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## Observational Study

# COVID-19 impact in Crohn's disease patients submitted to autologous hematopoietic stem cell transplantation

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## Abstract

### BACKGROUND

Severe acute respiratory syndrome coronavirus 2 is the virus responsible for coronavirus disease 2019 (COVID-19), a disease that has been blamed for inducing or exacerbating symptoms in patients with autoimmune diseases. Crohn's disease (CD) is an inflammatory bowel disease that affects genetically susceptible patients who develop an abnormal mucosal immune response to the intestinal microbiota. Patients who underwent hematopoietic stem cell transplantation (HSCT) are considered at risk for COVID-19.

### AIM

To describe for the first time the impact of COVID-19 in CD patients who had undergone autologous, non-myeloablative HSCT.

### METHODS

In this descriptive study a series of 19 patients were diagnosed with positive COVID-19. For two patients there were reports of the occurrence of two infectious episodes. Parameters related to HSCT, such as time elapsed since the procedure,

vaccination status, CD status before and after infection, and clinical manifestations resulting from COVID-19, were evaluated.

## RESULTS

Among the patients with COVID-19, three, who underwent Auto HSCT less than six months ago, relapsed and one, in addition to the CD symptoms, started to present thyroid impairment with positive anti-TPO. Only one of the patients required hospitalization for five days to treat COVID-19 and remained in CD clinical remission. Nine patients reported late symptoms that may be related to COVID-19. There were no deaths, and a statistical evaluation of the series of COVID-19 patients compared to those who did not present any infectious episode did not identify significant differences regarding the analyzed parameters.

## CONCLUSION

Despite the change in CD status in three patients and the presence of nine patients with late symptoms, we can conclude that there was no significant adverse impact concerning COVID-19 in the evaluated patients who underwent HSCT to treat CD.

**Key Words:** Inflammatory bowel disease; Crohn disease; SARS-CoV-2; COVID-19; Autologous hematopoietic stem cell transplantation; Stem cell therapy

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**Core Tip:** This report discusses the impact of coronavirus disease 2019 (COVID-19) on 50 patients with Crohn's disease (CD) who underwent autologous hematopoietic stem cell transplantation between 2013 and 2021. Of these patients, 19 were diagnosed with COVID-19, with two patients reporting two infectious episodes each and in three there was a change in the CD status. One patient required hospitalization, but there were no deaths. Overall, the study found no significant adverse impact of COVID-19 on these patients.

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## INTRODUCTION

Since 2020, the world has lived with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. The disease also known as coronavirus disease 2019 (COVID-19) is characterized primarily by respiratory failure and pneumonia but with different repercussions and clinical complications in the entire organism[1,2].

Crohn's disease (CD) is a chronic disease that occurs in genetically susceptible individuals as a result of an anomalous immune response of the mucosa to the intestinal microbiota[3].

Despite the improvement in the medical management of inflammatory bowel disease (IBD) and CD in recent years, some patients with CD become refractory or without any therapeutic drug options. Autologous hematopoietic stem cell transplantation (Auto HSCT) in these patients could be an alternative treatment option[4].

The impact of COVID-19 on CD and IBDs has received little attention despite the gut microbiota being considered one of the preferred targets of SARS-CoV-2[5].

COVID-19 has been described as triggering or responsible for relapses in patients with autoimmune diseases[6,7]. Hematopoietic stem cell transplant (HSCT) recipients are considered at increased risk of mortality and morbidity with COVID-19 due to severe immune dysfunction[8]. However, no data exists on outcomes and the COVID-19 clinical impact on patients with CD that underwent Auto HSCT.

Thus, this report aimed to present and discuss the impact of SARS-CoV-2 infection for the first time in patients who had severe and refractory CD to conventional treatments and underwent Auto HSCT.

## MATERIALS AND METHODS

The evaluated patients are part of studies registered in US Clinical Trials NCT 03000296 and IRD- CAAE 20 894719.1.0000.5629, infected or not by SARS-CoV-2. All consented to have their data published.

A unicentric longitudinal study was carried out in Hospital de Beneficência Portuguesa, São Jose do Rio Preto, Brazil on a group of 50 patients with CD who underwent an Auto HSCT between 2013 and 2021. The evaluation of HSCT patients in respect to COVID-19 and their clinical status was performed in 2022, and the Auto HSCT non-myeloablative

regimen data and details of the procedure they underwent are described in another publication elsewhere[9].

Patient information was organized in a database of 50 records with 12 variables. The records contained information on two patients who had had the disease twice. The variables obtained from each patient were age, sex, date of the HSCT, months elapsed from the transplant until the date of the infection by the virus, clinical symptoms observed during the infection, treatment provided for COVID-19, history of immunization, the origin of the vaccine, number of doses, and patient symptoms during and after COVID-19, in addition to the CD status before and after COVID-19. For this evaluation, we considered remission, CD status and any specific clinical or surgical treatment for the disease at any time after Auto HSCT.

For statistical analysis, the patients were organized into two groups, one formed by those who did not have a diagnosis of COVID-19 and the other by those who had a diagnosis of COVID-19. Patients who underwent HSCT after the onset of the pandemic were evaluated separately taking into account the same parameters. Statistical analysis was performed with Pearson's Chi square test, t-test and Fisher's exact test using the SPSS (version 23) software with a significance level of 0.05% being considering significant.

## RESULTS

The study consisted of 50 patients of both sexes, 28 (56%) female and 22 (44%) male. The mean age was  $38.12 \pm 9.273$  years, with the youngest patient being 17 and the oldest 57 years old. The clinical and demographic characteristics of the patients who underwent auto HSCT and contracted COVID-19 are shown in Table 1. In addition, data for the entire series are shown as Supplementary Tables 1-3. Table 2 shows the two groups of patients who had or did not have COVID-19.

Of the total, 31 patients (62%) did not have COVID-19, while 19 (38%) had the diagnosis confirmed by reverse transcription PCR. Among the patients with COVID-19, 12 (42.8%) were female and seven (31.8%) were male, nine (23.1%) had been previously vaccinated, while 10 (90.9%) still had not taken any doses of the vaccine against SARS-CoV-2.

Among the vaccinated patients, the Pfizer vaccine predominated with 23 immunized patients, followed by the Astra Zeneca vaccine with 20 patients immunized. In total 45 (90%) of the patients had received a COVID-19 vaccine. Of the patients who reported being vaccinated, 30% received two doses and 42% received three.

Before the diagnosis of COVID-19, 22 patients were in clinical remission of CD, while 28 had relapsed. After infection, 19 patients were in remission and 31 had relapsed. Thus, three patients relapsed after being infected with COVID-19. Twenty-one patients underwent Auto HSCT after 2019, the beginning of the pandemic with an analysis of the same variables as the initial group of 50 patients showing a mean age of 31 years (median of 35 years, 11 were female and 10 were male. In this group, eight became infected with COVID-19 while 13 did not. Therefore, the analysis of the results of this group of patients after 2019 do not differ statistically from the entire group studied.

The symptoms of patients who contracted COVID-19 were those usually described for the disease, such as fever, asthenia, cough, sore throat, and muscle pain with only one of the patients (15) requiring hospitalization for five days.

As additional data, two patients with two infectious episodes (22 and 40) had been in clinical remission, however, patient 40, after the first episode, started to show anti-TPO antibodies in addition to signs of CD activity. The other patient, 22, remained in clinical remission after the two infectious episodes.

Regarding the symptoms the patients had during the infectious episodes, in addition to the usual symptoms, diarrhea was mentioned in 15.8% and vomiting in 15%. After COVID-19, nine patients reported varied late symptoms and 5.3% reported persistent diarrhea and abdominal pain. Only one of the patients mentioned the presence of cognitive disorders. There were no COVID-19-related deaths in this case series.

The data in Supplementary Tables 1-3 complement the data described in the study.

## DISCUSSION

The SARS-CoV-2 virus is responsible for COVID-19, a disease that has impacted the entire world and is blamed for the induction and exacerbation of autoimmune diseases[6,7,10]. In addition to immunocompromised patients, HSCT recipients are part of a group of patients at greater risk of contracting COVID-19[11]. Allogeneic and auto HSCT recipients have increased mortality, morbidity, and clinical complication rates when contracting COVID-19[8,12-14]. A report on a group of patients undergoing transplantation showed a mortality rate for auto HSCT of 17% and for allogeneic HSCT it was 21%[8]. These data configure the severe conditions to which HSCT recipients are submitted in both modalities. There is a reason for evaluating a group of patients previously submitted to auto HSCT and its impact on CD.

CD courses with dysbiosis of the digestive system, which is the primary habitat and target of SARS-CoV-2. This is due to a high intestinal expression of ACE2 and TMPRSS2 receptors, which are abundant at this site[15].

The intestinal microbiome of people with COVID-19 or CD, compared to that of healthy people, shows a considerable reduction of anti-inflammatory bacteria[15]. Patients with COVID-19 have gastrointestinal manifestations during the infection, and the SARS-CoV-2 virus is believed to trigger CD in patients predisposed to the disease[16]. However, the effect of COVID-19 on gut health and inflammation among patients with inflammatory diseases remains uncertain, particularly in respect to the susceptibility and clinical impact of COVID-19 and its impact on the gut microbiota[5]. It is believed that the immune dysregulation caused by COVID-19 can trigger the onset of various autoimmune diseases, including in patients with active CD, which persist even after recovery from the infectious episode[17].

**Table 1 Demographic and clinical characteristics of Crohn disease patients coronavirus disease 2019 + underwent autologous hematopoietic stem cell transplantation (2013-2021; 19/50 pts)**

|     | Age (yr) | Sex | HSCT date | Elapsed months | Vaccina | Label vaccine (n) | CD status | COVID-19 | Months HSCT to COVID | Vaccination at infection time | Symptoms COVID-19 +                                                              | Treatment COVID-19+ | CD Status before COVID-19 pts + | CD Status after COVID-19 pts + | Delayed symptoms after COVID-19                      |
|-----|----------|-----|-----------|----------------|---------|-------------------|-----------|----------|----------------------|-------------------------------|----------------------------------------------------------------------------------|---------------------|---------------------------------|--------------------------------|------------------------------------------------------|
| 5   | 41-45    | F   | 2015      | 84             | No      | 0                 | Remission | Yes      | 76                   | No                            | Fever, flu-like symptoms, cough, body aches                                      | 0                   | Remission                       | Remission                      | 0                                                    |
| 7   | 56-60    | M   | 2015      | 78             | Yes     | (2) Az            | Remission | Yes      | 77                   | Yes                           | Fever, body aches, fatigue                                                       | 0                   | Remission                       | Remission                      | 0                                                    |
| 8   | 51-55    | M   | 2015      | 77             | No      | 0                 | Remission | Yes      | 76                   | No                            | Severe body aches, severe headache, physical and mental fatigue and diarrhea     | 0                   | Remission                       | Remission                      | Fatigue, muscle weakness, shortness of breath        |
| 12  | 31-35    | M   | 2016      | 71             | No      | 0                 | Relapsed  | Yes      | 59                   | No                            | Flu symptoms                                                                     | 0                   | Relapsed                        | Relapsed                       | 0                                                    |
| 14  | 41-45    | M   | 2016      | 69             | Yes     |                   | Relapsed  | Yes      | 68                   | Yes                           | Coryza and sore throat                                                           | 0                   | Relapsed                        | Relapsed                       | 0                                                    |
| 15  | 51-55    | F   | 2016      | 69             | Yes     | 0                 | Remission | Yes      | 68                   | No                            | Headache, diarrhea, hospital stay 5 days                                         | Iver, Cort e Azitro | Remission                       | Remission                      | Sleep disorders, headache                            |
| 20  | 31-35    | F   | 2017      | 57             | Yes     | (2) Az (1) Pf     | Remission | Yes      | 56                   | Yes                           | Headache, rashes, fever, cough and sore throat                                   | Azitro, Cort        | Remission                       | Remission                      | Loss of taste, nausea and alopecia                   |
| 22a | 26-30    | F   | 2017      | 55             | No      | 0                 | Remission | Yes      | 41                   | No                            | Flu-like symptoms, nausea, fatigue                                               | 0                   | Remission                       | Remission                      | 0                                                    |
| 22b | 26-30    | F   | 2017      | 55             | Yes     | (2) Az            | Remission | Yes      | 54                   | Yes                           | Cough                                                                            | 0                   | Remission                       | Remission                      | Diarrhea                                             |
| 24  | 41-45    | F   | 2017      | 50             | Yes     | (2) Az (1) Pf     | Relapsed  | Yes      | 49                   | Yes                           | Fever, sore throat, body aches, vomiting, headache, cough and worsening diarrhea | 0                   | Relapsed                        | Relapsed                       | Cough, headache and dizziness, burning in the throat |
| 27  | 41-45    | F   | 2018      | 45             | Yes     | (1) Az            | Remission | Yes      | 32                   | No                            | Body ache and sore throat                                                        | Azitro, Iver        | Remission                       | Remission                      | 0                                                    |
| 29  | 36-40    | F   | 2018      | 42             | Yes     | (2) Az (1) Pf     | Relapsed  | Yes      | 41                   | Yes                           | Sore throat, cough, runny nose, body ache, fever, indisposition                  | 0                   | Relapsed                        | Relapsed                       | 0                                                    |
| 31  | 36-40    | M   | 2019      | 33             | Yes     | 0                 | Relapsed  | Yes      | 24                   | Yes                           | Shortness of breath, cough and asthma                                            | Azitro, Cort        | Relapsed                        | Relapsed                       | Coognitive disorders                                 |
| 33  | 16-20    | F   | 2019      | 32             | No      | 0                 | Relapsed  | Yes      | 12                   | No                            | Headache, sneezing, body ache, runny nose                                        | 0                   | Relapsed                        | Relapsed                       | 0                                                    |
| 34  | 31-35    | F   | 2019      | 30             | Yes     | (3) Pf            | Relapsed  | Yes      | 29                   | Yes                           |                                                                                  | 0                   | Relapsed                        | Relapsed                       | 0                                                    |

|            |       |   |      |    |     |               |           |     |    |     |                                                                                                                                                                                    |   |           |           |                                                                    |
|------------|-------|---|------|----|-----|---------------|-----------|-----|----|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-----------|-----------|--------------------------------------------------------------------|
| <b>40a</b> | 31-35 | F | 2020 | 24 | No  | 0             | Relapsed  | Yes | 6  | No  | Loss of taste and smell, fever, tiredness, diarrhea, sore throat, headache and body pain. Loss of taste and smell, fever, tiredness, diarrhea, sore throat, headache and body pain | 0 | Remission | Relapsed  | Muscle weakness, sleep and cognitive disturbances with CD symptoms |
| <b>40b</b> | 31-35 | F | 2020 | 24 | Yes | (2) Az (1) Pf | Relapsed  | Yes | 23 | Yes | Sore throat, cough, runny nose, fever, headache and body ache                                                                                                                      | 0 | Relapsed  | Relapsed  | Muscle weakness, sleep and cognitive disturbances with CD symptoms |
| <b>41</b>  | 51-55 | F | 2020 | 24 | Yes | (2) Pf        | Relapsed  | Yes | 23 | Yes | Fever, body aches, sore throat and weakness                                                                                                                                        | 0 | Relapsed  | Relapsed  | Diarrhoea, severe abdominal pain                                   |
| <b>43</b>  | 46-50 | M | 2020 | 16 | Yes | 0             | Relapsed  | Yes | 6  | No  | Fever, stuffy nose, loss of smell and taste, and muscle aches                                                                                                                      | 0 | Remission | Relapsed  | 0                                                                  |
| <b>44</b>  | 36-40 | M | 2020 | 14 | Yes | 0             | Relapsed  | Yes | 4  | No  | Fever, headache, lack of appetite, tiredness, cough, weakness                                                                                                                      | 0 | Remission | Relapsed  | 0                                                                  |
| <b>50</b>  | 31-35 | F | 2021 | 5  | Yes | (2) Az (1) Pf | Remission | Yes | 3  | Yes | Fever, headache, body ache, sore throat, cough, tiredness, chest pain, vomiting, diarrhea                                                                                          | 0 | Remission | Remission | 0                                                                  |

CD: Crohn's disease; COVID-19: Coronavirus disease 2019; Azitro: Azitromycin, Cort: Corticosteroids, F: Female; Iver: Ivermectin; HSCT: Hematopoietic stem cell transplantation; M: Male; Az: Oxford/Astra Zeneca ChAdOx1-S; Cort: Corticosteroids; F: Female; Iver: Ivermectin; M: male; Pf: Pfizer Biontech BNT16-2b2.

COVID-19 shares similar characteristics with autoimmune diseases regarding clinical manifestations, immune responses, and pathogenic mechanisms. In addition, there are reports of several patients developing autoimmune diseases, such as Guillain Barre Syndrome, lupus, vasculitis, myopathies, and descriptions of isolated cases of multiple sclerosis and Still's disease[18-20].

In the current series of 50 patients with CD, and in the 19 patients who had COVID-19, there was no increase in the morbidity rate or presence of mortality, data that differ from the literature[8,12-14]. In the analysis of the series of patients submitted to autologous and allogeneic HSCT, we observed that they had onco-hematological diseases submitted to rescue chemotherapy, mobilization schemes with high doses of chemotherapy, and myeloablative conditioning. Our sample differs in using mobilization regimens with low doses of cyclophosphamide and a non-myeloablative conditioning regimen. This may explain the low morbidity, with only one case requiring hospitalization and then only on the ward. Another relevant data observed was the absence of deaths.

In the current patients, there was no change in CD status in most cases, with relapse in only three cases (40, 43 and 44). These patients had undergone HSCT less than six months prior to the infectious episode. This data corroborates the information on patients' vulnerability within the first year after auto HSCT[21].

There are reports that COVID-19 can affect the endocrine system and trigger changes in thyroid function, with clinical and biochemical manifestations and the development of antithyroid antibodies[22,23]. One of the cases in this study (40) that relapsed after an infectious episode presented endocrinological manifestations of CD with the presence of anti-TPO.

Post-COVID syndrome is currently recognized as a new disease in the context of SARS-CoV-2 infection. However, its pathogenesis is still not fully understood, with data that acute inflammation may be responsible for this clinical picture [24-27], Of our patients, nine reported clinical manifestations that may be related to the Post-COVID Syndrome. However,

**Table 2 General Statistics of the Crohn disease patients underwent to autologous hematopoietic stem cell transplantation and coronavirus disease 2019 (50 pts. 2013-2021), *n* (%) / mean  $\pm$  SD**

|                                            |           | COVID-19 positive patients, 19<br>(38%) | COVID-19 negative patients, 31<br>(62%) |                     |
|--------------------------------------------|-----------|-----------------------------------------|-----------------------------------------|---------------------|
| Sex                                        | Female    | 12 (42.85)                              | 16 (57.14)                              | 0.425 <sup>1</sup>  |
|                                            | Male      | 7 (31.81)                               | 15 (68.18)                              |                     |
| Age (yr)                                   |           | 39.11 $\pm$ 10.104                      | 37.52 $\pm$ 8.84                        | 0.562 <sup>2</sup>  |
| Elapsed time HSCT until evaluation (month) |           | 46.05 $\pm$ 24.19                       | 48.71 $\pm$ 28.12                       | 0.734 <sup>2</sup>  |
| Elapsed time HSCT until COVID-19 +         |           | 39.47 $\pm$ 26.57                       |                                         |                     |
| COVID-19 vaccination                       | Yes       | 9 (23.1)                                | 30 (76.9)                               |                     |
|                                            | No        | 10 (90.90)                              | 1 (9.1)                                 |                     |
| CD status before COVID-19                  | Relapsed  | 8 (28.57)                               | 20 (71.42)                              | 0.1500 <sup>3</sup> |
|                                            | Remission | 11 (50)                                 | 11 (50)                                 |                     |
| CD status after COVID-19                   | Relapsed  | 11 (35.48)                              | 20 (64.52)                              | 0.7661 <sup>3</sup> |
|                                            | Remission | 8 (42.10)                               | 11 (57.89)                              |                     |

<sup>1</sup>Pearson Chi-square test.<sup>2</sup>*t*-test.<sup>3</sup>Fisher's exact test.

CD: Crohn's disease; COVID-19: Coronavirus disease 2019; HSCT: Hematopoietic stem cell transplantation.

only one of the patients had cognitive disorders, and two patients had digestive manifestations and diarrhea and had relapsed.

## CONCLUSION

In conclusion, with the observed data, we can say that COVID-19 infection in CD patients who underwent non-myeloablative auto HSCT results in a low morbidity rate with no mortality and that patients in the first year after transplantation have an increased risk of contracting COVID-19 with the possibility of inducing relapse of their CD.

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