

## **Repercussions of COVID-19 pandemic impacts on non-metastatic HER2-negative breast cancer diagnosis and neoadjuvant treatment over patients' quality of life and mental health**

### **Repercussões dos impactos da pandemia COVID-19 no diagnóstico e tratamento neoadjuvante de câncer de mama HER2-negativo não metastático sobre a qualidade de vida e saúde mental das pacientes**

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**ABSTRACT**

**OBJECTIVE:** To understand if COVID-19 pandemic impacts on delays in non-metastatic HER2-negative breast cancer diagnosis and in the beginning/development of neoadjuvant chemotherapy, as well as on changes in treatment plan to Paclitaxel intensification doses, impaired patients' quality of life and mental health. **METHODS:** This is a cross-sectional study of 67 women diagnosed with non-metastatic HER2-negative breast cancer during the first sixteen months of COVID-19 pandemic and receiving neoadjuvant treatment due to pandemic impossibility of immediate definitive cancer surgery following the neoplasm diagnosis. Sociodemographic, Functional Assessment of Cancer Therapy Scale - General, Beck Anxiety and Depression Inventory were used for outcomes assessment. Inferential analysis was performed by Mann-Whitney, Pearson's chi-squared, and Fisher's exact tests. The adopted significance was 5%. **RESULTS:** The study revealed that the oncological diagnosis delays caused a worsening of the patients' physical (8 x 21; p = 0.001), functional (13 x 21; p = 0.03) and general (61 x 83; p = 0.004) well-being; retardment in the beginning of neoadjuvant chemotherapy decreased physical well-being (13 x 21; p = 0.01). Changes in treatment plan, to Paclitaxel doses intensification, had a negative effect on functional well-being (20 x 25.5; p = 0.04). COVID-19 pandemic impacts on neoplasm diagnosis and neoadjuvant treatment delays were also associated with psychosocial manifestations, including higher levels of severe anxiety (60% x 14.5%; p = 0.03 and 40% x 14%; p = 0.04) and depression (40% x 3.2%; p = 0.004 and 60% x 5.3%; p = 0.03) respectively. **CONCLUSION:** The present study shows that COVID-19 pandemic impacts on non-metastatic HER2-negative breast cancer patients' diagnosis and neoadjuvant chemotherapy impaired patients' quality of life and mental health.

**Keywords:** breast neoplasms, COVID-19, mental health, anxiety, depression

**RESUMO**

**OBJETIVO:** Compreender se a pandemia de COVID-19 tem impacto nos atrasos no diagnóstico não-metastático do cancro da mama HER2-negativo e no início/desenvolvimento da quimioterapia neoadjuvante, bem como nas alterações do plano de tratamento para as doses de intensificação de Paclitaxel, na deterioração da qualidade de vida e da saúde mental das pacientes. **MÉTODOS:** Este é um estudo transversal de 67 mulheres diagnosticadas com cancro da mama não-metastático HER2-negativo durante os primeiros dezasseis meses da pandemia de COVID-19 e que receberam tratamento neoadjuvante devido à impossibilidade de cirurgia neoadjuvante definitiva imediata após o diagnóstico da neoplasia. A avaliação sociodemográfica, avaliação funcional da escala de terapia do cancro - Geral, Inventário de Ansiedade e Depressão de Beck foram utilizados para a avaliação dos resultados. A análise inferencial foi realizada por Mann-Whitney, Pearson's chi-squared, e os testes exactos de Fisher. O significado adoptado foi de 5%. **RESULTADOS:** O estudo revelou que os atrasos no diagnóstico oncológico causaram um agravamento do bem-estar físico (8 x 21; p = 0,001), funcional (13 x 21; p = 0,03) e geral (61 x 83; p = 0,004) dos pacientes; o retardamento no início da quimioterapia neoadjuvante diminuiu o bem-estar físico (13 x 21; p = 0,01). Alterações no plano de tratamento, à intensificação das doses de Paclitaxel, tiveram um efeito negativo no bem-estar funcional (20 x 25,5; p = 0,04). Os impactos da pandemia de COVID-19 no diagnóstico da neoplasia e atrasos no tratamento neoadjuvante também foram associados a

manifestações psicossociais, incluindo níveis mais elevados de ansiedade grave (60% x 14,5%;  $p = 0,03$  e 40% x 14%;  $p = 0,04$ ) e depressão (40% x 3,2%;  $p = 0,004$  e 60% x 5,3%;  $p = 0,03$ ) respectivamente. **CONCLUSÃO:** O presente estudo mostra que a pandemia de COVID-19 tem impacto no diagnóstico não-metastático do cancro da mama HER2-negativo e na quimioterapia neoadjuvante que prejudica a qualidade de vida e a saúde mental das pacientes.

**Palavras-chave:** neoplasias da mama, COVID-19, saúde mental, ansiedade, depressão

## 1 INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapid spread required health authorities to implement restrictive measures for Coronavirus Disease 2019 (COVID-19) containment.<sup>1</sup> The pandemic scenario, associated with social isolation, uncertainties about the disease as well as high rates of infectivity, morbidity and mortality, evidenced and exacerbated mental health disorders (anxiety and depression) in the population.<sup>2,3</sup>

Well-being and mental health impairments of cancer patients stand out for the intersection between pandemic context and biopsychosocial issues inherent to the neoplasm. Breast cancer psychologically impacts women since its initial investigation; changes in body image and femininity performance, hospitalizations, and distressing symptoms (nausea, vomiting, diarrhea, pain and fatigue) are important predictors of anxiety, depression and poorer quality of life.<sup>4,5</sup>

The COVID-19 pandemic caused health systems overload, directly impacting on delays in cancer diagnosis and treatment, as well as forcing oncological services to adapt their treatment regimens.<sup>6</sup> Thus, due pandemic impossibility of immediate definitive cancer surgery performance following diagnosis, many non-metastatic HER2-negative breast cancer patients had to start neoadjuvant treatment.<sup>7</sup> Also, some services intensified Paclitaxel doses during this treatment progress, aiming to reduce patients' hospitalization days and the number of chemotherapy sessions.<sup>8</sup>

In this scenario, the present study aimed to understand if COVID-19 pandemic impacts on delays in non-metastatic HER2-negative breast cancer diagnosis and in the beginning/development of neoadjuvant therapy, as well as on changes in treatment plan to Paclitaxel intensification doses, impaired patients' quality of life and mental health. The knowledge of how these COVID-19 pandemic impacts psychologically impairs non-metastatic HER2-negative breast cancer patients is important once those impairments are limiting factors for cancer therapy adherence, influencing breast cancer treatment success.

## 2 METHODS

### 2.1 STUDY DESIGN AND INCLUSION/EXCLUSION CRITERIA

An analytical, descriptive observational cross-sectional study was conducted based on the interview of non-metastatic HER2-negative patients receiving neoadjuvant chemotherapy at Oncology and Chemotherapy Center of the Hospital Universitário Evangélico Mackenzie (CEON-HUEM), Curitiba, Paraná, Brazil.

The study included women, over the age of eighteen, diagnosed with non-metastatic HER2-negative breast cancer during the first sixteen months of COVID-19 pandemic and initially submitted to neoadjuvant treatment with Anthracyclines (Doxorubicin 60 mg/m<sup>2</sup> endovenous) and Cyclophosphamide 600 mg/m<sup>2</sup> infusion over three hours for four cycles every 14 days, associated with Paclitaxel 80 mg/m<sup>2</sup> infusion over one hour weekly for 12 weeks at CEON-HUEM due to pandemic impossibility of immediate definitive cancer surgery following neoplasm diagnosis.

Patients who had anxiety and depression disorders prior to breast cancer diagnosis were excluded, as were those who had cognitive deficits or neurological and psychiatric diseases with an impossibility of understanding and providing adequate answers to interview questions.

Following the eligibility criteria, 67 patients were selected and interviewed. All items from the STROBE checklist for cross-sectional studies were included in this manuscript.<sup>9</sup>

The present study followed Helsinki Declaration ethical principles, being approved by the Ethics and Research Committee of the Hospital Universitário Evangélico Mackenzie through Plataforma Brasil (CAAE 40337520.0.0000.0103). All patients who participated in the study signed the Free and Informed Consent Form in accordance with National Research Ethics Commission 466/2012 resolution.

### 2.2 OUTCOME ASSESSMENT MEASURES:

The interviews carried out with the selected patients consisted in the application of a sociodemographic questionnaire, Functional Assessment of Cancer Therapy Scale - General (FACT-G), Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI). FACT-G, BAI e BDI questionnaires were properly licensed and applied in their validated versions translated for Portuguese (Brazil).

The sociodemographic questionnaire was developed by the researchers themselves with 13 questions. The topics corresponded to patient's current social context, involving age, marital status, number of sons and daughters, economic situation (monthly income) and neoplasm clinical staging. It was also asked whether the patient or her first-degree relatives were

diagnosed with COVID-19. Impacts of the pandemic on delays in neoplasm diagnosis or beginning/development of neoadjuvant chemotherapy, as well as on changes in neoadjuvant treatment plan were evaluated by using four other questions. It is emphasized that although these questions were performed through sociodemographic questionnaire, and some patients did not know how to adequately inform at first, all the presented information was checked with medical records analysis.

According to Trufelli (2008) analysis of delays in breast cancer diagnosis and treatment at a public Brazilian hospital, we considered neoplasm diagnosis delay as a period of more than 90 days to cancer diagnosis confirmation with anatomopathological and immunohistochemical biopsies results from the identification of breast nodules by mammography. Retardment in neoadjuvant treatment initiation was considered as an interval greater than 15 days from neoplasm diagnosis confirmation to the beginning of neoadjuvant therapy. Delay in neoadjuvant chemotherapy development is defined as the time interval greater than 14 days between cycles of Anthracycline and Cyclophosphamide.<sup>10</sup> Changes in treatment plan may be understood as situations in which patients had their neoadjuvant chemotherapy plans changed to Paclitaxel intensification doses regimens (Paclitaxel 175 mg/m<sup>2</sup> for three hours for four cycles every 14 days).<sup>8</sup>

The FACT-G is a 27-question questionnaire developed by Cella (1997) and used to assess four health-related quality of life domains in cancer patients. The physical, social/family, and functional well-being domains are composed of seven questions each, while the emotional well-being domain is composed of six. For each question, five answers are possible, scoring from zero to four. The FACT-G is the sum of physical, emotional, social, and functional well-being, ranging from zero to 108. The higher the value, the better the quality of life.<sup>11,12</sup> This questionnaire was validated for Portuguese (Brazil) by Functional Assessment of Chronic Illness Therapy team.<sup>13</sup>

The BAI is a self-report scale created by Beck (1988) and used to assess the degree of anxiety in children and adults. The questionnaire consists of 21 questions related to the patient's anxiety symptoms in the last week. For each question, four answers are possible, scoring from zero to three points. The scale classifies anxiety as minimal (score 0-10), mild (11-19), moderate (20-30) or severe (31-63).<sup>14</sup> Validation of the questionnaire for the Portuguese (Brazil) language was performed by Cunha (2001).<sup>15</sup>

The BDI is a self-report scale created by Beck (1961) and used to assess levels of depression. Like BAI, it consists of 21 questions, each with four possible answers that score from 0 to 3 points. The scale classifies depression as minimal (score 0-9), mild (10-16),

moderate (17-29) or severe (30-63).<sup>16</sup> Validation of the questionnaire for Portuguese (Brazil) was also performed by Cunha (2001).<sup>15</sup>

It is important to emphasize that BAI and BDI proved to be effective for anxiety and depression assessment in psychiatric and non-psychiatric patients. Thus, both questionnaires could be used in the present study to assess outcomes in breast cancer patients.<sup>17</sup>

### 2.3 STATISTICAL ANALYSIS

The data obtained from the interviews were organized and stored in an Excel® spreadsheet. Then, statistical analysis was performed by using the IBM SPSS Statistics for Windows, Version 27.0 software (IBM Corp., Armonk, NY, USA).

Concerning the large standard deviations observed in patients' responses data analysis and the consequent distorted findings representation by arithmetic means, authors expressed the results by medians, minimum and maximum values (quantitative variables) or frequencies and percentages (qualitative/categorical variables).

Initially, the Kolmogorov-Smirnov test was performed evidencing a non-normal distribution of the sample ( $p < 0.05$ ). Thus, inferential analysis was performed with non-parametric tests - Mann-Whitney (continuous discrete variables from the FACT-G) - as well as Pearson's chi-squared and Fisher's exact tests (categorical variables from BAI and BDI)

Statistical analysis assumed a 95% confidence level and a 5% standard error. "p" values less than 0.05 were significant.

After data analysis, authors selected variables with statistically significant results and created Excel® graphs to didactically represent the main findings. Not statistically significant findings were also described in the results section.

### 2.4 SAMPLE SIZE

The present study population corresponded to the 80 women over the age of eighteen who were diagnosed with non-metastatic HER2-negative breast cancer during the first sixteen months of COVID-19 pandemic and receiving neoadjuvant chemotherapy at CEON-HUEM due to pandemic impossibility of immediate definitive cancer surgery following the diagnosis. Therefore, assuming a 95% confidence level and a 5% margin of error, the required sample size calculated was 67 patients.



### 3 RESULTS

Sixty-seven female patients, with a median age of 49 years, were interviewed. Of these women, 45% were married or in a stable union. Although 93% had sons or daughters, only 56.7% had social support in oncologic appointments. Most patients had completed high school education. Once CEON-HUEM is an institution linked to the Brazilian public health system (Sistema Único de Saúde - SUS), 37% of the interviewed patients classified their economic situation as a monthly income of up to one minimum wage.

By TNM cancer staging of the American Joint Committee on Cancer, most patients were classified as clinical stage II or III. Due pandemic impossibility of immediate definitive cancer surgery performance, all patients underwent neoadjuvant treatment.<sup>18</sup>

Concerning COVID-19 pandemic impacts over cancer diagnosis or neoadjuvant treatment, it was observed delays in 7.5% of neoplasm diagnosis, 15% of neoadjuvant treatment initiation, and 18% of neoadjuvant treatment development. Changes in neoadjuvant treatment plan occurred in 16.4% of the patients.

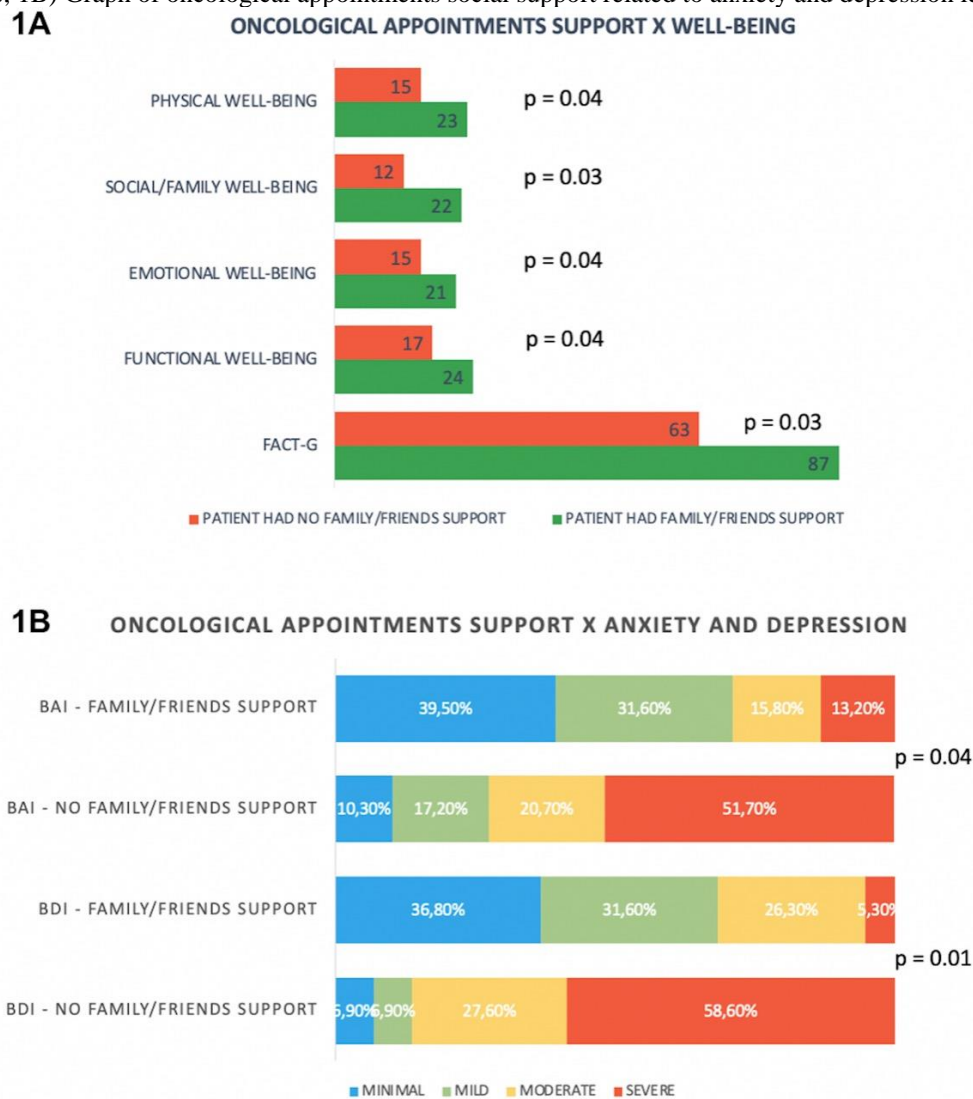
COVID-19 was reported in 7.5% of the patients and about 45% of their first-degree relatives. The information regarding COVID-19 diagnosis was confirmed by positive results in molecular and serological tests. Table 1 describes sociodemographic characteristics of the interviewed patients.

Table 1 - Sociodemographic characteristics of the interviewed patients.

VARIABLE	N (%)	MEDIAN (MIN-MAX)
Female, gender	67 (100)	
Age (years old)		49 (33-67)
Marital status		
Single	10 (14.9)	
Married / Stable union	30 (44.8)	
Divorced / Separated	16 (23.9)	
Widow	11 (16.4)	
Sons / Daughters		
Patients with sons and daughters	62 (92,5)	
Number of sons and daughters		2 (0-7)
Social support in oncologic appointments	38 (56.7)	
Schooling		
1 <sup>st</sup> to 4 <sup>th</sup> elementary school grade	11 (16.4)	
5 <sup>th</sup> to 8 <sup>th</sup> elementary school grade	7 (10.4)	
High school	31 (46.3)	
Technical education	8 (11.9)	
University education	10 (14.9)	
Economic situation (monthly income)		
Up to one minimum wage	25 (37.3)	
From one to two minimum wages	16 (23.9)	
From two to five minimum wages	16 (23.9)	
Above five minimum wages	10 (14.9)	
Neoplasm Clinical Staging		
IA	8 (11.9)	
II	32 (47.8)	
III	27 (40.3)	
COVID-19 pandemic effects over cancer diagnosis or systemic treatment		
Diagnosis delay	5 (7.5)	
Neoadjuvant beginning treatment delay	10 (14.9)	
Neoadjuvant treatment development delay	12 (17.9)	
Changes in neoadjuvant treatment plan	11 (16.4)	
COVID-19 diagnosis		
Patient	5 (7.5)	
Patients' first-degree relatives	30 (44.8)	

The FACT-G questionnaire showed that women who had social support by family/friends in oncologic appointments reported better well-being in all domains (physical, social/family, emotional and functional); psychosocial questionnaires (BAI and BDI) also described supporting benefits revealing much lower anxiety and depression levels than patients who consulted alone (Figure 1).

Figure 1 - Repercussions of family/friends support on oncological appointments over patients' well-being, anxiety, and depression levels. 1A) Graph of the relationship between oncological appointments social support and FACT-G domains; 1B) Graph of oncological appointments social support related to anxiety and depression levels.



In patients who had sons or daughters, the inferential analysis also showed a better physical (20 x 11; p = 0.02) and functional (26 x 21; p = 0.04) well-being, as well as lower levels of severe depression (4.8% x 40%; p = 0.03).

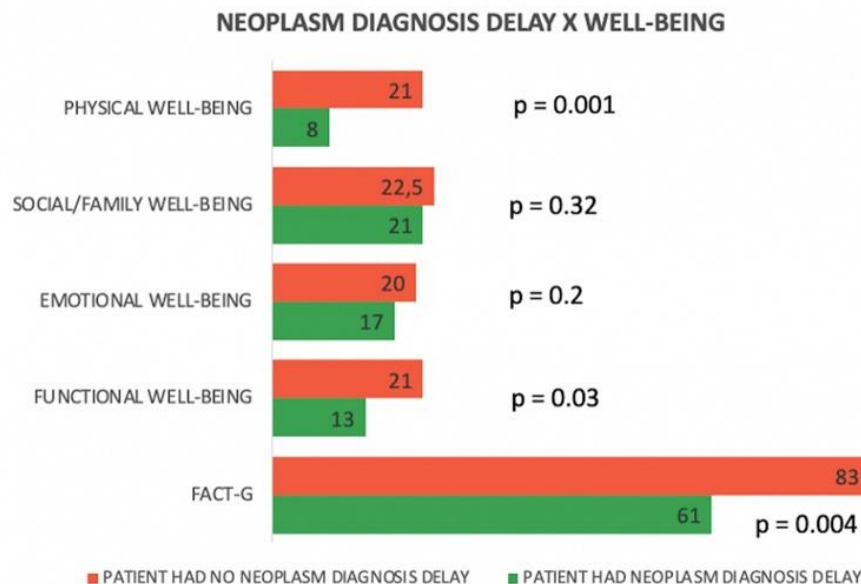
Better social/family well-being was found in women with higher schooling (26.5 x 20; p = 0.03) and better economic situation (25 x 20; p = 0.04). There was no statistically significant



relationship between patients' age and FACT-G domains. Also, no significant differences between ages, level of education or economic situation with anxiety and depression levels were observed.

Considering pandemic impacts on non-metastatic HER2-negative breast cancer diagnosis and neoadjuvant treatment, diagnosis delay was related to poorer physical, functional, and general patients' well-being (Figure 2). Retardment in the beginning of neoadjuvant treatment was also associated with worsening of physical well-being (13 x 21;  $p = 0.01$ ). Although no significant differences were found between neoadjuvant treatment development delays and the FACT-G domains, changes in treatment plan had a negative impact on functional well-being (20 x 25.5;  $p = 0.04$ ).

Figure 2 - Relationship between non-metastatic HER2-negative breast cancer diagnosis delay and FACT-G domains.

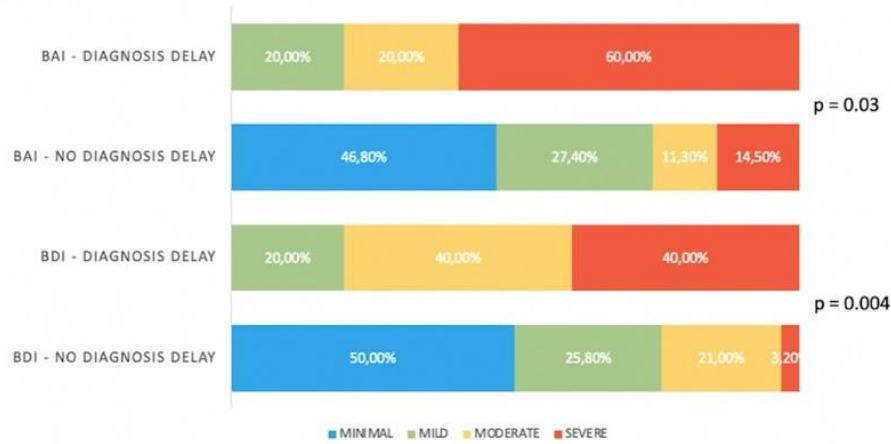


COVID-19 pandemic impacts on non-metastatic HER2-negative breast cancer diagnosis and neoadjuvant treatment were also associated with psychosocial manifestations. The present study showed that delays in diagnosis or in the beginning of neoadjuvant treatment were related to higher levels of anxiety and depression (Figure 3). No differences in anxiety and depression levels were observed in patients who had delayed neoadjuvant treatment development or changed the treatment plan.

Figure 3 - Psychosocial manifestations resulting from COVID-19 pandemic impact on delayed non-metastatic HER2-negative breast cancer diagnosis and beginning neoadjuvant treatment. **3A)** Graph of the relationship between neoplasm diagnosis delay and anxiety and depression manifestations; **3B)** Graph of the relationship between the beginning neoadjuvant treatment delay and anxiety and depression manifestations.

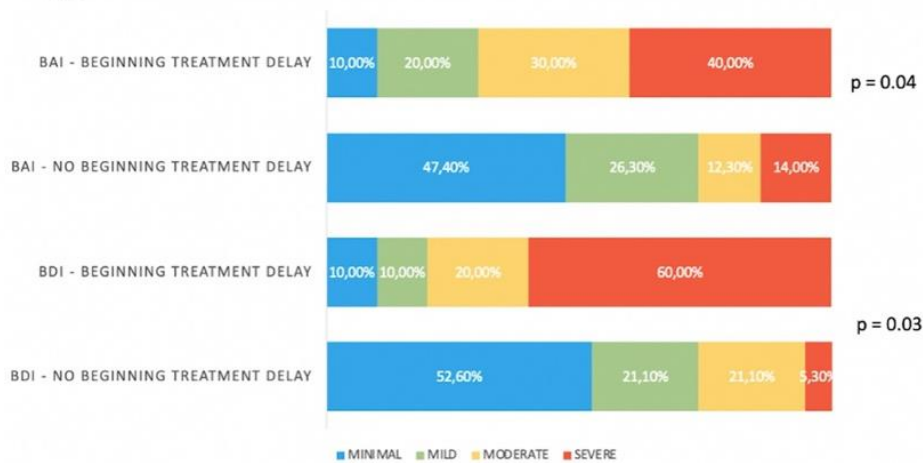
**3A**

**NEOPLASM DIAGNOSIS DELAY X ANXIETY AND DEPRESSION**



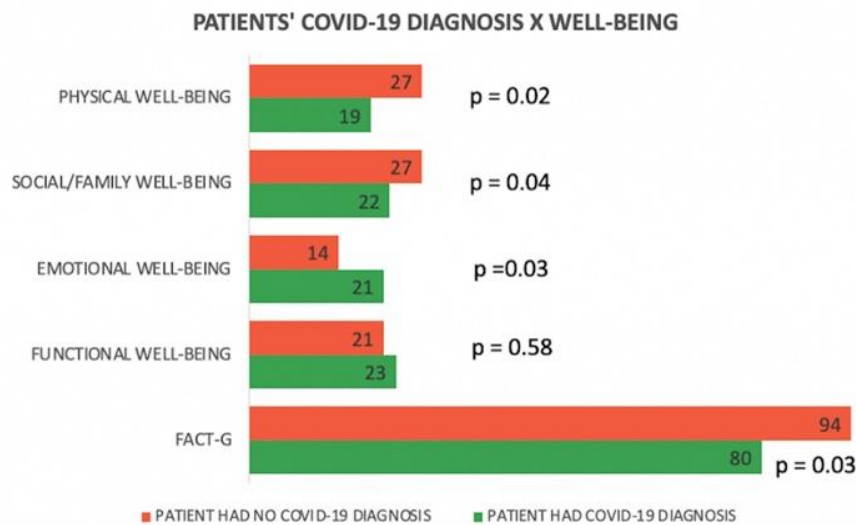
**3B**

**BEGINNING TREATMENT DELAY X ANXIETY AND DEPRESSION**



Concerning COVID-19 infection, non-metastatic HER2-negative breast cancer patients who acquired the disease had poorer physical, social, and general well-being. However, patients who were not diagnosed with COVID-19 showed greater impairment in emotional well-being (Figure 4). The inferential analysis did not reveal statistical significance between patients' diagnosis and anxiety/depression levels.

Figure 4 - Relationship between patients' COVID-19 diagnosis and FACT-G domains.



Regarding patients' first-degree relatives COVID-19 diagnosis, significant impairment was noticed in patients' emotional well-being ( $p = 0.04$ ). Although no significance was found, high levels of anxiety (76.7% x 67.5%;  $p = 0.24$ ) and depression (70% x 75.6%;  $p = 0.93$ ) in moderate and severe degrees were described in those who had and had not sick relatives, respectively.

During the interviews, the complementary complaint of unsatisfactory sexual activity by most women when answering BDI's last question regarding sex interest, attracted researchers' attention.

To better understand this complaint, BDI's last question score (discrete continuous variable with non-normal distribution according to the Kolmogorov-Smirnov test) was related to patients' sociodemographic variables and pandemic impacts on cancer diagnosis and systemic treatment, through the Mann-Whitney test.

Thus, the inferential analysis identified greater rates of complete sex interest loss in women who had delays in breast cancer diagnosis (75% x 22.6%;  $p = 0.02$ ) and systemic treatment development (60% x 32.7%;  $p = 0.03$ ). The other variables analyzed were not statistically significant.

#### 4 DISCUSSION

COVID-19 is the century's most widespread pandemic. Since December 2019, SARS-CoV-2 great transmissibility has contributed to the disease's high global morbimortality rates. On admission, patients frequently complain of acute respiratory distress syndrome, which may eventually progress to severe multisystem inflammatory syndrome.<sup>19</sup> Cancer, otherwise, is a

chronic inflammatory disease whose pathophysiology and treatment are related to immunological modulation. Liang (2020) revealed that cancer patients undergoing chemotherapy when infected by COVID-19 have a risk of requiring mechanical ventilation in the intensive care unit 3.5 times higher than general population.<sup>20</sup> The increased risk may be attributed to patients' immunosuppression and COVID-19 coping measures, which reduced the demand for health care, access, and availability of diagnostic services.<sup>21</sup> Thus, several studies in the literature have described neoplasms as an independent risk factor for SARS-CoV-2 infection worse prognosis.<sup>22</sup>

Anxiety and depression are limiting factors for cancer treatment adherence, being associated with patients' increased hospitalization time and oncologic complications.<sup>23</sup> Despite neoplasm inherent stress compromise mental health, the pandemic context evidenced and exacerbated anxiety and depression levels as well as decreased patients' quality of life. Thus, it is inferred that the current pandemic situation may trigger psychological and psychiatric manifestations, influencing oncological treatment success.<sup>22,24</sup>

The present study was carried out exclusively with SUS patients submitted to neoadjuvant treatment at a reference oncology center; women that had private appointments or private health insurance were not evaluated. Authors recommend the performance of new studies with private sector patients to verify whether the pandemic effects triggered different behaviors in different socioeconomic profiles.

A social support network formation with friends and family during oncologic appointments was essential for patients' better well-being along with lower levels of anxiety and depression. The inferential analysis also highlighted the importance of sons and daughters' involvement in shared decision-making and in supporting patients during such a challenging time. Despite the pandemic context and social isolation, oncological services should allow and encourage patients to be accompanied in their appointments, from diagnosis to full cancer treatment course, given the psychological benefits associated.<sup>25</sup>

Cancer diagnosis essentially involves three steps in the Brazilian public health scenario. The first step occurs from the first symptom (self-palpation or identification of breast nodules by mammography) to the first consultation with a general practitioner; the second stage occurs from the first consultation until accessing the specialized reference service; and the third, from the first evaluation in the specialized service to diagnostic confirmation, through anatomopathological and immunohistochemical results.<sup>10</sup> Considering COVID-19 pandemic context, Patt (2020) and Lôbo (2020) showed breast cancer diagnosis delays by reporting an 85-100% reduction in stereotactic core biopsies during pandemic peak.<sup>26,27</sup> Complementing

these findings, our study described that diagnoses delays prolonged patients' uncertainty and insecurities feelings, deteriorating physical and functional well-being, as well as their anxiety and depression levels.

According to the National Cancer Comprehensive Network (NCCN), after neoplasm diagnosis confirmation with biopsy and immunohistochemistry, non-metastatic HER2-negative patients may undergo immediate definitive surgical or, in case of impossibility, initiate neoadjuvant chemotherapy.<sup>8</sup> Since the COVID-19 pandemic has posed significant pressures on healthcare systems, Hawrot (2020) evidenced the significant increase ( $p < 0.001$ ) of neoadjuvant treatment in 2020 (43.9% overall) when compared to 2018 (16.4% overall).<sup>6</sup>

Although neoadjuvant chemotherapy favors the early initiation of neoplastic treatment in the current scenario, delays in the initiation and development of this therapy were also observed.<sup>28</sup> Our study was carried out with patients submitted to neoadjuvant chemotherapy, and contributing to the literature, we found an increase in anxiety and depression levels, as well as worsening of physical well-being in patients who had delays in the beginning of neoadjuvant treatment.

It is highlighted that in our service all elective surgeries were cancelled due pandemic context. Thus, by the fact that none non-metastatic HER2-negative breast cancer patient underwent immediate definitive surgical treatment following the neoplasm diagnosis, we couldn't evaluate this group of patients' well-being, anxiety, and depression levels. Further studies may assess this topic enabling the comparison of psychosocial impairments in neoadjuvant chemotherapy versus immediate oncological surgery interventions. Also, studies evaluating repercussions of the pandemic in metastatic patients would be interesting.

Considering neoadjuvant chemotherapy regimens for non-metastatic HER2-negative patients, the NCCN recommends that the treatment may be preferably performed with Anthracyclines (Doxorubicin 60 mg/m<sup>2</sup> endovenous) associated with Cyclophosphamide 600 mg/m<sup>2</sup> infused over three hours for four cycles every 14 days and Paclitaxel 80 mg/m<sup>2</sup> infused over one hour weekly for 12 weeks. An alternative pointed out by the guideline involves the same Anthracyclines (Doxorubicin 60 mg/m<sup>2</sup> EV) and Cyclophosphamide 600 mg/m<sup>2</sup> regimen, however, associated with Paclitaxel intensification doses (175 mg/m<sup>2</sup> infused over three hours for four cycles every 14 days). Due to pandemic context, after the beginning of neoadjuvant treatment with the preferred regimen, patients could have their treatment plans changed to Paclitaxel intensification doses. The change is supported once the alternative regimen reduces patients' hospitalization days and the number of chemotherapy sessions.<sup>8</sup>

Although chemotherapy regimens changes are consistent with the pandemic context, inferential analysis revealed that it affected patients' functional well-being. This occurred because high chemotherapy doses exposure is associated with greater side effects. Complementing the findings, Shinan (2020) showed that chemotherapy intensification regimens reduced the contact of breast cancer patients with their respective doctors, triggering patients' insecurity feelings and concerns about the effectiveness of the new regimen with fewer hospitalization days.<sup>29,30</sup>

The evidence that SARS-CoV-2 infection in breast cancer patients is associated with a poorer physical and social well-being is not pathophysiological fully comprehended. A hypothesis raised to explain the fact is that the impairments observed were related to COVID-19 clinical manifestations and social isolation. Zhang (2020) reported the characteristics and outcomes of 35 breast cancer patients infected by COVID-19, attributing overlapping symptoms of severe acute respiratory syndrome - dyspnea, fatigue, fever, anorexia, and signs of desaturation - and chemotherapy side effects as main responsible for the worsening of patients' physical well-being.<sup>31</sup>

As for social well-being, the worsening can be explained by the fact that infected patients are subjected to social isolation and must face the diseases alone. In this context, video calls appear as efficient tools to maintain a strengthened social support network despite physical distance. Since most patients of the study presented a less favored economic situation, only a few had accesses to these tools, negatively influencing social well-being. Further studies need to be carried out to better assess the impacts of video calls on cancer patients well-being and to elaborate measures allowing wide access of these tools, especially in elderlies who do not have expertise to use electronic devices.<sup>32,33</sup>

Otherwise, patients who were not infected by the virus showed a poorer emotional well-being. This can be explained by the fear of becoming infected, and that a possible contamination might be a complicating factor in their clinical condition. Worries of becoming contaminated and transmitting the virus to their closest people are also highlighted.<sup>34,35</sup>

Patients who had family members diagnosed with COVID-19 showed emotional well-being impairment. An interesting detail noticed was the high levels of anxiety and depression in both patients who had and had not family members infected. The event can be explained by the fact that, in addition to neoplasm inherent stress, the pandemic also triggered additional patients' concerns with family members who are or may become ill by COVID-19.<sup>36-38</sup>

During questionnaires application, women's sexuality complaints, such as decrease in libido and sexual interest, were especially noticed in those who had a delay in diagnosis and in



systemic treatment development. It is hypothesized that these complaints were related to psychological impairments evidenced by the COVID-19 pandemic. Further studies that address this issue in greater detail are required to propose strategies for sexual activity improvement performance.<sup>39,40</sup>

Although this paper is unique in answering specific questions about HER2-negative breast cancer patients' quality of life and mental health impairments related to COVID-19 pandemic impacts on neoplasm diagnosis and neoadjuvant treatment, some limitations also need to be acknowledged. First, the small sample size and the single center analysis limits the findings' external validity. Furthermore, the cross-sectional analysis also limits the inferences that can be drawn from this study. For instance, as our study was performed during the COVID-19 pandemic it is impossible to determine whether psychological symptoms increased during the pandemic as compared to before. Longitudinal studies with pre, during and post-COVID-19 pandemic measures would be needed to better understand its impact on cancer patients' psychological functioning. Hence, the results should be interpreted with caution and further studies that address psychological pandemic repercussions in breast cancer patients are necessary to replicate them in larger samples and identify COVID-19 effects in different clinical stages (especially in stage IV), cultures, and socioeconomic scenarios, providing a comprehensive approach in an unprecedented global public health context.

## 5 CONCLUSION

Through this study, it was evidenced that the pandemic impacts on delays in non-metastatic HER2-negative breast cancer diagnosis and in the beginning/development of neoadjuvant treatment were related to quality-of-life impairments - including sexual - and a higher incidence of anxiety and depressive disorders; changes in neoadjuvant treatment plans to chemotherapy cycles intensification regimens had a negative impact on the interviewees' functional well-being. Additionally, the analysis performed revealed that both personal and first-degree relatives COVID-19 diagnosis negatively affected non-metastatic HER2-negative breast cancer patients' quality of life. It was also observed that women who had family/friends support during oncologic appointments showed better well-being and lower levels of anxiety and depression, emphasizing their importance in shared decision-making, and coping with patients during such a challenging time.

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