MASTOLOGY

Official Journal of the Brazilian Society of Mastology

Volume 32, 2022

ISSN 2594-5394

Brazilian Society of Mastology

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BRAZILIAN SOCIETY OF MASTOLOGY

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ABOUT

Mastology is a publication of the Brazilian Society of Mastology. The responsibility for concepts emitted in the articles is exclusive of its authors

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National and international subscription and advertising: Brazilian Society of Mastology - Phone number: (21) 2220-7711 - Whatsapp (21) 98138-0034

PRODUÇÃO EDITORIAL

ZEPPELINI PUBLISHERS

ORIGINAL ARTICLE
https://doi.org/10.29289/2594539420210039

Survival analysis of patients with breast cancer and secondary brain metastasis: a retrospective cohort

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ABSTRACT

Introduction: The presence of brain metastases secondary to primary breast cancer implies a worse prognosis for those affected. Therefore, the aim of this study was to determine the median survival after the diagnosis of brain metastasis in patients with breast carcinoma in a center in northeastern Brazil. **Methods:** The medical records of 345 patients diagnosed with breast cancer, treated between 1998 and July 2018, were analyzed. Those with brain metastasis along with their treatment performed and survival were identified. **Results:** Nine (2.6%) patients had brain metastasis; the mean age was 56.8 years. The mean survival time determined by the Kaplan-Meier method was 23.8 months (95%CI 6.9–40.8). Seven patients (78%) died from the disease and two were lost to follow-up (22%); invasive carcinoma of no special type was the most frequent (78%). Molecular classification by immunohistochemistry was possible in seven patients: five luminal B subtype cases, one luminal A case and one triple-negative case; luminal B subtype was associated with longer survival: 23.3 months (95%CI 3.0–43.6). As for the initial clinical staging, according to the TNM Classification of Malignant Tumors, there was one IA case, one IIA case, three IIB cases and two IIIB cases. Three patients underwent modified radical mastectomy, and six underwent conservative treatment (quadrantectomy); there was no statistical difference in survival between the different forms of treatment (p=0.771). **Conclusion:** The median survival after diagnosis of brain metastasis from breast cancer was 23.80 months.

KEYWORDS: breast neoplasms; brain neoplasms; conservative treatment; survival rate; immunohistochemistry.

INTRODUCTION

Breast cancer is the most prevalent type of cancer in Brazil and worldwide[1]. Despite the advances that have made, mainly in the areas of prevention and treatment, breast cancer remains the main cause of cancer mortality in Brazil among women, with a mortality rate adjusted by the world population of 14.23 deaths/100,000 women, in 2019, according to Brazil's National Cancer Institute (INCA)[2].

The progression of primary breast cancer to metastatic forms, especially those with cerebral involvement, is an impacting factor for the increase in morbidity and mortality of this disease[3]. Breast cancer is the second type of cancer with the highest risk to develop brain metastases[4]. In these cases, in general, the prognosis is poor and quality of life and life expectancy of patients is substantially reduced. This negative impact on life varies according to the affected location of the central nervous system and the number of metastases at the time of diagnosis. As an example of this, according to a retrospective North American cohort study, approximately 80% of the 420 patients who presented with tumor spread to the brain or another region of the central nervous system died within the first year of follow-up[5]. Another aggravating factor is the fact that the diagnosis is not always made in a timely manner, due to the absence of clinical manifestations of these lesions until death[6].

In Piauí, the estimates for breast cancer for the 2020/2021 biennium are 590 new cases[7]. Despite this number of cases,

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Conflict of interests: nothing to declare. **Funding:** none.
Received on: 07/26/2021. **Accepted on:** 12/08/2021.

there are not many studies in the literature on the incidence of brain metastasis and analysis of survival time in this population. Accordingly, the main objective of the present study was to evaluate the median survival after the diagnosis of brain metastasis in a retrospective cohort of patients from an oncology clinic in Teresina, Piauí, Brazil.

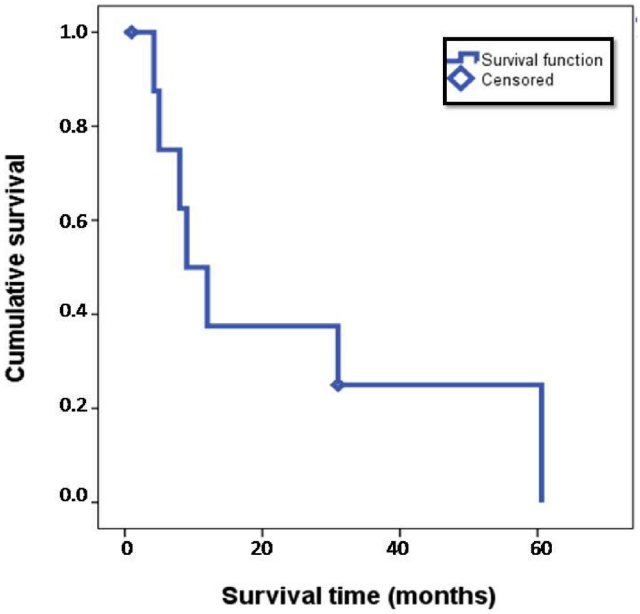
METHODS

The present study was conducted according to the STROBE statement for cross-sectional studies[8]. We analyzed the medical records of a cohort of 345 patients diagnosed with primary breast cancer, treated between January 1998 and June 2018, at a private clinic in Teresina, Piauí. The sample space had a 95% confidence level considering the female population of Piauí as 1,600,000 (according to the 2010 IBGE census), with a margin of error of 5.28%.

Those who had brain metastasis (12 cases) were identified. Three cases were excluded from the study because despite the presence of neurological symptoms, the diagnosis of tumor spread was only possible post mortem, which would compromise the determination of survival time; in addition, these cases did not have enough data regarding primary breast cancer to allow the assessment of prognostic factors. In the end, nine cases remained for descriptive analysis of variables and determination of survival rate and mean and median survival time using the Kaplan-Meier method. Median survival is understood as the time required for 50% of the sample to reach the outcome (death due to metastasis). To determine the statistical significance and confidence intervals of the influence of possible prognostic factors on survival (histological type, molecular subtype, tumor size, degree of differentiation and treatment), the log rank test was used by means of the IBM SPSS Statistics software 20. The study was approved by the Research Ethics Committee of UFPI – CAAE: 94518518.9.0000.5214. Substantiated approval :2.948.415.

RESULTS

Nine (2.6%) of the 345 patients had brain metastasis. The survival function determined using the Kaplan-Meier method is shown in Figure 1. The mean survival time was 23.80 months (95%CI 6.854–40.759), with a maximum value of 60.6 months and a minimum of 1 month (Figure 1); the median survival time was 9 months (95%CI 3.5–14.5); the 3-year overall survival found was 11.11%. The mean and median ages at diagnosis were respectively 56.8 and 50 years; the mean time between the diagnosis of breast cancer and the onset of brain metastasis was 36.9 months (range between 6 and 58 months). Seven patients (78%) died from the disease and two were lost to follow-up (22.22%), which were censored during the analysis.



Source: Prepared by the authors on the basis of study of online medical charts.

Figure 1. Survival curve of women diagnosed with brain metastasis secondary to primary breast cancer, treated at a private center in Piaui.

Invasive carcinoma of no special type was the histological type in nine cases; there was one case of papillary carcinoma (Table 1). Regarding the degree of differentiation, five cases had grade 2, two grade 3, and one grade 1. The average size of the largest dimension of the tumors in the analyzed cases was 1.96 cm (the largest with 3.5 cm and the smallest with 1 cm). There was no statistical difference in the risk of larger tumors progressing to metastasis. The presence of an undifferentiated histological grade had a median survival of 8.5 months (95%CI 7.5–9.5). There was no statistical increase in survival when comparing grades 2 and 3 (p=0.654).

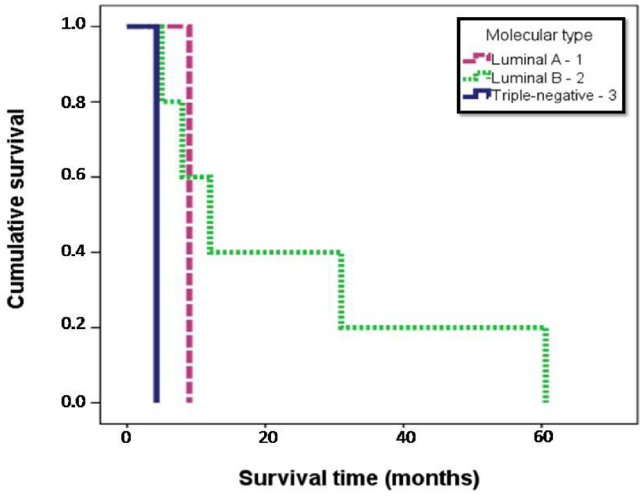
Molecular classification was possible in seven patients: five luminal B subtype, one luminal A case and one triple-negative case; patients with the luminal B subtype had a longer median survival – 23.3 months (95%CI 3.0–43.6; p=0.044<0.05). The triple-negative case had a lower median survival (4.25 months) (Figure 2). There was no study of germline mutations in hereditary breast cancer susceptibility genes in any of the cases.

As for clinical staging, there was one case of IA, one IIA, three IIB and two IIIB. Three (33%) of the patients underwent modified radical mastectomy, and six underwent conservative treatment (quadrantectomy). Three patients received neoadjuvant chemotherapy and five underwent adjuvant chemotherapy; in addition to these, three patients (30%) also used hormone therapy (tamoxifen). There was no statistical difference in survival when comparing the different treatments. (p=0.771).

Table 1. Characteristics of cases of primary breast cancer that developed brain metastasis.

Histological type	Histological grade	Molecular subtype	Treatment	Survival (months)
ICNST	3	Luminal B	neo CT+Sur+RT	60.60
ICNST	3	Luminal B	neo CT+Sur+RT	8.00
ICNST	3	Luminal A	Sur	9.00
ICNST	2	Luminal B	Sur+RT+CT+TMX	12.00
ICNST	1	NI	Sur+RT+CT+TMX	1.00
ICNST	2	Luminal B	Sur+RT+CT	5.00
ICNST	2	Triple-negative	Sur+RT+CT	4.25
ICNST	2	Luminal B	Sur+RT+CT	31.00
PC	NI	NI	NI	31.00

ICNST: invasive carcinoma of no special type; PC: papillary carcinoma; neo CT: neoadjuvant chemotherapy; CT: adjuvant chemotherapy; Sur: surgical procedure; RT: adjuvant radiotherapy; TMX: tamoxifen.
Source: Prepared by the authors on the basis of study of online medical charts.



Source: Prepared by the authors on the basis of study of online medical charts.

Figure 2. Survival curve of women diagnosed with brain metastasis secondary to primary breast cancer, according to molecular subtype.

DISCUSSION

In the present study, the median survival of patients with brain metastasis was 23.8 months (95%CI 6.9–40.8). We identified luminal B subtype as associated with a better outcome, with a median survival of 23.3 months (95%CI 3.0–43.6; p=0.044). The presence of an undifferentiated histological grade led to a worse prognosis, with a mean survival of 8.5 months (95%CI 7.5–9.5); however, there was no significant difference in survival when comparing grades 2 and 3 (p=0.654).

The mean time between the diagnosis of breast cancer and the onset of brain metastasis was 36.9 months (range between 6 and 58 months). Among the patients analyzed, seven (78%) died from the disease and two were lost to follow-up (22%), the latter being censored during the analysis. Survival time ranged from 1 – 60.6 months (Figure 2).

A Chinese study, published in 2019, using the Surveillance, Epidemiology, and End Results Database, analyzed the survival of 18,322 American patients diagnosed with metastatic breast cancer. Patients with brain metastasis had a worse prognosis when compared to those whose cancer progressed to metastases to other organs; they had a lower breast cancer-specific survival rate and lower overall survival; p<0.001, for both)[9]. This was observed in our cohort: the median survival found after the Kaplan-Meier analysis in our cohort was 9 months (95%CI 3.5–14.5 months), similar to the median value found in the US population (8 months for patients with brain metastasis with 95%CI 5.7–10.4 months)[9].

On the other hand, the overall 3-year survival rate found was 11%; lower than that found in the survival analysis of the US population, 19.90%[9]. An important limitation for this was our small number of cases of patients who developed brain metastasis in the present series.

Nine (2.6%) of the patients had brain metastasis in the present study; the mean age was 56.9 years, while the median age was 50 years. This number was similar to the median age of 56 years found in a European multicenter study that evaluated 668 patients with brain metastasis secondary to primary breast cancer. Furthermore, according to the literature, survival tends to decrease in patients with advancing age (over 40 years), when compared to younger patients (under 40 years)[10]. Only one patient in our sample was younger than 40 (31 years old).

Growing evidence indicates that the occurrence of distant metastases differs according to the histological subtype of primary breast cancer. According to the World Health Organization (WHO), there are 21 histological types of breast cancer, divided into non-invasive carcinomas, which include carcinomas in situ and Paget's disease, and invasive carcinomas, such as invasive

carcinoma of no special type (invasive ductal carcinoma) and other rarer types[11].

According to the literature, the most common histological type is invasive carcinoma of no special type[11]; this was also the most frequent type in patients who developed brain metastasis in the sample of the present study (88.89% of cases), as can be seen in Table 1. However, there was no statistically significant increase in risk in our sample, demonstrating that invasive carcinoma of no special type is most associated with brain metastasis (relative risk (RR) 3.75; 90%CI 0.35–18.56). However, this finding is in agreement with a multinational and multicenter cohort study, whose sample space involved 2,473 patients with primary breast cancer and brain metastasis. Invasive carcinoma of no special type was diagnosed in about 80% of these patients[12].

Among the invasive cancers of no special type, it is possible to see in Table 1 that three belonged to the most undifferentiated form, with one case being grade 1 (least undifferentiated) representing 11% of cases, and five grade 2 (56%). In one of the cases, it was not possible to assess the degree of tumor differentiation. When considering the degree of differentiation as a prognostic factor, there was no statistically significant difference in survival, when we compared the survival curves for grades 2 and 3 (p=0.654). Grade 3 patients had a median survival of 8.5 months (95%CI 7.5–9.5). The literature, in turn, points out that the more undifferentiated the tumor, the worse the prognosis tends to be, and therefore, the longer survival is usually found in patients diagnosed with grade 1 and 2 cancer; however, the small number of cases in our study severely limits this analysis[13]. Even with this good prognostic correlation, some cases of more differentiated histological grade may develop metastases, with the invasive ductal subtype being more commonly associated with this type of tumor dissemination[14].

Among the patients, there was also one case of papillary carcinoma with an unknown degree of differentiation, as shown in Table 1. Papillary carcinomas tend to have a better prognosis compared to invasive carcinoma of the no special type, and this patient had a 31-month survival rate[15].

Regarding size, the mean of the largest dimension of the tumors was 1.96 cm (ranging from 1 – 3.5 cm); there was no statistical difference in the association between a larger size of the primary tumor and the probability of progressing to brain metastasis. This limitation is possibly due to the small number of patients in our series. According to Wang et al. (2019), the size of the primary tumor is one of the variables with the worst prognosis for survival (hazard ratio HR>1, p<0.001), especially those with T4 classification[9].

Furthermore, the literature suggests that the survival time for patients with brain metastases differs significantly between the molecular subtypes of breast cancer. These are classified according to the presence or absence of estrogen (ER) and progesterone (PR) receptors or human epidermoid growth factor receptor 2 (HER2) in luminal A (ER+ and/or PR+ and HER2-), luminal B (ER+ and/or PR+ and HER2+), triple-negative (ER-, PR-, HER2-) and enriched or overexpressed HER2 (ER-, RP-, HER2+)[13]. Breast cancer subtypes with high expression of the HER2 marker and triple-negative (TN) are more prone to brain metastasis during the course of the disease, with triple-negative being associated with lower survival[15]. There is evidence that approximately 30% of primary breast cancers with HER2+ and about 50% of triple-negative cases progress with central nervous system invasion[16]. In the present study, molecular classification was possible in seven patients: luminal B subtype was the most prevalent (five cases); there was one luminal A case and one triple-negative case. There was a longer median survival (23.32 months) in those patients who had luminal B subtype (95%CI 3.01–43.63) and thereby a better outcome (Figure 2).

This result was consistent with that obtained by a retrospective French study that analyzed 4,118 patients with brain tumors secondary to breast cancer: the overall survival for HER2+/HR+ (luminal B) tumors was the highest (18.9 months; HR=0.57, 95%CI 0.50–0.64; p<0.0001)[17] when compared to the other molecular subtypes. Although the triple-negative subtype had a lower mean survival (4.25 months), accurate statistical analysis was not possible, because of the limiting factor of having only one patient with this characteristic in our series. Also, according to Darlix[17], patients with triple-negative tumors (HER2-/HR-) had a worse outcome, with an overall survival of 4.4 months (HR=1.55, 95%CI 1.42–1.69; p<0.0001)[17].

Another limitation of the present study was the fact that none of the nine cases (100%) included genetic tests, such as testing for the BRCA-1 gene. Nonetheless, five of them (55%) had an indication for genetic studies according to the NCCN (National Comprehensive Cancer Network), because primary breast cancer was diagnosed before the age of 50[18]. Furthermore, one of these five was within another criterion, as it met the triple-negative molecular classification. A French cohort study showed that positivity for BRCA-1 is associated with the development of high-grade tumors, as well as with a high rate of mitosis[19]. For a better approach, the American Society of Breast Surgeons, considering the results of a prospective multicenter study of genetic testing, currently recommends performing multigene panels in all breast cancer patients[20]. In addition, there are associations in the literature between this alteration and evolution with triple-negative tumors[21].

Regarding clinical staging (TNM) at the time of diagnosis, there was one case of IA, one IIA case, 3 IIB cases and two IIIB cases. The more advanced the stage at diagnosis, the worse the patient's prognosis tends to be. Patients diagnosed at stage 4, for example, have a median survival of 2 – 3 years[9]. It is important to emphasize, however, that in the estimation of survival, the TNM classification must be evaluated together with other individual factors. Its use for prognosis disregards variables such as

genetic, pathological (cell replication rate or tumor subtype) or treatment differences[22].

The factors are directly related to the therapeutic management of the patient. The spread of metastatic breast cancer makes treatment difficult, where the cancer is considered incurable and with a poor prognosis. The final objective of the treatment is therefore palliative to improve the patients' symptoms and delay the spread of the tumor[23]. In this cohort, 33% of the patients underwent modified radical mastectomy, and six underwent conservative treatment (quadrantectomy); three patients received neoadjuvant chemotherapy, five underwent adjuvant chemotherapy, while three patients (30%) also used hormone therapy (tamoxifen).

For patients with metastasis, the decision to treat with systemic chemotherapy or hormone therapy depends on a few factors: tumor location and extent, the presence of hormone receptors, age, menopausal profile, and disease-free period[23].

Primary tumor resection can increase patient survival when performed at early stages, and it also impacts disease recurrence[24]. In the management of metastatic tumors, however, evidence shows that aggressive local therapy does not lead to additional benefits to patient survival. However, in certain circumstances, surgical resection of the primary tumor of stage IV breast cancer works as palliative care in the control of ulcerations, bleeding and infections, and therefore, it should be considered in a multidisciplinary approach[23]. In the present study, all patients were operated on (100%), and adjuvant or neoadjuvant treatment was individualized. However, there was no statistically significant difference in survival when comparing the different forms of treatment (p=0.771).

An alternative for the treatment of brain metastasis is stereotactic surgery by radiotherapy. This type of intervention is indicated when the patient has less than four foci of brain metastasis. However, the prognosis is still guarded. In a cohort study with 50 patients, the median survival found after this approach was 33 months[25].

CONCLUSION

The median survival after diagnosis of brain metastasis from breast cancer was 23.8 months. The luminal B subtype was associated with a better outcome, with a mean survival of 23.3 months

AUTHORS' CONTRIBUTIONS

SCV: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. FECSF: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft. GMA: Investigation, Data curation, Methodology, Writing – original draft, Visualization. LLSB: Investigation, Data curation, Formal Analysis, Writing – original draft, validation. MACN: Investigation, Data curation, Formal analysis, Visualization, Writing – original draft.

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CASE REPORT
https://doi.org/10.29289/2594539420210053

Changing the molecular profile of primary and metastatic breast cancer identified by Foundation One: case report

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ABSTRACT

Objective: To describe a case report of a patient who presented with bilateral breast cancer with progression to metastatic disease, in which immunohistochemical profile of the primary and metastatic tumor was divergent. **Methods:** This was a study with a descriptive narrative and reflective design, of the case report type, based on secondary data, with information and images obtained from the electronic medical records of the MVSoul system used in the oncology center of a private hospital in the Federal District in Brazil. Data collection was derived from the analysis of data and images of the electronic medical record. **Case report:** A patient presented with bilateral metastatic breast cancer, and the primary and metastatic breast tumors showed a difference in immunohistochemical profile. Accordingly, we highlight the rarity of the case, the need for biopsies of metastatic lesions because of the molecular heterogeneity of breast cancer and possible discrepancy between the primary tumor and metastases. Spreading knowledge about diagnostic tests and personalized treatment according to tumor molecular characteristics is also essential, especially when the patient does not have a satisfactory therapeutic response, as in the reported case, since the patient had metastases with different molecular profiles confirmed only by of tumor DNA sequencing.

KEYWORDS: breast neoplasms; metastasis; biopsy; cytogenetic analysis.

INTRODUCTION

Breast cancer is the most common type of malignant neoplasm in Brazilian women, with an annual incidence of 66,280 cases (29.7%), and it was the main cause of cancer death In 2020, where 18,068 (16.4%) deaths from breast cancer were registered[1]. According to international guidelines, breast cancer is uncommon in women under 40 years of age, representing less than 7% of all diagnosed cases[2]. Even rarer is the involvement of a second contralateral primary breast cancer, corresponding to a mean annual incidence rate of 0.5%[3,4]. Over the years, scientific discoveries have shown that this neoplasm has significant molecular heterogeneity, and an immunohistochemical evaluation of the disease is essential to characterize the status of the progesterone (PR) and estrogen (ER) receptors, HER2 expression and Ki67 cell proliferation index[2,5]. According to these data, breast carcinoma is classified as luminal A, luminal B, HER2-positive or triple-negative (TN).

Breast cancer has extensive molecular heterogeneity, so it cannot be seen as a single entity, since patients with different molecular subtypes have differences in survival and different therapeutic possibilities[6]. Luminal tumors are those enriched by hormone receptors (ER and/or PR) and include special types, such as tubular, cribriform, lobular and mucinous carcinomas. On the basis of Ki67, a cut-off point of 14% was established to distinguish luminal A and B tumors. By definition, luminal A tuors are those that are hormone receptor positive, HER2-negative and Ki67-positive up to 14%, while luminal B ones are those that are hormone receptor-positive and HER2-positive or -negative and have a Ki67 index greater than 14%[7]. Those tumors that do not express the HER2 protein or hormone receptors are called triple-negative tumors, and they are more aggressive[8-10].

Generally, the characteristics of metastatic breast cancer, like other types of cancer, are similar to those of the initial disease. However, more and more studies demonstrate a

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Conflict of interests: nothing to declare. **Funding:** none.
Received on: 10/29/2021. **Accepted on:** 12/31/2021.

divergent molecular profile between the initial breast tumor and the recurrent or[11] metastatic one, which can be attributed to the cellular heterogeneity of the cancer, as well as the selective expression of receptors by cell clones at the end of the initial treatment[11]. All this makes it often necessary to biopsy the new lesion, especially when the patient does not have a satisfactory therapeutic response[12].

A study carried out with a large cohort of patients in the Stockholm region (Sweden) estimated that, at relapse, 32%, 41% and 15% of patients showed a change in ER, PR and HER2 status, respectively[11,13,14]. It also highlights that women with initially ER-positive tumors who transformed into ER-negative had a significantly increased risk of death by 48% compared to stable ER patients[11].

Another multicenter cohort study, PriMet, retrospectively evaluated 635 breast cancer patients between 1980 and 2010. Discrepancies in hormone receptors and HER2 status between primary tumor and recurrent disease were observed in 18.7% and 21.6% of cases, respectively[15,16]. Regarding hormone receptor presence, positivity in the primary tumor and its absence in the relapsed disease were more frequent, while for the expression of HER2, the opposite was observed[16].

Cancer treatment is undergoing an essential shift with the use of molecularly targeted drugs for selected subsets of patients with various tumor types, resulting in more effective and safer treatment. Diagnostic tests that show individual genomic alterations are essential for the successful application of personalized therapy[17]. Parallel (or "next generation") DNA sequencing, successfully applied in the research environment to elucidate the complexity of the cancer genome, is becoming an attractive clinical diagnostic technology because it can accurately detect most genomic changes in all therapeutically relevant cancer genes in a single trial[18].

Given the complexity of this disease, it is necessary to promote effective interventions, and it is essential to better understand the relevant molecular characteristics and their influence on prognosis. Likewise, it is essential to know the therapeutic possibilities to achieve the best possible prognosis and longer disease-free survival for the patient.

Therefore, the present work is justified by the importance of disseminating knowledge about a cancer whose prognosis and treatment depend on its molecular characteristics.

METHODS

This was a study with a descriptive design of a narrative and reflective character, of the case report type, based on secondary data, with information and images obtained from the electronic medical record of the MVSoul system used in the oncology center of a private hospital in the District Federal. The information was collected through the analysis of data and images from the electronic medical record.

CASE REPORT

A 39-year-old patient came to the outpatient clinic in 2004 with a complaint of a palpable lump in the right breast. Breast ultrasound revealed two breast nodules, which were biopsied: 1. Invasive ductal carcinoma (IDC), grade II, 0.7x0.5 cm in the lower left quadrant. 2. IDC, grade II, 0.3x0.2 cm in the upper left quadrant. Clinical status T1N0M0. Immunohistochemistry showed ER+, PR++, HER2++, Ki67++, FISH negative. Patient underwent left quadrantectomy with negative sentinel lymph node (SL) investigation, followed by radiotherapy and use of tamoxifen for five years.

She was under clinical follow-up when, in 2009, at the age of 44, after ending the use of tamoxifen, she had recurrence of the skin neoplasm. We opted for a right radical mastectomy with axillary dissection and a left prophylactic mastectomy with negative SL. Anatomopathology (AP) of the right breast surgical specimen showed IDC, grade II, 3x2x1.5 cm, skin infiltration, with four compromised lymph nodes of 15 resected, pT4pN2 M0, ER+, PR+, HER2-negative and Ki67 10%, while the AP prophylactic mastectomy of the left breast found a second primary tumor: IDC, grade I, 1.4 cm, luminal B, LS negative. Chemotherapy was started with AC-T (docetaxel) regimen, external radiotherapy in the breast plastron and use of adjuvant anastrozole for five years (until 2014), because at that time the patient was postmenopausal.

In May 2017, three years after anastrozole was discontinued, follow-up examinations showed suspected disease progression to the bones, lungs, and mediastinum. Bone biopsy (sternum) showed AP compatible with metastatic adenocarcinoma, immunohistochemistry: ER 80%, PR negative, Ki67 50%, HER2 negative. At this point, she was on faslodex for five cycles, showing clinical worsening and rapid progression of the disease to the liver. She then opted for the Foundation One genetic test, which indicated no detectable genetic alterations. There was a change of treatment to chemotherapy with paclitaxel+bevacizumab for six cycles, when there was new disease progression to the bones during treatment.

The regimen was changed to eribulin for four cycles, with a good initial response, but followed by a new one for progression, this time for the lungs and mediastinum. With the arrival of CDK4/6 inhibitors, palbociclib with letrozole was chosen for four cycles, however, with further worsening of the disease in bones, lungs and liver.

In view of the extensive history and lack of therapeutic response, a new bone biopsy (iliac) was performed, where AP confirmed IDC with ER 60%, PR negative and HER2 negative. Material was sent again to Foundation One, and the result was different from the previous ones, including HER2 amplification.

Once HER2 amplification was verified, the patient started using trastuzumab emtansine every 21 days, combined with letrozole and denosumab, with excellent clinical, metabolic and radiological complete response for a year and a half. There was then focal progression of the disease in the central nervous system, where she underwent radiosurgery and then started a double block with Herceptin and Perjeta. To date, the patient uses double HER2 blockade, with clinical stability and no evidence of disease (Figure 1).

DISCUSSION

Breast cancer is the most common type of malignant neoplasm in Brazilian women, with an annual incidence of 66,280 cases (29.7%), and the main cause of cancer death. In 2020, 18,068 (16.4%) deaths from breast cancer were identified[1]. According to international guidelines, breast cancer is uncommon in women under 40 years of age, accounting for less than 7% of all diagnosed cases[2]. The involvement of a second contralateral primary breast cancer is even rarer, corresponding to an average annual incidence rate of 0.5%[3].

Research carried out by the Cooperative Breast Cancer Group in Denmark evaluated 68,466 patients with breast cancer between 1978 and 2012, of which only 4% had a second contralateral primary tumor, and the prognosis was considerably worse when compared to unilateral disease[4]. There are many risk factors for breast cancer; however, for contralateral disease, these factors are not well established[5].

Over the years, scientific discoveries have also shown that breast tumors have remarkable molecular heterogeneity, and an immunohistochemical evaluation of the disease is essential to characterize PR and ER status, HER2 expression and Ki67[2] index.

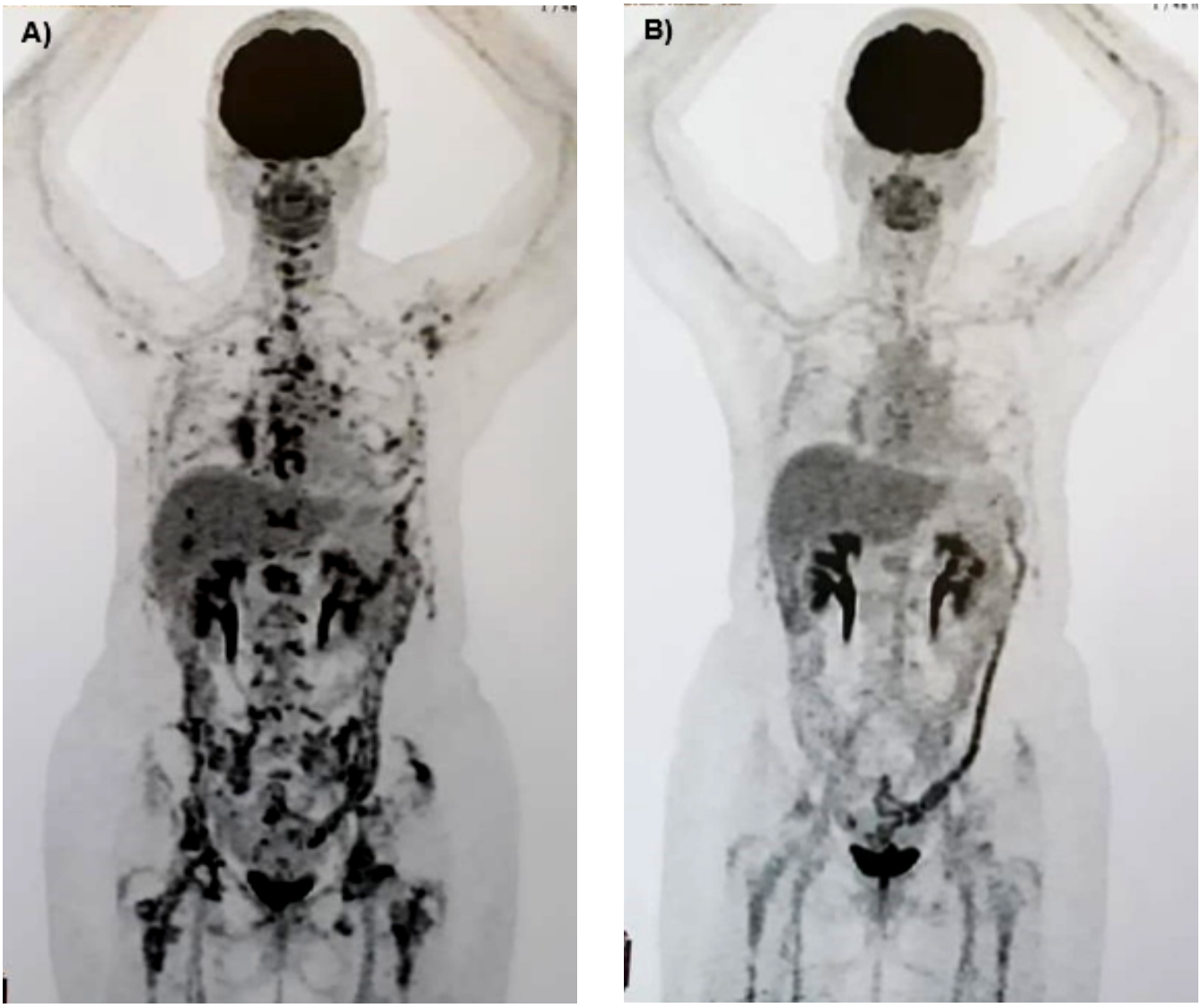

Figure 1. A) PETCT of the patient before starting treatment with trastuzumabe entansina combined with letrozol and denosumabe; B) PETCT of the patient at the end of treatment with trastuzumabe entansina combined with letrozol and denosumabe.

And it is according to each molecular subtype that survival rate is determined and therapeutic possibilities defined[6].

Luminal tumors are those enriched by hormone receptors (ER and/or PR) and include special types such as tubular, cribriform, lobular and mucinous carcinomas. On the basis of the Ki67 level, a cohort point of 14% was established to distinguish luminal A and B tumors. By definition, luminal A tumors are those that are hormone receptor-positive, HER2-negative and Ki67-positive up to 14%, while luminal B ones are those that are hormone receptor-positive and HER2-positive or -negative with Ki67 index greater than 14%[7]. Those that do not express the HER2 protein and do not have hormone receptors are called triple-negative (TN) tumors and are more aggressive[8-10].

Luminal A tumors are those with the lowest metastatic potential, while luminal B and HER2-positive tumors have as main metastatic sites the central nervous system, liver and lung, as well as bones. TN tumors metastasize to any location[11].

The British Columbia Cancer Agency followed patients with early-stage breast cancer diagnosed between 1986 and 1992 and found high rates of brain metastases in the HER2 overexpressed (28.7%) and TN (22%) groups[15].

A retrospective cohort performed at Seoul National Hospital (South Korea) analyzed 1,432 patients with stage I to III breast cancer who underwent surgery and systemic treatment when indicated, with a mean follow-up of 53 months. The five-year breast cancer-free interval, according to subtype, was 93.9% for luminal A, 94.2% for luminal B with HER2 positive, 91.4% for luminal B with HER2 negative, 83.1% for HER2 positive and 81.9% for TN. The overall five-year survival rate was 98.3%, 95.8%, 98%, 90.8% and 89.9% for luminal A, luminal B with HER2 negative, luminal B with HER2 positive, HER2 positive and TN, respectively[12].

An Asian study evaluated recurrence rates according to molecular subtype and found: 5% for luminal A, 7.8% for luminal B with HER2 negative, 6.6% for luminal B with HER2 positive, 13.1% for HER2 positive and 16.7% for TN[13]. Kennecke and coworkers (2010) followed 313 women with breast cancer for 93 months and observed that the site of distant recurrence varied according to molecular subtype: in luminal A and B, the most common pattern of recurrence was in the bones, while for HER2-positive and TN, visceral involvement was more common[14].

The molecular characteristics of metastatic breast cancer, like other types of cancer, are often similar to those of the initial disease. However, more and more studies have shown a divergent molecular profile between the initial tumor and the recurrent or metastatic one. This can be attributed to the cellular heterogeneity of cancer and the selective expression of receptors by cell clones after the initial treatment[11]. Because of this, biopsy of the new lesion is often necessary, especially when the patient does not have a satisfactory therapeutic response. A large cohort study of patients in the Stockholm region estimated that, at relapse, 32%, 41% and 15% of patients showed a change in ER, PR and HER2 status, respectively.

It is noteworthy that women with initially ER-positive tumors who transformed into ER-negative had an increased risk of death by about 48% when compared with stable ER patients[11]. PriMet, a multicenter cohort study, evaluated 635 breast cancer patients between 1980 and 2010. Discrepancies in hormone receptors and HER2 expression between primary tumor and recurrent disease were observed in 18.7% and 21.6 % of cases, respectively. The positivity in the primary tumor and its absence in the recurrent disease were more frequent for hormone receptors, while for HER2 expression, the opposite was observed[16].

The treatment of breast cancer is undergoing an essential change with the use of molecular-targeted drugs, based on a better understanding of this molecular heterogeneity and resulting in a more effective and safer treatment. Diagnostic tests that show individual genomic alterations are essential for the successful application of personalized therapy[17] based on tumor DNA sequencing. This clinical diagnostic technology has been extremely attractive because it can accurately detect most genomic changes in all therapeutically relevant tumor genes[18]. Speeding up the selection of effective drugs based on the identification of gene mutations in tumor DNA becomes essential, since patients with metastatic breast cancer carry a history of several previously received therapeutic lines, as in this case, resulting in reduced tumor cell sensitivity to the drugs used[19].

CONCLUSIONS

A patient presented with tumors in both breasts, metastatic and with different immunohistochemical profile between the primary tumor and the metastasis. Thus, the rarity of the case, the need for rebiopsy of metastatic or recurrent lesions due to the molecular heterogeneity of breast cancer and possible discrepancy between the primary and recurrent tumors are highlighted. Spreading knowledge about diagnostic tests and personalized treatment, considering their molecular characteristics, is also essential, especially when the patient does not have a satisfactory therapeutic response, as in the case reported, since the patient had lesions with different molecular profiles confirmed only with tumor DNA sequencing.

AUTHORS' CONTRIBUTION

IFVM: Data curation, Methodology, Writing – original draft, Writing – review & editing. PWS: Methodology, Writing – original draft. ADC: Methodology, Writing – original draft. JSS: Data curation, Writing – original draft. AVLS: Data curation, Writing – original draft.

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ORIGINAL ARTICLE
https://doi.org/10.29289/2594539420210059

Hematological ratios as prognostic indicators in patients with triple-negative breast cancer in southern Brazil

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ABSTRACT

Introduction: The heterogeneous nature and intrinsically aggressive tumor pathology of the triple negative breast cancer subtype results in an unfavorable prognosis and limited clinical success. The use of hematological components of the systemic inflammatory response for patients with triple-negative breast cancer can add important prognostic information to the criteria traditionally used for cancer patients, since inflammation can promote tumor progression support by affecting the stages of tumorigenesis. **Objectives:** The aim of this study was to evaluate the hematological parameters neutrophil/lymphocyte, monocyte/lymphocyte and platelet/lymphocyte ratios as prognostic indicators in patients with triple-negative breast cancer. **Methods:** This was a single-center retrospective observational study in an oncology referral hospital in the South region of Brazil. Electronic medical records of patients diagnosed with triple-negative breast cancer from 2012 to 2016 were reviewed and analyzed using SPSS. **Results:** The low blood cell ratio groups had significantly higher overall survival than the high blood cell ratio groups. Univariate analysis also confirmed the correlation of patients in the high blood cell ratio groups with unfavorable results. **Conclusions:** Hematological components of the systemic inflammatory response are promising prognostic indicators. More studies on the subject should be carried out to assist in future medical decision-making so these parameters of easy assessment and low cost can be introduced in clinical practice.

KEYWORDS: breast cancer; triple negative breast neoplasms; prognosis; blood cell count.

INTRODUCTION

Breast cancer became in 2020 the leading cause of global cancer incidence — with around 2.3 million new cases — as well as the fifth leading cause of cancer mortality worldwide, with 685,000 deaths[1]. It is estimated that approximately 12% to 20% of breast cancer cases diagnosed annually are of the triple-negative histological subtype. Triple-negative breast cancer (TNBC) is characterized by the lack of expression of estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER-2)[2].

The heterogeneous nature and inherently aggressive tumor pathology of this breast cancer subtype result in an unfavorable prognosis, where clinical success is limited by the lack of targeted therapy and with a tendency for early recurrence[3,4]. Accordingly, this histological subtype requires new approaches, including assessment tools that complement conventional methods. More and more studies support the involvement of inflammation in cancer prognosis, as inflammation is related to the development, progression, metastasis and recurrence of the disease[5-10].

Neutrophils, lymphocytes, monocytes and platelets, hematological components of the systemic inflammatory response, have been reported as prognostic factors in several types of tumors, including breast cancer, due to their influence on neoplastic processes. Neutrophil, monocyte, platelet, and lymphocyte counts, in the form of neutrophil/lymphocyte (NLR), monocyte/lymphocyte (MLR), and platelet/lymphocyte (PLR) ratios, are inflammatory biomarkers that serve as auxiliary tools to add prognostic information to the criteria. traditionally used in cases of cancer patients[5-8].

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Conflicts of interest: nothing to declare. **Funding:** none.
Received on: 11/16/2021. **Accepted on**: 01/17/2021.

Thus, the aim of this study was to evaluate NLR, MLR and PLR as prognostic indicators in patients with TNBC, to contribute information to assist in future clinical practice and medical decision-making.

METHODS

Patients

This was a single-center, retrospective observational study, in which we identified patients whose diagnosis and treatment for TNBC had been performed at a referral oncology hospital in southern Brazil, between 2012 and 2016. The study obtained the informed consent of patients and ethical approval from the Ethics Committee of the teaching hospital, in accordance with the Declaration of Helsinki (1964) and Resolution 466/2012 of the National Health Council/Ministry of Health of Brazil.

Eligible patients were female, aged 18 years or older, diagnosed with triple-negative breast cancer and registered in the electronic medical record system available at the referral hospital. Patients who did not sign an informed consent form and whose TNBC was not characterized as the primary tumor were excluded. Duplicate patients and those with missing clinical data or incomplete or absent pathological and laboratory results were also excluded.

Clinicopathological characteristics

According to pathology reports, we identified tumors lacking immunohistochemical expression of ER, PR and HER-2 receptors. We then reviewed the electronic medical records of these patients to check their age and medical history, occurrence of metastases, recurrence or death. Pathological characteristics were determined, including the classification of malignant tumors (TNM), involvement of lymphatic vessels, blood vessels and axillary and sentinel lymph nodes.

Laboratory data

A complete blood count was performed as part of the routine clinical evaluation before surgery. NLR, MLR and PLR were defined as the absolute count of neutrophils, monocytes and platelets divided by the absolute lymphocyte count, being calculated from the pretreatment complete blood count performed within six months before diagnosis. To investigate the association of blood cell ratios with death outcome, a graphical representation was performed based on the receiver operating characteristic curve (ROC curve).

Statistical analysis

Qualitative variables were provided as frequency and percentage, while the quantitative as mean and standard deviation. Through the ROC curve, the ratio cut-offs for the outcome of death were estimated according to the Youden index. The associations of the ratios with the clinicopathological characteristics were analyzed using the chi-square test or Fisher's exact test when appropriate, and age results were compared using Student's t-test. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Overall survival time was defined from the date of diagnosis to the date of death/last record, and progression-free time was defined from the date of diagnosis to the date of first relapse or death/last record. Hazard ratio (HR) was determined by Cox proportional hazard regression analysis, with 95%CI. We used the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) for the analyses, and a significance level of 0.05 was adopted.

RESULTS

Patients

A database consisting of 2890 records of patients with histopathologically confirmed breast cancer was reviewed, and 42 records of patients with histological subtype triple-negative were included after the screening process and checking eligibility criteria (Figure 1). In this study, 95.2% of the samples for anatomopathological analysis came from surgical samples and only 4.8% from biopsies. Baseline clinicopathological characteristics are shown in Table 1. The mean time between diagnosis and death or closure was 47.1 months (range 1–60 months) and death occurred in 13 (31%) of the 42 patients. The mean time between diagnosis and progression or closure was 37.7 months (range 0–60 months) and progression occurred in 21 (50%) of the 42 patients. The mean age of the patients was 54.8 years (range, 33.09–89.8 years) and 9 (21.4%) of the patients were 40 years old or younger. The NLR, MLR and PLR were determined for all patients and ranged from 0.44 to 9.71 (mean, 2.77; median, 2.05; SD, 1.81), 0.12 to 2.00 (mean, 0.44; median, 0.35; SD, 0.34) and 61.57 to 594.34 (mean, 204.54; median, 159.35; SD, 117.57), respectively.

Cut-off points for NLR, MLR and PLR

ROC curve analysis was performed to determine optimal cut-off values for pretreatment NLR, MLR and PLR (Figure 2). The cut-off values of NLR, MLR and PLR were 2.13, 0.55 and 203.55, respectively, indicating the highest Youden index (maximum point of sensitivity and specificity). Eligible patients were stratified into two groups (low and high) according to cut-offs. Twenty-two patients (52.4%) were classified in the low NLR group (NLR<2.13) and 20 (47.6%) in the high NLR group (NLR≥2.13). Likewise, 32 (76.2%) of the patients were classified in the low MLR group (MLR<0.55), while 10 (23.8%) in the high MLR group (MLR≥0.55). Regarding PLR, 25 (59.5%) of the patients were classified in the low group (PLR<203.5) and the other 17 (40.5%) in the high group (PLR≥203.5).

Association of NLR, MLR and PLR with prognosis

There was no significant correlation between pretreatment NLR, MLR and PLR and clinicopathological indices such as age at diagnosis, histological grade, tumor size, lymph node status, invasion of skin, blood vessels or lymphatic vessels, molecular phenotype and locoregional recurrence (p>0.05) (Table 1). We found that the low NLR, MLR and PLR groups had significantly higher overall survival (OS) (NLR log rank p=0.010, MLR log rank p=0.003 and PLR log rank p=0.000) than the high NLR, MLR and PLR groups (Figure 3). In the analysis of progression-free survival (PFS) (Figure 4), there was no significant difference between the high and low NLR groups (log rank p=0.166), nor between the high and low MLR groups (log rank p=0.072). However, there was a significant difference in PFS for PLR (log rank p=0.003). Univariate analysis also confirmed the correlation of patients in the high NLR, MLR and PLR groups with unfavorable outcomes. The chance of death at any time during follow-up increased 4.72-fold for NLR≥2.13 (95%CI 1.29–17.22, p=0.019), 4.56-fold for MLR≥0.55 (95%CI 1.52–13.72, p=0.007) and 11.02-fold for PLR≥203.5 (95%CI 2.42–50.05, p=0.002) in relation to low NLR, MLR and PLR.

DISCUSSION

In recent years, several studies in literature have demonstrated the important role of blood cell ratios as significant biomarkers for breast cancer and other solid tumors, such as colorectal cancer, gastric cancer, ovarian cancer, non-small cell lung cancer, and others[9-18]. Despite the technical-scientific advances on the subject, for breast cancer, studies on the predictive value of pretreatment hematological ratios in the Brazilian population

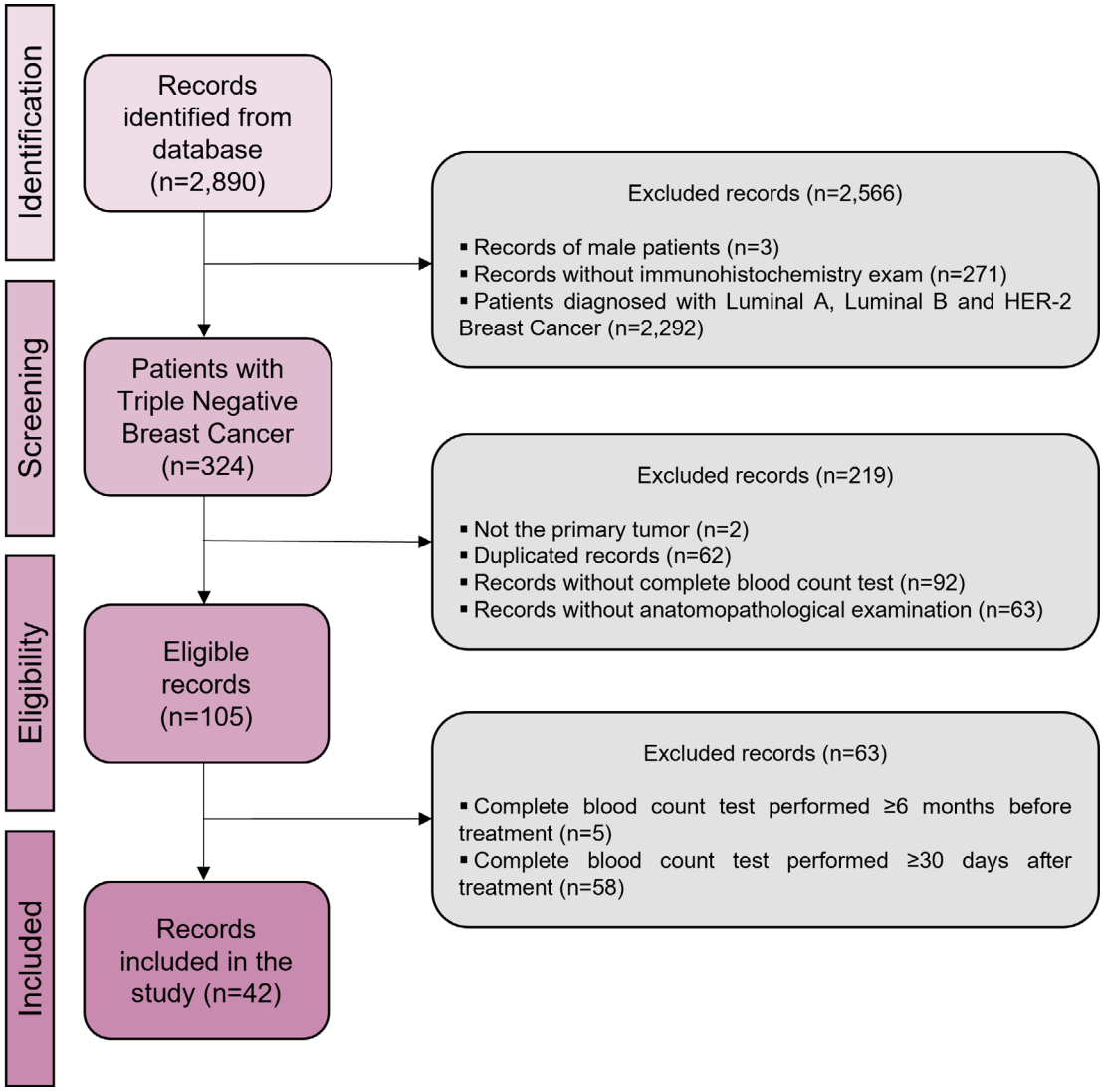


Figure 1. Records screened and included in the study.

are rare, especially for TNBC, known to be an aggressive cancer due to its high nuclear grade, high mitotic index and greater tendency for regional and distant metastases. The use of hematological components of the systemic inflammatory response for patients with TNBC can add important prognostic information to the criteria traditionally used in cases of cancer patients.

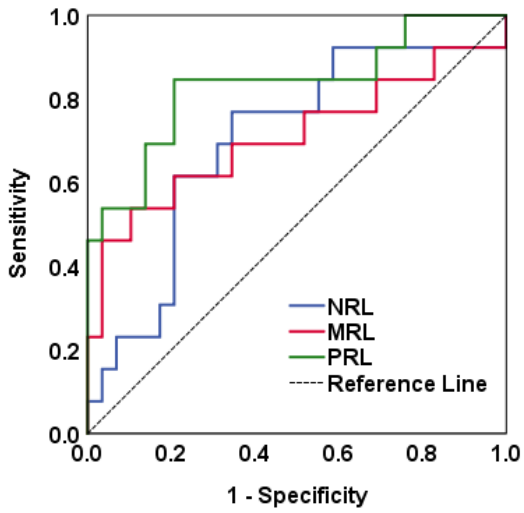
In the present study, we demonstrated that high PLR is a statistically significant predictor of worse OS and PFS (p=0.000, p=0.003, respectively) among women with TNBC. When compared to other pretreatment hematological ratios and factors associated with survival, such as the occurrence of recurrence, the high PLR group again showed significantly unfavorable results. On the other hand, the NLR and MLR groups did not show statistically significant results in the PFS analysis (p=0.166, p=0.072, respectively). The prognostic effect of NLR, MLR and PLR was consistent with the clinicopathological findings, since the groups with high NLR, MLR and PLR values, which were associated with a worse OS, also had unfavorable clinicopathological results in relation to the low NLR, MLR and PLR groups.

Two recent meta-analyses corroborate the findings of this study, suggesting that breast cancer patients with a high level of PLR are associated with a significantly worse prognosis and shorter

Table 1. Clinicopathological baseline characteristics of 42 patients with triple-negative breast cancer.

Characteristics		NLR<2.13 (n=22)		NLR≥2.13 (n=20)		p-value	MLR<0.55 (n=32)		MLR≥0.55 (n=10)		p-value	PLR<203.5 (n=25)		PLR≥203.5 (n=17)		p-value
		n	%	n	%		n	%	n	%		n	%	n	%	
Age at diagnosis	Mean and SD	54.18	12.25	55.47	16.17	0.770	52.57	12.57	61.93	16.90	0.066	53.89	13.26	56.13	15.55	0.619
Histological grade	G1+G2	2	9.1	3	15.0	0.656	3	9.4	2	20.0	0.577	3	12.0	2	11.8	1.000
	G3	20	90.9	17	85.0		29	90.6	8	80.0		22	88.0	15	88.2	
T	T1	5	23.8	3	15.0	0.754	7	22.6	1	10.0	0.288	7	28.0	1	6.3	0.207
	T2	10	47.6	9	45.0		15	48.4	4	40.0		12	48.0	7	43.8	
	T3	2	9.5	4	20.0		5	16.1	1	10.0		3	12.0	3	18.8	
	T4	4	19.0	4	20.0		4	12.9	4	40.0		3	12.0	5	31.3	
N	N0	12	57.1	9	45.0	0.686	19	61.3	2	20.0	0.158	16	64.0	5	31.3	0.167
	N1	4	19.0	4	20.0		4	12.9	4	40.0		3	12.0	5	31.3	
	N2	1	4.8	0	0.0		1	3.2	0	0.0		1	4.0	0	0.0	
	N3	2	9.5	4	20.0		4	12.9	2	20.0		2	8.0	4	25.0	
	N4	2	9.5	3	15.0		3	9.7	2	20.0		3	12.0	2	12.5	
Invasion of skin	No	14	77.8	12	75.0	1.000	22	84.6	4	50.0	0.066	16	84.2	10	66.7	0.417
	Yes	4	22.2	4	25.0		4	15.4	4	50.0		3	15.8	5	33.3	
Invasion of blood vessels	No	20	90.9	17	94.4	1.000	28	90.3	9	100.0	1.000	22	88.0	15	100.0	0.279
	Yes	2	9.1	1	5.6		3	9.7	0	0.0		3	12.0	0	0.0	
Invasion of lymphatic vessels	No	9	40.9	8	40.0	0.952	14	43.8	3	30.0	0.490	12	48.0	5	29.4	0.228
	Yes	13	59.1	12	60.0		18	56.3	7	70.0		13	52.0	12	70.6	
Molecular phenotype	Basal-like	13	59.1	17	85.0	0.063	22	68.8	8	80.0	0.696	17	68.0	13	76.5	0.731
	Non-basal-like	9	40.9	3	15.0		10	31.3	2	20.0		8	32.0	4	23.5	
Chemotherapy	Neoadjuvant	8	40.0	10	58.8	0.254	14	46.7	4	57.1	0.693	7	30.4	11	78.6	**0.004**
	Adjuvant	12	60.0	7	41.2		16	53.3	3	42.9		16	69.6	3	21.4	
Recurrence	No	13	59.1	9	45.0	0.361	19	59.4	3	30.0	0.152	17	68.0	5	29.4	**0.014**
	Yes	9	40.9	11	55.0		13	40.6	7	70.0		8	32.0	12	70.6	
Locoregional recurrence	No	16	72.7	16	80.0	0.723	25	78.1	7	70.0	0.678	20	80.0	12	70.6	0.714
	Yes	6	27.3	4	20.0		7	21.9	3	30.0		5	20.0	5	29.4	
Distant recurrence	No	16	72.7	10	50.0	0130	21	65.6	5	50.0	0.465	19	76.0	7	41.2	**0.023**
	Yes	6	27.3	10	50.0		11	34.4	5	50.0		6	24.0	10	58.8	
Death	No	19	86.4	10	50.0	**0.011**	26	81.3	3	30.0	**0.005**	23	92.0	6	35.3	**0.000**
	Yes	3	13.6	10	50.0		6	18.8	7	70.0		2	8.0	11	64.7	
Progression	No	13	59.1	8	40.0	0.217	19	59.4	2	20.0	**0.030**	17	68.0	4	23.5	**0.005**
	Yes	9	40.9	12	60.0		13	40.6	8	80.0		8	32.0	13	76.5	

NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio; SD: standard deviation; bold: with significant p.

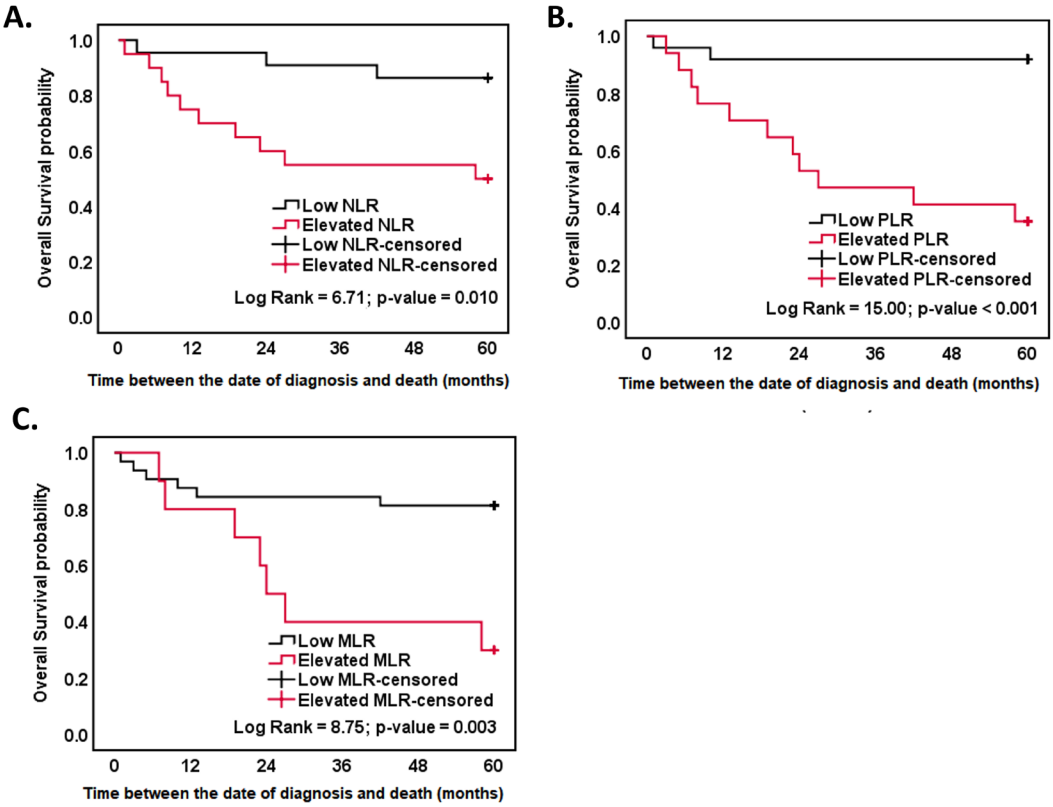


The areas under the curve for each parameter were 0.70 (p=0.040), 0.71 (p=0.033) and 0.83 (p=0.001), respectively.
NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

Figure 2. Receiver operating characteristic curve evaluating the cut-off points of the neutrophil/lymphocyte, lymphocyte/monocyte and platelet/lymphocyte ratios to predict overall survival and progression-free survival in the study.

disease-free survival, as well as a higher risk of recurrence compared with the low PLR group[14,19]. These findings can be explained by the fact that platelets are associated with the inflammatory process. Inflammation, known as one of the hallmarks of cancer, can contribute to several factors, altering the microenvironment and possibly accelerating tumor progression by releasing growth factors that support proliferative signaling and survival factors that limit cell death, facilitating angiogenesis, invasion and metastasis[20]. Thus, platelets end up playing an important role in tumor progression, by releasing pro-angiogenic proteins and protecting tumor cells from cytotoxic natural killer (NK) cells, responsible for controlling the spread of neoplastic cells. As a consequence, platelets end up potentiating the metastatic capacity of tumor cells[11,13,21]. Therefore, PLR is an excellent indicator of tumor activity.

Systematic literature reviews and meta-analyses have reported that the high NLR group is associated with worse survival in patients diagnosed with multiple cancers[12,22]. The analysis conducted by Jia et al. revealed that high levels of NLR prior to neoadjuvant therapy are associated with a worse prognosis, particularly TNBC[6]. In addition to being reported in breast cancer, the potential prognostic value of NLR has been reported in colorectal cancer, hepatocellular carcinoma, bladder cancer, lung cancer,



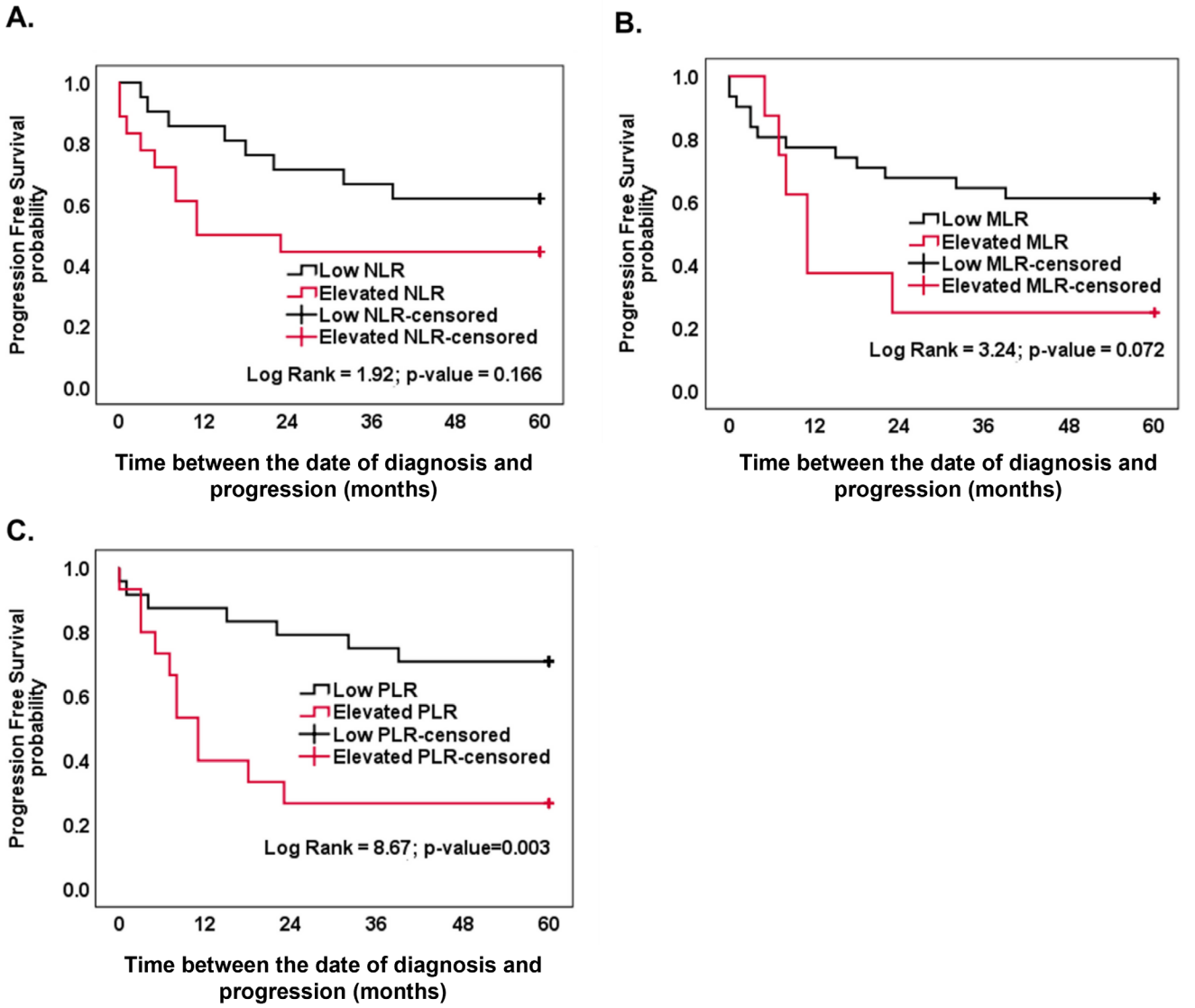
(A) Median overall survival was 54.95 months in the patients in the low neutrophil/lymphocyte ratio group and 38.55 months in the high neutrophil/lymphocyte ratio group. (B) Median overall survival was 51.1 months in the patients in the low monocyte/lymphocyte ratio group and 34.6 months in the patients in the high monocyte/lymphocyte ratio group. (C) Median overall survival was 55.64 months in the low platelet/lymphocyte ratio group and 34.65 months in the high platelet/lymphocyte ratio group.
NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

Figure 3. Correlation between overall survival of patients with triple-negative breast cancer and pretreatment blood cell ratios.

pancreatic cancer, prostate cancer and renal cell cancer[6,7,12]. In this study, the NLR obtained a significant difference only in the analysis of OS (p=0.010). However, our findings corroborate with the literature, since high NLR increased the chance of death at any time during the follow-up by 4.7 times (95%CI 1.29–17.22, p=0.019) compared to low NLR. These findings can be explained by the ability of neutrophils to inhibit the immune system and promote tumor growth, suppressing lymphocyte activity and T cell response. Therefore, NLR is considered a negative prognostic factor, being associated with low survival of cancer patients[6,7,12-14].

Huszno et al.[7] did not identify prognostic value between MLR and OS in patients with breast cancer and with TNBC. In our study, although there was a significant difference only in the analysis of OS (p=0.003), high MLR increased the chance of death by 4.56 times (HR: 4.56 95%CI 1.5–13.72, p=0.007). Therefore, more studies are needed to confirm our results.

To the best of our knowledge, this study was the first to evaluate the prognostic association of pretreatment blood cell ratios in patients with triple-negative subtype breast cancer for SG and PFS in patients from South Brazil. However, there are three important limitations that must be taken into account when interpreting our findings. Our main limitation refers to the sample size. Although we identified 324 patients with TNBC, as this was a retrospective, single-center study, there were several losses due to missing data and loss to follow-up, which resulted in only 42 eligible patients being included in the study. Unfortunately,



(A) Median progression-free survival was 43.8 months in the patients in the low neutrophil/lymphocyte ratio group and 30.6 months in the high neutrophil/lymphocyte ratio group. (B) Median progression-free survival was 41.5 months in the patients in the low monocyte/lymphocyte ratio group and 23.1 months in the high monocyte/lymphocyte ratio group. (C) Median progression-free survival was 47.2 months in the patients in the low platelet/lymphocyte ratio group and 22.5 months in the high platelet/lymphocyte ratio group.
NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

Figure 4. Correlation between progression-free survival of patients with triple-negative breast cancer and pretreatment blood cell ratios.

it was not possible to perform more robust analyses to obtain detailed information on the prognostic association of pretreatment hematologic ratios in patients with TNBC due to the sample size. In addition, it should be borne in mind that markers of the systemic inflammatory response may be influenced by factors such as acute and/or chronic infections and drug use.

CONCLUSIONS

In conclusion, the hematological components of the systemic inflammatory response are promising prognostic indicators, as they allow determining the specific needs of a patient through minimally invasive tests such as the blood cell count, helping to choose individualized approaches, and possibly helping to optimize the results for the patients. However, our findings need to be validated in larger retrospective, cohort or prospective studies. More studies on the subject should be carried out with the aim of introducing these parameters of easy assessment and low cost of performance in clinical practice in Brazil.

ACKNOWLEDGMENTS

To Cristiane Bündchen (Research Support Center, Universidade Federal de Ciências da Saúde de Porto Alegre) for statistical advice, and to all the students and researchers indirectly involved in this study for their technical-scientific assistance.

AUTHORS' CONTRIBUTION

CMB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MDB: Conceptualization, Data curation, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CGB: Conceptualization, Data curation, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RJVA: Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – review & editing. LMD: Methodology. GKC: Methodology. KAT: Methodology.

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ORIGINAL ARTICLE
https://doi.org/10.29289/2594539420220010

Real-world data on metastatic breast cancer in Goiânia, Brazil: a 17-year analysis (1995–2011)

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ABSTRACT

Introduction: Most of the data on metastatic breast cancer (MBC) originate from hospital-based studies or controlled trials involving specific populations and controlled treatments. In this respect, few population-based studies have analyzed the profile of MBC in low- and middle-income countries. **Objective:** To describe the epidemiological profile of women with de novo MBC using data from a population-based cancer registry (PBCR). **Methods:** An ecological study conducted in a PBCR in Goiânia, Brazil, for the 1995–2011 period. Women with MBC at diagnosis were included and the standardized incidence rate and annual percent change (APC) over the period were calculated. The women's clinical and demographic characteristics and data on diagnosis and treatment were analyzed. **Results:** Overall, 5,289 cases of breast cancer were registered in the Goiânia PBCR, 277 (5.2%) at metastatic stage. The adjusted incidence was 8.9/100,000 in 1995 and 6.04/100,000 in 2011 (APC: 1.1; p=0.6). Most of the patients (70.3%) were receiving care within the public healthcare system and the mean age at diagnosis was 54.7±14.5 years. Additional data for a subpopulation of 156 patients were identified at the city's two main treatment centers. According to immunohistochemistry, 53 women (67.1%) had hormone receptor-positive cancer. Of these, 14.0% (6/43) received endocrine therapy as first-line systemic treatment and 48.5% (17/35) as second-line treatment. A comparison of clinical data between the 1995–2003 and 2004–2011 periods revealed no significant differences in age, histological grade, locoregional staging, the presence of symptoms at diagnosis, or in treatment. **Conclusion:** This study population of women with MBC consisted predominantly of locally advanced tumors and the luminal-like subtype. The incidence rate of MBC in Goiânia did not change over the 17-year period. Most cases received chemotherapy as first-line systemic treatment irrespective of the tumor phenotype.

KEYWORDS: breast neoplasms; neoplasm metastasis; incidence; epidemiology.

INTRODUCTION

Breast cancer is a heterogenous pathology involving different patterns of tumor biology that are reflected in individualized clinical behavior and response to treatment[1-4]. As a result of population screening, there has been an increase in the number of incident cases diagnosed at the initial stages in various countries[5-7]; however, no reduction has been seen in the number of women diagnosed with de novo metastatic carcinoma[4,6,7].

Patients with metastatic breast cancer (MBC) receive a continuous regime of palliative treatment, resulting in elevated financial costs due to the high cost of the medications and the need to frequently undergo tests and hospitalization for clinical support[8,9]. The median 5-year survival of these women, however, remains poor, ranging from 15% to 35%[10-12].

In recent years, increased knowledge of tumor biology, advances in disease diagnosis, and access to new therapeutic agents have increased the overall survival of patients with MBC[13,14]. Although these advances have resulted in more personalized management of the metastatic disease, they have also introduced new challenges associated with controlling adverse events[8,15]. Therefore, epidemiological and population-based evaluations of women with MBC can contribute towards elaborating and implementing measures for more effective management of these patients.

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Conflict of interests: nothing to declare. **Funding:** none.
Received on: 03/22/2022. **Accepted on:** 04/16/2022.

Currently, most of the data on MBC originate from retrospective hospital-based studies or controlled trials involving specific populations and controlled treatments[13,14,16]. In this respect, few population-based studies have analyzed the profile of MBC in low- and middle-income countries[10-12,16-18].

Since population-based cancer registries record incident cases of cancer in a defined population over a period of time, their use in real-world studies allows a wider exploratory analysis to be conducted and confers the possibility of external validation. Therefore, the objective of this study was to describe the patient profiles and patterns of care in MBC in the city of Goiânia, Brazil.

METHODS

An ecological, population-based clinical study was conducted with women with MBC in the city of Goiânia, Brazil. The cases were extracted from the Goiânia population-based cancer registry database for the period between 1995 and 2011[10].

Goiânia cancer registry, Goiás

The Goiânia population-based cancer registry was created in 1986 and has been recording all new cases of cancer in residents of the city of Goiânia uninterruptedly since its creation to the present day[4,10,19].

Criteria for the selection of cases

All incident cases for which the variable "extent of the disease" was described as "metastatic" or "unknown" were potentially eligible for inclusion in the study.

Cases

The cases registered as metastatic at diagnosis were classified as de novo metastatic disease. This classification is based on the clinical report, imaging tests, and/or a histology report showing the presence of metastatic disease at sites other than the breast and axillae[8,15].

All the cases of breast cancer for which the variable "extent of the disease" was registered as "unknown" in the cancer registry were reviewed by performing an active search in the patient's medical records at the Araújo Jorge Hospital of the Association for the Combat of Cancer in Goiás and at the Universidade Federal de Goiás Teaching Hospital, two reference centers for cancer treatment in the city of Goiânia. The medical records of patients with a diagnosis of metastatic disease were then reviewed and constituted the subsample of the population-based registry.

Cases of breast carcinoma in situ were excluded from the study, as were those without histological confirmation and cases in which diagnosis had only been recorded on the death certificate.

Variables selected for analysis

The demographic variables *age at diagnosis*, *age at menarche*, *family history of breast or ovarian cancer*, and *type of access to treatment* (public or private healthcare system) were retrieved from the medical records at the city's treatment centers.

The site and morphology of the tumor were coded in accordance with the International Classification of Diseases for Oncology, third edition (ICD-O-3). The cases included the morphological codes 8500/3, 8520/3, and 8521/3[20,21]. Sarcomas (8800/3) and other morphological types (anaplastic carcinoma and spindle-cell neoplasms) were classified as "other subtypes".

Histological grade was classified as G1, G2, or G3 according to the Bloom-Richardson grading system[22]. Locoregional staging was classified according to the tumor-node-metastasis (TNM) staging system, as defined in the American Joint Committee on Cancer's (AJCC) cancer staging manual, 8th edition[23,24].

Immunohistochemical estrogen and progesterone receptor expression was considered positive or negative according to the report from each laboratory. Human Epidermal growth factor Receptor-type 2 (HER2) expression was considered positive when reported as three crosses (3+) or when amplification was confirmed by immunofluorescence. Tumor phenotype classification was determined following the recommendations of the 2017 St. Gallen International Expert Consensus Conference[25].

Data on the site of metastasis were collected from the medical records at the two participating institutes. The site of metastatic lesions and the presence of associated clinical symptoms were evaluated, as well as whether aspiration and/or biopsy of the lesions had been performed. Treatment data were collected on the type of surgery performed for the primary tumor and/or for metastasis and any systemic treatments given.

Statistical analysis

The database was constructed using Microsoft Office Excel®, version 2003 (Microsoft Corporation, Redmond, WA, USA). The frequency of all the variables was established and a central tendency analysis was conducted to determine the mean age.

The crude incidence rate was defined as the ratio between the number of new cases of MBC diagnosed annually and the number of women exposed to the risk of developing the disease at the mean point of the respective year, with the result being expressed as a coefficient per 100,000 women[26]. The number of women exposed to the risk of cancer was defined as the female population of the city of Goiânia in the respective year according to the census population count for the years 2000 and 2010 and the intercensal population counts for the other years[27].

The standardized incidence rate was calculated based on Segi's world standard population and expressed per 100,000 inhabitants[28,29]. Due to the rarity of this event, the rates were smoothed to a three-year mean.

The temporal analysis of the clinical and therapeutic characteristics was performed by comparing the 1995–2003 period with the 2004–2011 period. Statistical analysis was performed using MedCalc for Windows (MedCalc Software, Ostend, Belgium), version 18.11. The chi-square test was used to compare two proportions (of independent samples), expressed as a percentage. P-values <0.05 were considered statistically significant.

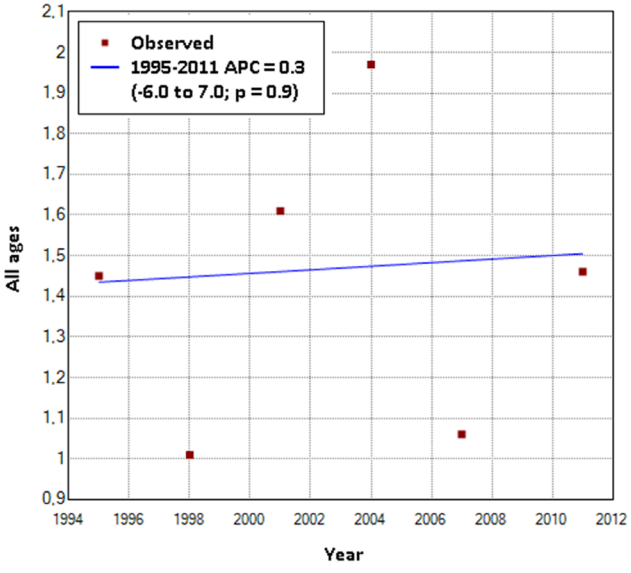
The annual percent change (APC) and the average APC (AAPC) in the rate of MBC were calculated for the total sample and according to the age group (<50, 50–69, and ≥70 years), with age being the only variable for which data were available in all cases. The relevant 95% confidence intervals (95%CI) were calculated, with p-values <0.05 being considered statistically significant. The Poisson regression model was used for these calculations and the software program used was JoinPoint Regression, version 4.7.0.0, of February 2019 (National Cancer Institute, USA)[30].

Ethical aspects

The Internal Review Board at the Araújo Jorge Hospital of the Goiás Association for the Combat of Cancer approved the study protocol under CAAE No. 61987716.0.0000.0031. All the recommendations for good clinical practice outlined in the Brazilian National Health Council's resolution 466/2012 and the Helsinki Declaration were followed.

RESULTS

Between 1995 and 2011, 5,289 cases of breast cancer were registered in Goiânia and 277 (5.2%) were diagnosed as de novo metastatic disease. The adjusted incidence rate was 8.9/100,000 in 1995 and 6.04/100,000 in 2011 (Figure 1). There was no difference in the proportion of metastatic cases between the 1995–2003 period (n=129; 46.6%) and the 2004–2011 period (n=148; 53.4%; p=0.2) or in the trend during the periods (APC: -1.1; -5.2–3.2; p=0.06).



*Average APC (AAPC) 0.3; -6.0 to 7.0; p=0.9.

Figure 1. Trend in the standardized incidence rate of metastatic breast cancer in the city of Goiânia, Brazil, between 1995 and 2011, adjusted for age.

In the subsample of 156 cases identified in the two treatment centers, the majority (70.3%) were patients receiving care in the public healthcare system. The mean age was 54.7±14.5 years (mean±standard deviation [SD]). Eighty-eight women (88/129; 68.2%) had a single metastatic lesion and 65 (65/129; 50.4%) had a visceral disease at diagnosis (Table 1).

Ten patients were subjected to resection of the metastatic lesion (10/108; 9.2%). Four of these patients had lesions in the brain and three in distant lymph nodes (mediastinal, cervical, and contralateral axillary lymph nodes). A further twenty women were subjected to percutaneous biopsy (20/108; 18.5%) for confirmation by cytology or histology. Of the 50 women subjected to breast surgery, 40 underwent radical mastectomy and 10 conservative breast surgery.

Endocrine therapy was prescribed as first-line treatment for 14.0% (6/43) of the patients with hormone receptor-positive cancer, and for 48.5% (17/35) of the patients, as second-line therapy. Of the 24 women with HER2-positive breast cancer, three were given trastuzumab as first-line treatment (3/24; 12.5%) and two as second-line treatment for the metastatic disease (Tables 2 and 3).

There was no change in the distribution pattern of cases of MBC in the time periods analyzed here concerning histological grade, locoregional staging, the presence of symptoms at diagnosis, or the type of oncological treatment given. Between 2004 and 2011, there was a decrease in the number of luminal-HER2-positive cases and a reduction in the percentage of patients using the private healthcare system compared to the 1995-2003 period (Table 4). There was a reduction in the APC in women over 70 years of age (APC: -4.8; -9.3–-0.1; p<0.001); however, there was no statistically significant difference for any of the other age groups. There were no statistically significant differences in the AAPC as a function of the age group (Figure 2).

DISCUSSION

This population-based study describes the profile of MBC in the city of Goiânia, Brazil. Around 5.0% of breast cancer cases were metastatic at diagnosis, a finding that is similar to that of other hospital-based studies conducted both in Brazil[3,31] and in countries with population-based mammography screening, including the United States, Denmark, and the Netherlands[2,6,7,32]. Therefore, genetic factors or exposure to risks may have made these women more susceptible to diagnosis at an advanced stage, not being detected through the screening policy adopted in Brazil[5]. Nevertheless, it was impossible to establish whether these women had undergone mammography screening. Likewise,

Table 1. Sociodemographic and clinical characteristics of 277 women with metastatic breast cancer between 1995 and 2011.

Characteristics	Cases (n)	%	Characteristics	Cases (n)	%
Age at diagnosis (years)			Total n*	89	100.0
≤49	103	37.2	Estrogen receptor status		
50–59	75	27.1	Positive	53	67.1
≥60	99	35.7	Negative	26	32.9
Total n*	277	100.0	Total n*	79	100.0
Skin color/ethnicity			Progesterone receptor status		
White	98	55.4	Positive	42	55.3
Brown	69	39.0	Negative	34	44.7
Black	5	2.8	Total n*	76	100.0
Others	5	2.8	C-erb-B status		
Total n*	177	100.0	Positive	24	33.8
Age at menarche (years)			Negative	47	66.2
<11	10	21.8	Total n*	71	100.0
12–13	18	39.1	Tumor phenotype		
>13	18	39.1	Luminal	34	47.9
Total n*	46	100.0	Luminal-HER2	16	22.5
Family history			Pure HER2	8	11.3
Breast cancer, first-degree relatives	9	13.7	Triple-negative	13	18.3
Breast cancer, second-degree relatives	6	9.1	Total n*	71	100.0
Ovarian cancer, first-degree relatives	3	4.5	Staging (T)		
None	48	72.7	T0	3	2.3
Total n*	66	100.0	T1	12	9.3
Presence of symptoms			T2	22	17.1
Yes	103	81.8	T3	25	19.4
No	23	18.2	T4	67	51.9
Total n*	126	100.0	Total n*	129	100.0
Histological type			Staging (N)		
Carcinoma, not otherwise specified	19	14.0	N0	31	25.2
Ductal carcinoma	107	78.6	N1	40	32.5
Lobular carcinoma	6	4.4	N2	37	30.1
Sarcoma and others	4	3.0	N3	15	12.2
Total n*	136	100.0	Total n*	123	100.0
Histological grade			Type of healthcare		
G1	11	12.3	Public	90	70.3
G2	51	57.3	Private	38	29.7
G3	27	30.4	Total n*	128	100.0

*The number of individuals for whom data were available.

a more in-depth analysis of the respective risk factors could not be performed.

Over the 17-year period analyzed (1995–2011), no trend was found towards any changes in the incidence of MBC. This finding showed that the opportunistic screening carried out in the city of Goiânia has not been successful in reducing the incidence of advanced breast cancer. This fact is even more evident when comparing data with those of other Brazilian populations, for example, comparing data from the Goiânia population-based cancer registry with data from the city of Barretos and surrounding region where there is population-based mammography screening[33]. In the area covered by screening, there were significantly

Table 2. Anatomical site of metastasis and treatment given to women with metastatic breast cancer at diagnosis in Goiânia, Brazil (n=277).

	Cases (n)	%
Number of metastatic sites*		
1	88	68.2
2	31	24.0
≥3	10	7.8
Total n†	129	100.0
Site of metastasis		
Bone	36	27.9
Visceral	41	31.8
Visceral+bone	24	18.6
Central nervous system	11	8.5
Skin, subcutaneous tissue cells or distant lymph nodes	17	13.2
Total n†	129	100.0
First-line systemic treatment		
Chemotherapy (≥2 drugs)	94	86.2
Chemotherapy (1 drug)	6	5.5
Endocrine therapy	9	8.3
Total n†	109	100.0
Surgery for resection of the primary tumor		
Yes	50	40.6
No	73	59.4
Total n†	123	100.0
Surgery for resection of metastases		
Yes	10	9.2
No	98	90.8
Total n†	108	100.0

*At the time of initial diagnosis; †Number of individuals for whom data were available.

fewer cases detected at stage III compared to Goiânia. However, for cases with a metastatic disease already at diagnosis, the incidence was similar[33].

The subsample analyzed revealed a predominance of large tumors at diagnosis, with skin involvement and clinically compromised lymph nodes, reflecting difficulty to access disease diagnosis. This fact could probably be explained by the predominance of users of the public healthcare system in this study, since there are limitations to access within this system that are not found in the private healthcare system[17,34,35]. Nevertheless, the other clinical and demographic characteristics of the sample analyzed here were similar to those of the population with non-metastatic disease[36].

Palliative endocrine therapy is the systemic treatment of choice for women with metastatic disease and hormone-positive tumors in the absence of visceral crisis[8,15,25]. In itself, this is a more accessible and less expensive treatment than chemotherapy, a fact that is particularly important bearing in mind the progressive increase in the costs of cancer treatment[9]. In addition, endocrine therapy is associated with lower rates of adverse events and better quality of life, with no negative effect on progression-free survival or overall survival[37,38]. Therefore, the underutilization of endocrine therapy found in this study may reflect an inappropriate approach to treatment according to current recommendations and even according to the standard clinical practice within the time period studied[8,15,37].

In the subgroup of women with HER2-positive tumors, the small number of patients who received anti-HER2 therapy is noteworthy. This finding could be explained by the predominance of patients receiving care within the public healthcare system where trastuzumab only became available for the treatment of metastatic HER2-positive breast cancer in 2017[34,39]. In years to come, with increased access to targeted therapy, a reduction should be seen in the rates of chemotherapy alone, with the introduction of CDK 4/6 inhibitors and anti-HER therapy[8,14].

Data on the extent and the site of the metastatic lesions are crucial for planning treatment and evaluating individual prognosis[12,40]. In this study, despite the predominance of lesions at a single anatomical site, there was a high prevalence of visceral lesions and symptomatic disease at diagnosis. These data may partially explain the choice of chemotherapy as a first-line systemic treatment, even in cases of luminal tumors[8,25].

Subjecting women with metastatic disease to breast surgery remains controversial and is usually reserved for selected cases[8,41,42]. However, scientific evidence at the time evaluated by this study was limited to retrospective, non-controlled studies showing better overall survival in patients subjected to breast surgery[41]. In this study, around 40% of the patients had been subjected to some type of breast surgery, a finding that could also be explained by the better local control that was achieved[42]. A population-based study conducted in the United States also found a similar rate of breast surgery in this population[43]. However, in the context of public health in low- and medium-income countries, the possibility of inadequate systemic staging at diagnosis and confirmation of the metastatic disease in the first months following breast surgery deserves special emphasis[8,35,44].

The temporal analysis performed in this study failed to reveal any significant changes in the clinical characteristics or in the treatment provided despite the advances in diagnosis and treatment that have occurred in recent years[8]. This fact is probably due to the predominance of users of the public healthcare system in this study population. Nevertheless, a hospital-based study conducted in São Paulo included metastatic patients who received similar cancer treatment irrespective of whether they were clients of the private or public healthcare sector. In that series too, no statistically significant changes were found in the

Table 3. Description of the systemic treatment given as first- or second-line treatment according to the immunohistochemical characterization of tumor subtype.

	Systemic treatment	Anthracyclines	Taxanes	Tamoxifen	Aromatase inhibitors
	Tumor subtype	n (%)	n (%)	n (%)	n (%)
First-line	HR(+)/HER2(-) (n=34)*	25 (73.5)	16 (47.0)	3 (8.8)	3 (8.8)
	HR(+)/HER2(+) (n=9)*	7 (77.8)	4 (44.4)	-	1 (11.1)
	HR(-)/HER2(+) (n=7)*	7 (100.0)	4 (57.1)	-	-
	HR(-)/HER2(-) (n=11)*	10 (90.9)	7 (63.6)	-	-
2nd line	HR(+)/HER2(-) (n=29)*	3 (10.3)	1 (3.4)	12 (41.4)	5 (17.2)
	HR(+)/HER2(+) (n=6)*	1 (16.6)	1 (16.6)	2 (33.3)	-
	HR(-)/HER2(+) (n=4)*	-	-	-	-
	HR(-)/HER2(-) (n=5)*	-	-	-	-

	CMF	Platinum-based	Capecitabine	Gemcitabine	Vinorelbine	Trastuzumab
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
First-line	1 (3.0)	-	-			-
	1 (11.1)	-	-			1 (11.1)
	-	1 (14.3)	-			2 (28.5)
	1 (9.1)	-	-			-
2nd line	-	4 (13.8)	3 (10.3)	4 (13.8)	1 (3.4)	-
	-	1 (16.6)	1 (16.6)	1 (16.6)	-	1 (16.6)
	-	2 (50.0)	1 (25.0)	2 (50.0)	1 (25.0)	1 (25.0)
	-	4 (80.0)	1 (20.0)	3 (60.0)	1 (20.0)	-

*Total number of individuals for whom data were available for the respective line of systemic treatment. Each patient could have received more than one drug per line of treatment. CMF: Cyclophosphamide, methotrexate, 5-fluorouracil; HR: hormone receptor.

frequency distribution of the treatments carried out between 2000 and 2012[45]. Taken together, these data may reflect the progress of breast cancer treatment in the period, with a qualitative improvement in treatments already in use rather than the implementation of new treatment modalities.

Over the 17 years of analysis, a statistically significant alteration was found in only two variables. The reduction in the luminal-HER2 cases identified in immunohistochemistry is due to the small sample size. On the other hand, the increase in the proportion of public healthcare system users probably reflects the local socio-economic conditions[17,35]. Nevertheless, despite the difficulties of the Brazilian healthcare model[10,16,34], the data found in this series are in agreement with international population samples and reinforce the concept of cancer treatment globalization[11-14,16].

Limitations of this study include data missing from the population-based cancer registry database and from the medical records. These limitations are inherent to retrospective studies and do not affect the credibility or relevance of the results obtained[46]. The intersection of the population-based data made it possible to increase the robustness of this study by adding information on clinical, pathological, and treatment variables in patients with MBC. In theory, this real-world study, conducted in a city located in Brazil's Midwest, may reflect several other populations in low- and middle-income countries.

CONCLUSIONS

Around 5% of the women with breast cancer in Goiânia between 1995 and 2011 had MBC, of which the most common subtype was luminal breast cancer. There was no change in the incidence trends over the 17 years of the study. Almost 90% of the patients received chemotherapy as first-line treatment and, of the patients with hormone receptor-positive tumors, only 14% received endocrine therapy as first-line treatment. The use of anti-HER2 treatment was also remarkably low. Therefore, further studies are required to identify the biomarkers that could anticipate the diagnosis of

Table 4. Temporal distribution of clinical and therapeutic variables in the 1995–2003 and 2004–2011 periods in women with metastatic breast cancer at diagnosis in the city of Goiânia, Brazil.

	1995–2003 (n=129)		2004–2011 (n=148)		Absolute difference (%)	95%CI (%)	p-value†
	Cases (n)	%	Cases (n)	%			
Age at diagnosis (years)							
≤49	50	38.8	53	35.8	3.0	-8.2 to 14.2	0.6
50–59	37	28.7	38	25.7	3.0	-7.4 to 13.4	0.5
≥60	42	32.5	57	38.5	6.0	-5.3 to 16.9	0.2
Total n*	129	100.0	148	100.0			
Presence of symptoms							
Yes	40	75.5	63	86.3	10.8	-2.85 to 25.19	0.1
No	13	24.5	10	13.7	‡	‡	‡
Total n*	53	100.0	73	100.0			
Histological grade							
G1/G2	31	72.1	31	67.4	4.7	-14.18 to 22.94	0.6
G3	12	27.9	15	32.6	‡	‡	‡
Total n*	43	100.0	46	100.0			
Tumor phenotype							
Luminal	10	41.6	24	51.1	9.5	-14.41 to 31.45	0.4
Luminal-HER2	9	37.5	7	14.9	22.6	1.85 to 43.76	0.03
Pure HER2	2	8.4	6	12.7	4.3	-14.49 to 18.09	0.5
Triple-negative	3	12.5	10	21.3	8.8	-11.91 to 24.68	0.3
Total n*	24	100.0	47	100.0			
Staging (T)							
T0–2	19	31.7	18	26.1	5.6	-9.83 to 21	0.4
T3–4	41	68.3	51	73.9	‡	‡	‡
Total n*	60	100.0	69	100.0			
Staging (N)							
N0	19	32.8	12	18.5	14.3	-1.1 to 29.19	0.06
N1	19	32.8	21	32.3	0.5	-15.62 to 16.82	0.9
N2–3	20	34.4	32	49.2	14.8	-2.62 to 30.91	0.09
Total n*	58	100.0	65	100.0			
Access to treatment							
Public healthcare	32	60.4	58	77.3	16.9	0.82 to 32.54	0.04
Private healthcare	21	39.6	17	22.7	‡	‡	‡
Total n*	53	100.0	75	100.0			
First-line systemic treatment							
Chemotherapy (≥2 drugs)	41	89.1	53	84.2	4.9	-9.14 to 17.44	0.4
Chemotherapy (1 drug)	1	2.2	5	7.9	5.7	-4.51 to 15.2	0.1
Endocrine therapy	4	8.7	5	7.9	0.8	-9.91 to 13.26	0.8
Total n*	46	100.0	63	100.0			
Surgery for primary tumor							
Yes	22	44.0	28	38.3	5.7	-11.52 to 22.84	0.5
No	28	56.0	45	61.7	‡	‡	‡
Total n*	50	100.0	73	100.0			
Surgery for metastasis							
Yes	2	4.5	8	12.5	8.0	-4.17 to 18.78	0.1
No	42	95.5	56	87.5	‡	‡	‡
Total n*	44	100.0	64	100.0			

*Number of individuals for whom data were available for each variable. †Chi-square test. ‡For the dichotomous variables, the same proportion of difference and the same significance level values were maintained.

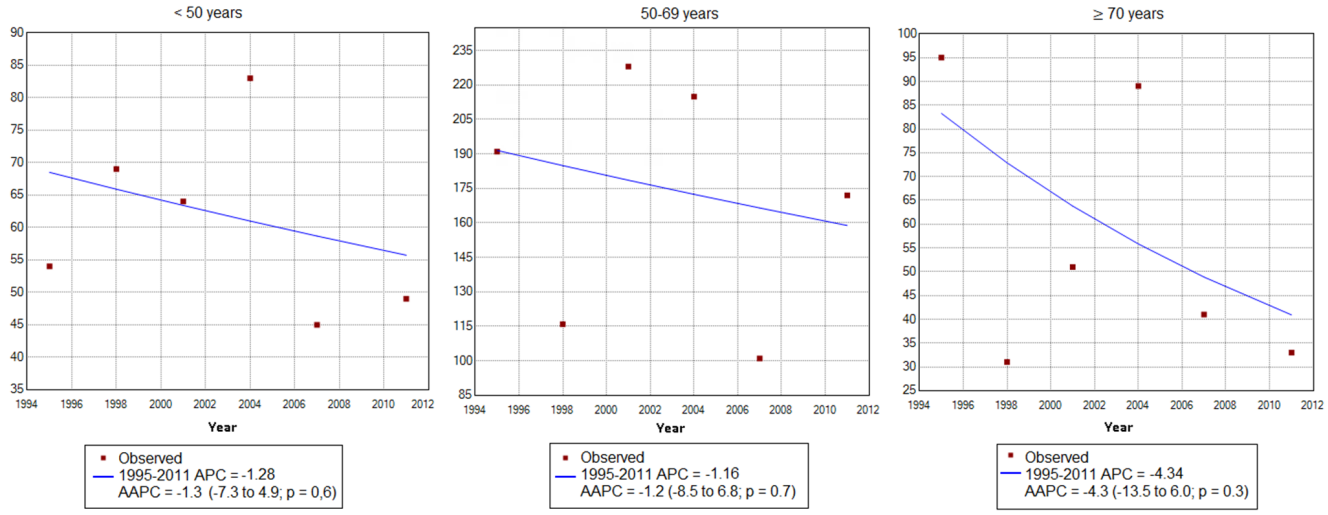


Figure 2. Trend in the standardized incidence rate of metastatic breast cancer in the city of Goiânia, Brazil, between 1995 and 2011, by age group.

breast cancer before it becomes metastatic. Finally, appropriate health policies need to be implemented to ensure the availability of new agents for use in systemic rescue therapy, including anti-HER2 agents and cyclin-dependent kinase inhibitors.

AUTHORS' CONTRIBUTION

LRS: Conceptualization, Data curation, Formal analysis, Resources, Writing – original draft, Writing – review & editing. RFJ: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. RDN: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. EM: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Visualization, Writing – review & editing. JCO: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. MPC: Conceptualization, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE
https://doi.org/10.29289/2594539420210066

Repercussions of the COVID-19 pandemic on breast cancer treatment in a referral hospital in Santos-SP, Brazil

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ABSTRACT

Objective: Considering that breast cancer has the fifth highest mortality rate in the world, this study aims to evaluate the repercussions of the COVID-19 pandemic on the treatment, both surgical and systemic, of patients with cancer in general and those with breast cancer at Hospital Guilherme Álvaro (Santos, Brazil), between March 1st, 2019 and February 28, 2021. **Methods**: For this purpose, data were collected from both the hospital's surgery record book and electronic medical records of patients who were followed up in the Mastology and Oncology sectors at Hospital Guilherme Álvaro. This information was tabulated, estimating the total number of surgeries, whether: benign elective surgeries, diagnostic surgeries, surgeries of cancer in general, surgeries exclusive to mastology, of cancer in mastology, benign surgery in mastology, and plastic reconstructive surgery. The percentage ratio between these numbers was calculated. **Results**: A 49% reduction in total surgeries was observed, comparing the period prior to the pandemic (2019–2020) with the pandemic period (2020–2021), with a decrease of 24.6% in the number of general cancer surgeries except for mastology, and 19.6% of surgeries exclusive to mastology. In other words, there was a total reduction of 22.9% in all oncological surgeries. Moreover, there was a decrease of 11.5% in the total number of patients treated with chemotherapy. In 2020, of the 214 new cases, 116 (54.2%) were mastology patients, being 45.8% of other oncology clinics. **Conclusion**: Thus, it is concluded that the reduction in the number of aesthetic, benign, and reconstructive surgeries was expected, as observed in the decrease in the number of chemotherapies, which could be due to a limitation on medical appointments. The number of diagnostic surgeries remained stable, which could lead to positive outcomes for oncology patients. It is not possible to predict the next repercussions of the COVID-19 pandemic on breast cancer treatment while the pandemic endures, requiring more studies on this topic.

KEYWORDS: COVID-19; breast neoplasms; neoadjuvant therapy.

INTRODUCTION

Breast cancer is the fifth with the highest mortality rate worldwide and has a high incidence among young women in Brazil[1,2]. Recently, it became the most diagnosed type of cancer, surpassing lung cancer[1]. Its early diagnosis, in addition to advances in treatment, has shown better results and greater survival for patients[3]. However, in December 2019, a new disease called COVID-19, caused by the SARS-CoV-2 virus, was detected in Wuhan, China. A pandemic was declared by the World Health Organization (WHO) in March 2020. Faced with this new situation, breast cancer screening and treatment were hampered[4,5].

Although breast surgery is of great importance in the treatment, as it aims to remove the entire tumor with free margins, neoadjuvant chemotherapy (NC) has gained prominence during the pandemic, and there is a decrease in the probability of recurrence and increase in the survival of patients who undergo this procedure[6,7]. The purpose of NC is to reduce mass in locally-advanced tumors and to allow the use of efficient surgical and radiotherapy treatments[7].

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Conflict of interests: nothing to declare. **Funding:** none.
Received on: 01/13/2022. **Accepted on:** 02/24/2022.

Until recently, the indication for NC was based on inoperable T3-T4/N2-N3 tumors (inflammatory breast cancer; inoperable tumor due to invasion of the skin or thoracic structures; clinically coalesced and/or fixed axillary lymph nodes; lymph node metastases beyond the axillary chain) or operable tumors in need of reduction to perform conservative surgery (tumor greater than 5 cm or between 2 and 5 cm with an unfavorable tumor/breast ratio for conservative surgery)[6,8,9].

However, after the beginning of the pandemic, the recommendation for breast cancer treatment has changed. For new cases diagnosed after this period, it has been recommended to start systemic treatment with neoadjuvant endocrine therapy or neoadjuvant chemotherapy with anti-HER2 blockade, if the disease was positive for HER2[10]. As HER2 and triple negative tumors are more aggressive molecular subtypes, there are discussions for starting the treatment with chemotherapy and target therapy (HER2 subtype) before surgery in tumors larger than 1 cm, whereas in tumors smaller than 1 cm, surgery should not be postponed[11]. In addition, this should be considered in three situations: if the disease progresses during NC; if it is a malignant phyllodes tumor; or breast sarcoma[10]. It should be noted that, according to a systematic literature review and meta-analysis published in July 2021, the ideal time to perform breast surgery after the completion of the NC is four to eight weeks[12].

Both the chemotherapy and radiotherapy used in the treatment and the cancer itself have immunosuppressive effects, making cancer patients vulnerable to infections[13]. Therefore, the recommendations for such patients also include limiting their exposure to SARS-CoV-2, encouraging telemedicine appointments whenever possible and restricting visits to wards with immunocompromised patients[4,13].

Another important measure implemented to contain the advance of the new coronavirus was to consider many of the breast cancer treatment surgeries as elective[8]. Nevertheless, the choice to postpone such therapy is only possible when the patient is not at risk of life, or when it is possible to use less invasive methods such as chemotherapy and radiotherapy[14]. Thus, as in other services, the Mastology Department of Hospital Guilherme Álvaro, located in Santos (state of São Paulo, Brazil), expanded the indications for neoadjuvant care, restricted surgeries, and maintained outpatient care only for emergencies[15].

Even though it is proven that these noninvasive methods can delay definitive surgical treatment for a period of time, the duration of restrictive measures during the pandemic remains indetermined[14]. The impact of postponing tumor resection and the administration of invasive therapies for an extended period of time on the outcome and survival of these patients is still uncertain[13]. Furthermore, in this context, the impact that cancer illness has on the physical and mental health of patients can have psychological effects such as anxiety, depression, anguish, and acute stress[16]. This situation, in addition to the fear of infection with the new coronavirus or the waste of health resources, would favor the reduction of diagnoses and the quality of cancer treatment[16].

Hence, this study aims to assess the repercussion of the COVID-19 pandemic on the number of elective and oncological surgeries and chemotherapy treatments performed at Hospital Guilherme Álvaro, a major oncology reference center in Baixada Santista, state of São Paulo, Brazil.

METHODS

This is a cross-sectional and retrospective study, based on surgeries performed at Hospital Guilherme Álvaro, a public tertiary hospital located in the city of Santos, Brazil, from March 1st, 2019 to February 28, 2021. Data were obtained from the hospital's surgery record book, whose content was based on information such as date of surgery, patient's name, age, anesthetic risk, underlying pathology, surgical procedure, type of anesthesia, name of anesthesiologist, name of surgery resident, name of surgeon, time of the surgery, and destination of the patient after the surgical procedure; and electronic medical records of patients who were followed up in the Mastology and Oncology Departments of the institution.

These data were transcribed into a table on the computer, using the Microsoft Excel Office 2016 program, and the statistical analysis was later performed in the same program.

The analyzed variables were: benign elective surgeries, diagnostic surgeries, general cancer surgeries, and surgeries exclusive to mastology. In the latter group, it was observed which surgeries were related to breast cancer and whether adjuvant or neoadjuvant chemotherapy were administered.

Among the inclusion criteria, it is worth highlighting patients treated by the mastology team during the period stipulated by the research; patients treated by the surgical team of Hospital Guilherme Álvaro during the same period; and patients with breast diseases treated by the Oncology Clinics of *Rede Hebe Camargo de Combate ao Câncer* [Hebe Camargo Network for Combating Cancer], at Hospital Guilherme Álvaro. Patients whose data in the medical records were incomplete for the study, or patients treated outside the stipulated period, were not evaluated.

Data were monthly tabulated, estimating the total number of surgeries, as well as how many of them were benign, diagnostic, of cancer in general, exclusive to mastology, of cancer in mastology, benign surgeries in mastology, and plastic reconstructive. In addition, it was verified how many patients underwent chemotherapy, considering the patients who were already being treated prior to the pandemic and the new cases that emerged during that period. The percentage ratio between these numbers was estimated and the Z-test, a null hypothesis statistical calculation based on the Z statistics, was applied, which establishes whether

the difference between the sample mean and that of the population is large enough to be statistically significant.

The pre-pandemic period was considered to be that between March 1st, 2019 and February 28, 2020; and the pandemic period, as that between March 1st, 2020 and February 28, 2021.

This study was submitted and approved by the Research Ethics Committee of Hospital Guilherme Álvaro and Fundação Lusíada (UNILUS), approved by Plataforma Brasil (Certificate of Presentation for Ethical Consideration — CAAE: 51960121.6.0000.5436), and complied with the code of ethics of the 1964 Declaration of Helsinki and all its subsequent updates. Furthermore, the study has own funding and the authors have no conflicts of interest to declare.

RESULTS

After data collection, tables were monthly compiled to obtain the results. During the analyzed period, from March 1st, 2019 to February 28, 2020, 3,118 general surgeries were performed; and from March 1st, 2020 to February 28, 2021, 1,591 general surgeries, totaling a sample of 4,709 (Table 1).

By analyzing the data on general surgery, an association with statistical significance can be observed in the number of surgeries performed for benign pathologies, cancer in general, and plastic reconstructive procedures when comparing the pre-pandemic period with the pandemic period ($p<0.01$). Meanwhile, with regard to surgeries performed by the mastology sector, there was an association with statistical significance for surgeries performed for breast cancer and breast reconstructions when correlating the pre-pandemic and the pandemic periods ($p<0.01$) (Table 1).

According to data obtained from the Hebe Camargo Network, the number of cases undergoing treatment and new cases of chemotherapy, before and during the pandemic, can be verified. However, it was not possible to establish an association with statistical significance between the obtained results (Table 2).

DISCUSSION

After the beginning of the COVID-19 pandemic, the recommendation for breast cancer treatment has changed. The new indication is based on initiating neoadjuvant systemic or endocrine therapy whenever possible, in addition to having medical appointments via telemedicine, thus restricting visits to wards with immunocompromised patients. Elective surgical treatment would only be indicated again if there was a decrease in infection rates for at least two consecutive weeks in the hospital region[17]. A problem faced by the patients treated at Hospital Guilherme Álvaro was the lack of structure for some of these changes such as the impossibility of arranging medical appointments via telemedicine.

Thus, a 49% reduction in total surgeries at the hospital was observed when comparing the pre-pandemic period (2019–2020) with the pandemic period (2020–2021), with a 24.6% drop in the number of oncological surgeries except for mastology and 19.6% in the number of oncological surgeries in mastology. Therefore, there was a total reduction of 22.9% in all oncological surgeries. Likewise, a study conducted in England also observed a 16.4% decrease in the number of patients receiving

Table 1. Total number of general and mastology surgeries in periods prior to and during the pandemic.

	Pre-pandemic	During the pandemic	Z-test (p-value)	Difference between proportions	Confidence Interval	
	Surgery of cancer in general				-95%	+95%
Total surgeries	3,118	1,591				
Benign	2,471 (79.25%)	1,143 (71.84%)	<0.01	7.41%	4.90	10.00
General diagnostic	131 (4.20%)	93 (5.85%)	0.01	-1.64%	-2.90	-0.40
Cancer in general	272 (8.72%)	205 (12.88%)	<0.01	-4.16%	-6.00	-2.30
Plastic reconstructive	24 (0.77%)	0 (0.00%)	<0.01	0.77%	0.30	1.20
	Mastology					
Cancer	138 (4.43%)	113 (7.10%)	<0.01	-2.68%	-4.00	-1.30
Benign	19 (0.61%)	4 (0.25%)	0.09	0.36%	-0.10	0.80
Diagnostic	35 (1.12%)	28 (1.76%)	0.07	-0.64%	-1.30	0.10
Reconstructive	19 (0.61%)	1 (0.06%)	<0.01	0.55%	0.20	0.90
Cancer + immediate reconstructive	5 (0.16%)	3 (0.19%)	0.8241	-0.03%	-0.30	0.20
Non-oncological aesthetic	4 (0.13%)	1 (0.06%)	0.5143	0.07%	-0.10	0.30

Source: Prepared by the authors.

Table 2. Total number of chemotherapies in periods prior to and during the pandemic.

	Pre-pandemic	During the pandemic	Z-test (p-value)	Difference between proportions	Confidence Interval	
	Chemotherapy				-95%	+95%
Undergoing treatment	3,719 (94.1%)	3,283 (94%)	0.8555	0.10%	-0.98	1.18
New cases	233 (5.9%)	214 (6%)	0.8555	-0.10%	-0.98	1.18

Source: Prepared by the authors.

treatment in the first half of 2020 after breast cancer diagnosis compared with 2019, and the authors expected an even greater reduction[18]. This scenario had repercussions on the treatment of cancer patients during the pandemic, mainly because cancer is a progressive chronic disease and, in its initial phase, it can be controlled or even cured by surgical treatment[17].

When analyzing the surgeries performed by the mastology team of Hospital Guilherme Álvaro, there was a decrease in their absolute number during the pandemic period (31.8%). However, if only oncological surgeries are considered, there is an increase of 2.67% ($p<0.01$). This is probably due to the fact that surgeries performed for aesthetic and benign purposes are not being prioritized during the pandemic period, after considering their risks and benefits[4].

Another relevant finding was the sharp decrease of 94.7% of reconstructive surgeries in the 2020–2021 period compared with 2019–2020, a decrease proportional to the number of total surgeries, 0.55% ($p<0.01$). As in Brazil, Walter et al. found, in a study conducted in the United States of America, that 19% of physicians reported the suspension of immediate breast reconstruction surgeries during the pandemic at their institutions[19]. This situation reflects the recommendations of medical entities and societies, which indicate the careful selection of patients eligible for surgical treatment during this pandemic period[18].

Consequently, not performing this procedure can be harmful to patients, as it is proven that immediate reconstruction has benefits both in improving self-image and in the quality of life and mental health in the long term. Another advantage would be not to subject the patient to more than one procedure, given the anesthetic risks inherent in the surgical process itself[20,21].

Furthermore, in a research conducted in Londrina (state of Paraná, Brazil), the authors observed that women diagnosed during the pandemic had lower emotional and physical scores when compared with previously diagnosed patients[22]. We must also consider the effects of the psychological factor on those who have had treatment suspended due to fear of the progression of the disease while awaiting a new date for their definitive treatment.

As the recommendation of health agencies was to perform neoadjuvant therapy to reduce tumor size and postpone surgery during the peak of the pandemic, an increase in the number of this procedure was expected[7,15]. Nevertheless, there was a decrease of 11.5% in the total number of patients treated with chemotherapy during the pandemic[13,15]. One factor that may have contributed to this finding is that, although the indications and protocols for NC are well-established in the literature, in Brazil there are some barriers, especially in the public sector, related to the delay in diagnosis, the difficulty of infrastructure, and the incorporation of medicines[23]. Nonetheless, as the data were not statistically significant ($p=0.85$), further studies are necessary for a reliable and accurate interpretation.

In 2020, of the 214 new cases, 116 (54.2%) were from mastology patients, whereas 45.8% were from other oncology clinics. This predominance of new mastology cases in the chemotherapy sector could constitute a good prognostic factor, considering that it would reduce the likelihood of recurrence of the disease and increase survival[7]. One of the limitations found for the analysis of this information was the fact that the Instituto Hebe Camargo did not divide chemotherapy data by sector, which began to be done in 2020. Thus, it became difficult to compare the number of breast cancer chemotherapies from the periods prior to and during the pandemic. In addition, medical records were unavailable and could not be computed.

In comparison, a study conducted at Hospital Central da Aeronáutica in Rio de Janeiro (state of Rio de Janeiro, Brazil) evaluated surgeries in mastology during the pandemic period compared with the pre-pandemic period. The authors verified a decrease in the number of surgeries in mastology (28.6%) and an increase in the indications for neoadjuvant care (133%) in the same period[15,24]. These results can be compared with our findings, as both studies showed a total decrease in the number of surgical interventions. While in the present study it was not possible to obtain statistically significant results with regard to neoadjuvant chemotherapy, the research carried out in Rio de Janeiro reached a result that confirms the hypothesis of a possible increase in the number of NC[15,24].

In view of these results, we can assess that the reduction in the number of aesthetic, benign, and reconstructive (elective) surgeries was expected due to the orientation to patients to avoid unnecessary visits to the hospital, once the risks and benefits were analyzed. Nevertheless, we also observed a decrease in the number of chemotherapies, which may be due to the limitation of outpatient care. Meanwhile, the number of diagnostic

surgeries remained stable and may bring positive results to the prognosis of cancer patients.

Another beneficial aspect is due to the fact that the Hospital Guilherme Álvaro maintained a number of breast cancer surgeries, during the pandemic period, similar to that of the analyzed pre-pandemic period. However, it is worth mentioning that at the end of March 2021 the elective surgeries at the institution were suspended, and only those deemed urgent and emergency cases were performed, in exceptional situations. This change can be explained by the fact that, so far, March was the month with the worst repercussions of the pandemic in the State of São Paulo, with a mortality of 9.1 thousand people until March 23[25].

The psychological factor of patients who had treatment suspended and were unable to undergo reconstructive surgery must also be considered, as they remain anxious and afraid of the disease while waiting for a new date for their definitive treatment. Therefore, even though it is proven that these non-invasive methods can delay definitive surgical treatment for a period of time, the duration of restrictive measures during the pandemic remains indetermined[14]. The impact of postponing tumor resection and the administration of invasive therapies over an extended period of time on the outcome and survival of these patients is still uncertain, in such a way that further studies on this topic are necessary[13].

CONCLUSIONS

We verified a reduction in the number of aesthetic, benign, and reconstructive surgeries, as well as in the number of chemotherapies, which may be due to the limitation of outpatient care. Moreover, the number of diagnostic surgeries remained stable and may bring positive results to the prognosis of cancer patients. As long as the pandemic continues, it will not be possible to fully predict the next repercussions of COVID-19 on the treatment of breast cancer, which indicates the need for more long-term research on this topic.

ACKNOWLEDGEMENTS

The authors would like to thank all the professionals who worked on the COVID-19 front line, directly or indirectly.

AUTHORS' CONTRIBUTION

MAK, EBLS, TCM, RCTR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing — original draft, Writing — review & editing. MFHP: Data curation, Formal analysis, Investigation, Supervision, Writing — review & editing.

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REVIEW ARTICLE
https://doi.org/10.29289/2594539420210051

Integrative review on breast cancer screening in the transgender population: what do we know?

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ABSTRACT

The lack of formal breast cancer screening guidelines for the transgender population and the unpreparedness of health professionals to provide adequate health care to this population are described in the literature. The objective of this integrative review was to present the proposals for breast cancer screening in the transgender population, based on the literature, being searched in the Medline, PubMed, SciELO, and Lilacs databases. The articles that addressed breast cancer screening in the female and/or male transgender population were selected, in addition to the associated studies with the use of hormone therapy and breast cancer in transgender people, using the terms such as "transgender people," "early cancer diagnosis," and "breast." Of the 38 articles selected, 24 address recommendations for breast cancer screening in the female and/or male transgender population. There is limited population-based information on mammography screening in transgender people, which ultimately affects the analysis of cancer incidence in this population. The literature supports screening in the male transgender profile (similar to the female cisgender). In transgender females, recommendations are implemented based on expert's opinions, such as mammographic screening after 5 years of hormone use. More studies on this subject are needed.

KEYWORDS: transgender persons; early detection of cancer; breast.

INTRODUCTION

Breast cancer is recognized as the most common malignant disease in the female population, representing 13% of all cancer deaths in women worldwide[1-3].

Mammography is still the best method for breast cancer screening and has been proven to reduce mortality due to this type of cancer[1-3]. In Brazil, according to the Guidelines for the Early Detection of Breast Cancer, from the Ministry of Health, mammographic screening is recommended for women aged 50–69 years for a period of every 2 years. On the one hand the Brazilian Society of Mastology, the Brazilian College of Radiology, and the Brazilian Federation of Gynecology and Obstetrics recommend mammographic screening in women aged 40–74 years, annually, who are at usual risk[3].

Breast cancer affects not only women but also men in about 1% of cases[1,3,4]. As breast cancer in men is rare, there are no Brazilian guidelines for screening in men. Data from the American Society of Clinical Oncology suggest screening only in high-risk male patients, including the group of patients who have undergone breast cancer surgery and have proven genetic mutations[4].

However, it is noteworthy that despite the guidelines for breast cancer screening in cisgender women and in special situations in high-risk cisgender men, breast cancer can also affect transgender men and women[5-7].

Transgender is an umbrella term to describe a group of diverse individuals who cross or transcend culturally defined gender categories. This transgender population is composed of individuals who have gender incongruence with the biological sex assigned at birth and may be male, female, or non-binary (who are identified as neither male nor female sex, regardless of the biological sex at birth)[5,8,9].

Gender diversity is an area in a society marked by stigmas, causing failure in health care due to the lack of access and interest in the medical services for this population[5,8,9]. Briefly, the topic can be understood as having two main aspects:

1) the need to know the impact of hormonal treatments on the development of breast cancer; and
2) the need to educate these people as far as the early detection of this disease is concerned.

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Conflict of interests: nothing to declare. **Funding:** none.
Received on: 10/19/2021. **Accepted on:** 03/02/2022.

Thus, gender identification has peculiarities that deserve medical attention. This population lacks satisfactory studies and statistical significance regarding both the incidence of breast cancer and the possible ways of screening[8-11].

The main data recently published by Spizzirri et al.[5] point out the fact that Brazilian individuals with gender diversity represent approximately 2% of the country's adult population (almost 3 million people) and are homogeneously located throughout the country, reiterating the urgency of public health policies for these individuals in the five Brazilian subregions[5].

Given the relevance of the subject and the deficiency of research and studies on breast cancer screening in transgender people, the review aimed to present the main proposals for breast cancer screening in this population, described in the literature.

METHODS

This is an integrative review, in which the literature search was carried out in the search platforms PubMed, Medical Literature Analysis and Retrieval System Online (MEDLINE) databases, LILACS, and SciELO, using the following DECs and MeSH descriptors such as "transgender people," "early cancer diagnosis," and "breast."

The population included in this selection is female and/or male transgender people, in studies where the suggestion of different types of breast cancer screening was described (diagnostic intervention for breast cancer detection). As an outcome, it is expected that, in face of a standardized screening of this population, taking into account possible hormonal and surgical treatments, there will be an improvement in the quality of care provided to this population.

The extraction of data from the articles was carried out in a separate form, independently by two of the six authors. Duplicates (eight articles), abstracts, letters to journal editors, gray literature, and book chapters, as well as those that did not present in the title, abstract, or text the subject addressed in this review were excluded. It is worth mentioning that the studies repeated in the different databases were only excluded after being read in their entirety in order to avoid exclusion errors.

The main eligibility criteria articles were made available online in English, Portuguese, and Spanish, which addressed breast cancer screening in female and/or male transgender people. Articles that studied the encountered limitations by the transgender population in breast screening and studies that associated the use of hormone therapy and breast cancer in transgender people were also considered eligibility criteria.

For a better knowledge of important issues related to the transgender population, we complemented the review with the objective of identifying publications not captured by the electronic search, secondary references of articles, as well as additional searches of the literature on known and hypothesized cancer risk factors, the occurrence of cancer (incidence or prevalence) in a defined population of transgender persons, and the potential mechanisms by which exposure to these factors may affect cancer risk in this population.

Regarding the ethical issue of research by the National Health Council (Conselho Nacional de Saúde – CONEP), an evaluation was not necessary by an Ethical Research Committee (comitê de ética em pesquisa – CEP) according to Resolution No. 466/2012.

RESULTS

Of a total of the initially identified 76 articles, 38 were excluded. The flowchart about the selection of the articles is shown in Figure 1.

The articles that met all the selection criteria and made easier to answer the question of this review were selected (38 articles). Of this total, 24 were used to prepare the tables in this study. Of these 24 studies, 15 address the recommendation of screening in female and male transgender people, 8 articles address screening only in transgender males, and 1 article recommends screening only in transgender females.

The main results that were obtained by analyzing the articles from the bibliographic search and the proposed methodology are shown in Tables 1 and 2. The tables present the recommendations for breast cancer screening in the transgender population, which were divided into males[12-34] and females[12-16,18,20-23,27,28,31,33-35]. The tables also mention the references related to this review.

Regarding the proposed form of screening for the male transgender population, most articles suggest maintaining screening for transgender men with natal or residual breast tissue, in line with current guidelines for cisgender women[12-25]. Regarding the transgender female population, all studies indicate mammographic screening after 5 years of hormone (estrogen) use[12-16,18,20-22,27,28,31,33,35].

To finalize the screening proposals, Table 3 summarizes the publication of the joint national position of the Brazilian College of Radiology and Imaging Diagnosis, the Brazilian Society of Endocrinology and Metabology, and the Brazilian Society of Clinical Pathology, coordinated by Vieira and collaborators, national reference in breast cancer screening recommendations for the transgender population[6].

DISCUSSION

Transgender and nonbinary people have unique health care needs, which stems from gender-affirming hormone therapy and/or surgical interventions performed by this population[11,13,16,21,26,31]. The relationship between hormonal treatments in the sexual transition of female and male transgender people and the incidence of breast cancer is still discussed in the literature[13,16,26,31].

As the transgender community gains visibility and recognition, health disparities become more apparent[14,24,30]. Despite the efforts to become more inclusive, access to health care for this population is a challenge because it is a system built on a binary model. Another major challenge in caring for the

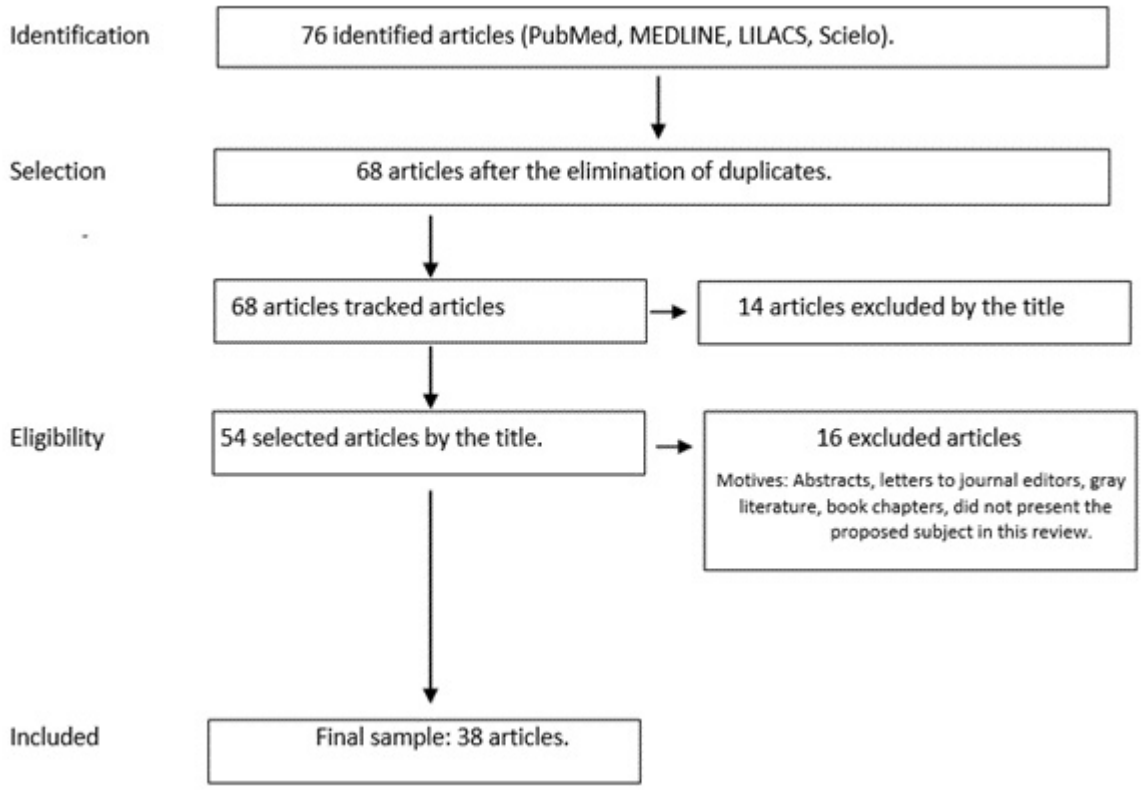

Figure 1. Flowchart of the selection of articles for the integrative review identification.

Table 1. Recommendations for breast cancer screening in the transgender male population found in the review.

Breast cancer screening recommendation in transgender males	Number (and respective reference) of articles found with this recommendation
Screening for transgender men with natal or residual breast tissue, according to current guidelines for cisgender women	15 articles[12-23,32-34]
Biennial mammography in transgender men who used hormone therapy aged 50–69 years	6 articles[24-29]
Annual MRI and mammography for transgender men aged 25–30 years. Consideration of prophylactic bilateral mastectomy for patients with BRCA2	1 article[30]
Annual mammogram for transgender men aged 40 years and above	1 article[31]

Table 2. Recommendations for breast cancer screening in the transgender female population found in the review.

Breast cancer screening recommendation in transgender females	Number (and respective reference) of articles found with this recommendation
Annual mammogram for transgender women with more than 5 years of hormone therapy, BMI>35 kg/m^2 or a family history of breast cancer Breast ultrasound and magnet resonance imaging or mammography with displacement mammography for those with breast prostheses	2 articles[13,34]
Mammography for transgender women undergoing hormone therapy for more than 5 years	3 articles[15,23,27]
Mammography every 2 years for transgender women aged 50 years and above who have been on hormone therapy for more than 5 years	5 articles[12,14,21,28,35]
Annual or biennial mammography for transgender women aged 50 years or above who are undergoing hormone therapy for more than 5 years and with additional risk factors: BMI>35 kg/m^2; family history of breast cancer	6 articles[16,18,20,22,31,33]

BMI: Body mass index.

Table 3. Recommendations for breast cancer screening in the male and female transgender population, according to the Joint Positioning of the Brazilian Society of Clinical Pathology, Brazilian Society of Endocrinology and Metabology, and Brazilian College of Radiology and Diagnostic Imaging.

Breast cancer screening recommendation in transgender males	Follows recommendations for cisgender women when bilateral mastectomy is not performed After bilateral mastectomy, mammographic screening is not recommended
Breast cancer screening recommendation in transgender females	Annual or biennial mammography, starting at age 50, in patients using hormone therapy for at least 5 years

transgender community is the scarcity of scientific and medical knowledge[16,28,30-33].

Most health professionals receive less or no training to provide clinically and culturally appropriate health care to these patient groups[7,14,34,35].

To date, no study is able to support a biological difference between transgender women and cisgender men, and between transgender men and cisgender women, since the incidence of breast cancer should be attributed to biological sex[27,29].

Transgender men or male transgender people

Hormone therapy for transition helps this population to modify some physical or visual characteristics to become more phenotypically like a man. In this scenario, with the use of testosterone, the suppression of the period of breast development (depending on the age at the beginning of hormone therapy), an increase in lean muscle mass, and a male-standard body development[13,16,20,36] are expected. Such characteristics, which are potentially affected, are noticed in the first month of testosterone use, as well as an increase in skin oiliness and libido around 3 months after the start of therapy (directly related to testosterone levels in the blood and inversely proportional to the luteinizing hormone levels)[13,16,20,36].

Concomitant with the external changes, histological evaluations of the endometrium of transgender men showed it to be atrophic and inactive, similar to the result observed in postmenopausal cisgender women without estrogen therapy. The menstrual period ceases approximately 2–6 months after initiation of testosterone hormone therapy. This process is faster when the therapy is used intramuscularly[13,16,20,36].

As in the female transgender population, the relationship between hormone therapy and the onset of breast cancer is not well established[14,20,36]. One of the postulated pathways is peripheral aromatization in the breast and adipose tissue, which converted dehydroepiandrosterone into estradiol and estrone, in postmenopausal women. Another hypothetical mechanism is the direct stimulation of androgen receptors. Normal breast cells as well as breast cancer cells express androgen receptors in large numbers[13,16]. Chotai and colleagues[20], in their study including 1,849 breast cancer patients, revealed that androgen receptor positivity was inversely related to clinical stage, histological tumor grade, and mitotic stage, suggesting an association of positivity between androgen receptors and less aggressive tumors[20].

Regarding the published studies of breast cancer in male transgender people, Blok and colleagues[29], with a sample of 1,229 men, identified four cases of invasive breast cancer, with a mean age of 46 years. Kiely[27], in a cohort of 5,135 transgender people using cross-hormonal therapy, described 10 case reports of breast cancer: 7 cases in transgender men, 2 in transgender women, and 1 in a nonbinary patient. From this perspective, there are few cases of breast cancer in transgender described, proving to be an uncommon disease, but not absent[24,28].

Gender-affirming mastectomy techniques vary significantly in relation to the amount of residual breast tissue, which has unknown implications for postoperative breast cancer incidence and the need for screening. Clinical examination remains the most commonly reported method of post-mastectomy malignancy detection[21,36]. For those who opted for a complete mastectomy, two authors recommend an annual clinical examination of the chest wall and armpits[21,27,28]. In the case of patients with a greater amount of residual breast tissue, they can be considered alternative imaging modalities, although the efficacy and cost-utility of these techniques have yet to be proven[21,27,28,36-38].

Preoperative patient counseling about the risk of breast cancer after masculinizing mastectomy, in addition to the unknown implications of residual breast tissue and long-term exposure to androgens, is essential[15,16,31,34].

There is still no established breast cancer screening guidelines for the transgender male population. However, some authors suggest screening based on the presence of breast tissue and risk factors[15,24,26,27,30,34,35].

According to the study by Pivo and colleagues[32], for transgender men, risk factors inherent to the female genotype should be considered, such as age, race, reproductive history, and family history of breast and ovarian cancers[13]. The study by Kiely[27] considered modifiable and non-modifiable factors for breast cancer risk, including family and personal history of breast and ovarian cancer, body mass index >35 kg/m^2 in menopausal women, early menarche, late menopause, and moderate or high alcohol consumption[27].

Based on the guidelines of the Brazilian Society of Clinical Pathology, the Brazilian Society of Endocrinology and Metabology, and the Brazilian College of Radiology and Diagnostic Imaging, breast cancer screening for transgender men is limited to the type of examination, age, and periodicity. Mammography is recommended biennially for transgender men who are not having

bilateral mastectomy and aged 50–69 years (as well as indicated for cisgender women at usual risk). For transgender men with bilateral mastectomy, screening is not indicated[6].

Transgender women or female transgender people

Transgender women undergo hormone therapy with estrogen in conjunction with antiandrogen drugs, such as spironolactone, to inhibit the action of testosterone. The effects of hormone therapy include breast growth, decreased facial hairiness, increased capillary volume, altered body fat distribution, and decreased testicle size. Approximately from 3 to 6 months, it is possible to visualize the beginning of these phenotypic changes; however, it is only 2 or 3 years of hormone therapy in which the maximum growth of the breasts is evidenced[26,31,33,34]. The degree of breast development appears to be independent of the type and dose of hormone treatment used. Once the maximum development of female characteristics is reached, it is necessary to reduce the offered hormonal dose[19,31].

After this process, the breast of the transgender woman has the same characteristics as the breast of a cisgender woman, with an exposure to develop benign tumors as well as malignant lesions. In addition, the potential increased risk of breast cancer with the use of exogenous hormones has not been completely elucidated, which makes it a challenge to assess the most appropriate screening recommendation in this population[22,31]. The potential risk goes beyond the increased risk of breast cancer in cisgender postmenopausal women undergoing estrogen hormone replacement therapy and is supported by the literature of case reports of breast cancer in transgender women[29,33,34].

Regarding the studies that present case reports of breast cancer cases in transgender females, Hartley and colleagues[31] described 22 transgender women with breast cancer after a literature review including 18 articles. The average age was 51.5 years, where 7 of them reported a first-degree relative with breast cancer and 1 had a confirmed mutation in the BRCA2 gene. Among the types of cancer, most were represented by adenocarcinomas (13 cases, 59.3%); BIA-ALCL (breast implant-associated anaplastic large-cell lymphoma) (3 cases, 13.6%); ductal carcinoma in situ (1 case, 4.5%); secretory carcinoma (1 case, 4.5%), malignant phyllode tumor (1 case, 4.5%); and Paget's carcinoma associated with invasive ductal carcinoma (1 case, 4.5%) and without histological classification (2 cases, 9.1%)[31].

Regarding the duration of hormone use, transgender women who presented with breast cancer used hormone therapy for an average of 18 years, with a predominance of luminal type tumors[12,22,29,33,34].

In the Dutch study by Blok and colleagues[29], in a group of 2,260 transgender women, 15 cases of invasive breast cancer were identified, with an average age of 52 years, which was comparatively lower than the average age (61 years) of involvement of Dutch cisgender women[29]. The incidence of breast cancer in these women was considered higher than the risk in Dutch cisgender men (0.4 expected cases), but below the expected benchmark for Dutch women (72 expected cases)[29].

The correlation of information obtained from the 15 articles selected in this review (Table 1) suggests mammographic screening in transgender women undergoing hormone therapy, after 5 years of use, although there is no consensus regarding its periodicity and age[12-16,18,20-23,27,28,31,33]. Screening mammography is not currently recommended for transgender women who are not using hormones, except in patients with other known risk factors, for example, those with Klinefelter syndrome[4,11].

According to the Brazilian societies, breast cancer screening in transgender women should be performed if they have been using hormone therapy for more than 5 years, with intervals of 1 or 2 years, starting at the age of 50 years. If hormone therapy is not used, screening is not indicated[6].

Some of these women opt for breast augmentation surgery with the use of breast implants. The surgery itself does not interfere with breast cancer risk, but it does affect the monitoring. In these cases, according to the studies by Schmidt and colleagues[21] and Hartley and colleagues[31], the use of ultrasound and magnetic resonance imaging of the breasts or mammography with the displacement of the breast implants is suggested for screening.

Awareness and education of these patients play an important role in shared decision-making, but more research is needed to define standards of care and breast cancer screening in this population[8,9,23].

CONCLUSIONS

Summarizing the main guidelines for breast cancer screening in transgender people, the literature describes the screening process for transgender men with natal or residual breast tissue, according to the current guidelines for cisgender women; and for the female transgender population, mammographic screening is indicated after 5 years of hormone use, but without consensus regarding the age of initiation and termination of this screening.

The severity and complexity of breast cancer, associated with the lack of robust data in the literature on the incidence and screening of this pathology in the group of transgender patients, indicate the need for further studies for a better understanding and applicability of the guidelines proposed in the literature.

AUTHORS' CONTRIBUTION

MJGC: Conceptualization, Data curation, Formal Analysis, Writing – original draft. RFAD: Conceptualization, Writing – review & editing. CBC: Conceptualization, Data curation, Writing – review & editing. BG: Visualization, Writing – original draft. IMLC: Methodology, Visualization. JMG: Writing – review & editing.

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REVIEW ARTICLE
https://doi.org/10.29289/259453942021056

Free nipple graft: current indications and applications of a centenary breast surgery technique – an integrative review

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ABSTRACT

Introduction: Free nipple graft is a mammaplasty technique first described about 100 years ago. Its indication, restricted to reduction mammoplasty earlier, has been expanding into areas in mastology intervention, such as transgender and oncological surgery. **Aim:** The aim of this study was to evaluate the efficacy and outcomes of the technique. **Methods:** Electronic literature search was conducted, using PubMed and LILACS databases. The search strategy consisted of the keywords, MeSH terms, and free text words and variants for the free nipple graft and its application in reduction and mammaplasty, transgender, and oncoplastic surgery. **Results:** A total of 397 articles were found and, after inclusion and exclusion criteria, 15 were selected. Their outcomes have been shown, despite lack of standardized scores, as well as clinical trials to postulate better scientific evidence on its use and indications, that the technique, analyzed in over 1290 patients, achieved high safety rates and reproducibility. **Conclusion:** Aesthetics and patients satisfaction were found positive, as recommended by the authors in different studies discussed in this article.

KEYWORDS: free nipple graft; mammaplasty; transgender; breast neoplasms

INTRODUCTION

The surgical technique of free nipple graft (FNG), or areola autograft (Figures 1-3), was first described about 100 years ago by the Hungarian-American doctor named Max Thorek in 1922[1,2]. Its application was originally meant exclusively to reduction mammaplasty, but later expanded its role into areas of mastology intervention, such as oncoplastic surgery[3] and chest adjustment surgery in transgender males[4,5]. Despite the wide utilization and usefulness of FNG in mastology, this technique lacks reviews and secondary studies in literature that evaluate the efficiency and outcomes of its use. Thus, the importance of a single technique as FNG on interventional surgical treatment of multiple disorders related to breast such mammary hypertrophy, gender dysphoria, and even in potential life-threatening diseases, like cancer, is an emerging topic in mastology studies.

Symptomatic mammary hypertrophy is a medical condition that directly affects the physical and emotional health of the patients. Headache, cervical and back pain, as well as self-esteem problems are frequently related to this condition[6]. Randomized clinical trials (RCTs) have shown that conservative therapy is ineffective in improving symptoms and that reduction

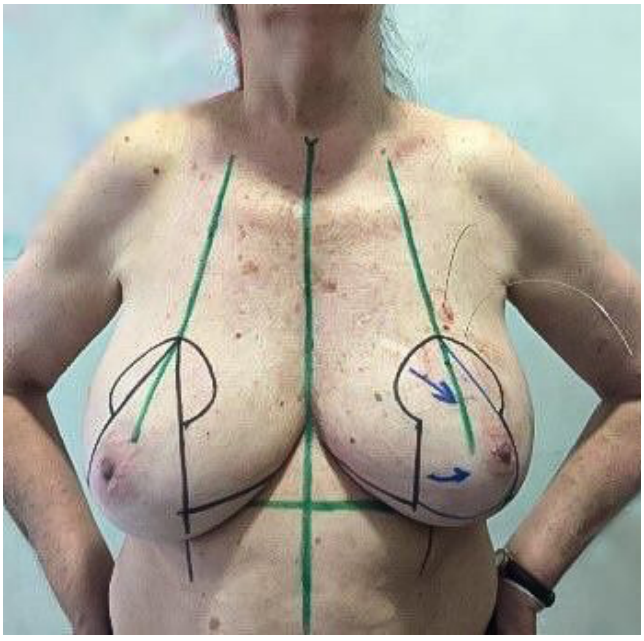

Figure 1. Preoperative marks that guide the surgical approach and incision sites. The upper blue arrow indicates the position where replacement of the nipple graft should be implanted.

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***Corresponding author:** rfapleon@hotmail.com
Conflict of interests: nothing to declare. **Funding:** none.
Received on: 11/03/2021. **Accepted on:** 02/21/2022.

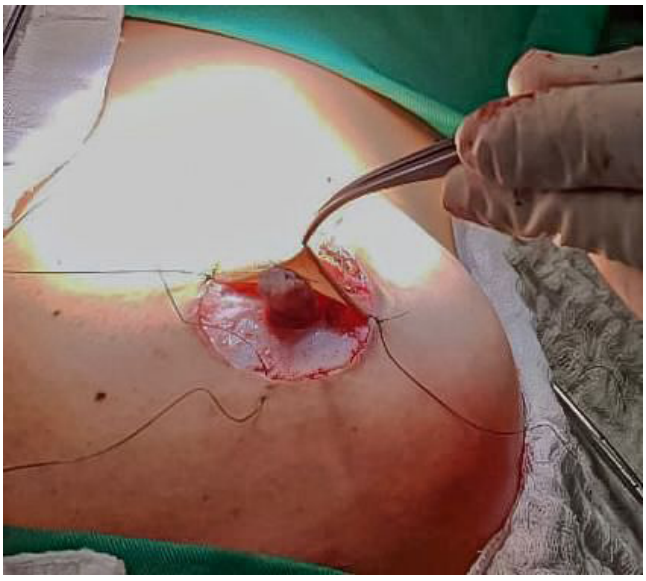

Figure 2. The nipple areolar complex is de-epithelized, as a graft, that must be preserved in a saline solution while breast parenchyma is resected.

Figure 3. Reinsertion of the areola graft in the breast resected with sutures.

mammaplasty surgery remains the only intervention with the ability to reduce the patients'[7] physical and psychological complaints, with approximately 129,000 surgeries being performed in 2017 with this purpose, according to the National Association of Plastic Surgeons[8].

In this scenario, the technique first described by Thorek[1,2] in 1922, i.e., FNG, represented a mark in mammoplasty reduction at the time, due to its ability to maintain the nipple areolar complex (NAC), compared to underexplored by prior used techniques, such glandular and skin excision described by Frenchmen Morestin in 1908[1]. Despite its aesthetic functional limitations, related to insufficient breast projection and total loss of sensibility and lactation function of the nipple[1,2,9-11], FNG remains the first choice technique in patients with gigantomastia weighing 1000 g and ptotic breasts[11]. Moreover, modifications of the original technique are providing new alternatives for indicating the use of FNG[9-11].

In the past few years, sociocultural changes and a better understanding on gender dysphoria have been increasing the demand for masculinizing transgender procedures of the chest wall, in which mastectomy is one of the most efficient approaches on improving psychological outcomes of dissociation between body gender and biological sex experienced by these patients[5]. Literature reviews and comparative analysis on different surgical techniques have shown that double incision-free nipple graft (DIFNG), an adaptation of Thorek's technique, is the first choice in selected patients, as it promotes aesthetic satisfying outcomes and optimization of the relocation of the NAC, as well as lower rates of reoperations and anatomic limitations when compared to other chest wall masculinizing transgender techniques[4,5].

Breast cancer is the most prevalent malignant neoplasia in women. According to the World Health Organizations (WHO), approximately 2.2 million women were diagnosed with the disease in 2020[12]. The progress in understanding and treatment of the disease made interventions possible, which, in addition to being curative, also provides a better aesthetic functional outcome in patients who undergo mastectomies and breast reconstruction. In this scenario, FNG has been indicated as an alternative option in the maintenance of the NAC in women who would be initially excluded from reconstructive surgery using the nipple-sparing mastectomy (NSM) due to anatomical limitations of the breasts, such as ptotic breasts and gigantomastia. Therefore, women who would be excluded from NSM can undergo FNG surgery and, in a two or a single surgical time, undergo NSM, maintaining the NAC and elevating their psychological and self-esteem.

OBJECTIVES

This literature review seeks to provide an updated synthesis of knowledge about the FNG technique and its outcomes related to aesthetics satisfaction, functionality, and safety profile, as well as to analyze its incorporation and applicability in several intervention areas involved in mastology and plastic surgery.

METHODS

A structured electronic literature search was conducted, using PubMed and LILACS databases. The search strategy consisted of the keywords, MeSH terms, and free text words and word variants for the FNG and its application in reduction mammaplasty, transgender, and oncoplastic surgery. In PubMed databases, a search was conducted using the keywords, such as "breast neoplasms" OR "transgender" OR "mammaplasty" AND "free nipple graft." The Mesh terms in PubMed were "Breast Neoplasms" [Mesh]) OR ("Transgender Persons" [Mesh]) OR ("Mammaplasty" [Mesh])) AND free nipple graft. In LILACS databases, the keywords were "breast neoplasms" OR "transgender" OR "mammaplasty" AND "nipple."

The PICO question was formulated: breast neoplasms, transgender, and mammaplasty as the problems in question; FNG as an intervention; other mammaries surgical techniques and noninterventional treatments as a control and aesthetics; and patients satisfaction, safety profile, and reproducibility as outcomes.

Date of publication was limited to the past 10 years. The following filter was applied: language (English). A hand search of bibliographies was conducted to identify any additional articles by two of the authors. All titles and abstracts were independently reviewed by two of the authors. All study types, such as RCTs, case-control, cohort, reviews, and case studies, were eligible for inclusion.

The different study designs and the heterogeneity of the outcomes reported in the studies precluded the possibility of pooling data across the studies. Therefore, a narrative synthesis was conducted.

RESULTS

A total of 397 articles were found (209 in PubMed and 188 in LILACS databases) and, after inclusion and exclusion criteria, 15 were selected according to PRISMA 2020 presentation in Figure 4. Results are summarized in Table 1.

From the selected articles, only four evaluated the traditional application of FNG in reduction mammaplasty, comparing it to other technique interventions and analyzing its current concepts and surgical complications[13-16]. A total of 824 patients and 1648 operated breasts were analyzed, with an average of 1250 g of resected parenchyma. The other six articles[17-22] refer to the applicability of FNG in oncoplastic surgery, in which a total of 123 patients and 238 mastectomies have been analyzed. Finally, five articles deal with FNG utility in masculinizing transgender surgery[23-27], with 343 patients and 721 mastectomies analyzed.

Roje et al.[13] performed a retrospective study involving 59 patients, with a mean age of 48.5 years old (p=0.271) and 1050 g of parenchyma removed (p=0.009). The study compared the inferior pedicle, inverted T-scar, and FNG techniques based on aesthetic and functional outcomes and, therefore, determined a more suitable technique for each patient. The authors emphasizes the importance of FNG technique for reduction mammaplasty, since it provides a possibility of parenchyma resection in patients at high surgical risk, such as smokers (OR=61.92; p=0.008). Moreover, it is able to be performed in reduced surgical time, aspect directly related to lower complication rates (OR=1.05; 95%CI 1.01–1.1; p=0.019). When compared to other techniques, it has been elected as first choice in patients with macromastia, those with ptotic breast, or those who are at high surgical risk.

Robert et al.[14], in a retrospective analysis of 715 mammaplasty reduction surgeries, with a mean age of 38 years old, 27 kg/m^2 of body mass index (BMI) and suprasternal notch-nipple distance of 31.6 cm, when comparing the FNG technique to the superior pedicle technique, found that the FNG had lower overall surgical complication rates (OR=1.57; 95%CI 0.73–3.38 vs. OR=2.64; 95%CI 1.54–4.61). In addition, it allows a greater parenchyma resection (average 1100 g vs. 501 g; p<0.0001). However, authors narrow the FNG technique use only in patients with ptosis or macromasty[14,15] due to functional impairments involved in its application, such as total loss of NAC sensibility, nipple hypopigmentation, and insufficient breast projection, being preferable to use techniques with greater vascular safety profile in nonselected patients, since FNG has higher rates of areolar necrosis when compared to the inferior pedicle technique (61 vs. 4.7%; p<0.0045).

One of the major problems historically related to FNG is a partial loss of mammary projection [9-11,14]. This aspect was approached by Karsidag et al.[15] who reported a better projection and aesthetic outcome through a modification of the original Thorek´s technique, using a dermoglandular flap associated with a suture of pectoralis major within the parenchyma. It provided a satisfactory breast contour and projection in all 24 patients with severe macromastia over 1000 g and breast ptosis, with a mean distant suprasternal notch nipple of 48.5 cm. The outcomes were analyzed comparing preoperative and postoperative photographs, as well as a questionnaire filled out by the surgeon that considered patients' satisfaction and lasting breast projection for 1 year. Finally, the authors recommend the adoption of their modified technique for surgeons experienced in performing original FNG. Moreover, the authors highlight, as an advantage, the fact that the technique can be easily performed and exchanged intraoperatively, If an occlusion of nipple perfusion, such as ischemia, is identified, it can be converted into a pedicle technique, which may offer a higher vascular safety profile.

Fırat et al.,[16] in their prospective study, in which 26 patients who underwent free nipple graft vertical mammaplasty using the Graf dermoglandular flap mastopexy as a novel autoprosthesis procedure with an average follow-up period of 22 months were evaluated for a conical breast shape with better projection and upper pole fullness after surgery. The average weight of removed breast tissue was 1634 g for the right breast and 1630 g for the left breast. The mean sternal notch-nipple distance was 37.1 cm,

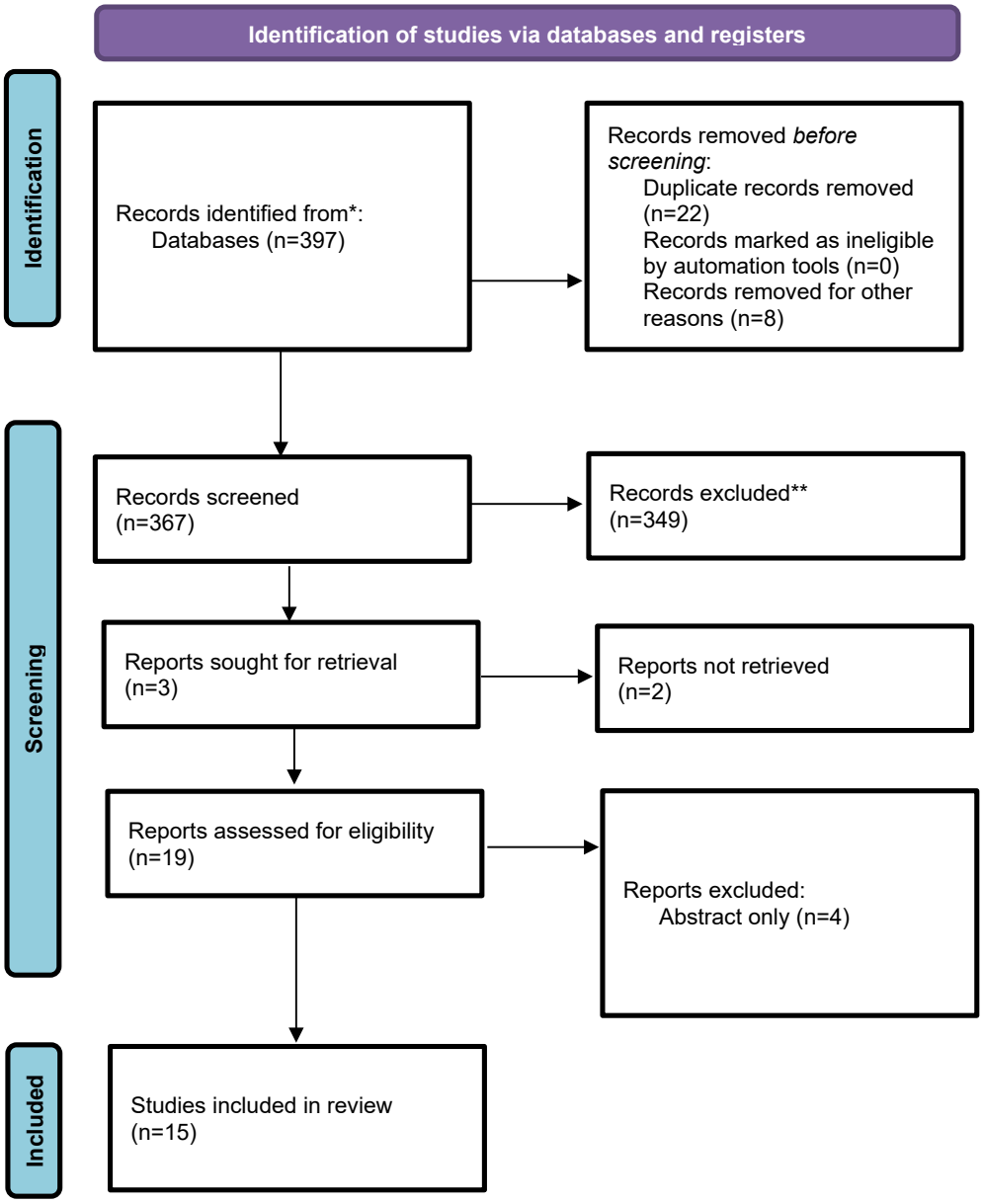

Figure 4. Prisma flow diagram.

and the mean nipple-submammary fold distance was 20.7 cm. The authors concluded that novel autoprosthesis technique yields a conical breast shape with better projection and upper pole fullness, thereby providing a better long-term aesthetic outcome than previous procedures for treating patients with gigantomastia. The examinations performed 2 years postoperatively clearly show that the autoprosthesis increased breast projection and preserved breast shape in the long term. This technique is easy to perform and highly suitable for patients with gigantomastia.

The role of FNG in reduction mammaplasty for decades prospected new possibilities for its use. Kijima et al.[17] explored FNG as a reconstructive plastic modified technique, associated with partial mastectomy in breast cancer conservative treatment. The authors reported a case of a 65-year-old woman who suffered from a bilateral ductal carcinoma in situ, who would have a compromised reconstruction surgery aesthetic result, in case of being submitted to the conventional pedicled technique, due to ptotic breasts. In this case, doctors opted to perform a partial bilateral mastectomy followed by a breast amputation with FNG. The modified technique was able to achieve a satisfactory oncological safety outcome in all quadrant areas, considering that the removal of the NAC from its original site

Table 1. List of articles according to title, author, year of issue, procedures, number of patients, and results.

Title/theme	Author and year of issue	Procedures and number of patients	Results
Mammaplasty			
Current trends in breast reduction	Roje et al.[13]	Retrospective cohort analysis of 59 patients who suffered from symptomatic macromasty and underwent surgical intervention from 1995–2011.	The free nipple graft technique is preferred for macromasty in smoker patients at high surgical risk.
Complications of breast reduction about 715 breasts	Robert et al.[14]	Retrospective cohort analysis of 715 patients who underwent a reduction mammaplasty in multiple techniques.	The free nipple graft has lower general rates of complications compared to the pedicle technique. Yet, its functional and aesthetic limitations as well as its high risk of mammillary necrosis restrict its use to severe macromasty and ptosis.
Reduction mammaplasty using the free-nipple-graft vertical technique for severe breast hypertrophy: improved outcomes with the superior dermaglandular flap	Karsidag et al.[15]	Prospective cohort study of 24 patients who suffered from severe mammary hypertrophy operated from 2003–2009.	The modified free nipple graft technique has shown to be effective in maintaining breast projection in all patients within the study. Experienced surgeons in superior pedicle technique used in reduction mammaplasty can adopt the suggested technique free nipple graft associated with superior dermoglandular flap.
An autoprosthesis technique for better breast projection in free nipple graft reduction mammaplasty	Fırat et al.[16]	26 patients who underwent free nipple graft vertical mammaplasty combined with the Graf dermoglandular flap mastopexy procedure were evaluated for a conical breast shape with better projection and upper pole fullness after surgery.	The novel autoprosthesis technique described yields a conical breast shape with better projection and upper pole fullness, thereby providing a better long-term aesthetic outcome than previous procedures for treating patients with gigantomastia.
Oncoplastic surgery			
Oncoplastic surgery combining partial mastectomy with breast reconstruction using a free nipple-areola graft for ductal carcinoma in situ in a ptotic breast: report of a case.	Kijima et al.[17]	Case report of a 65-year-old patient with ductal carcinoma in situ associated with ptotic breast.	The free nipple graft technique can be performed with reduced surgical time when compared to the inferior pedicle technique and it is indicated for the treatment of carcinoma in situ in women with ptotic breast.
Free nipple grafting: an alternative for patients ineligible for nipple-sparing mastectomy?	Doren et al.[18]	Retrospective cohort analysis of 15 ineligible patients for nipple-sparing mastectomy who underwent free nipple graft free nipple graft in order to maintain the nipple areolar complex.	In case of anatomical incompatible criteria for nipple-sparing mastectomy, free nipple graft is a viable option. The graft success rates were 95%, and the complication rates including loss of projection and hypopigmentation were, respectively, 19% and 27%.
Free nipple grafting and nipple sharing in autologous breast reconstruction after mastectomy.	Egozi et al.[19]	A prospective analysis of 13 patients who underwent free nipple graft after mastectomy with autologous reconstruction.	The free nipple graft technique achieved high aesthetic satisfaction rates: 4.6 out of 5 in Nahabedian score, as well as low rates of complications. Only 1 out of 13 grafts did not succeed and 24% of the nipples did not maintain pigmentation.
Nipple-sparing mastectomy and ptosis: using a free nipple graft with tissue expander reconstruction	Ghidei et al.[20]	Retrospective cohort of 14 patients submitted to free nipple graft in an oncological center.	The proposed free nipple graft intervention allowed women with breast ptosis to undergo NSM with preservation of the nipple areolar complex. Graft-taking was 100%. Yet, complications such as mammillary necrosis, hypopigmentation, and loss of sensibility were observed, respectively, in 7, 14, and 100% of the cases.
Revisiting the free nipple graft: an opportunity for nipple-sparing mastectomy in women with breast ptosis.	Chidester et al.[21]	A series of case reports on three women with breast cancer who were ineligible for nipple-sparing mastectomy and underwent a free nipple graft procedure.	Women who were previously excluded for nipple-sparing mastectomy were able to maintain nipple areolar complex integrity with free nipple graft with no oncological harm.

Continue...

Table 1. Continuation.

Title/theme	Author and year of issue	Procedures and number of patients	Results
One-stage breast reconstruction using the inferior dermal flap, implant, and free nipple graft	King et al.[22]	A reconstruction using free nipple graft was performed following a wise pattern skin incision in 16 patients and 19 breasts. A prospective database was kept from it.	The inferior dermal flap with implant and free nipple graft is an excellent single-stage reconstruction option. This method offers a potentially safe, reliable, and aesthetically acceptable outcome for women with larger, ptotic breasts.
Transgender surgery			
Long-term changes in free nipple graft morphology and patient-reported outcomes in gender-affirming mastectomies	Timmerman et al.[23]	Data from two prospective cohorts were collected: 67 transgender men after a mastectomy with free nipple grafts and 150 cisgender men (reference sample). Both groups were compared to establish the long-term changes in nipple-sparing mastectomy morphology and compare these to cisgender male nipple-sparing mastectomy outcomes.	Satisfaction for size, shape, and flatness decreased significantly after postoperative day 30 in transgender men compared to cisgender men.
Our experience in mastectomy for transgenders female to male – A 90 cases cohort study	Wolf et al.[24]	Retrospective cohort of 180 mastectomies performed in 20 years in transgender men.	The two main techniques performed with the best indicators of satisfaction and complications were nipple-sparing mastectomy flap and nipple-sparing mastectomy graft.
The nipple split sharing vs. conventional nipple graft technique in chest wall masculinization surgery: can we improve patient satisfaction and aesthetic outcomes?	Bustos et al.[25]	Retrospective cohort analysis of 68 transgender patients who underwent free nipple graft or nipple split intervention.	The nipple split and the conventional free nipple graft techniques did not show statistically significant complication rates. Yet, the nipple split had higher satisfaction rates compared to conventional free nipple graft technique
Modified nipple flap with free areolar graft for component nipple-areola complex construction: outcomes with a novel technique for chest wall reconstruction in transgender men	Frey et al.[26]	Retrospective cohort analysis including 50 transgender patients who underwent free areolar graft technique.	The techniques allow nipple-sparing mastectomy reconstruction in an effective and safe way. General complication rates were 10%.
A review of 101 consecutive subcutaneous mastectomies and male chest contouring using the concentric circular and free nipple graft techniques in female-to-male transgender patients	Knox et al.[27]	Retrospective analysis of 101 transgender patients who underwent either free nipple graft or concentric circular surgical techniques.	The concentric circular technique showed better aesthetic results in a score proposed by the study. However, the free nipple graft technique showed lower rates of complications.

reduces recidivation, in addition to a shortened surgical time when compared to other techniques used in oncological surgeries such as the pedicle technique[13,18]. Besides, FNG provides a better outcome regarding breast symmetry, due to the possibility of positioning nipple intraoperatively according to surgeon metrics. Therefore, authors highly recommend FNG application in the conservative oncological treatment of women with ptotic breasts in early stages of cancer.

The use of FNG in oncological mastology continues to be explored by Doren et al.[18] and Egozi et al.[19]. The nipple-sparing mastectomy (NSM) is a consolidated technique to achieve aesthetic results in mammary reconstruction[5,18,19]. However, in some cases, due to anatomical limitations and exposition factors, there is a contraindication to surgery using NSM, being left to perform a prior reconstruction followed by NSM in two surgical times. In retrospective cohort study by Doren et al.[18], 15 patients who were previously excluded from NSM due to previous areolar incision (n=2), breast parenchyma weighing >700 g (n=2), ptosis (n=1), radiation therapy (n=5), and patient's desire for autologous reconstruction (n=5) underwent a modified technique NSM associated with FNG in a single surgical time. A total of 26 areolar grafts were analyzed with a mean age of 47 years old, and 518.5 g of breast parenchyma. The graft viability was 95%, and the complication rate for loss of projection and hypopigmentation were, respectively, 19% and 27%. Doren et al.[18] concluded that FNG is a viable option for patients who do not fit classic indications and, therefore, is initially excluded from nipple-sparing surgery. The complication rates of FNG in oncoplastic surgery are similar

to those of reduction mammaplasty surgeries performed with the technique. Moreover, it spares patients from a doubled surgical time and its complications. Egozi et al.[19] retrospectively studied 7 patients in whom 13 FNG surgeries were performed. Initially, those patients were not excluded from NSM, as they were at high risk of mammillary necrosis. The mean age of the patients was 39.7 years old, and the mean BMI was 30.1 kg/m^2. All of them suffered from ptotic breasts (Regnault's grade II or III), and the average of parenchyma resected was 953 g. Finally, the authors reported a taking of 12 (93%) out of 13 grafts, with only 3 (24%) had hypopigmentation, and regarding a rate scale, based on Nahabedian patient satisfaction score, the FNG intervention achieved 4.6 out of 5. Therefore, FNG use is highly recommended by the authors owing to its high aesthetic satisfaction and low complication rates, potentially sparing patients from mammillary necrosis[18].

Ghiedei et al.[20] in their retrospective cohort study verified, as a primary outcome, the graft viability and postoperative complications in women who suffered from ptotic breasts. They underwent skin-sparing mastectomy, with oncoplastic purpose, followed by FNG in a single surgical time, aiming to maintain the integrity of NAC. In the retrospective study of 14 patients analyzed from 2014 to 2017, 10 suffered from invasive breast carcinoma and 4 underwent prophylactic mastectomy due to high-risk familiar history of breast cancer. The authors found that the use of FNG is able to maintain NAC integrity after mastectomy in women with ptosis, as well as achieved high rates of aesthetic satisfaction and free resection margins in an oncological perspective[18,19]. However, complications such as partial nipple necrosis, hypopigmentation, and loss of NAC sensibility were found, respectively, in 7, 14, and 100% of the patients observed in the study, reinforcing the need for a captious analysis on the indication and guidance of FNG due to complications which may impact the patient's self-esteem and quality of life.

The FNG intervention in breast oncology continues to be explored in the literature in the cases report by Childester et al.[21], in which a series of cases of three different women suffering from breast ptosis and carcinoma in situ underwent five NSMs, followed by FNG in a single surgical time. Analysis found that 1 (20%) out of 5 areola grafts was not successful, though it did not require postoperative debridement. The authors concluded that FNG was able to maintain NAC and free oncological margin [18-21] when undergoing FNG and skin-sparing mastectomy in a single surgical time.

King et al.[22] conducted a prospective study on 16 patients with breast cancer who underwent reconstruction surgery, using an inferior dermal flap associated with free nipple graft in a one-stage procedure and analyzed oncological safety and postoperative complications. Patient average age was 54 years, and average operative time was 165 min. There were no immediate complications requiring reoperation. All retroareolar biopsies were benign and no locoregional recurrences have occurred. Two nipples had partial necrosis of the lower pole but healed with conservative treatment. No patients required any subsequent procedures to their reconstructed breast. Although authors reinforce this type of procedure is proper for only a minority of patients who are suitable for immediate reconstruction, such as those who have a large ptotic breast and who have a low likelihood of disease involving the nipple, they concluded that FNG associated with dermal flap is a safe method of implant-based reconstruction, giving an excellent cosmetic result in a single procedure.

Society has experienced a paradigm shift concerning gender and sexuality in the past few years. This context expanded the areas of intervention in mastology and plastic surgery. The demand for transgender mammaplasty surgery has been rising in recent years, and FNG mastectomy is highlighted as one of the first choice techniques for chest wall masculinizing surgery in these patients [4,5].

Timmerman et al.[23] performed an observational, cross-sectional study, with data collected from two prospective cohorts transgender men (n=57) after a mastectomy with free nipple grafts and cisgender men (n=150) as a reference sample. Demographics and 3D images were collected for both groups. NAC measurements were performed on the 3D images at four time points (i.e., 7, 30, 90, and 365 days postoperative) in transgender men and once in cisgender men. NAC width and height in trans men changed from 21.5±2.7 to 23.8±3.9 mm (p<0.001) and 16.2±2.5 to 14.7±3.0 mm (p=0.01) within a year, respectively. The mean NAC width and height in cisgender men were 28.1±5 and 20.7±4 mm, being significantly larger than that in transgender men. Satisfaction for size, shape, and flatness decreased significantly after postoperative day 30 (p=<0.05) in transgender men. Therefore, authors conclude morphology and satisfaction with the NACs in transgender men significantly decreased over time. They enforce that understanding and incorporating these differences into preoperative counseling and surgical planning might help increase patient satisfaction in a long-term status and not only in an immediate postoperative analysis.

In retrospective cohort of 90 patients and 180 mastectomies by Wolf et al.[24], two techniques NAC pedicle (41.1%) and NAC graft (41.1%), which is a modification of the original FNG technique, were the most used surgical procedures in transgender patients in the series of procedures performed by a single surgeon. A mean age of 22.4 years old and 467 g of resected breast parenchyma were analyzed, and the authors found that, although high satisfaction and low complication rates were found in total mastectomies, it is necessary to establish a clinical-surgical classification based on breast weight and symmetry, as well as clinical trials to define which technique is more suitable for transgender patients.

Bustos et al.[25] compared intraoperative and postoperative outcomes of two techniques, either based on FNG, used in chest wall transgender surgery, the DIFNG and the nipple split technique

performed in a total of 34 transgender patients, with a mean age of 24 years old and BMI of 32.2 kg/m^2, retrospectively analyzed from 2017 to 2019. Both techniques did not have statistical difference concerning intraoperative and postoperative complication rates; however, the nipple split technique achieved a higher satisfaction rate according to patients (90.7 vs. 58.1%, p<0.05) calculated by a Likert scale questionnaire. Thus, the authors concluded that the nipple split FNG is able to achieve good aesthetic results with low complication rates and a high security profile and that it should be recommended as a first choice in transgender mastectomies instead of DIFNG.

Frey et al.[26] analyzed symmetry and plasticity of NAC, as a primary outcome, in 50 transgender patients who underwent DIFNG from March 2015 to October 2016. The mean age of patients was 30.6 years old, and the mean weight of resected breast parenchyma was 627.8 g. The authors concluded DIFNG has a satisfactory safety profile. General complication rates including seromas, cellulitis, and hematomas were about 10%, and specific aesthetic-related complications that needed reintervention to adjust size or symmetry of NAC were about 8%. Therefore, the authors recommend the adoption of the technique in transgender mastectomies due to its high aesthetic and success rates.

Knox et al.[27] reviewed 101 masculinizing mastectomies surgeries comparing two consolidated techniques in transgender patients: FNG and circular concentric. The authors found FNG had lower complication rates (12.7% vs. 37%; p<0.01). In addition, they found circular concentric technique achieved better aesthetic outcomes in the score proposed by the authors based on scar healing and breast shape ranging from 1 to 5 (circular concentric score 3.39 vs. 2.62 FNG; p<0.01). Therefore, the authors reduce the recommendation for the FNG technique in patients with BMI>27 kg/m^2 and distance nipple inframammary fold longer than 7 cm and patients who might be at a high surgical risk. Furthermore, the authors reinforce the need for standardized evaluation scores and clinical trials to define, with a higher evidence-based conduct, the most suitable technique for transgenders masculinizing mastectomies.

DISCUSSION

A variety of surgical applications has been described for the free nipple graft technique. The data from the present literature and research have shown promising results that may provide plastic and mastology surgeons with an evidence-based incentive to adopt the FNG technique in its broad spectrum of intervention.

Moreover, the possibility to modify Thorek's original technique[14,15] was explored in this study as a viable way to improve aesthetic problems in reduction mammaplasty, such as insufficient breast projection. This possibility was already discussed in literature back to the 90s by Romano et al.[9] and Abramson et al.[10]

Some restrictions to the FNG use, described in the past decades, which limited its use to strict cases of reduction mammaplasty with over 1 kg per breast to be resected, or sternal notch-nipple distance longer than 35 cm, were already questioned by Colen et al.[11] The authors suggest that FNG may achieve equal or better aesthetic and functional outcomes compared to traditional reduction mammaplasty techniques, such as inferior pedicle, not only in its classic indications for gigantomastia or breast weighing >1 kg but also in cases of preeminent ptosis, inverted nipple, and fatty breasts. Transgender individuals who underwent surgery using FNG had average breast parenchyma resection of 490 g in the studies[24-26]. That gives support to Colen et al.[11] questioning on limitations to FNG use in parenchyma weighing 1000 g to be resected and suggests misconception of those prior restrictions related to FNG indications.

As a subtype of free skin graft, FNG had already been studied in some references back to the 2000s when it was seen that inclusion criteria for breast conservative surgery continued to evolve, including lower quadrants mastectomy and large breasts. Spear et al.[28]. reviewed on 11 women with macromastia who underwent lumpectomy followed by mammaplasty reduction, using FNG in 8 out of 22. The authors have already determined the importance of this gathered oncoplastic procedure, in that the potential for disfigurement after breast conservative treatment would increase, especially in some risk patients, such as women with macromastia. Authors found similar results compared to some in this article[17,22] when it comes to recognize the importance of a coordinated oncoplastic program and the benefits in boosting self-esteem in those patients, but Spear et al.[28] also reinforced the need for better define and improve algorithms for selecting women who might benefit from this type of the procedure, since patients with macromastia are at higher surgical risk when compared to most patients. In the articles[17-22] found in this revision, none of them have proposed a standardized algorithm neither for macromastia nor for ptotic breasts in oncoplastic treatment.

Some limitations to this revision were also found. Except Robert et al.[14], none of the studies analyzed a broad population with a standardized statistic score of outcomes, such as risk ratio and aesthetic results when it comes to compare various techniques used in reduction mammaplasty, oncoplastic, and transgender surgery. In this manner, a reduced sample limits a significant statistical analysis. Besides, a historical problem concerning difficulties in performing clinical trials related to surgical interventions[29] was also present in the literature concerning FNG as no RCT was found in the databases, which may reduce methodological and evidence strength of this study.

Another fact that must be considered is the lasting of the aesthetics results, especially in transgender surgeries. Timmerman et al.[23] were the only authors who approached a lasting satisfaction over 1 year in contrast of the other articles on transgender surgery[24-27]. This aspect could be more explored since nonlasting results may have impact on self-esteem and morbidity problems in those patients[5].

Despite these considerations regarding methodological and articles limitations, it is important to emphasize a broad applicability of FNG technique and its limited dissemination and

use in breast surgery. Notwithstanding inconveniences related to FNG technique, such total loss of nipple sensibility, areolar depigmentation, and flattening of the papilla over time, it is also necessary to reinforce the low rate of loss of graft as well as aesthetic result similar or better to those found using conventional mammaplasty techniques. Moreover, in cases of oncological surgeries, in which maintaining NAC would not be possible after mastectomy in ptotic or bulky breasts, FNG may be used for the maintenance of the NAC or correction of malposition of it after conservative or radical mastectomies[17,18].

CONCLUSIONS

The literature data analysis provides a broad view of possibilities in breast surgery using the FNG technique and its safety profile. This study represents a potential impact on both experienced and learner surgeons when providing the most complete and updated information about a technique with a large spectrum of intervention in mammaplasty, oncological, and transgender surgery. Furthermore, we reinforce the need for adequate interventional trials and standardized aesthetic functional scores in order to define with a better level of evidence the usefulness of FNG.

AUTHORS' CONTRIBUTION

RP: Conceptualization, Methodology, Formal Analysis, Investigation, Writing – original draft. AA: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. CN: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. CE: Supervision, Project Administration, Formal Analysis, Writing – review & editing.

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REVIEW ARTICLE
https://doi.org/10.29289/2594539420210057

Global impact of pandemic by SARS-CoV-2 on breast cancer diagnosis and screening

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ABSTRACT

Introduction: The pandemic related to the new coronavirus is characterized by high rates of contamination, transmissibility, and mortality. The measures of social isolation adopted by the World Health Organization and corroborated by several countries, with a view to avoiding or minimizing the transmission of COVID-19, can lead to the reduction of the capacity of screening and diagnosis of diseases, such as breast cancer. **Objective:** This study aimed to analyze the diagnostic indexes and mamaria malignancy diagnosis test, such as mammogram, during the COVID-19 pandemic period. **Methodology:** Systematic review of the literature based on studies found in the PubMed, SciELO, LILACS, and ScienceDirect databases. **Results:** The six selected articles demonstrate a reduction in the diagnosis of breast cancer during the pandemic, although with discordant rates. Outcomes such as reduced number of mammograms and change in tumor stage were also analyzed. **Conclusion:** It is essential to maintain care with the screening, diagnosis, and treatment of breast cancer, in order to minimize the damage caused over more than 1 year of COVID-19 pandemic.

KEYWORDS: coronavirus; early detection of cancer; neoplasms; SARS-CoV-2.

INTRODUCTION

The SARS-CoV-2 virus infections are first recorded in December 2019 in Wuhan, China. Spreading globally, due to the inherent characteristics of the virus, there was a need to implement measures to contain viral propagation, such as social distancing and the relocation of health services, in order to meet new global demands. Therefore, many countries have chosen to temporarily suspend their screening and diagnosis programs for breast cancer, which is the world's most common neoplasm among women[1].

In Brazil, according to Bessa[2], the National Health Agency recommended that non-urgent visits, examinations, or surgeries be postponed. The State has a screening program for the diagnosis of breast cancer through the Unified Health System in women aged between 50 and 69 years. Despite government efforts, even before the pandemic, it is estimated that, together with the search for private care, only 60% of screening coverage occurs in the country.

In this context of changes in the functionality of health systems resulting from the COVID-19 pandemic, the study aimed to analyze the overall impact on the number of diagnoses of breast neoplasms and on mammograms. Through a systematic review, pre-pandemic and pandemic comparative data are described.

METHODS

This study consists of a systematic literature review so that submission to the Ethics and Research Committee was not necessary. Articles indexed in the electronic databases PubMed, SciELO, LILACS, and ScienceDirect were manually collected from August 28 to 31, 2021. Cross-sectional and retrospective observational studies were selected using the following descriptors and keywords: (Diagnosis) AND (Breast Neoplasms) AND (COVID-19), which were obtained according to the Health Science Descriptors (DeCS).

The inclusion criteria for the selection of articles for systematic review were predetermined and include relationship between the number of breast cancer diagnoses before and during the COVID-19 pandemic; articles with real data presentation; and

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Conflict of interests: nothing to declare. **Funding:** none.
Received on: 01/07/2022. **Accepted on:** 04/01/2022.

articles with translation into at least one of the following languages: English, Portuguese, or Spanish. The exclusion criteria were also predetermined for the search, being excluded: editorial articles; articles whose publication has been made in languages other than those mentioned above; and articles with speculative data.

In this search for the present study, 263 results were found on the PubMed platform, 174 articles on the ScienceDirect platform, and 5 articles on the LILACS platform, with no results on the SciELO platform. Only one of the articles was duplicated, so after reading the titles, 36 studies were selected to read the abstract and, after reading the respective abstracts, 21 articles remained. These 21 studies were read in full by three reviewers and selected independently so that they met the inclusion and exclusion criteria, leaving, at the end, 6 articles.

Of the 263 articles found on the PubMed platform, 262 remained after the exclusion of the duplicate, so that 229 of them were excluded after reading the title and 12 after reading the abstract for not meeting the pre-established requirements. Of the 19 articles read in full, 10 were excluded due to the absence of the outcome of the relationship between the number of breast cancer diagnoses during the pandemic, 4 were excluded because they were guidelines or editorial letters, and 1 was excluded because it referred to simulations with unrealistic data from population models. Of the 174 studies located on the ScienceDirect platform, 171 were excluded after reading the title and 2 were excluded after reading the abstract, so the article read in full was included in the review. Of the five articles found on the LILACS platform, four studies were excluded after reading the title and one was selected to integrate the systematic review. Finally, data were extracted on the characteristics of the studies, results, and outcomes. The flowchart of the process of identification and selection of studies is presented in Figure 1.

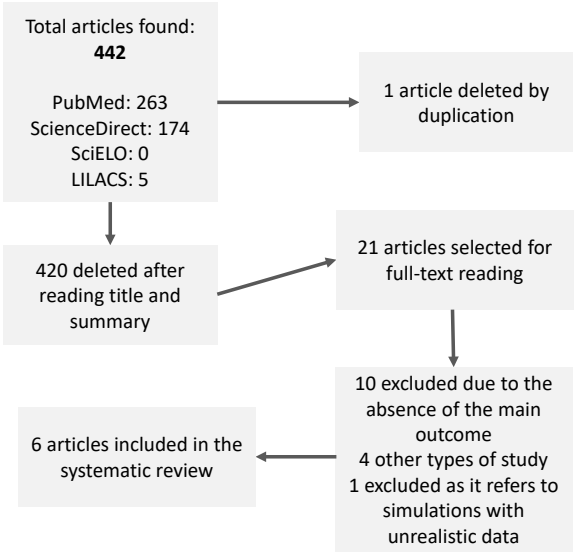

Figure 1. Search strategy flowchart. Passo Fundo (RS), 2021.

RESULTS

All articles included were published in 2020 or 2021, written in English, with impact factors ranging from 4,018 to 11,059. Regarding origin, two studies are from the Netherlands[3,4], one from Belgium[5], one from Brazil[6], one from Croatia[1], and one from Italy[7]. The outcomes addressed by the studies were decreased in breast cancer diagnoses, reduction in the number of tests performed, and changes in the stage of cancer.

In the Brazilian article, coming from Fortaleza, Ceará, mammography and breast ultrasound examinations had the greatest impact due to the pandemic, with a decrease of 95% and 100%, respectively, which led to a reduction of up to 60% of diagnoses, since the number of new cases of breast cancer was 23 in May 2019 and 8 in May 2020[6]. When comparing two distinct periods, it was noted that, in northern Italy, between May 2019 and July 2019, 15,942 mammograms were performed and 223 individuals were diagnosed with breast cancer (221 women and 2 men), but in the same quarter of 2020, only 9,052 mammograms were performed and 177 patients were diagnosed (174 women and 3 men). In addition, in 2020, there was a statistically significant reduction in the diagnosis of breast cancer in situ (from 17% of breast cancer diagnoses in 2019 to 6.8% in 2020), but the rate of cT1, cT2, and cT3 tumors diagnosed in May to July 2020 did not differ significantly from the 2019 tumors. In contrast, cT4 tumors increased from 4 (1.8%) in 2019 to 14 (7.9%) in 2020 and the number of breast cancers with metastatic lymph nodes (cN+) at the time of diagnosis increased from 28 (12.5%) in 2019 to 42 (23.7%) in 2020[7].

In the Netherlands, the incidence of breast tumors detected at screening decreased during weeks 12–13 of 2020, almost zeroed during weeks 14–25, and increased during weeks 26–35. The decrease in incidence was observed in all age groups and occurred mainly for cTis, cT1, ductal carcinoma in situ, and stage I tumors. Due to the suspension of the breast cancer screening program and its restarting with reduced capacity, the incidence of tumors detected by screening decreased by 67% during weeks 9–35 of 2020, which equates to about 2,000 possibly delayed breast cancer diagnoses. Despite this, until August 2020, there was no evidence of a transition to breast cancer at higher stages after the restart of screening[3].

A 24% reduction in newly diagnosed breast cancer cases in Croatia was seen during April, May, and June 2020 compared to the same period in 2019. However, during the whole of 2020, only 1% fewer new cases were reported than in 2019, 6% less than expected[1]. In Belgium, female breast cancer diagnoses in the screening population (50–69 years) decreased by 56% in April

2020, but it was possible to resume screening for these tumors, with only 6% of diagnoses missing by the end of 2020[5].

DISCUSSION

Breast cancer screening in the asymptomatic population leads to early diagnosis and treatment[8]. During the COVID-19 pandemic, there were problems in accessing cancer care services, which includes screening[9], raising some concerns about the delay, and decreased diagnoses of the disease[5]. This context can have deleterious long-term effects, since it was estimated that the delay of each month in diagnosis is associated with a 1.8% higher probability of a more advanced stage of cancer[1].

As can be seen in Table 1, the six articles selected for systematic review demonstrate a reduction in the diagnosis of breast cancer during the COVID-19 pandemic, although these rates present some disagreements. Lôbo et al.[6] reported a 60% reduction in diagnoses, the highest rate found, but these data are related to a restricted population, since they correspond to the city of Fortaleza (Ceará, Brazil). In addition, these rates also disagree with those presented by the National Cancer Institute[10] which demonstrates 59,700 new cases in 2019 and 66,280 in 2020, so that in Brazil, there was a 10% increase in new cases of the disease.

Toss et al.[7], Eijkelboom et al.[3], Vrdoljak et al.[1], and Eijkelboom et al.[4] demonstrated similar rates of diagnostic reduction in the first half of 2020, with 24, 37, 24, and 35% decrease, respectively. These values also disagree with those analyzed in the same studies by Vrdoljak et al.[1] and Peacock et al.[5], which demonstrate a reduction of 1 and 6%, respectively, when compared to the whole year 2019 and 2020. The explanation for these data may lie in the fact that, as cancer care services returned to work, an increase in screening volumes may have reduced the deficit in accumulated mammograms, as demonstrated in the study by Miller et al.[11], which brought up new diagnoses of the disease.

Regarding breast cancer screening tests, when analyzing the article by Lôbo et al.[6], it was evidenced a 95% decrease in the rate of mammograms in the period from March to June 2020 compared to 2019 in Brazil, while in the study by Toss et al.[7], in Italy, there was a 43% reduction in these rates from May to July 2020, compared to the previous year. The discrepancy of these data may occur due to the fact that the pandemic in Italy began earlier than in Brazil and had its peak waves of SARS-Cov-2 in different stages.

When comparing Brazilian studies, Lôbo et al.[6] with Bessa[2], there is a difference in results, because Bessa[12], based on DATASUS, showed a 42% drop in the rate of mammograms throughout the

Table 1. Outcomes found in the systematic search.

Reference	Analyzed site	Analyzed period	Breast cancer diagnostic reduction (%)	Mammography reduction (%)	Tumor stage (%)
1. Lôbo et al.[6]	Fortaleza, Ceará, Brazil	From March to June 2020, compared to the same period in 2019	60 of reduction in diagnostics	95	–
2. Toss et al.[5]	Province of Modena, northern Italy	From May to July 2020, compared to the same period in 2019	24 of reduction in diagnostics	43	IN SITU: decrease of 68 IIA: decrease of 12 Stage III: increase of 10 Stage I, IIB e IV no significant changes
3. Eijkelboom et al.[2]	Holland	From February to August 2020, compared with the same period in 2018 and 2019	37 of reduction in diagnostics	–	IN SITU: decrease of 57 Stage I: decrease of 43 Stage II: decrease of 25 Stage III: decrease of 16 Stage IV: decrease of 4
4. Vrdoljak et al.[1]	Croatia	Year 2020 compared to 2019	24 of reduction in diagnostics from April to June 2020, if compared with the same period in 2019 1 of reduction in diagnostics for the whole of 2020	–	–
5. Eijkelboom et al.[3]	Holland	From February to April 2020, compared with the same period in 2018 e 2019	35 of reduction in diagnostics	–	IN SITU: decrease of 38 Stage I: decrease of 39 Stage II: decrease of 32,5 Stage III: decrease of 38 Stage IV: decrease of 15
6. Peacock et al[4]	Belgium	2020 compared to year 2019	6 of reduction in diagnostics	–	–

country and that the most affected state was Rondônia, with 67%. However, in the study by Lôbo et al.[6], it is only in Fortaleza, Ceará, there was a 95% decrease, which is similar to the data demonstrated by Collado-Mesa et al.[12], whose decrease in mammograms was 98% in Florida, USA. From March to June 2020, the same period as evidenced by Lôbo et al.[6], the article by Song et al.[16] showed a 38% reduction in mammograms expected compared to 2019 in the United States. In another study conducted in the United States[13], from March to May 2020, the absolute deficit in the American population in breast screening associated with the COVID-19 pandemic was estimated at 87.3% compared to the same time period in 2019.

In the analysis of the selected articles, a significant reduction of 68% of the tumor in situ is found in the study by Toss et al.[7] and of 57% is found in the study by Eijkelboom et al.[3], demonstrating the proximity of the data. Already in the study by Eijkelboom et al.[4], this rate is also decreased, but with a value of 38%. Stage I had similar results in the articles by Eijkelboom et al.[3] and by Eijkelboom et al.[4], with a decrease of 43 and 39%, respectively. However, in the study by Toss et al.[7], this stage does not present significant changes, as well as IIB and IV in the same article. Stage II demonstrates a decrease of 12, 25, and 32.5% in the studies by Toss et al.[7], Eijkelboom et al.[3], and Eijkelboom et al.[4], in that order, in which the disparity of the data between the first and the other articles is perceived. Stage III shows decrease in the study by Eijkelboom et al.[3] of 16% and approximately double in the study by Eijkelboom et al.[3], with 38%. However, Toss et al.[7] presented a discrepancy in the data, with an increase of 10%. Stage IV showed a slight decrease of 4% in the study by Eijkelboom et al.[3] and a more significant percentage of 15% in the study by Eijkelboom et al.[4].

In relation to increased mortality due to delay and decrease in diagnoses, Yong et al.[14] estimated the long-term clinical impact of breast cancer screening interruptions in Canada, using a validated mathematical model, which demonstrated an increase of 110 deaths between 2020 and 2029 due to a 3-month break in the disease screening service. Another study[15] estimated the impact of COVID-19 on screening and treatment of breast cancer at Sharpless, using CISNET cancer simulation, which demonstrated an increase of more than 5,000 deaths in the next decade in the United States.

This context of reduced diagnosis and screening tests demonstrated by systematic review occurs both due to the reduced operational status of imaging clinics and due to the fear of patients seeking health services[16]. However, even in the midst of the pandemic, other pathologies, such as breast cancer, have not stopped emerging and continue to cause high morbidity and mortality. In this sense, since the COVID-19 pandemic persists for more than 1 year, it is important that breast cancer care services continue to function, with due care, in order to perpetuate care for the pathology.

Although some studies present discordant rates, this review demonstrates the reduction in the number of tests performed for breast cancer screening, as well as the decrease in diagnoses of the disease in all sites studied by the analyzed articles. In addition, it is also suggested, as a consequence of the reduction in screening, changes in the staging of breast cancer. However, more studies are needed to confirm these findings. Even so, considering the data that indicate worsening in the stage of the disease, it is essential to maintain care with the screening, diagnosis, and treatment of breast cancer, aiming to minimize the damage caused over more than 1 year of COVID-19 pandemic.

AUTHORS' CONTRIBUTION

ADDA: Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. AKD: Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. GVBS: Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. MB: Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. VAS: Conceptualization, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. ESG: Conceptualization, Investigation, Methodology, Validation, Writing – original draft. LLA: Conceptualization, Data curation, Investigation, Project administration, Supervision, Validation, Writing – review & editing. LMW: Conceptualization, Data curation, Investigation, Project administration, Supervision, Validation, Writing – review & editing

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