Humoral immunity improves with a booster dose of SARS-CoV-2 vaccine in patients with inflammatory bowel disease on immunosuppressants

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Abstract

Purpose

Patients with inflammatory bowel disease (IBD) are often treated with immunosuppressants and immunobiologics. We evaluated the humoral response after vaccination against SARS-CoV-2 in patients with IBD compared to a healthy population.

Methods

Patients with IBD, enrolled in a tertiary outpatient unit, were followed-up with serial blood collections between September 2021 and September 2022. IgG antibody titers against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were measured before and one month after the administration of the two doses of the different vaccination regimens. The results were compared with those of a healthy control group obtained during the same period.

Results

Mean pre-vaccination antibody titers were 430.3 AU/mL and 90.5 AU/mL in the IBD (46 participants) and control (92 participants) groups, respectively. After two doses of vaccine, the titers significantly increased in both groups (IBD, 8038.4 AU/mL; control, 7697.5 AU/mL; p < 0.001). One month after the second dose, no significant difference was observed between the two groups (p = 0.731). In the IBD group, there was a difference between vaccination schemes, with higher titers in those who received Pfizer, younger patients (p < 0.005), and those with a previous COVID-19 infection (p < 0.012).

Conclusion

The use of immunosuppressants and immunobiologics did not affect the overall humoral response to the COVID-19 vaccine in patients with IBD. However, specific vaccine regimens, age, and previous coronavirus infection significantly affected the response. This study reinforces the positive impact of booster doses and safety of SARS-CoV-2 vaccination.

Introduction

The coronavirus pandemic peaked in April 2021, reaching 4,000 deaths per day [1, 2]. Brazil has the second highest number of deaths from COVID-19 and the third highest number of diagnosed cases, with approximately 698,000 deaths and 35 million people infected. Currently, more than 80% of the population (170 million Brazilians) is vaccinated with at least two doses of different vaccines [3]. Considering the negative numbers related to the pandemic, it is crucial to identify populations at greater risk of severe COVID-19 infection [4] and define when to recommend vaccination and boosters as a priority [5]. According to the Brazilian Society of Immunization and the Ministry of Health, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine should be administered in four doses to the population with conditions that compromise the immune system, as is the case in patients with inflammatory bowel disease (IBD) receiving immunosuppressive or immunobiological therapy [6, 7]. Recently, a fifth dose of the vaccine has been considered for this group, as their humoral response to vaccines may be reduced compared with that of the general population. Populations with chronic inflammatory conditions, such as patients with IBD, should be aware of these recommendations.

Crohn's disease (CD) and ulcerative colitis (UC), the two major forms of IBD, are complex inflammatory disorders with progressively increasing incidences worldwide [8, 9]. Although the etiopathogenesis of IBD is not completely understood, a large body of evidence indicates the existence of underlying defects in innate and adaptive immunity [10, 11] and abnormal immune reactivity against gut commensal microorganisms [12, 13]. Owing to its chronic nature, in which the clinical course is typically characterized by relapse and remission, patients usually require regular and continuous maintenance treatment, often with immunosuppressive/immunomodulatory therapy [14]. These drugs have potentially serious side effects, including acute and chronic opportunistic infections [15]. Despite this, patients with IBD usually have a consistent benefit from the use of these medications, both in the short- and long-term. However, humoral response to COVID-19 vaccines and the need for vaccine boosters in this group of patients using immunosuppressants or immunobiologics are still not fully established [16, 17]. Therefore, it is of paramount importance to understand the pandemic pattern and the role of vaccination in this population, which involves the risk of progression to severe disease and the humoral response achieved and maintained after complete immunization with different vaccines [18, 19].

The introduction of SARS-CoV-2 vaccines has led to dramatic reductions in transmission, hospitalization, and death [19]. Previous studies on the effectiveness of COVID-19 vaccination focused on responses to commonly administered vaccines worldwide, especially adenovirus and mRNA vaccines, such as BioNTech Pfizer, Moderna, and AstraZeneca [20–22]. Recent studies on patients with IBD have shown that post-vaccination adverse events are similar to those in the general population, with no increased risk of disease exacerbation [23, 24]. However, the frequent use of immunosuppressants and immunobiologics for the maintenance treatment of patients with IBD has been implicated in variable responses to vaccines. For example, there is evidence of an impaired immune response to vaccines against pneumococcus [25], influenza virus [26], and hepatitis B virus [27] in patients with IBD using immunosuppressants [28, 29]. These data make the effectiveness of COVID-19 vaccination in patients with IBD questionable. In addition, the optimal level of protection, defined as the immune response required to protect an individual from SARS-CoV-2 infection,
has not yet been established. Hence, this prospective study aimed to evaluate the humoral response to different types of vaccines against SARS-CoV-2 in patients with IBD and compare the response with that in a healthy population.

**Methods**

**Ethical considerations**

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee of the Pedro Ernesto University Hospital of the State University of Rio de Janeiro (CAAE: 48541221.1.0000.5259). All the enrolled patients provided written informed consent before participating in the study.

**Study design and selection of patients**

This prospective, single-center, observational, longitudinal study enrolled patients who were followed-up regularly at the Inflammatory Bowel Disease Outpatient Unit, Piquet Carneiro Polyclinic of the State University of Rio de Janeiro, a tertiary referral center, between September 2020 and September 2021. Eligible individuals were patients aged between 15 and 75 years with a diagnosis of IBD (CD or UC), supported by routine clinical, endoscopic, histological, and imaging parameters. Patients who had not been vaccinated against COVID-19 were consecutively selected to participate, regardless of the current therapy for IBD. Convenience sampling was conducted during the study period. A total of 35 patients with CD, 11 with UC, and 92 controls without comorbidities were included in this study. The exclusion criteria included prior SARS-CoV-2 infection, the presence of other autoimmune diseases, HIV/AIDS, individuals who did not sign the informed consent form, pregnant women, refusal to vaccinate, those with unclassified IBD, those in the postoperative period of less than 6 months or with total colectomy, those with evidence of abdominal abscess or colonic mucosal dysplasia, and those with cancer or acute or chronic enteric infection (e.g., *Clostridioides difficile*).

**Study protocol and procedures**

Between September 2021 and September 2022, blood samples were collected from all individuals enrolled in the study at three different time points: before vaccination and at one and six months after the second dose of the vaccine. The vaccines analyzed in this study were AstraZeneca (non-replicating viral vector), BioNTech Pfizer (mRNA), CoronaVac (inactivated virus), and Janssen (non-replicating viral vector). Sample collection was performed at the IBD outpatient unit in a reserved room after vital signs were checked by the nursing team. After collection, samples were registered in the MV Seoul system using patient registration data. After identification, the samples were centrifuged and stored at -20°C until the date of shipment (within one week) to the UNADIG-Fiocruz/RJ Diagnostic Center.

The titers of immunoglobulin G (IgG) antibodies against the SARS-CoV-2 spike receptor-binding domain were determined using a chemiluminescent microparticle immunoassay. For qualitative (N, against the nucleoprotein) and quantitative (S, against the S1 subunit of the receptor binding domain of the SARS-CoV-2 spike protein) determination of IgG antibodies, we ran an automated immunoassay SARS-CoV-2 IgG (for N) and SARS-CoV-2 IgG II Quant assay (for S) (Abbott Laboratories, Abbott Park, IL, USA), using the Architect i2000sr platform (Abbott, IL, USA), according to the manufacturer's recommendations. The assay uses paramagnetic microparticles coated with a nucleoprotein or the S1 subunit of the receptor-binding domain of the spike protein. The response (in relative light units) was based on IgG II standard/calibrator estimates, reflecting the quantity of IgG antibodies present. Overall, the assay showed 99.37% sensitivity and 99.5% specificity. Qualitative results were considered positive when the N nucleoprotein index s/c was ≥ 1.4. Seropositivity was defined as ≥ 50 arbitrary units (AU)/mL.

The results were registered in the MV Soul system, signed, and made available in the electronic records of patients or on the MV website. All data, including adverse events collected over one year of follow-up, were stored on the Google Chrome digital platform in a password-protected spreadsheet format accessible only to the researcher. Additional information is provided in the eAppendix of the Supplement. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting Guidelines for Observational Studies.

**Statistical analysis**

Statistical analyses were performed using the Statistical Package for Social Science software for Windows (Version 24, Statistic Package for Social Science, Inc., Chicago, IL, United States). Graphs were constructed using Prism software version 9.1.2 for Windows (GraphPad Software, San Diego, CA, USA). The characteristics of patients with IBD and the control group were summarized using descriptive statistics, with means and standard deviations for continuous variables and counts and percentages for categorical variables. Antibody titers between the two groups were compared using the Mann–Whitney U test. A pairwise Wilcoxon rank-sum test was used to compare the effect of the vaccines on antibody titers between two different time points. Similarly, groups were compared according to the vaccination schedule. Multiple comparisons between the vaccination schemes in each group were performed using the Kruskal–Wallis test. Multivariate linear regression was performed to assess the influence of variables on antibody titers using the variation in antibody titers before vaccination and one month after vaccination as the outcome. All tests were two-tailed, and significance was set at p < 0.05.

**Results**

Ninety patients with IBD were recruited, and pre-vaccination blood samples were collected for serological assays. Those who refused follow-up (n = 13), those with an insufficient blood volume in the first sample (n = 3), those who did not return for further collections without justification or because they
did not respond to telephone contact (n = 19), and those who refused more doses of vaccines (n = 9) were excluded. The final sample size was 46. Antibody titers against the surface protein of SARS-CoV-2 (anti-s IgG) before vaccination and one month after the second dose were analyzed in 46 patients with IBD and 92 patients in the control group. Similarly, six months after the second dose, patients with IBD were followed up with antibody measurements. Patients in the IBD group were vaccinated with the first dose between days 1 and 25 after the first blood collection (median, 7.6 days). The control group was vaccinated with the first dose between 1 and 29 days after the first collection (median, 6.1 days). The sociodemographic and clinical profiles of the participants in the IBD and control groups are presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and demographic characteristics of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IBD (n = 46)</td>
</tr>
<tr>
<td>Age in years (mean [range])</td>
<td>34.8 [16–60]</td>
</tr>
<tr>
<td>Male Gender (%)</td>
<td>39.2</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>9</td>
</tr>
<tr>
<td>White (%)</td>
<td>63</td>
</tr>
<tr>
<td>Vaccine (%)</td>
<td></td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>43.5</td>
</tr>
<tr>
<td>CoronaVac</td>
<td>17.4</td>
</tr>
<tr>
<td>Biontech Pfizer</td>
<td>30.4</td>
</tr>
<tr>
<td>Janssen/different schemes</td>
<td>8.7</td>
</tr>
<tr>
<td>Previous coronavirus infection (%)</td>
<td>21.7</td>
</tr>
<tr>
<td>Asymptomatic/mild symptoms (%)</td>
<td>96</td>
</tr>
<tr>
<td>CD (%)</td>
<td>76</td>
</tr>
<tr>
<td>UC (%)</td>
<td>24</td>
</tr>
<tr>
<td>CD Localization (%)</td>
<td></td>
</tr>
<tr>
<td>L1 (terminal ileum)</td>
<td>28.5</td>
</tr>
<tr>
<td>L2 (colon)</td>
<td>28.5</td>
</tr>
<tr>
<td>L3 (ileocolon)</td>
<td>40.0</td>
</tr>
<tr>
<td>L4 (upper GI tract)</td>
<td>3.0</td>
</tr>
<tr>
<td>UC Extension (%)</td>
<td></td>
</tr>
<tr>
<td>E1 (Proctosigmoiditis)</td>
<td>18</td>
</tr>
<tr>
<td>E2 (Left colitis)</td>
<td>18</td>
</tr>
<tr>
<td>E3 (Pancolitis)</td>
<td>64</td>
</tr>
<tr>
<td>CD Behavior (%)</td>
<td></td>
</tr>
<tr>
<td>B1 (nonstricturing nonpenetrating)</td>
<td>60.0</td>
</tr>
<tr>
<td>B2 (stricturing)</td>
<td>31.4</td>
</tr>
<tr>
<td>B3 (penetrating)</td>
<td>8.6</td>
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<tr>
<td>P (perianal)</td>
<td>23.0</td>
</tr>
<tr>
<td>Therapy (%)</td>
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</tr>
<tr>
<td>Salicylate / none</td>
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</tr>
<tr>
<td>Biologic only</td>
<td>15.2</td>
</tr>
<tr>
<td>Thiopurine only</td>
<td>32.6</td>
</tr>
<tr>
<td>Combotherapy</td>
<td>32.6</td>
</tr>
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</table>

Prior COVID-19 infection and vaccination schemes
In the IBD group, 21.7% of patients reported a previous COVID-19 infection before vaccination. Of these, only two patients had a moderate infection. The remaining patients were either asymptomatic or exhibited only mild symptoms. The vaccination scheme with two doses of AstraZeneca, Pfizer, Coronavac, or one dose of Janssen was administered to 43.5%, 30.4%, 17.4%, and 4.35% of the patients, respectively. Two patients received the first two doses of different vaccines. For comparison purposes, owing to the small number of patients, we gathered the same group of patients who received Janssen's vaccine and those who received the first two doses of different schedules.

In the control group, only 16.3% had COVID-19 before vaccination, and all cases were asymptomatic or mild. The vaccination scheme with two doses of AstraZeneca, Pfizer, Coronavac, or one dose of Janssen was carried out in 62%, 18.5%, 16.3%, and 0% of patients, respectively. Three individuals received the first two doses of the vaccine. For comparison purposes, owing to the small number of patients, we grouped in the same group the patients who received Janssen's vaccine and those who received the first two doses of different schedules.

Comparison of antibody titers in the IBD and control groups

In patients with IBD, the mean antibody titers were 430.3 AU/mL before vaccination and 8038.4 AU/mL after the two vaccine doses. In the control group, the mean antibody titers were 90.5 AU/mL before vaccination and 7697.5 AU/mL after the two vaccine doses (Fig. 1). In both groups, there was a significant increase in antibody titers after administration of the two vaccine doses (p < 0.001). When comparing the antibody titers one month after the second dose, no difference was detected between the IBD and control groups (p = 0.731).

Potential association between pre- and post-vaccination antibody titers and vaccination schemes

The mean antibody titers of control participants vaccinated with Janssen/different regimens, Coronavac, AstraZeneca, and Pfizer were 14431.4 AU/mL, 1397.3 AU/mL, 4498.3 AU/mL, and 25648.1 AU/mL, respectively. In the IBD group, the mean antibody titers were 2477.6 AU/mL, 1140.4 AU/mL, 4017.3 AU/mL, and 19313 AU/mL, respectively.

Individual analysis by vaccination scheme showed that, in both groups, the AstraZeneca, Coronavac, and Pfizer vaccines significantly increased the antibody titers (Table 2). However, patients receiving Janssen or different regimens did not show a significant increase in antibody titers (p > 0.05) (Fig. 2).
Table 2
Comparative analysis of vaccination schemes in cases and controls

<table>
<thead>
<tr>
<th>Vaccine Scheme</th>
<th>Descriptive statistics</th>
<th>Control</th>
<th>IBD</th>
<th>p</th>
<th>IBD</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-vaccination</td>
<td>One month after 2nd dose</td>
<td>p</td>
<td>Pre-vaccination</td>
<td>One month after 2nd dose</td>
</tr>
<tr>
<td>CV</td>
<td>N</td>
<td>17</td>
<td>17</td>
<td>&lt;0.001</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>30.9</td>
<td>1397.3</td>
<td>86.9</td>
<td>1140.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>6.8</td>
<td>1255.5</td>
<td>48.6</td>
<td>1240.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>64.6</td>
<td>854.7</td>
<td>111.4</td>
<td>890.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>6.8</td>
<td>315.5</td>
<td>6.8</td>
<td>91.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>245.8</td>
<td>3742.5</td>
<td>327.8</td>
<td>2669.7</td>
<td></td>
</tr>
<tr>
<td>AZ</td>
<td>N</td>
<td>57</td>
<td>57</td>
<td>&lt;0.001</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>83.7</td>
<td>4498.3</td>
<td>147.3</td>
<td>4017.3</td>
<td></td>
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<tr>
<td></td>
<td>Median</td>
<td>8.3</td>
<td>2224.9</td>
<td>7.6</td>
<td>1979.5</td>
<td></td>
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<tr>
<td></td>
<td>SD</td>
<td>214.0</td>
<td>6085.2</td>
<td>255.5</td>
<td>5032.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min</td>
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<td>143.0</td>
<td>6.8</td>
<td>100.0</td>
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<tr>
<td></td>
<td>Max</td>
<td>1229.4</td>
<td>32767.2</td>
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<tr>
<td>Pfizer</td>
<td>N</td>
<td>15</td>
<td>15</td>
<td>0</td>
<td>14</td>
<td>14</td>
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<tr>
<td></td>
<td>Mean</td>
<td>200.8</td>
<td>25648.1</td>
<td>1096.0</td>
<td>19313.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>6.8</td>
<td>23346.6</td>
<td>10.7</td>
<td>12061.3</td>
<td></td>
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<tr>
<td></td>
<td>SD</td>
<td>554.1</td>
<td>13650.9</td>
<td>3594.7</td>
<td>17537.2</td>
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<tr>
<td></td>
<td>Min</td>
<td>6.8</td>
<td>10493.3</td>
<td>0.1</td>
<td>433.0</td>
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<tr>
<td></td>
<td>Max</td>
<td>2144.4</td>
<td>58875.8</td>
<td>13521.5</td>
<td>57196.8</td>
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<tr>
<td>Janssen/different schemes</td>
<td>N</td>
<td>3</td>
<td>3</td>
<td>0.109</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>8.1</td>
<td>14431.4</td>
<td>201.8</td>
<td>2477.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>6.8</td>
<td>12818.3</td>
<td>22.9</td>
<td>2774.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>2.2</td>
<td>10491.0</td>
<td>369.0</td>
<td>1962.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>6.8</td>
<td>4840.3</td>
<td>6.8</td>
<td>159.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>10.6</td>
<td>25635.5</td>
<td>754.8</td>
<td>4202.6</td>
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</table>

AZ, AstraZeneca; CV, CoronaVac; SD, standard deviation; Min, minimum; Max, maximum.

When comparing the different vaccine schemes in the control group, there was a clear superiority of the Janssen and Pfizer schemes over CoronaVac (p = 0.015 and p < 0.0001, respectively), and Pfizer over AstraZeneca (p < 0.0001). In patients with IBD, the Pfizer system induced higher antibody titers than the AstraZeneca (p < 0.0001) and CoronaVac (p = 0.01) systems (Fig. 2).

A comparison of the different vaccine schemes was also performed during the follow-up period of up to 6 months after the second dose. Six months after the second dose, all vaccine regimens showed a significant increase in antibody titers, whereas vaccination with Pfizer continued to induce relatively higher antibody titers (Fig. 3).

**Potential association between antibody titers and specific features of patients with IBD**

To estimate the relationship between the clinical and demographic characteristics of the patients and antibody titers after the vaccination schemes, we analyzed the data using linear regression. Significant individual differences were observed in relation to the vaccination scheme (p < 0.0001), with a negative association with older age (p < 0.005) and a positive association with a history of COVID-19 (p = 0.012) (Table 3). We then used multiple linear regression to estimate the relationship between vaccine response and variables with greater power of association with antibody titers (Fig. 4).
was associated with lower concentrations of antibodies compared with the general population, unlike what was observed with other therapeutic regimens. As shown in previous studies in patients with IBD, iniximab was associated with attenuated serological responses to SARS-CoV-2 infection, which increases the risk of COVID-19 [34].

Nonetheless, the decay of antibody titers over time following SARS-CoV-2 vaccination reported in studies with non-immunosuppressed cohorts [32, 33], which increases the risk of COVID-19 [34], has raised concerns related to patients with IBD, particularly regarding the frequent use of immunosuppressants. As shown in previous studies in patients with IBD, infliximab was associated with attenuated serological responses to SARS-CoV-2 infection [35]. Similarly, decreased durability of the humoral response to SARS-CoV-2 infection was detected among patients receiving anti-TNF therapy compared to those receiving other medications, including other biologicals [36], which could impact long-term immunity [37]. In another study of 370 participants using different drugs to treat IBD, the use of anti-TNF and tofacitinib was associated with lower concentrations of antibodies compared with the general population, unlike what was observed with other therapeutic regimens [38]. In contrast, the results of this study showed that the antibody titers in patients with IBD were similar to those in the general population.

Potential association between antibody titers and the therapeutic regimen for IBD

Considering the different therapies used, including salicylate or none (0), immunosuppressant only (1), biological only (2), and combined therapy (3), we did not find any differences in antibody titers between the distinct therapeutic groups in the pre-vaccination analyses and 1 month after the second dose (p > 0.05). (Fig. 5).

Discussion

Shortly after the appearance of the first case of SARS-CoV-2 infection in 2019, great efforts were directed towards the investigation and development of effective and safe vaccines capable of containing the viral spread worldwide. However, initial clinical trials did not include patients using immunosuppressants/immunomodulatory drugs, thus raising doubts about the capacity for seroconversion and maintenance of antibodies over time in these individuals. It was only in December 2020, the date on which the worldwide vaccination campaign began, new data emerged regarding the post-vaccination humoral immune responses in this population.

In this study, the outpatient unit from which all patients with IBD and samples were analyzed belonged to a tertiary referral center that received patients with different levels of complexity, most of whom were using biological and/or immunomodulatory therapy. Therefore, all the patients in this study had a priority indication for vaccination. It is important to highlight the small number of Brazilian studies on patients with IBD regarding COVID-19 and SARS-CoV-2 vaccination, especially those involving vaccines with limited global coverage, as is the case with CoronaVac. Considering this, we aimed to contribute to the study of humoral immune responses that develop after vaccination against COVID-19 in patients with IBD. Moreover, the current study analyzed individuals in the transition from the pre- to post-vaccination era, collecting data before and after the available vaccination schemes. This study focused on the evaluation of antibody titers before, one month after, and six months after the two standard doses of the different vaccination schemes. In patients with IBD, antibody titers at different time points were analyzed according to different vaccination schemes, clinical characteristics of the patients, and outcomes. In addition, the results of the IBD group were compared with those of a control group of healthy individuals with sociodemographic characteristics similar to those of the IBD group.

As is already well established in the global literature, vaccination against COVID-19 has contributed significantly to the control of the pandemic. In a retrospective study conducted in Italy, Mattiuzzi et al. demonstrated that the vaccine significantly reduced SARS-CoV-2 infections, hospitalizations, intensive care unit stays, and deaths in the general population [30]. Likewise, in patients with CD or UC, vaccination was shown to be effective and safe, protecting them from the most severe outcomes in a similar way to the general population, as concluded by Lev-Tzion et al., from Israel [31]. However, important variations among countries regarding the types of vaccines, interval between doses, transmissibility rate, and negative outcomes of the infection need to be acknowledged and require further investigation. Therefore, the paucity of local data prompted us to evaluate the pattern of antibody titers in the IBD population, emphasizing comparison with a control group, which might help us understand the influence of medications used in the treatment of IBD on the vaccine response.

Nonetheless, the decay of antibody titers over time following SARS-CoV-2 vaccination reported in studies with non-immunosuppressed cohorts [32, 33], which increases the risk of COVID-19 [34], has raised concerns related to patients with IBD, particularly regarding the frequent use of immunosuppressants. As shown in previous studies in patients with IBD, infliximab was associated with attenuated serological responses to SARS-CoV-2, which were further impaired by combination therapy with immunomodulators [35]. Similarly, decreased durability of the humoral response to SARS-CoV-2 infection was detected among patients receiving anti-TNF therapy compared to those receiving other medications, including other biologicals [36], which could impact long-term immunity [37]. In another study of 370 participants using different drugs to treat IBD, the use of anti-TNF and tofacitinib was associated with lower concentrations of antibodies compared with the general population, unlike what was observed with other therapeutic regimens [38]. In contrast, the results of this study showed that the antibody titers in patients with IBD were similar to those in the general population.
after two doses of the vaccine against the coronavirus, regardless of the therapy used. Our findings are in line with the data from Kappleman et al., who demonstrated a high rate of seroconversion in 95% of patients in a cohort of 317 individuals with IBD after two doses of mRNA vaccines [39]. Similarly, Melmed et al. reported seroconversion in 99% of patients with IBD after two doses, regardless of the medication used to treat IBD [40].

This study revealed other relevant associations with humoral responses in patients with IBD. In addition to reporting seroconversion and antibody titers similar to those in the general population after two doses of the vaccine, we also observed that the titers changed according to the specific characteristics of the individuals. As expected and consistent with other studies, increasing age was significantly associated with lower antibody titers, an effect probably attributable to immunosenescence [41]. A significant independent association between age and antibody titers appeared in the multiple linear regression model, showing the expected negative association. Nevertheless, it is important to call attention to note that this study analyzed a cohort of patients with IBD who were younger than those in most previous studies [38, 42, 43]. Such differences in average age among patients in different studies may render data on the impact of age on the response to vaccine. In addition, among the several characteristics of the IBD group, the model revealed higher antibody titer concentrations in patients who were vaccinated with two doses of Pfizer vaccine compared with the other vaccine regimens. This finding is similar to that of Alexander et al., who compared mRNA and adenovirus-based vaccines [38]. Moreover, analysis of the model indicated significantly higher serological responses in patients previously infected with COVID-19, which may be explained by the immunological memory generated by B lymphocytes after infection, as previously proposed [44].

This study had some limitations that must be acknowledged. First, the sample size was relatively small. The number of patients who received Janssen or two doses of different vaccines as a standard dose was small, which explains the absence of seroconversion in this group when the titers were evaluated one month after the second dose. Second, the analysis performed six months after the second dose was biased because of the emergence of booster doses. During this period, only the IBD group was vaccinated with booster doses, preventing comparison with the control group and long-term follow-up of antibody titers. Moreover, many initial losses have occurred, largely due to low vaccine acceptance. As COVID-19 is still regarded as a new disease, with vaccine development still in progress, global acceptance is relatively slow, similar to what occurred at the beginning of vaccination against influenza in 2009, as analyzed by Bulths et al. [45]. Although SARS-CoV-2 vaccine hesitancy is a relatively common problem worldwide, partly fueled by misinformation [46], this should not exempt local governments and health system decision-makers from their responsibilities and roles in education and divulgation of quality information, all critical for the rapidity and range of vaccine coverage and protection of the population. Finally, as observed in most studies with similar designs, an isolated and single-center study of antibody titers measuring IgG antibodies against the spike protein (IgG anti-s) may not accurately reflect humoral immunity and the immune response as a whole. Considering the complexity of adaptive and innate responses against SARS-CoV-2, the interpretation of vaccine immunity must be part of the broad context of immunology [47].

However, the lowest-cost and simplest way to assess humoral responses to different types of vaccines is through the measurement of antibodies. Additionally, because COVID-19 is still considered a new disease, each process that involves protection against the development of the disease must be considered, making it a fundamental part of the construction of knowledge [48]. Currently, the Ministry of Health of Brazil, in agreement with the World Health Organization, recommends a second booster dose four months after the first. As noted by Loubet et al., the choice of a campaign with booster doses is based on the spread of new variants over time, in addition to scientific evidence of a decline in humoral response after full vaccination, mostly with two doses of the vaccine [49]. There is still much to learn about the coronavirus pandemic, and several studies have been published on this topic. This study showed that awareness regarding booster doses in patients with IBD receiving immunosuppressive therapy should remain, as the current results indicate that a booster dose of the COVID-19 vaccine enhances the antibody response. Finally, the results of this study contribute to reinforcing the safety of SARS-CoV-2 vaccination in patients with IBD under immunosuppressive therapeutic agents.

Declarations

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Conflict of interest. The authors declare that they have no competing interests.

Ethical approval. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee of the Pedro Ernesto University Hospital of the State University of Rio de Janeiro (CAAE: 48541221.1.0000.5259).

Consent to participate. All the enrolled patients provided written informed consent before participating in the study.

Data availability. Materials such as protocols, analytical methods, and study materials are available upon request from interested researchers. The raw data supporting the conclusions of this manuscript will be made available by the authors without undue reservation to any qualified researcher.

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References


SARS-CoV-2 antibody titers in control individuals and patients with IBD

The humoral immune response to vaccination against SARS-CoV-2 spike protein was evaluated by measuring pre- and post-vaccination antibody titers. Medians with interquartile ranges and individual values are shown. The analysis was performed using the Kruskal–Wallis test, in which multiple comparisons between the vaccination schemes in each group were carried out using the Dunn's test, and Wilcoxon matched-pairs signed rank test for pre- and post-vaccination results.

IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
Figure 2

SARS-CoV-2 antibody titers in response to different vaccination schemes

The humoral immune response to vaccination against SARS-CoV-2 spike protein was evaluated by measuring pre- and post-vaccination antibody titers in control individuals (A) and patients with IBD (B). Medians with interquartile ranges and individual values are shown. The analysis was performed using the Kruskal-Wallis test, in which multiple comparisons between the vaccination schemes in each group were carried out using the Dunn’s test, and Wilcoxon matched-pairs signed rank test for pre- and post-vaccination results.

IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
Figure 3

Effect of previous natural covid infection in the short and long-term SARS-CoV-2 antibody titers in response to vaccination

The humoral immune response to vaccination against SARS-CoV-2 spike protein was evaluated by measuring pre- and post-vaccination (1 month and 6 months after vaccination) antibody titers. Medians with interquartile ranges and individual values are shown. The analysis was performed using the Kruskal–Wallis test, in which multiple comparisons between the vaccination schemes in each group were carried out using the Dunn's test, and Wilcoxon matched-pairs signed rank test for pre- and post-vaccination results.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
Figure 4

Multiple linear regression of predicted SARS-CoV-2 antibody titers modeled based on the combined rates of age, previous history of natural COVID-19 infection, and the vaccination scheme.

Log10-transformed individual values are shown, with a median and 95% confidence interval (lines).

RMSE: 0.5196
P < 0.0001
RSq: 0.3479

RSq, R squared; RMSE, root-mean-square error; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019
Figure 5

Effect of the therapeutic regimen for IBD in SARS-CoV-2 antibody titers in response to vaccination

The humoral immune response to vaccination against SARS-CoV-2 spike protein was evaluated by measuring pre- and post-vaccination antibody titers, according to the different therapeutic regimens. Medians with interquartile ranges and individual values are shown. The analysis was performed using the Kruskal–Wallis test, in which multiple comparisons between the vaccination schemes in each group were carried out using the Dunn's test, and Wilcoxon matched-pairs signed rank test for pre- and post-vaccination results.

IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Supplementary Files

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- CostaDatabase.xlsx