

# Treatment delay and treatment pattern modifications among epithelial ovarian cancer patients during the COVID-19 pandemic: A retrospective cohort study

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## Funding information

Conselho Nacional de Desenvolvimento Científico e Tecnológico,  
Grant/Award Number: 310262/2021-6;  
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES EPIDEMIAS,  
Grant/Award Number: 88887.506852/2020-00

## Abstract

**Background and Objectives:** The coronavirus disease 2019 (COVID-19) pandemic disrupted healthcare access and medical treatment, including oncological care. Treatment delay in ovarian cancer could impact survival. We aimed to assess if there were delays and treatment changes in a cohort of epithelial ovarian cancer patients.

**Methods:** A retrospective cohort of epithelial ovarian cancer patients included cases diagnosed during the first 22 months of the COVID-19 pandemic in the state of Sao Paulo and those diagnosed in the 22 months preceding the outbreak. Time-to-treat was measured in days. In each group, surgery and chemotherapy proportions were assessed according to healthcare insurance status.

**Results:** A 56.2% reduction in epithelial ovarian cancer diagnosis was identified during the pandemic group compared to the prepandemic group; fewer patients were diagnosed in stage I ( $p < 0.01$ ). Time-to-treat increased from 18.9 to 23 days ( $p < 0.01$ ). Surgery in the public sector fell from 74.6% to 65.3% during the pandemic, compared to 87.1% to 68.8% in the private sector.

**Conclusion:** There were fewer overall diagnoses, reduced stage I diagnosis, increased time-to-treat, and a reduction in the proportion of patients submitted to surgery. Brazil's public healthcare system demonstrated a higher resiliency to treatment change than the private sector.

## KEYWORDS

COVID-19, ovarian cancer, surgery, treatment

## 1 | INTRODUCTION

In January 2020, a new infectious disease was described in China, with the first known patients presenting symptoms in December 2019. This contagious respiratory disease was caused by a virus now known as SARS-CoV-2 and was named coronavirus disease 2019 (COVID-19). On March 11, 2020, the World Health Organization declared COVID-19 a pandemic.<sup>1</sup>

The first reported COVID-19 case happened on February 26, 2020. This patient was a 61-year-old male with a travel history to Italy. On March 20, 2020, less than a month later, Brazil's Ministry of Health declared COVID-19 to have achieved community transmission in all national territory.<sup>2</sup> The disease proceeded to spread quickly in the country, with a distribution pattern towards the interior.<sup>3</sup>

As a result of the pandemic and governmental responses to the disease spread, healthcare access has been reduced. This has

impacted access to timely care in cancer care.<sup>4</sup> Thus, the pandemic has affected the healthcare system's ability to perform prevention, early diagnosis, and treat cancer patients.<sup>5</sup> These challenges are also noted among ovarian cancer patients, which could potentially impact ovarian cancer treatment quality, if not addressed.<sup>6</sup>

Cancer care delay may have a substantial impact on a patient's staging. This may represent the difference between having a curable or incurable disease. A modeling study in the United Kingdom shows that cancer care delay could impact mortality up to 10 years after the pandemic.<sup>7</sup>

This study aims to verify the impact of the COVID-19 pandemic on a cohort of epithelial ovarian cancer patients in the State of Sao Paulo, Brazil. Our main goal is to assess if there were differences in time between diagnosis and treatment among these patients during the pandemic compared to the prepandemic control group. In each group individually, we also verified if there were any differences between surgery and chemotherapy rates and if those expressed correlations with healthcare provider status. Last, we aimed to verify if the distance traveled for treatment differed in both groups.

## 2 | MATERIALS AND METHODS

This study is designed as a retrospective cohort analysis. We obtained a file including several pieces of information about each patient, provided publicly by the Fundacao Oncocentro de Sao Paulo (FOSP). Using these variables, we divided epithelial ovarian cancer patients into two groups: those whose diagnosis occurred from March 2020 up to December 2021, thus amounting to 22 months, and a control group of those diagnosed during the previous 22 months.

Our main goal was to assess if the time between diagnosis and treatment presented any changes after the beginning of the COVID-19 pandemic. We restricted this analysis to patients who had already started treatment during this 22-month period. We imposed this restriction to avoid bias since patients in the control group could have differences between diagnosis and treatment that the first group could not match. Furthermore, patients diagnosed previous to the pandemic but not yet treated when it began could be affected by it.

We also aimed to analyze if other variables differed between these two groups, such as: age, staging; if the patient was submitted to chemotherapy; if surgery was performed; the distance between the patient's city of residence and the city where the hospital was located. We also tracked whether the patient's treatment was in the public healthcare system or private treatment.

Last, we aimed to assess if there were changes in treatment patterns between the prepandemic and pandemic groups. In this step, groups were not restricted to patients who already had begun treatment; our goal in this analysis was not to assess the time up to treatment but rather the existence of treatment or not. We evaluated each group individually to see if there was a difference in the performance of chemotherapy and surgery according to the treatment provider.

A data file containing patients in the Hospital Cancer Registry (HCR), provided publicly by FOSP, was obtained. We proceeded to include all patients with the International Disease Code of C56, which corresponds to ovarian cancer. Patients were required to be residents of the State of Sao Paulo and have no previous cancer diagnosis or treatment. Patients were excluded if they had missing data regarding age, distance traveled, staging, or presented tumors not included in the epithelial histology.

We included in the control group patients diagnosed from May 2018 up to February 2020, and in the analysis group, patients diagnosed from March 2020 up to December 2021. For the analysis regarding time from diagnosis to treatment, we excluded from both groups patients who had not received treatment during the timeframe of their groups. Conversely, we excluded patients with unknown provider status for the analysis regarding changes in treatment patterns and possible association with an insurance provider.

Our file contained the following variables considered during the analysis. Age was available, expressed in years. The interval between diagnosis and treatment was available in the data file, described in days. Surgery and chemotherapy status were available separately as binary variables, thus present or absent. The staging was grouped as I, II, III, or IV. Treatment provider was classified as public healthcare or private treatment. Distance is expressed in kilometers and was calculated from available data: using the city of residence and the city of treatment, we applied the Haversine formula using publicly available latitude and longitude coordinates for each city. Thus, patients treated in the same city they resided in had a distance variable of zero.

We compared both groups using the Wilcoxon-Mann-Whitney test to analyze the interval between diagnosis and treatment. We used this same test to verify if there was a difference between the distance traveled between the two groups and their ages. We compared both groups staging variables using the Chi-square test. We also performed the Chi-square test to compare both groups' surgery status and chemotherapy status rates.

As for the analysis of possible treatment pattern modifications, we analyzed each group individually. We used the Chi-square test for each of them to determine whether there was a difference in surgery and chemotherapy rates according to the healthcare provider status.

Additionally, we performed an exploratory analysis using the Chi-square test in each of the groups of the treatment pattern analysis to verify if there was a correlation between staging and healthcare provider status, which, if present, could work as a confusion variable.

Data manipulation and statistical analysis were conducted using the software RStudio version 1.4.1717 (2021-05-24).

## 3 | RESULTS

Using the method above, we included 650 patients in the time-to-treat analysis; 198 patients were treated during the COVID-19 pandemic, and 452 patients were treated in the control group. This

represents a 56.2% reduction from the prepandemic period to the pandemic period. Table 1 summarizes the characteristics of both groups.

It is worth noting the mean time between diagnosis and treatment was 23 days in the pandemic group and 18.9 days in the prepandemic group, and the Wilcoxon-Mann-Whitney for this association has a  $p < 0.01$ . Additionally, the pandemic group has a lower percentage of patients diagnosed and treated in stage I. The Chi-square test has a  $p < 0.01$ . Among patients diagnosed and treated before the pandemic began, 82.1% received surgery. This value is 65.7% in the pandemic group, and the Chi-square test has a  $p < 0.01$ . As for chemotherapy rates, an increase is identified, from 76.3% in the prepandemic group to 84.8% in the pandemic group. The Chi-square test has a  $p$  value of 0.019 for this analysis. Values for age, distance traveled, and healthcare provider status was similar between both groups, and statistical tests did not show a difference regarding these variables.

For the treatment pattern analysis, a total of 293 patients were included in the pandemic-affected group, and 663 patients were

included in the control group, amounting to 958 patients. This displays a 55.8% reduction in the pandemic period compared to the prepandemic interval. Statistical analysis was performed separately in each group regarding healthcare provider status and treatment-related variables.

The pandemic group included 213 patients treated in the public healthcare system and 80 patients treated privately. Table 2 describes the age, surgery, and chemotherapy status of each of these groups. Statistical tests did not show a difference between public and private-treated patients regarding all variables. The exploratory analysis did not demonstrate clinical staging differences between healthcare provider status groups.

The control group included 516 patients treated in the public healthcare system and 147 patients treated privately. Results for each variable according to the healthcare provider status group are shown in Table 3. The surgery rate in the public healthcare group was 74.6%, while this value was 87.1% in the private treatment group. Chi-square test results in a  $p < 0.01$ . Age and chemotherapy status

**TABLE 1** Characteristics of ovarian cancer patients diagnosed and treated in the State of Sao Paulo before and during the COVID-19 pandemic

|                                      | Pandemic (N = 198) | Pre-pandemic (N = 452) | Overall (N = 650) | p value |
|--------------------------------------|--------------------|------------------------|-------------------|---------|
| Time between diagnosis and treatment |                    |                        |                   |         |
| Mean (SD)                            | 23.0 (29.3)        | 18.9 (35.9)            | 20.1 (34.0)       | <0.01   |
| Median [min, max]                    | 14.0 [0, 143]      | 0 [0, 405]             | 1.00 [0, 405]     |         |
| Age                                  |                    |                        |                   |         |
| Mean (SD)                            | 59.2 (12.2)        | 57.4 (13.0)            | 58.0 (12.8)       | 0.11    |
| Median [min, max]                    | 60.0 [23.0, 84.0]  | 58.5 [19.0, 87.0]      | 59.0 [19.0, 87.0] |         |
| Distance traveled                    |                    |                        |                   |         |
| Mean (SD)                            | 49.2 (80.0)        | 40.5 (70.2)            | 43.1 (73.4)       | 0.13    |
| Median [min, max]                    | 14.6 [0, 443]      | 0 [0, 393]             | 0 [0, 443]        |         |
| Healthcare provider                  |                    |                        |                   |         |
| Private                              | 52 (26.3%)         | 108 (23.9%)            | 160 (24.6%)       | 0.58    |
| Public                               | 146 (73.7%)        | 344 (76.1%)            | 490 (75.4%)       |         |
| Surgery status                       |                    |                        |                   |         |
| No Surgery                           | 68 (34.3%)         | 81 (17.9%)             | 149 (22.9%)       | <0.01   |
| Surgery                              | 130 (65.7%)        | 371 (82.1%)            | 501 (77.1%)       |         |
| Chemotherapy status                  |                    |                        |                   |         |
| Chemotherapy                         | 168 (84.8%)        | 345 (76.3%)            | 513 (78.9%)       | 0.019   |
| No chemotherapy                      | 30 (15.2%)         | 107 (23.7%)            | 137 (21.1%)       |         |
| Staging                              |                    |                        |                   |         |
| I                                    | 29 (14.6%)         | 128 (28.3%)            | 157 (24.2%)       | <0.01   |
| II                                   | 14 (7.1%)          | 38 (8.4%)              | 52 (8.0%)         |         |
| III                                  | 82 (41.4%)         | 160 (35.4%)            | 242 (37.2%)       |         |
| IV                                   | 73 (36.9%)         | 126 (27.9%)            | 199 (30.6%)       |         |

Abbreviation: COVID-19, coronavirus disease 2019.

**TABLE 2** Characteristics of ovarian cancer patients diagnosed during the COVID-19 pandemic in the state of Sao Paulo grouped by healthcare provider status

|                     | Public (N = 213)  | Private (N = 80)  | Overall (N = 293) | p value |
|---------------------|-------------------|-------------------|-------------------|---------|
| Age                 |                   |                   |                   |         |
| Mean (SD)           | 56.7 (14.2)       | 58.2 (16.1)       | 57.1 (14.7)       | 0.31    |
| Median [min, max]   | 59.0 [13.0, 84.0] | 60.0 [14.0, 85.0] | 59.0 [13.0, 85.0] |         |
| Surgery status      |                   |                   |                   |         |
| Surgery             | 139 (65.3%)       | 55 (68.8%)        | 194 (66.2%)       | 0.67    |
| No Surgery          | 74 (34.7%)        | 25 (31.3%)        | 99 (33.8%)        |         |
| Chemotherapy status |                   |                   |                   |         |
| Chemotherapy        | 140 (65.7%)       | 53 (66.3%)        | 193 (65.9%)       | 1       |
| No chemotherapy     | 73 (34.3%)        | 27 (33.8%)        | 100 (34.1%)       |         |

Abbreviation: COVID-19, coronavirus disease 2019.

**TABLE 3** Characteristics of ovarian cancer patients diagnosed before the COVID-19 pandemic in the State of Sao Paulo, grouped by healthcare provider status

|                     | Public (N = 516)  | Private (N = 147) | Overall (N = 663) | p value |
|---------------------|-------------------|-------------------|-------------------|---------|
| Age                 |                   |                   |                   |         |
| Mean (SD)           | 55.4 (15.9)       | 54.6 (16.2)       | 55.2 (15.9)       | 0.57    |
| Median [min, max]   | 58.0 [3.00, 89.0] | 57.0 [4.00, 91.0] | 58.0 [3.00, 91.0] |         |
| Surgery status      |                   |                   |                   |         |
| Surgery             | 385 (74.6%)       | 128 (87.1%)       | 513 (77.4%)       | <0.01   |
| No surgery          | 131 (25.4%)       | 19 (12.9%)        | 150 (22.6%)       |         |
| Chemotherapy status |                   |                   |                   |         |
| Chemotherapy        | 319 (61.8%)       | 92 (62.6%)        | 411 (62.0%)       | 0.94    |
| No chemotherapy     | 197 (38.2%)       | 55 (37.4%)        | 252 (38.0%)       |         |

did not present statistically significant differences between groups. The exploratory analysis did not find differences in staging regarding healthcare provider status.

The comparison between both groups' surgery rates, grouped by healthcare provider status, is illustrated in Figure 1.

## 4 | DISCUSSION

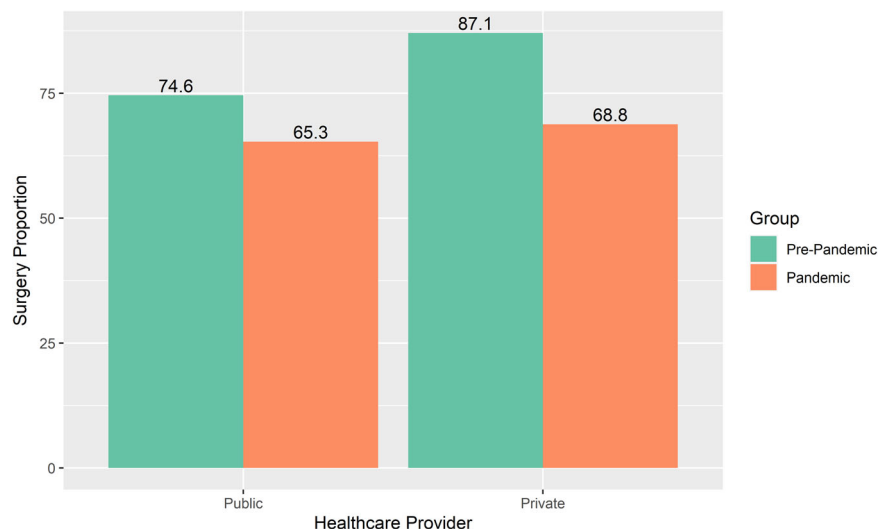
We identified an approximate 4-day increase in the interval between diagnosis and treatment among patients diagnosed during the COVID-19 pandemic compared to those diagnosed in the 22-month interval before the pandemic. Additionally, patients diagnosed and treated during the pandemic presented themselves at more advanced stages of the disease, and fewer were submitted to surgery. On the other hand, chemotherapy rates have risen during the pandemic period. Also, there were 56.2% fewer ovarian cancer diagnoses in the HCR. These results support our main hypothesis that the COVID-19 pandemic

impacted the treatment of ovarian cancer patients in the State of Sao Paulo.

This study's strengths include the number of patients in both analyses, the longitudinal nature of the study's design, and the presence of several individual-level variables which contribute to the investigation. Limitations of this study arise from its retrospective nature, the heterogeneity of the COVID-19 pandemic behavior during the 22-month timeframe in the State of Sao Paulo, the binary nature of surgery and chemotherapy status variable, and the reduced reach of the HCR among privately treated patients. These limitations, however, do not seem to invalidate the results obtained.

A review study aimed to elaborate recommendations for gynecological cancer management during the pandemic.<sup>8</sup> This research recommends that newly diagnosed ovarian cancer patients be submitted to surgery as early as possible, in a maximum of 2–3 weeks. Mean time-to-treat during the pandemic exceeded this threshold. Furthermore, these numbers do not account for the undiagnosed patients, which certainly will be impacted by longer delays or no access to any form of treatment at all.

**FIGURE 1** Ovarian cancer surgery proportion as percentages grouped by healthcare provider for prepandemic and pandemic groups



A study presenting a single-center retrospective cohort of patients referred to evaluation by a gynecologic oncologist in the United States before and during the pandemic presents a series of divergent results compared to our research.<sup>9</sup> A 32% decline in patients referrals was seen in the mentioned study, however, no decrease was found among patients with ovarian disease. Furthermore, ovarian disease surgery maintained similar activity before and during the pandemic. Finally, an 8.8 days decrease in time-to-treat among all patients with gynecological cancer was found, from 33.5 days before the pandemic to 24.7 during the outbreak. There is no immediate answer for these disparities. It is likely the answer is multifactorial, including hypothesis such as primary care structural differences, impact of the pandemic in each setting, resource availability and differences in restrictive measures.

An Austrian study has demonstrated a 49% reduction in ovarian cancer diagnosis, considering 106 ovarian cancer patients.<sup>10</sup> A different Austrian study, encompassing a more extensive timeframe, identified a 45% reduction in new gynecological cancer diagnoses during the lockdown period and a 44% reduction between the two Austrian lockdowns in 2020.<sup>11</sup> These results are similar to those seen in this study. However, in that study, there were no statistically significant differences between ovarian cancer stages upon diagnosis, unlike seen in our research. It is possible these differences were not detectable in a study with fewer patients. However, it is also possible to see a difference in healthcare resource availability in both scenarios. This might emerge from a difference in impact upon general physician access and ultrasound availability, or patients with fewer symptoms might not be willing to risk exposure to COVID-19, unaware they might be developing severe disease.

A study from India with a cohort of ovarian cancer patients has shown a 14-day delay in treatment during the pandemic.<sup>12</sup> There are methodological differences that limit comparison. Mainly, the mentioned study actively collected retrospective patient data; our study used systematically institutional registered data. A significant number of patients in our study presented 0 days between diagnosis

and treatment, suggesting diagnosis upon surgery. It is unclear if this arises from the method used to record data, or a clinical feature, such as the number of patients submitted to surgery without prior oncological ambulatorial investigation. Lack of access to specialized care or surgeries happening in urgency and emergency scenarios are possible explanations for this event.

A multicenter prospective cohort study in France has also demonstrated the impact of the COVID-19 pandemic on ovarian cancer care.<sup>13</sup> In that study, 34.6% of ovarian cancer patients had their surgeries postponed or canceled. While quantitative comparisons are not possible due to significant methodological differences, these results converge to those found in this current analysis.

A case series of Japanese and Korean patients has reported evidence of chemotherapy delay and interruption due to COVID-19 suspicion among ovarian cancer patients.<sup>14</sup> A different case series of Japanese patients with suspected or confirmed gynecological malignancies also demonstrated treatment delay due to concerns related to COVID-19.<sup>15</sup> These results are convergent to our research and also reinforce the perception of the widespread impact of COVID-19 among ovarian cancer patients from different countries.

A survey among gynecologic oncology specialists and trainees in Turkey identified a change in ovarian cancer treatment patterns.<sup>16</sup> This study reported that 50% of physicians administered more neoadjuvant chemotherapy cycles to patients who had already completed their chemotherapy. Furthermore, 12.9% of physicians delayed advanced ovarian cancer surgery or referred these patients. Similar to our research, these results demonstrate surgery reduction and treatment delay among ovarian cancer patients.

Regarding the impact of the pandemic on cancer care and its correlation with healthcare provider status, a retrospective cohort study has compared a Canadian publicly funded hospital results with an American privately funded cancer care center results.<sup>17</sup> In the mentioned study, there was a higher chance of cancer treatment delay and treatment modification in the publicly funded cancer care center compared to the private-funded hospital. Treatment

modification in that study was fundamentally associated with postponed or canceled surgery. Another study, a survey among healthcare professionals in India involved in the care of gynecologic cancer patients, assessed the difference between government and private hospitals.<sup>18</sup> This study identified that government hospitals had higher patient concentration rates than private hospitals before the pandemic. Government hospitals in this study reported higher proportions of practice decrease during the pandemic. Results from both studies diverge from our findings. There was a 9.3% decrease in surgery rates among patients treated in the public healthcare system, from 74.6% to 65.3% in our study; in the privately-treated group, this reduction was 18.3%, from a total of 87.1% before the pandemic to 68.8% during it. Thus, in our scenario, public and nonpublic treated patients had converging surgery rates after the pandemic began. Further studies are necessary to better comprehend the reasons behind this resiliency of the public healthcare system upon sudden and significant pressures, and also the reasons behind the previous gap between public and insurance-based treated groups.

Interpreting the changes in chemotherapy rates is challenging since this data was available as a binary variable. Studies considering the issue of chemotherapy have focused on changes in the neoadjuvant modality.<sup>12,13</sup> Due to our data's nature, we cannot analyze similar hypotheses. It is possible the changes identified in this cohort are associated with the reduction of stage I patients in the pandemic group.

Before the pandemic, studies have considered ovarian cancer and its relationship with geospatial variables.<sup>19</sup> Geographical location has been found to be an independent predictor of advanced-stage ovarian cancer mortality; however, this significance was largely reduced after considering other variables associated with appropriate treatment. In the previously mentioned Indian cohort, the authors hypothesized travel restrictions played a role in treatment delay.<sup>12</sup> It has been shown cancer surgery can be safely performed during the COVID-19 outbreak, given a COVID-19-free path is obtained; whether that requires changing previously established referral paths depends on local epidemiological concerns.<sup>20</sup> Our study found no differences in the distance traveled between both treatment groups. The goal of this analysis was mainly to help identify if missing, undiagnosed patients might be residing farther from treatment centers. While there is no association in this research, this analysis is limited by a few factors. First, since the distance was considered simply as a difference between two different cities, it potentially underestimates travel time for patients living in large cities. Secondly, distances were calculated as a straight line. These results might change when considering exact addresses and travel time instead of distances.

## 5 | CONCLUSION

The COVID-19 pandemic has impacted ovarian cancer care in the State of Sao Paulo. A significant reduction in ovarian cancer diagnosis has also been accompanied by larger intervals between diagnosis and

treatment. This includes fewer initial stages of diagnosis and reduced surgery rates among these patients, which might impact cancer mortality in the coming years. The public healthcare system displayed a higher resiliency to treatment changes compared to the insurance-based healthcare system. Distance did not seem to play a role in healthcare access for ovarian cancer patients during the pandemic, but further studies are necessary due to limitations in distance calculation in this analysis.

## AUTHOR CONTRIBUTIONS

*Conceived and designed the study:* Vinicius Cesar Moterani and Francisco Jose Candido dos Reis. *Collected and analyzed data:* Vinicius Cesar Moterani and Francisco Jose Candido dos Reis. *Helped with writing the first draft of the manuscript:* All authors. *Provided critical insight and revision to manuscript:* All authors.

## ACKNOWLEDGMENTS

We want to thank all members of Fundacao Oncocentro Sao Paulo for their continued work, which makes such data available and research like this possible. This project was funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)—Programa CAPES EPIDEMIAS (Grant Number: 88887.506852/2020-00). F. J. Candido dos Reis (Grant Number: 310262/2021-6) was funded by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT


The data regarding patient characteristics can be downloaded from the FOSP website at <http://www.fosp.saude.sp.gov.br/fosp/diretoria-adjunta-de-informacao-e-epidemiologia/rhc-registro-hospitalar-de-cancer/banco-de-dados-do-rhc/>

## ETHICS STATEMENT

The study followed the Declaration of Helsinki. According to Resolution 510/2016 of the National Health Council of Brazil, research that uses publicly available data without patient identification does not require approval from an Ethics Committee.

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**How to cite this article:** Moterani VC, Moterani NJW, Candido dos Reis FJ. Treatment delay and treatment pattern modifications among epithelial ovarian cancer patients during the COVID-19 pandemic: a retrospective cohort study. *J Surg Oncol*. 2022;1-7. doi:10.1002/jso.27048