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ABOUT

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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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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.

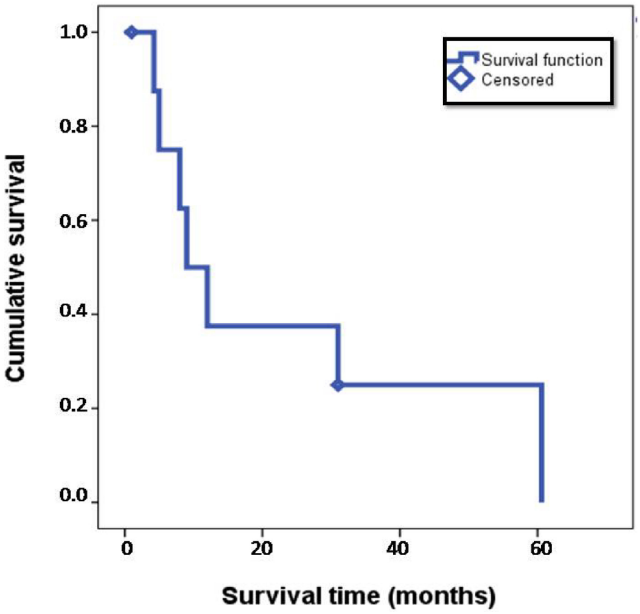
METHODS

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).

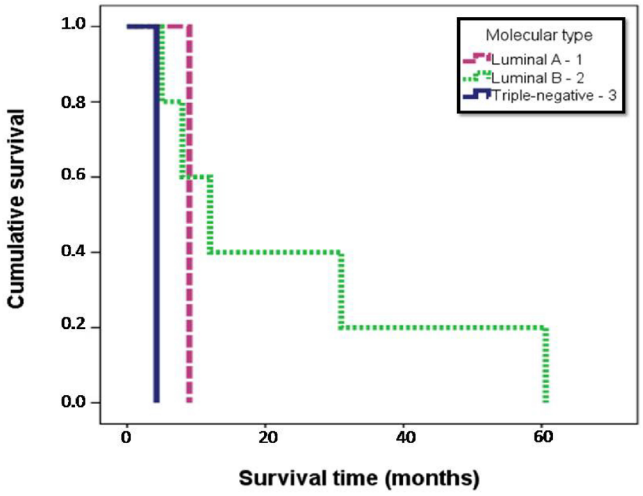
Molecular classification was possible in seven patients: five luminal B subtype, one luminal A case and one triple-negative case; patients with the luminal B subtype had a longer median survival – 23.3 months (95%CI 3.0–43.6; p=0.044<0.05). The triple-negative case had a lower median survival (4.25 months) (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
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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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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.

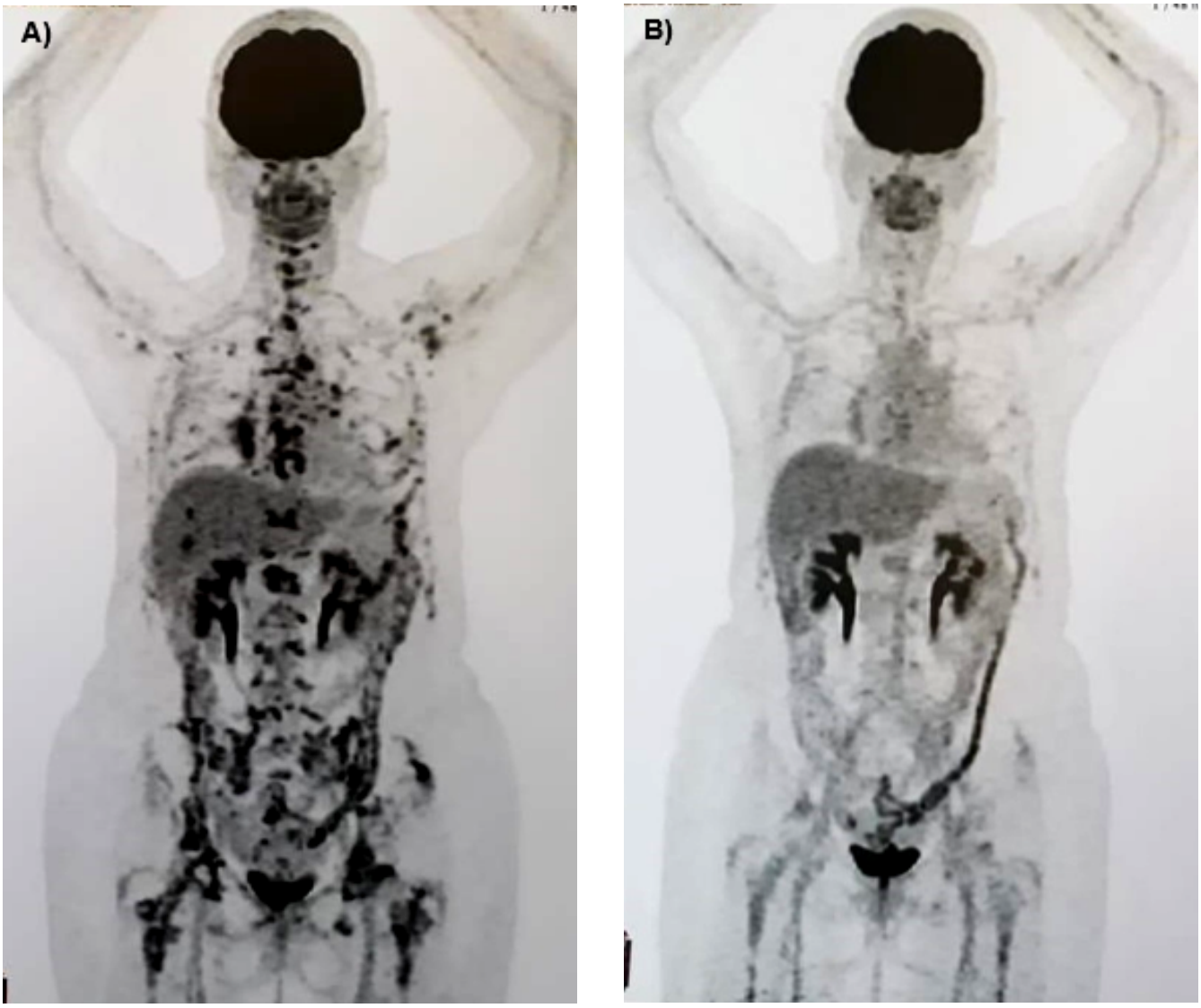

Figure 1. A) PETCT of the patient before starting treatment with trastuzumabe entansina combined with letrozol and denosumabe; B) PETCT of the patient at the end of treatment with trastuzumabe entansina combined with letrozol and denosumabe.

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
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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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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

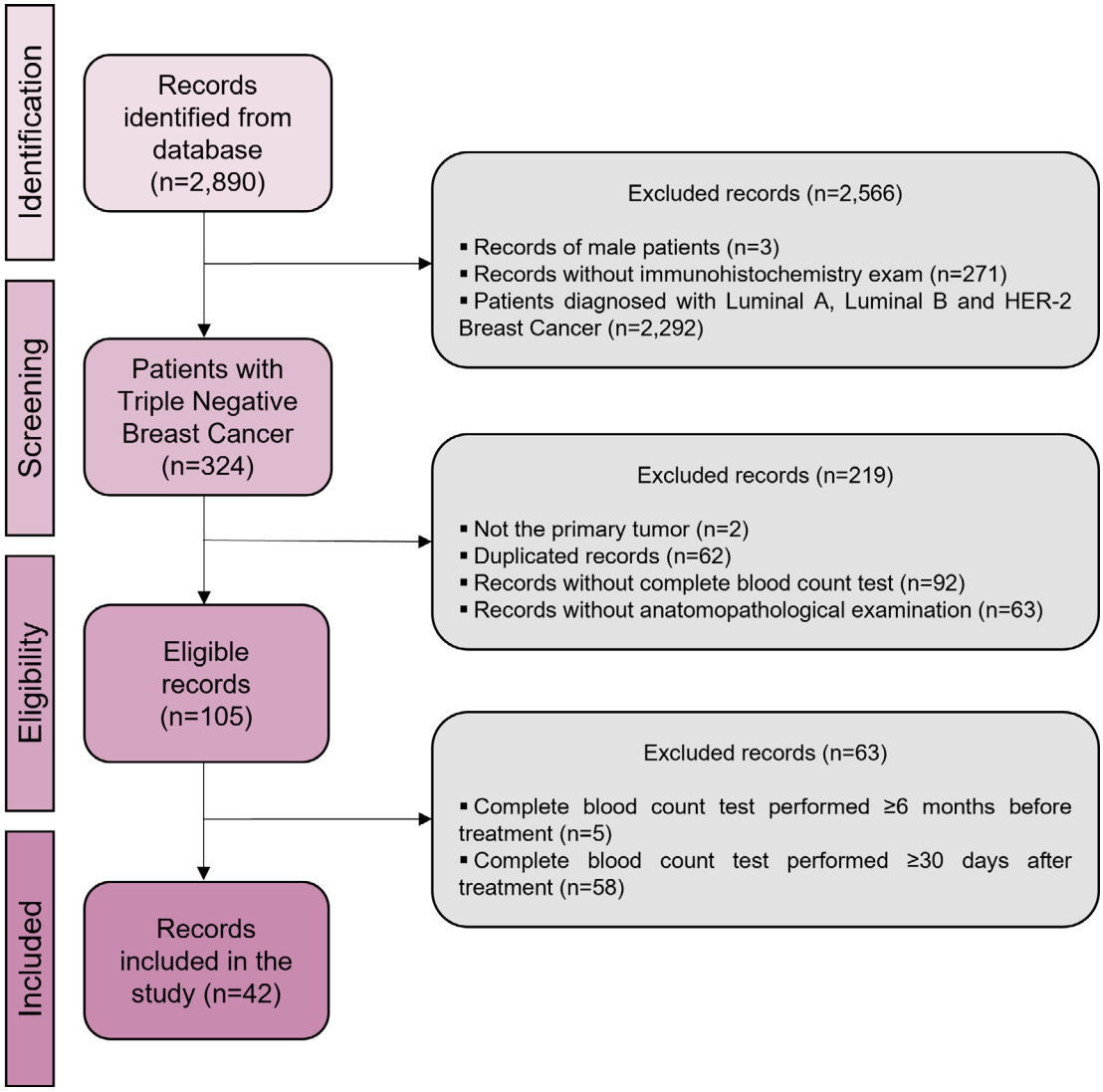


Figure 1. Records screened and included in the study.

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.

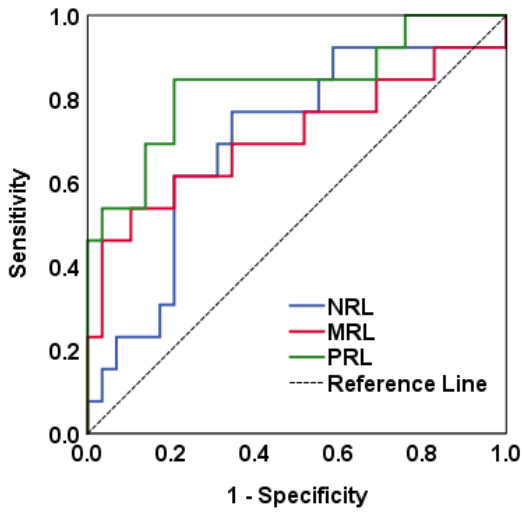
In the present study, we demonstrated that high PLR is a statistically significant predictor of worse OS and PFS (p=0.000, p=0.003, respectively) among women with TNBC. When compared to other pretreatment hematological ratios and factors associated with survival, such as the occurrence of recurrence, 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.

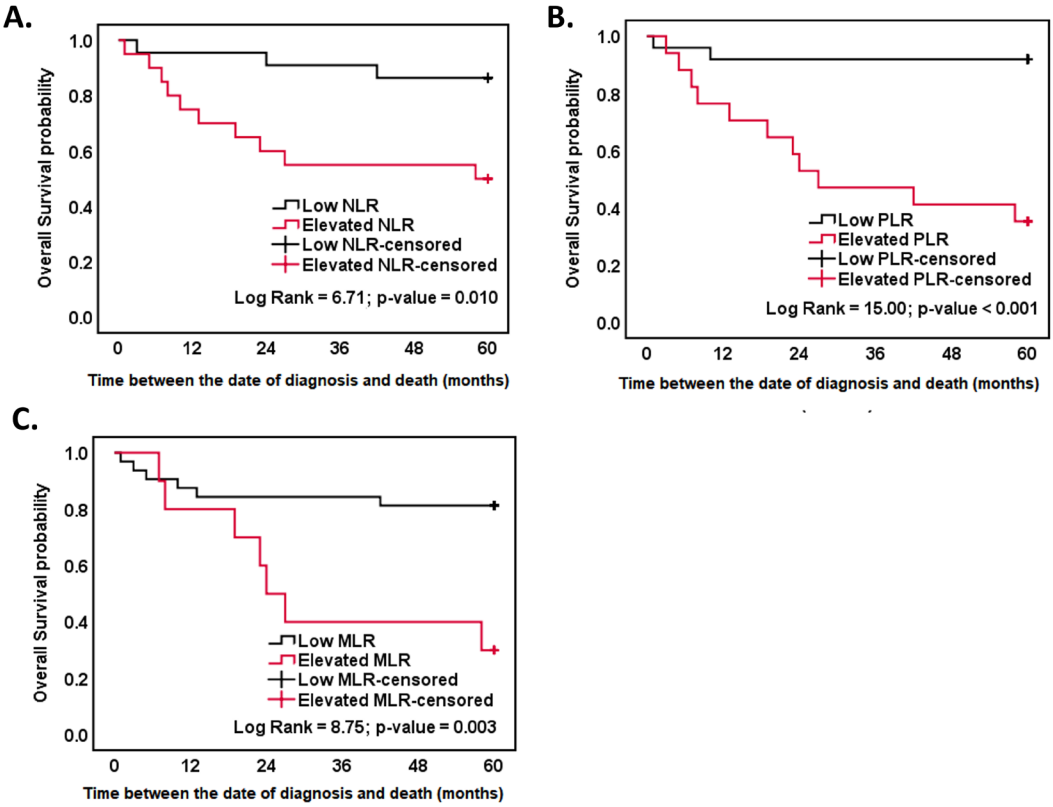


The areas under the curve for each parameter were 0.70 (p=0.040), 0.71 (p=0.033) and 0.83 (p=0.001), respectively.
NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

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,



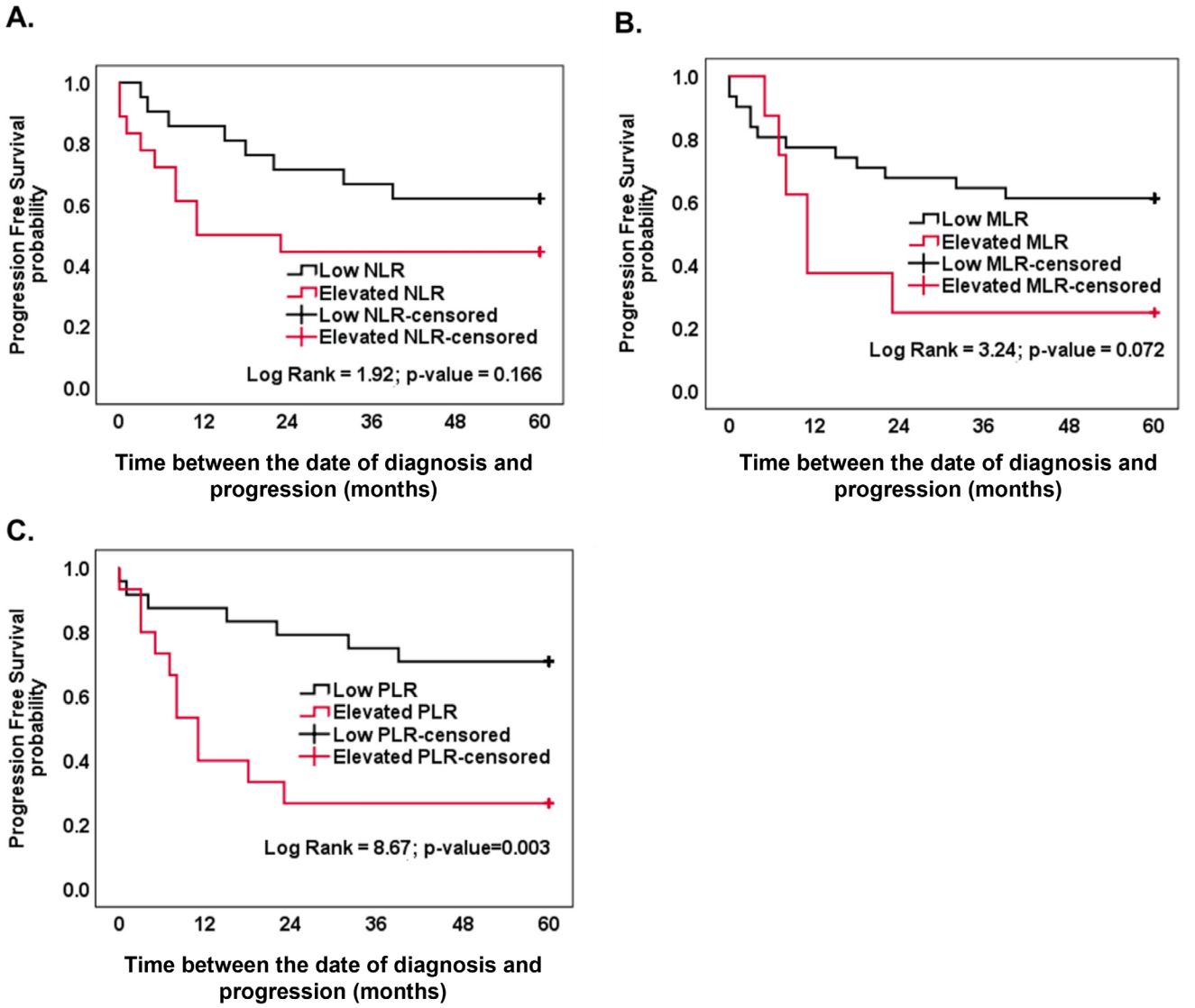
(A) Median overall survival was 54.95 months in the patients in the low neutrophil/lymphocyte ratio group and 38.55 months in the high neutrophil/lymphocyte ratio group. (B) Median overall survival was 51.1 months in the patients in the low monocyte/lymphocyte ratio group and 34.6 months in the patients 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.

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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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