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ORIGINAL RESEARCH

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Association of anemia and neutrophil-lymphocyte ratio with overall survival in breast cancer patients

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Abstract

Objective: The neutrophil-lymphocyte ratio (NLR) has been shown to correlate with disease progression and survival in a number of cancers. In this study we explore this ratio and a number of other blood-derived factors, including platelet-lymphocyte ratio (PLR) and hemoglobin levels, for their prognostic value with overall survival in breast cancer patients. **Methods**: A retrospective study was conducted with data from the medical records of patients with breast cancer (n = 303) collected from a breast cancer treatment and research clinic. The data included clinical staging at diagnosis, tumor size, axillary lymph node involvement, presence or absence of metastases, tumor histology, tumor grade, hormone receptor, treatments received (surgery, chemotherapy, hormonotherapy), overall survival, NLR, PLR, anemia, leukocytosis, neutrophilia, and lymphopenia. Cox regression was used to verify the influence of the variables on five-year overall survival of patients following their initial diagnosis. **Results**: Patients with NLR >4 showed association with staging >II ($p < 0.05$), with the presence of metastasis ($p < 0.0001$), and with negative hormone receptor ($p < 0.0001$). A hemoglobin <12 g/dL associated with staging >II ($p < 0.0001$), with the presence of metastasis ($p < 0.0001$), and with negative hormone receptor ($p < 0.05$). High values of NLR and PLR were associated with shorter overall survival by Kaplan-Meier survival curves ($p < 0.001$ and $p = 0.021$, respectively). After multivariate regression, tumor size, lymph node status, metastasis, NLR and anemia remained as factors that independently influenced mortality at 5 years. NLR >4 increased the risk of death by 7.76 times ($p < 0.001$) and hemoglobin <12 mg/d increased the risk of death by 2.47 times ($p = 0.037$). **Conclusions**: NLR and anemia are factors that independently correlate with overall survival in breast cancer patients. These factors have the advantage of being derived from simple and inexpensive blood testing.

Keywords

Neutrophil-lymphocyte ratio; Anemia; Hemoglobin; Overall survival; Breast cancer

1. Introduction

Breast cancer is the most frequently diagnosed cancer in women worldwide, with the exception of non-melanoma skin cancers in some countries. There were over 2.26 million cases of breast cancer diagnosed in 2020 [1]. In Brazil, 66,280 new cases were estimated for the year 2021, and the number of deaths was 18,068 women [2].

The main prognostic factors already known for breast cancer are age, tumor size, lymph node involvement, tumor histological grade, hormone receptor status, Human Epidermal growth factor Receptor-type 2 (HER-2), proliferation index and vascular invasion [3, 4]. Additional prognostic factors continue to be explored and may contribute to patient management. Analysis of blood factors may prove to be of particular value since these tests are readily available and inexpensive to perform.

Neutrophil-lymphocyte ratio (NLR) has been shown to be a promising prognostic factor for many cancers [5, 6]. NLR is a marker of systemic inflammatory response, which is related to the occurrence, progression and prognosis of cancer patients. Patients with higher NLR have more advanced and aggressive tumors, resulting in lower overall survival and disease-free survival, regardless of other prognostic factors. In breast cancer, increased NLR correlates with classical prognostic factors such as larger tumor size, lymph node involvement, metastasis and high-grade tumors [7], and is an independent prognostic factor for overall survival [8].

Another index derived from the blood count is the platelet-lymphocyte ratio (PLR). According to some studies, this index has a prognostic value analogous to NLR: higher values are associated with shorter survival in patients with breast cancer [9]. Another study demonstrated that hemoglobin levels are

TABLE 1. Characteristics of patients included in the study according to NLR and anemia (median, minimum and maximum values, or *n* and %).

	Median, minimum and maximum values, or *n* and %			
Item	NLR ≤4	NLR >4	Hemoglobin <12 g/dL	Hemoglobin ≥12 g/dL
	n = 272	n = 31	n = 32	n = 271
Age (years)	52 (25–86)	54 (28–86)	52 (25–86)	50 (25–86)
Race				
White	185 (68.01%)	17 (54.84%)	19 (59.37%)	183 (67.53%)
Non-white	87 (31.99%)	14 (45.16%)	13 (40.63%)	88 (32.47%)
Hormonal status				
Menacme	117 (43.01%)	14 (45.16%)	14 (43.75%)	117 (43.17%)
Menopause	155 (56.99%)	17 (54.84%)	18 (56.25%)	154 (56.83%)
Hormone receptor				
Positive	224 (82.35%)*	15 (48.39%)	20 (62.5%)	220 (81.18%)$^{+}$
Negative	48 (17.65%)	16 (51.61%)	12 (37.5%)	51 (18.82%)
Staging				
≤II	181 (66.54%)**	12 (38.71%)	9 (28.13%)	184(67.9%)$^{++}$
>II	91 (33.46%)	19 (61.29%)	23 (71.87%)	87 (32.1%)
Metastasis				
Yes	56 (20.59%)	17 (54.84%)	18 (56.25%)	55 (20.3%)
No	216 (79.41%)***	14 (45.16%)	14 (43.75%)	216 (79.7%)$^{+++}$

**p < 0.0001 compared to negative hormone receptor status; **p < 0.05 compared to staging >II; ***p < 0.0001 compared to presence of metastasis; $^{+}p < 0.05$ compared to negative hormone receptor status; $^{++}p < 0.0001$ compared to staging >II; $^{+++}p < 0.0001$ compared to presence of metastasis.*

also useful to predict survival in breast cancer patients. The presence of anemia at diagnosis (Hemoglobin (Hb) <12 g/dL) was associated with reduced local relapse-free survival, lymph node metastasis-free survival, distant metastasis-free survival, relapse-free survival, and overall survival [10].

Thus, it is clear that preoperative blood tests offer several promising parameters that can contribute to treatment decisions in breast cancer. Our study aims to determine the association of anemia, NRL and PLR with overall survival in breast cancer and to provide an additional set of factors to aid in patient management.

2. Materials and Methods

A retrospective study was conducted by collecting data from the medical records of patients diagnosed with breast tumors and treated at the Mastology Clinic.

The study population was derived from women seen at the Mastology Outpatient Clinic of a free care hospital located in Southeast Brazil. Most patients seen at the hospital are of lower socioeconomic status. Demographic characteristics recorded in the database were age and race. In Brazil, there is a great miscegenation in the population. Thus, we divide women into white and non-white races: 202 (66.7%) patients were white, 101 (33.3%) were non-white. The median age was 52 (25–86) years.

The inclusion criterion was a histologically confirmed diagnosis of breast malignancy. Exclusion criteria were; male gender, presence of associated infectious diseases, use of immunosuppressive drugs, immunosuppressive diseases and comorbidity with another type of cancer. The recorded data were age, parity, comorbidities, hemoglobin level, cell counts of neutrophils, lymphocytes and platelets, clinical staging, surgeries performed, chemotherapy administered, pathological staging, histological type, lymph node involvement, histological grade, immunohistochemistry for hormone receptors, ki-67 and HER-2 and overall survival. Blood collection was performed before the first treatment (surgery or neoadjuvant chemotherapy). NLR was obtained by dividing the number of neutrophils by the number of lymphocytes. PLR was obtained by dividing the number of platelets by the number of lymphocytes. As there are several studies in the literature referring to NLR and PLR cut-off values, we decided to adopt them as our cut-off values. Thus, we used a cut-off point of 4 for NLR [7, 11] and 185 for PLR [7, 12]. The hemoglobin value that defines anemia is already well established by the World Health Organization and was used in our study.

According to the immunohistochemical staining, tumors were divided into “hormone receptor positive” and “hormone receptor negative”. Patients with immunohistochemistry showing negative hormone receptors and positive HER-2 (+++), and patients showing negative hormone receptors and HER-2 negative were included in the “hormone receptor negative” group [13].

Data were analyzed with SPSS (Statistical Package for Social Science for Windows, IBM, Armonk, USA) version 20.0.

Chi-square test or Fisher's exact test were used to compare prognostic factors with NLR and hemoglobin. The Kaplan-Meier method was utilized for 5-year overall survival, and the comparison between the curves was performed by the log-rank Cox-Mantel test. Cox regression was used to verify the influence of the variables on mortality within 5 years. Initially, a univariate analysis was performed to determine the variables associated with mortality. Those with $p < 0.20$ were included in the model for multivariate analysis. Backward elimination was used to obtain the final model, eliminating the variables with values of $p > 0.05$ in descending order. A p-value < 0.05 was considered statistically significant.

3. Results

Characteristics of 303 patients included in the study according to NLR and anemia are described in Table 1.

Kaplan-Meier survival curves are shown in Figs. 1,2. NLR >4 and PLR >185 were associated with shorter overall survival ($p < 0.001$ and $p = 0.021$, respectively).

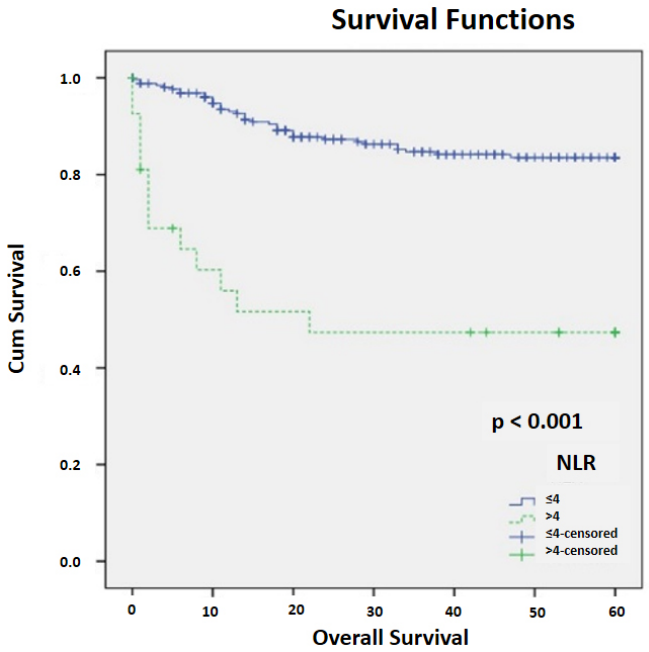

FIGURE 1. Survival curve according to NLR.

The univariate analysis of Cox regression showed that tumor size, lymph node status, presence of metastasis, chemotherapy, NLR and anemia are eligible to participate in the multivariate analysis model ($p < 0.20$); PLR did not meet the criteria ($p = 0.414$) (Table 2).

After multivariate regression, tumor size, lymph node status, metastasis, NLR and anemia remained as factors that independently correlate with mortality at 5 years. NLR >4 increased the risk of death by 7.76 times ($p < 0.001$) and hemoglobin <12 mg/d increased the risk of death by 2.47 times ($p = 0.037$) (Table 3).

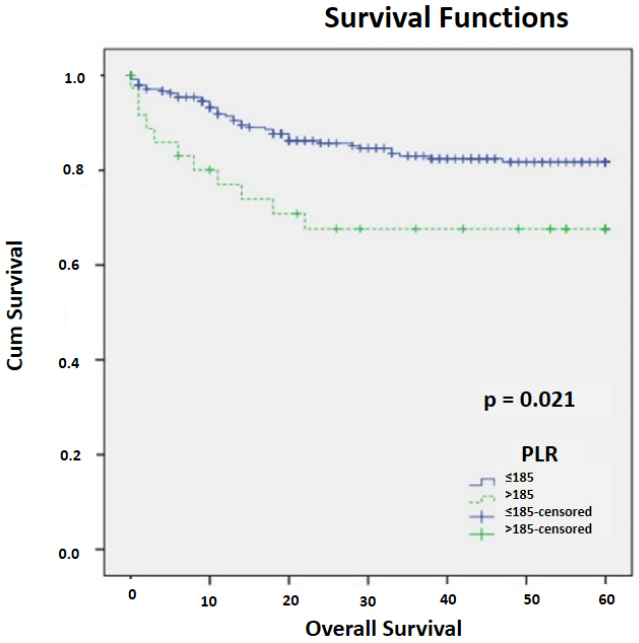

FIGURE 2. Survival curve according to PLR.

4. Discussion

NLR and PLR are simple indices obtained from the blood count, and are associated with known prognostic factors in cancer patients [12, 14]. These relationships may also independently relate to the overall survival of these patients. Recent studies have demonstrated a great potential for these ratios in clinical practice [6, 15].

Our data demonstrated that a high NLR resulted in an almost eight-fold increase in the risk of death within 5 years (Hazard Ratio (HR) 7.76, 95% Confidence interval (CI) 2.82–21.31, $p < 0.001$), regardless of other patient-specific factors or tumor characteristics. Previous studies with breast cancer have HR ranging from 1.45 to 24.87 for overall survival. A meta-analysis including 15 studies and 8563 patients showed an HR of 2.56 (95% CI 1.96–3.35, $p < 0.001$) [8]. Possibly, this variation in results is due to the different cut-off points used in the analyzes and due to the inclusion or exclusion of patients with metastases.

Another factor that influenced patients' overall survival was anemia. Patients with breast cancer and hemoglobin levels <12 g/dL had a hazard ratio (HR) of 2.47 (95% CI 1.06–5.77; $p = 0.037$) compared to patients with normal hemoglobin. Despite the population differences, this result was similar to the findings of a study with more than 2000 patients (HR 2.85, 95% CI 2.20–3.68, $p < 0.001$) [10]. The hemoglobin levels may be related to prognostic factors in a variety of tumors, including breast cancer [10, 16–18], ovarian [19–21] and ovarian borderline tumors [22], oral squamous carcinoma [23], lung, colorectal and liver tumors [18]. The presence of anemia before neoadjuvant chemotherapy was associated with poorer pathological response and lower survival [24]. Research shows that the relationship between anemia and cancer is mediated by the systemic inflammatory response. The infiltrating tumor cells and tissue macrophages secrete cytokines, such as IL-1, IL-6, INF-ɣ and TGF-β, capable of inhibiting erythropoiesis

and leading to anemia [25].

TABLE 2. Univariate analysis: factors influencing mortality in 5 years of breast cancer patients.

Variables	HR (95% CI)	*p*
Age	1.03 (0.97–1.08)	0.367
Menopause		
No (ref)		
Yes	1.00 (0.25–3.91)	0.997
Clinical staging		
O/I/II (ref)		
III/IV	0.60 (0.05–6.57)	0.675
Size		
T0/T1 (ref)		
T2	11.54 (1.16–115.06)	0.037
T3/T4	9.46 (0.79–11.92)	0.076
Axillary lymph nodes		
N0 (ref)		
N1	3.10 (0.84–11.41)	0.089
N2	13.77 (1.98–95.69)	0.008
N3	3.18 (0.43–23.55)	0.258
Metastasis		
No (ref)		
Yes	63.79 (9.36–434.77)	<0.001
Grade		
I (ref)		
II	0.77 (0.17–3.54)	0.737
III	1.75 (0.33–9.27)	0.513
Estrogen receptor		
Negative (ref)		
Positive	0.99 (0.32–3.07)	0.984
Surgery		
No (ref)		
Yes	0.64 (0.14–2.99)	0.566
Chemotherapy		
No (ref)		
Yes	0.46 (0.15–1.44)	0.183
Radiotherapy		
No (ref)		
Yes	1.91 (0.44–8.33)	0.389
Hormonotherapy		
No (ref)		
Yes	9.54 (0.52–175.38)	0.129
NLR		
≤4 (ref)		
>4	9.54 (0.52–175.38)	0.129
PLR		
≤185 (ref)		
>185	2.00 (0.38–10.58)	0.414
Platelets	1.00 (1.00–1.00)	0.778
Anemia		
No (ref)		
Yes	2.88 (0.78–10.60)	0.112
Leukocytosis		
No (ref)		
Yes	1.24 (0.27–5.64)	0.779
Neutrophilia		
No (ref)		
Yes	0.39 (0.02–6.71)	0.515
Lymphopenia		
No (ref)		
Yes	1.39 (0.15–13.09)	0.771

TABLE 3. Multivariate analysis: factors that influence mortality in 5 years of breast cancer patients.

Variables	HR (95% CI)	*p*
Size		
T0/T1 (ref)		
T2	12.53 (1.45–108.10)	0.022
T3/T4	14.96 (1.70–131.98)	0.015
Axillary lymph nodes		
N0 (ref)		
N1	2.00 (0.71–5.62)	0.189
N2	9.31 (2.77–31.23)	<0.001
N3	3.49 (0.85–14.31)	0.083
Metastasis		
No (ref)		
Yes	40.24 (12.51–129.37)	<0.001
NLR		
≤4 (ref)		
>4	7.76 (2.82–21.31)	<0.001
Anemia		
No (ref)		
Yes	2.47 (1.06–5.77)	0.037

Regarding PLR, although there was a clear difference between the groups with higher and lower values according to the Kaplan-Meier curve, the relation was not an independent factor for patients' overall survival. Zhu *et al*. [14] reviewed the literature and found that, although PLR was generally associated with lower overall survival (HR 1.55, 95% CI 1.07–2.25, $p = 0.022$), when only studies with a sample of less than 400 women were analyzed, the association between PLR and overall survival was not statistically significant (HR 1.34, 95% CI 0.34–5.23, $p = 0.674$).

The predictive value of NLR and PLR in the prognosis of breast cancer patients is due to their association with cancer-induced inflammatory response. Tumor cells have the ability to secrete factors that manipulate the immune system in their favor, leading to local and systemic inflammation, allowing tumor growth and progression, angiogenesis, invasion of other tissues and metastasis [26]. A study demonstrated that patients receiving chemotherapy had an increase of total CD8+ T cells after 3 months, with a decreased ratio of CD4:CD8, and patients with an inferior health status had more granulocytic cells, but lower levels of granulocytic myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), that can suppress the immune response [27].

Neutrophils and platelets play an important role in tumor development. Neutrophils are involved in tumor initiation, growth and metastasis by producing substances such as MMP9 (angiogenic factor) and reactive oxygen and nitrogen species, and by promoting immunosuppression by means of cytokine release and amino acid depletion [28]. Platelets, besides stimulating angiogenesis and tumor growth through the release of platelet-derived growth factor (PDGF), platelet-activating

factor (PAF) and vascular endothelial growth factor (VEGF), also protect circulating malignant cells by adhering to them and preserving them from elimination by the immune system, thus facilitating the occurrence of metastases [29]. On the other hand, studies show that lymphocytes can be associated with better prognosis and greater response to therapy in cancer patients [30]. A study found that the absolute number of lymphocytes positively influenced survival at 5 years [12]. This fact can be explained by the antitumor potential of these cells, which have the capacity to inhibit tumor growth and induce tumor cell death by cytotoxicity [31].

The main limitation of the present study was that it did not assess survival separately for each breast cancer molecular subtype. Studies with a larger sample may verify the validity of NRL and anemia as predictors of survival in each subtype and for each stage of breast cancer.

On the other hand, our study demonstrated the independent role of these parameters in the overall survival of breast cancer patients. The association of NLR with prognostic factors and survival in breast cancer is already described in the literature, but there are not many studies describing the relationship between anemia and survival, making this a strong point of our study. The discovery of new prognostic factors that correlate with breast cancer survival will provide additional tools allowing the clinician to choose the optimal treatment, individualized for each patient. For example, these findings may help the oncologist choose more aggressive treatments for women with anemia and an NLR greater than 4. In addition, these blood count parameters can be studied as potential targets for new therapies in this type of cancer. We emphasize that the NLR and hemoglobin measurements are readily obtained from a simple and low-cost clinical examination of a blood sample.

5. Conclusions

The relationship between the immune system and cancer remains an area of active study. NLR and hemoglobin levels are promising prognostic factors that are associated with overall survival in breast cancer patients, with the advantage of being parameters that are readily determined at low cost.

AUTHOR CONTRIBUTIONS

RSN, BMTM and EFCM designed the research study. RCS, REF, TCG, LMS, RSN, BMTM and EFCM performed the research. RSN and LMS analyzed the data. RCS, REF, TCG, LMS and RSN wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Federal University of Triângulo Mineiro (approval number: CAAE 20801413.1.0000.5154).

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CONFLICT OF INTEREST

The authors declare no conflict of interest. EFCM is serving as one of the Editorial Board members of this journal. We declare that EFCM had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Enrique Hernandez.

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