) patients, respectively. Regarding patients with UC, pancolitis (E3) was the most frequent disease extension type among those with SARS-CoV-2 positive serology, being present in 9 (75%) patients. Extra-intestinal manifestations (EIM) were present in 6 (23.1%) patients (TABLE 1).

The most frequently used medications were thiopurines (53.8%), mesalamine/sulfasalazine (42.3%) and tumor necrosis factor (TNF) antagonists (38.4%). Corticosteroids were used by 5 (19.2%) of the patients, in all of them due to relapses.

Contact with family members or coworkers with flu-like symptoms was observed in 16 (61.5%) and 13 (50%) patients, respectively. Patients also reported that none of the people with whom they had contact required hospital admission.

Regarding protection measures, mask use was informed by 231 (99.1%) patients, strict adherence to social distance measures was reported by 69 (29.6%), and partial adherence by 143 (61.4%) patients. Suitable personal hygiene measures were observed in 208 (89.3%) patients.

TABLE 1. Demographic and clinical characteristics of patients with inflammatory bowel disease in relation to the results of the SARS-CoV-2 serological markers.

Characteristics and clinical variables	SARS-CoV-2 serological markers				P
	Positive (n=26)		Negative (n=207)		
	38.6±11.6		41.8±14.2		
Age (mean±SD)	n	%	n	%	0.27
Gender					< 0.003
Female	20	76.9	95	45.9	
Male	6	23.1	112	54.1	
Smoking					0.22
Yes	1	3.9	28	14.1	
No	25	96.1	179	85.9	
IBD type					0.30
Crohn's disease	14	53.8	113	54.6	
Ulcerative colitis	12	46.2	74	45.4	
Age at the time of IBD diagnosis [†]					0.98
A1	3	11.5	22	10.6	
A2	18	69.2	142	68.6	
A3	5	19.2	43	20.8	
Localization of CD [‡]					0.82
L1	2	14.3	31	23.3	
L2	2	14.3	17	12.8	
L3	9	64.2	80	60.2	
L4	1	7.2	5	3.7	
Behavior of CD [‡]					0.88
B1	5	35.7	39	29.3	
B2	3	21.4	32	24.1	
B3	6	42.9	62	46.6	
P	4	28.6	51	38.3	0.44
B1p	1	3.8	15	7.2	
B2p	1	3.8	10	4.8	
B3p	2	7.7	26	12.6	
Extent of UC [‡]					0.25
E1	3	25.0	27	36.5	
E2	1	8.3	15	20.3	
E3	8	66.7	32	43.2	
Extraintestinal manifestations [‡]					0.04
Yes	6	23.1	19	9.2	
No	20	76.9	188	90.8	
Type of IBD treatment					
Mesalazine	11	42.3	61	29.5	0.18
Azathioprine	14	53.8	122	58.9	0.60
Corticosteroids	5	19.2	15	7.2	0.049
Infliximab	7	26.9	80	38.6	0.12
Adalimumab	5	19.2	33	15.9	0.78
Certolizumab	1	3.8	2	0.9	0.30
Vedolizumab	1	3.8	6	2.8	1.00
Ustekinumab	4	15.3	16	7.7	0.25
Combination therapy*	7	26.9	62	29.9	0.45
Exposure to persons with flu-like symptoms					<0.001
Yes	16	61.5	30	14.5	
No	10	38.5	177	85.5	
Exposure to persons with COVID-19 diagnosis					<0.001
Yes	13	50.0	21	10.1	
No	13	50.0	186	89.9	
Reported previous symptoms**					<0.001
Yes	18	69.2	28	13.5	
No	8	30.8	179	86.3	

CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel disease. [†]The Montreal Classification of IBD: age at diagnosis: A1: <16years, A2:16–40 years, A3: >40 years; localization of CD: L1: Ileal, L2: Colonic, L3:Ileo-colonic, L4: isolated upper GI tract; Behavior of CD: B1:inflammatory, B2:stenosing, B3: fistulizing, P: perianal disease; extent of UC: E1:proctitis, E2:left colitis, E3:pancolitis; SD *combination therapy: infliximab plus azathioprine. **Most common symptoms; fever, cough, sore throat, runny nose and myalgia.

Factors associated with positive SARS-Cov-2 serological markers

The univariate analysis revealed the following results:

- i) The female sex was significantly associated with the presence of positive SARS-Cov-2 serological markers ($P < 0.003$; OR: 3.93; 95%CI: 1.51–10.20) [TABLE 1].
- ii) The use of corticosteroids was associated with a significantly increased rate of positive SARS-Cov-2 serological markers ($P = 0.049$; OR: 3.05; 95%CI: 1.01–9.23).
- iii) The presence of extra-intestinal manifestations was significantly associated with positive SARS-Cov-2 serological markers ($P = 0.004$; OR: 2.97; 95%CI: 1.06–8.29).
- iv) Previous contact with individuals with flu-like symptoms ($P < 0.001$; OR: 9.44; 95%CI: 3.92–22.75) or with confirmed diagnosis of COVID-19 ($P < 0.001$; OR: 8.85; 95%CI: 3.63–21.60) were significantly associated with the presence of positive SARS-Cov-2 serological markers (TABLE 1).
- v) No associations were found between positive SARS-Cov-2 serological markers and age, skin color, smoking status, location and behavior of CD, extent of UC, use of thiopurines, mesalamine/sulfasalazine or biological agents and protection measures ($P > 0.05$).

The multivariate analysis revealed the following independent risk factors for positive SARS-Cov-2 serological markers: previous contact with individuals with flu-like symptoms ($P = 0.001$; OR: 8.68; 95%CI: 2.51–29.98) and previous contact with individuals with confirmed diagnosis of COVID-19 ($P = 0.001$; OR: 7.94; 95%CI: 2.41–26.13) (TABLE 2).

Reports on the presence of previous symptoms suggestive of COVID-19

Forty-six (19.7%) patients reported at least one symptom suggestive of COVID-19 prior to the search for serological markers for SARS-Cov-2 but did not undergo a confirmatory examination at the time. Among these patients, 18 presented positive serological markers for SARS-Cov-2. The univariate analysis revealed that the presence of reported previous symptoms was associated with a significantly increased rate of positive SARS-Cov-2 serological markers ($P < 0.001$; OR: 10.16; 95%CI: 3.81–27.11). The multivariate analysis revealed that the presence of reported previous symptoms was an independent risk factor for positive SARS-Cov-2 serological markers ($P = 0.004$; OR: 7.43; 95%CI: 1.91–28.89).

DISCUSSION

To date, this is the first study to assess the prevalence of SARS-CoV-2 serological markers in a cohort of IBD patients followed at a Brazilian tertiary referral center. This study was carried out nearly two months after the first confirmed case of COVID-19 in Southeast Brazil (State of São Paulo) and coincided with the main phase of the local epidemic in 2020, in which there was a significant increase in the cases of COVID-19 in our region.

Initial studies have shown that SARS-CoV-2 infection is relatively uncommon in patients with IBD^(25,26). In a cohort of 6,000 IBD patients from Nancy (France) and Milan (Italy), a cumulative incidence of 0.25% was found, which was similar to the general figures reported in these countries at that time (0.17%)⁽²⁷⁾. In contrast to the initial reports, a study conducted at a single center in Spain showed that approximately 10% of IBD patients had a confirmed diagnosis of COVID-19⁽²¹⁾.

Two studies that assessed the prevalence of COVID-19 in IBD patients using SARS-CoV-2 serological markers and SARS-CoV-2 RNA (RT-PCR) reported rates of 3% and 21%, respectively^(28,29). The study by Gubatan et al.⁽²⁸⁾, conducted in Northern California, demonstrated a 3% prevalence of the disease, comparable to that of the population in general. This retrospective study included patients who underwent the nasopharyngeal test for SARS-CoV-2 due to the presence of possible symptoms related to COVID-19; therefore, it cannot provide information about the previous exposure to SARS-CoV-2 infection in patients with IBD⁽²⁸⁾. Another study conducted at a reference center in IBD in Bergamo, Italy, in which SARS-CoV-2 serological markers were measured using a rapid test in 90 patients with IBD using biological therapy, reported a 21% prevalence rate. It is important to highlight that in this study, some patients reported previous symptoms of COVID-19; however, they were asymptomatic at the time of the test, thus providing information regarding previous exposure to COVID-19⁽²⁹⁾. These contrasting results regarding the prevalence of SARS-CoV-2 serological markers can partly be explained by the characteristics of the COVID-19 pandemic in different locations around the world, added to the characteristics of local populations and the use of different test methodologies (serology or PCR). Higher heterogeneity has been observed in the sensitivity of the different serological tests for SARS-CoV-2⁽²³⁾ and this depends on the assay setup and timing in the course of the disease, where the test is performed⁽²³⁾.

TABLE 2. Predictors of positive SARS-CoV-2 serological markers among IBD patients.

Clinical variables	Univariate analyses			Multivariate analyses		
	OR	95%CI	P	OR	95%CI	P
Female	3.93	1.51–10.20	<0.003	–	–	–
Extraintestinal manifestations	2.97	1.06–8.29	0.004	–	–	–
Use of corticosteroids	3.05	1.01–9.23	0.049	–	–	–
Contact with persons with flu-like symptoms	9.44	3.92–22.75	<0.001	8.68	2.51–29.98	0.001
Contact with persons with COVID -19 diagnosis	8.85	3.63–21.60	<0.001	7.94	2.41–26.13	0.001

OR: odds ratio; CI: confidence interval.

Data of SARS-CoV-2 serology screening carried out by School of Medicine of Ribeirão Preto and Ribeirão Preto Municipal Health Department of in early May 2020 found a 1.4% prevalence in the general population of the Ribeirão Preto city⁽³⁰⁾. We herein found that 11.2% of IBD patients followed at our institution had serological markers of previous SARS-CoV-2 infection. These contrasting results of the prevalence of SARS-CoV-2 serological markers in IBD patients and the general population from the same geographic area can be attributed to different reasons. In the aforementioned population survey, the determination of SARS-CoV-2 serological markers was carried out on a single occasion in early May 2020, through the rapid test. On the other hand, our study carried out from May 26 to September 30, 2020, the main phase of the local epidemic in 2020, the presence of SARS-CoV-2 serological markers was determined using the chemiluminescence methodology. Thus, studies with different methodologies and designs cannot be compared. Among the IBD patients with positive serological markers for SARS-CoV-2, 69.2% reported previous symptoms possibly related to COVID-19 in the months preceding serological testing. However, it is important to note that about one third of IBD patients in our series with positive SARS-CoV-2 serology results were completely asymptomatic, corroborating the clinical presentation of COVID-19⁽³⁾, which adds to the known difficulties in diagnosing this disease. All patients with IBD included in our study complete the symptom questionnaire, their clinical data were reviewed using the electronic medical record, and a serological test was performed in the absence of symptoms for more than 2 weeks.

In our study, the female sex and presence of EIM (especially articular manifestations) were significantly associated with the presence of positive SARS-CoV-2 serological markers. A higher prevalence of SARS-CoV-2 serological markers in females was also demonstrated in an Italian study⁽²⁹⁾. A possible explanation for this result is the lower rates of absenteeism for outpatient consultations in women we observed in our service. Despite the restrictive measures taken for the COVID-19 pandemic, it was shown that frequent visits to clinics or hospitals are associated with increased risks of acquiring SARS-CoV-2 infection⁽³¹⁾. This explanation may also apply to EIM, given that patients with IBD and these manifestations generally need to go more often to healthcare facilities. They are more frequently in need of clinical evaluation and more prone to receive intravenous drug treatment and concomitant use of immune suppressants, conditions that might be associated with an increased risk of acquiring SARS-CoV-2 infection.

The risk of SARS-CoV-2 infection in patients with IBD, similar to what is observed in the general population, is associated with close contact with individuals diagnosed with COVID-19⁽²⁰⁾. In our study, 50% of the IBD patients had close contact with other individuals with COVID-19 diagnosis, especially in familial (55%) and work environments (35%).

In our series, except for the use of systemic corticosteroids, no associations were found between positivity of serological markers for SARS-CoV-2 and the different classes of drugs used in the treatment of IBD. Corticosteroids was reported to be associated with higher risk of infection and hospitalization among patients with COVID-19 and IBD^(18,32-34). These results are in line with previous reports, in which corticosteroids (particularly ≥ 20 mg of prednisolone or its equivalent) are associated with an increased risk of infection, with an even more likely association with increased chances of complications due to COVID-19^(18,32-34). Corticosteroids affect the immune system through several mechanisms, such as

decreased expression of inflammatory cytokines and inhibition of adhesion molecules, inducing apoptosis of activated lymphocytes.

Despite the higher prevalence of positive serological markers for SARS-CoV-2 being associated with the use of corticosteroids, none of the patients in our study presented an unfavorable evolution requiring hospitalization, reinforcing the potentially favorable course of COVID-19 in the context of IBD^(21,22,27). However, considering higher risk of infection and complications among patients with COVID-19 and IBD it is recommended that corticosteroids should be used with caution. IBD patients who are taking systemic corticosteroids (especially prednisone >20 mg/d) should have their doses gradually tapered or switched to budesonide during the COVID-19 pandemic but should not be stopped at once^(18,32-34). More recent studies have shown that corticosteroids do not increase the risk of SARS-CoV-2 infection and were associated with worse prognosis and higher risk of hospitalization among patients with COVID-19 and inflammatory bowel diseases^(35,36).

Our study has some limitations that must be considered. First, because of the restrictive measures adopted to combat the pandemic by COVID-19 in our hospital, only patients who were receiving intravenous medications or whose needs could not be completely met by telemedicine had to attend visits in person. This may have affected the representativeness of our sample. Second, we were not able to recruit a control group from the general population due to the difficulties prevailing during the pandemic period. Lastly, during the pandemic, our institution's clinical management protocols recommended COVID-19 testing only in patients with cough, dyspnea, and fever. It is therefore possible that, amongst our patients with lighter symptoms, such as mild headache, runny nose, or sore throat, some might have actually had the infection, a fact that may have influenced our sample size and results.

Despite these limitations, our study has strengths that deserve to be highlighted. First, we provided new epidemiological data, as there are currently no published reports on the prevalence of COVID-19 among IBD patients in Brazil. Second, we identified some predictors of increased susceptibility to COVID-19 among IBD patients, in particular, the female sex, EIM, and use of corticosteroids, despite such associations were not found in the multivariate model. Third, we used an accurate serological test, which has higher sensitivity and specificity rates for the identification of SARS-CoV-2 serological markers, thus greatly reducing the chances of incorrect results, however, it has been described, as for other different serological testing methodologies, that a small percentage of patients using immunosuppressive and biological therapy may present a false negative result⁽³⁶⁾. Although the Siemens COV2T assay for the detection of antibodies against SARS-CoV-2 is highly specific and with a sensitivity 14 days after the onset of symptoms COVID-19 close to 100%⁽³⁵⁾, there are few studies on the quantification of serological markers SARS-CoV-2 using CLIA method so far; as such, further studies on the accuracy and clinical significance of this assay should be conducted^(37,38).

In conclusion, our results demonstrate that COVID-19 is not uncommon in patients with IBD and findings that are in agreement with those from other studies. The female sex, EIM, use of systemic corticosteroids, and close contact with family members or coworkers diagnosed with COVID-19 were factors associated with increased positivity to SARS-CoV-2 serological markers. Further studies with longer follow-up periods will be needed to not only confirm these findings but also to clarify the long-term evolution of SARS-CoV-2 infection in patients with IBD.

ACKNOWLEDGMENTS

The authors are grateful to Amanda Sacha Paulino Tolentino Alustau and Rafaella Queiróz Marques de Mendonça for data collection, Tiago Alexandre Cocio, Ana Rosa Bavaresco Pereira, Nádia Bittar Garcia and Alice Barros Chagas for processing of biological samples. Special thanks to Professor Marisa M. Mussi from the Department of Pediatrics and Childcare at the Ribeirão Preto Medical School for assigning the serology kits, making this study possible.

Authors' contribution

Ferreira SC participated in the study design, data collection, data analysis, data interpretation, and manuscript writing. Parra RS and Feitosa MR participated in the data analysis, interpretation and critical revising. Feres O participated in the manuscript

critical revising. Santana RC and Troncon LEA participated in the study design and in the manuscript critical revising. All authors contributed to the analysis and interpretation of data, revision of the manuscript, adding important intellectual content, granted final approval of the version to be published and agreed to be accountable for all aspects of the work, therefore ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Orcid

Sandro da Costa Ferreira: 0000-0001-7698-6599.

Rogério Serafim Parra: 0000-0002-5566-9284.

Marley Ribeiro Feitosa: 0000-0002-4440-2023.

Omar Feres: 0000-0003-3593-0526.

Rodrigo de Carvalho Santana: 0000-0002-5887-8663.

Luiz Ernesto de Almeida Troncon: 0000-0002-8599-2410.

Ferreira SC, Parra RS, Feitosa MR, Feres O, Santana RC, Troncon LEA. Prevalência e fatores preditivos associados à positividade dos marcadores sorológicos do SARS-COV-2 em pacientes com doença inflamatória intestinal em um centro de referência em DII. *Arq Gastroenterol.* 2022;59(2):170-6.

RESUMO – Contexto – Dados relacionados às taxas de exposição ao SARS-CoV-2 em pacientes com doenças inflamatórias intestinais (DII) são escassos.

Objetivo – Nosso objetivo foi determinar a prevalência de marcadores sorológicos do SARS-Cov-2 e os fatores preditivos de positividade em pacientes com DII. **Métodos** – Este foi um estudo transversal observacional realizado no período de maio a setembro de 2020. Os marcadores sorológicos SARS-CoV-2 foram determinados por imunoenensaio de quimioluminescência em 233 pacientes com DII sem evidência de sintomas de COVID-19. A idade dos pacientes foi 36,6±11,1 anos, 118 pacientes eram do sexo masculino (50,6%) e 63,1% tinham doença de Crohn. Os dados clínicos dos pacientes foram extraídos de prontuários médicos eletrônicos individuais e complementados por meio de uma entrevista estruturada. **Resultados** – Vinte e seis dos 233 pacientes com DII apresentaram marcadores sorológicos positivos para SARS-CoV-2 (11,2%). Sexo feminino ($P<0,003$), manifestações extra-intestinais ($P=0,004$), uso de corticosteroides ($P=0,049$) e contato prévio com indivíduos com sintomas gripais ($P<0,001$) ou diagnóstico confirmado de COVID-19 ($P<0,001$), foram associados a um aumento significativo da taxa de positividade para marcadores sorológicos do SARS-Cov-2. Não foi observada diferença significativa em relação à adesão às medidas de proteção e positividade dos marcadores sorológicos para o SARS-Cov-2 ($P>0,05$). **Conclusão** – A infecção prévia pelo SARS-CoV-2 não é tão incomum em pacientes com DII e sua prevalência em nossa série foi de 11,2%. A positividade aos marcadores sorológicos SARS-CoV-2 foi associada ao sexo feminino, manifestações extra-intestinais, uso de corticosteroides e contato com indivíduos com suspeita ou diagnóstico confirmado de COVID-19. Estudos com períodos de acompanhamento mais longos são necessários para confirmar esses achados.

Palavras-chave – Doenças inflamatórias intestinais; COVID-19; marcadores sorológicos.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020;382:727-33.
2. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. *Nature.* 2020;579:265-9.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395:497-506.
4. Li Q, Guan X, Wu P, Wang X, Zhou L, Tonget Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med.* 2020;382:1199-1207.
5. Leung K, Wu JT, Liu D, Leung GM. First-wave COVID-19 transmissibility and severity in China outside Hubei after control measures, and second-wave scenario planning: a modelling impact assessment. *Lancet.* 2020;395:1382-93.
6. Wu D, Wu T, Liu Q, Yang Z. The SARS-CoV-2 outbreak: What we know. *Int J Infect Dis.* 2020;94:44-8.
7. Mahase E. Covid-19: WHO declares pandemic because of “alarming levels” of spread, severity, and inaction. *BMJ.* 2020;368:m1036.
8. Cucinotta D, Vanelli M. World Health Organization declares COVID-19 a pandemic. *Acta Biomed.* 2020;91:157-60.
9. Magro F, Abreu C, Rahier JF. The daily impact of COVID-19 in gastroenterology. *United Eur Gastroenterol J.* 2020;8:520-7.
10. Ong J, Young BE, Ong S. COVID-19 in gastroenterology: A clinical perspective. *Gut.* 2020;69:1144-5.
11. Jeong DY, Kim S, Son MJ, Son CY, Kim JY, Kronbichler A, et al. Induction and maintenance treatment of inflammatory bowel disease: A comprehensive review. *Autoimmun Rev.* 2019;18:439-54.
12. Kirchgessner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. *Gastroenterology.* 2018;155:337-46.e10.
13. Andersen NN, Jess T. Risk of infections associated with biological treatment in inflammatory bowel disease. *World J Gastroenterol.* 2014;20:16014-9.
14. Monteleone G, Ardizzone S. Are patients with inflammatory bowel disease at increased risk for covid-19 infection? *J Crohn's Colitis.* 2020;14:1334-6.
15. Kennedy NA, Jones GR, Lamb CA, Appleby R, Arnott I, Beattie RM, et al. British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic. *Gut.* 2020;69:984-90.
16. Din S, Kent A, Pollok RC, Meade S, Kennedy NA, Arnott I, et al. Adaptations to the British Society of Gastroenterology guidelines on the management of acute severe UC in the context of the COVID-19 pandemic: A RAND appropriateness panel. *Gut.* 2020;69:1769-77.

17. Feitosa MR, Parra RS, de Camargo HP, Ferreira SDC, Troncon LEA, da Rocha JJR, et al. COVID-19 quarantine measures are associated with negative social impacts and compromised follow-up care in patients with inflammatory bowel disease in Brazil. *Ann Gastroenterol*. 2021;34:39-45.
18. Al-Ani AH, Prentice RE, Rentsch CA, Johnson D, Ardalán Z, Heerasing N, et al. Review Article: Prevention, Diagnosis and Management of COVID-19 in the Inflammatory Bowel Disease Patient. *Aliment Pharmacol Ther*. 2020;52:54-72.
19. Fiorino G, Allocca M, Furfaro F, Gilardi D, Zilli A, Radice S, et al. Inflammatory bowel disease care in the COVID-19 pandemic era: the Humanitas, Milan experience. *J Crohns Colitis*. 2020;14:1330-3.
20. Taxonera C, Sagastagoitia I, Alba C, Mañas N, Olivares D, Rey E. 2019 novel coronavirus disease (COVID-19) in patients with inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2020;52:276-83.
21. Guerra I, Algaba A, Jiménez L, Mar Aller M, Garza D, Bonillo D, et al. Incidence, Clinical Characteristics, and Evolution of SARS-CoV-2 Infection in Patients With Inflammatory Bowel Disease: A Single-Center Study in Madrid, Spain. *Inflamm Bowel Dis*. 2021;27:25-33.
22. Satsangi J. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006;55:749-53.
23. Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Spijker R, Taylor-Phillips S, et al. Antibody tests for identification of current and past infection with SARS-CoV-2. *Cochrane Database Syst Rev*. 2020;6:CD013652.
24. Caruana G, Croxatto A, Coste AT, Opota O, Lamoth F, Jatón K, et al. Diagnostic strategies for SARS-CoV-2 infection and interpretation of microbiological results. *Clin Microbiol Infect*. 2020;26:1178-82.
25. Higgins PDR, Ng S, Danese S, Rao K. The Risk of SARS-CoV-2 in Immunosuppressed IBD Patients. *Crohn's Colitis* 360. 2020;2:otaa026.
26. Bezzio C, Saibeni S, Variola A, Allocca M, Massari A, Gerardi V, et al. Outcomes of COVID-19 in 79 patients with IBD in Italy: An IG-IBD study. *Gut*. 2020;69:1213-7.
27. Allocca M, Fiorino G, Zallot C, Furfaro F, Gilardi D, Radice S, et al. Incidence and Patterns of COVID-19 Among Inflammatory Bowel Disease Patients From the Nancy and Milan Cohorts. *Clin Gastroenterol Hepatol*. 2020;18:2134-5.
28. Gubatan J, Levitte S, Balabanis T, Patel A, Sharma A, Habtezion A. SARS-CoV-2 Testing, Prevalence, and Predictors of COVID-19 in Patients with Inflammatory Bowel Disease in Northern California. *Gastroenterology*. 2020;159:1141-44.e2.
29. Norsa L, Cosimo P, Indriolo A, Sansotta N, D'Antiga L, Callegaro A. Asymptomatic Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Patients With Inflammatory Bowel Disease Under Biologic Treatment. *Gastroenterology*. 2020;159:2229-31.e2.
30. Universidade de São Paulo. Faculdade de Medicina de Ribeirão Preto. Relatório final. Avaliação da prevalência de marcadores virológicos e sorológicos do SARS-CoV-2 na população de Ribeirão Preto: um inquérito epidemiológico. Available from: https://www.apcdrp.com.br/arquivos/paginas/uploads/Relatorio_Final_do_Inquerito.pdf
31. Mao R, Liang J, Shen J, Ghosh S, Zhu LR, Yang H, et al. Implications of COVID-19 for patients with pre-existing digestive diseases. *Lancet Gastroenterol Hepatol*. 2020;5:425-7.
32. Brenner EJ, Ungaro RC, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, 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;159:481-91.e3.
33. Rubin DT, Feuerstein JD, Wang AY, Cohen RD. AGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: Expert Commentary. *Gastroenterology*. 2020;159:350-7.
34. Cappello M, Busacca A, Guida L. The course of Covid 19 in Inflammatory Bowel Disease: protective role of TNF antagonists Response to: Corticosteroids, but not TNF Antagonists, are Associated with Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results from an Int. *Gastroenterology*. 2020;S0016-5085:34920-9
35. Ungaro RC, Brenner EJ, Agrawal M, Zhang X, Kappelman MD, Colombel JF. Impact of Medications on COVID-19 Outcomes in Inflammatory Bowel Disease: Analysis of More Than 6000 Patients From an International Registry: Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) Research Group. *Gastroenterology*. 2022;162:316-9.e5.
36. Wetwittayakhlang P, Albader F, Golovics PA, Hahn GD, Bessissow T, Bitton A, Afif W, Wild G, Lakatos PL. Clinical Outcomes of COVID-19 and Impact on Disease Course in Patients with Inflammatory Bowel Disease. *Can J Gastroenterol Hepatol*. 2021;30:2021:7591141.
37. Florin L, Maelegheer K, Vandewal W, Bernard D, Robbrecht J. Performance Evaluation of the Siemens SARS-CoV-2 Total Antibody and IgG Antibody Test. *Lab Med*. 2021 2;52:e147-e153.
38. Cerino P, Gallo A, Pierri B, Buonerba C, Concilio DD, Cuomo MC, et al. Seroprevalence of SARS-CoV-2 Assessed by Four Chemiluminescence Immunoassays and One Immunocromatography Test for SARS-Cov-2. *Front Public Heal*. 2021;29:9:649781.

