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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

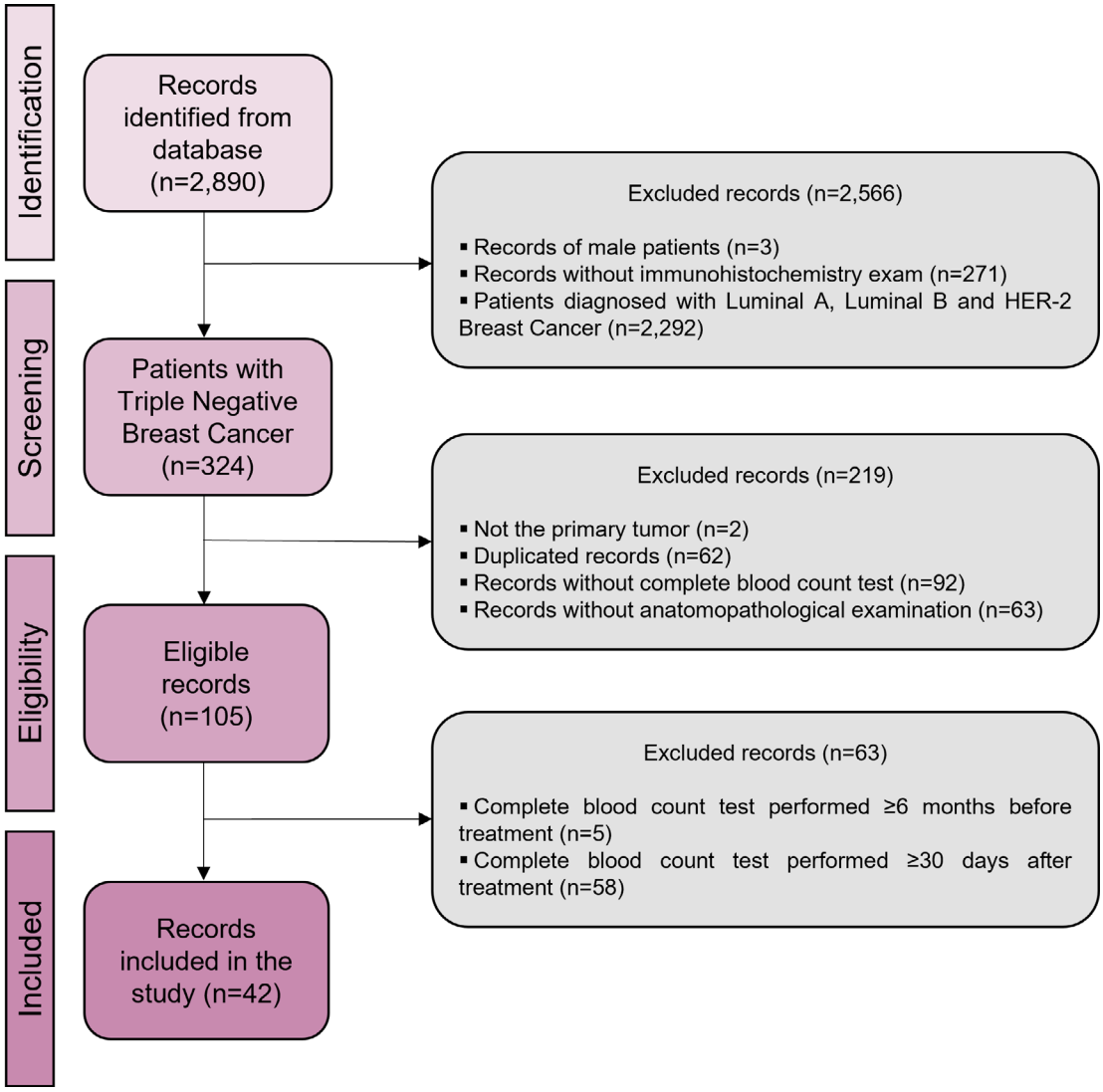


Figure 1. Records screened and included in the study.

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.

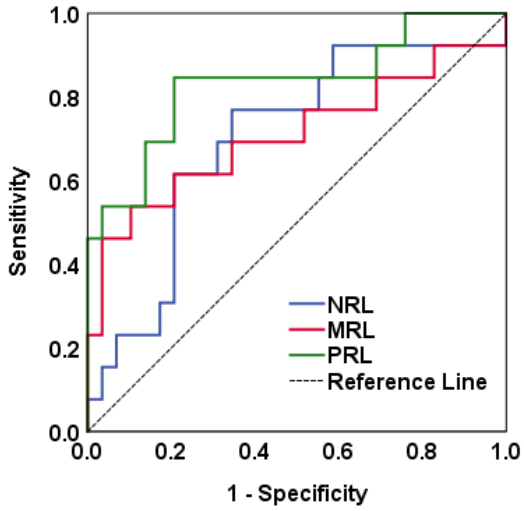
In the present study, we demonstrated that high PLR is a statistically significant predictor of worse OS and PFS (p=0.000, p=0.003, respectively) among women with TNBC. When compared to other pretreatment hematological ratios and factors associated with survival, such as the occurrence of recurrence,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

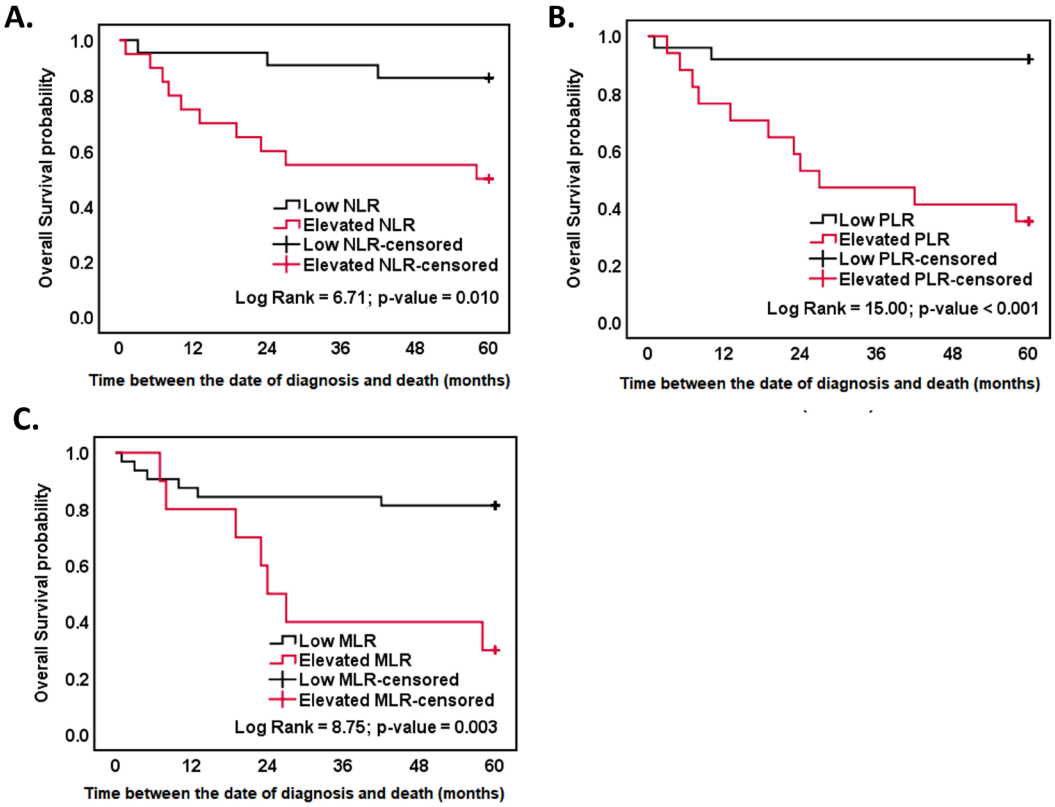


The areas under the curve for each parameter were 0.70 (p=0.040), 0.71 (p=0.033) and 0.83 (p=0.001), respectively.
NLR: neutrophil/lymphocyte ratio; MLR: monocyte/lymphocyte ratio; PLR: platelet/lymphocyte ratio.

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,



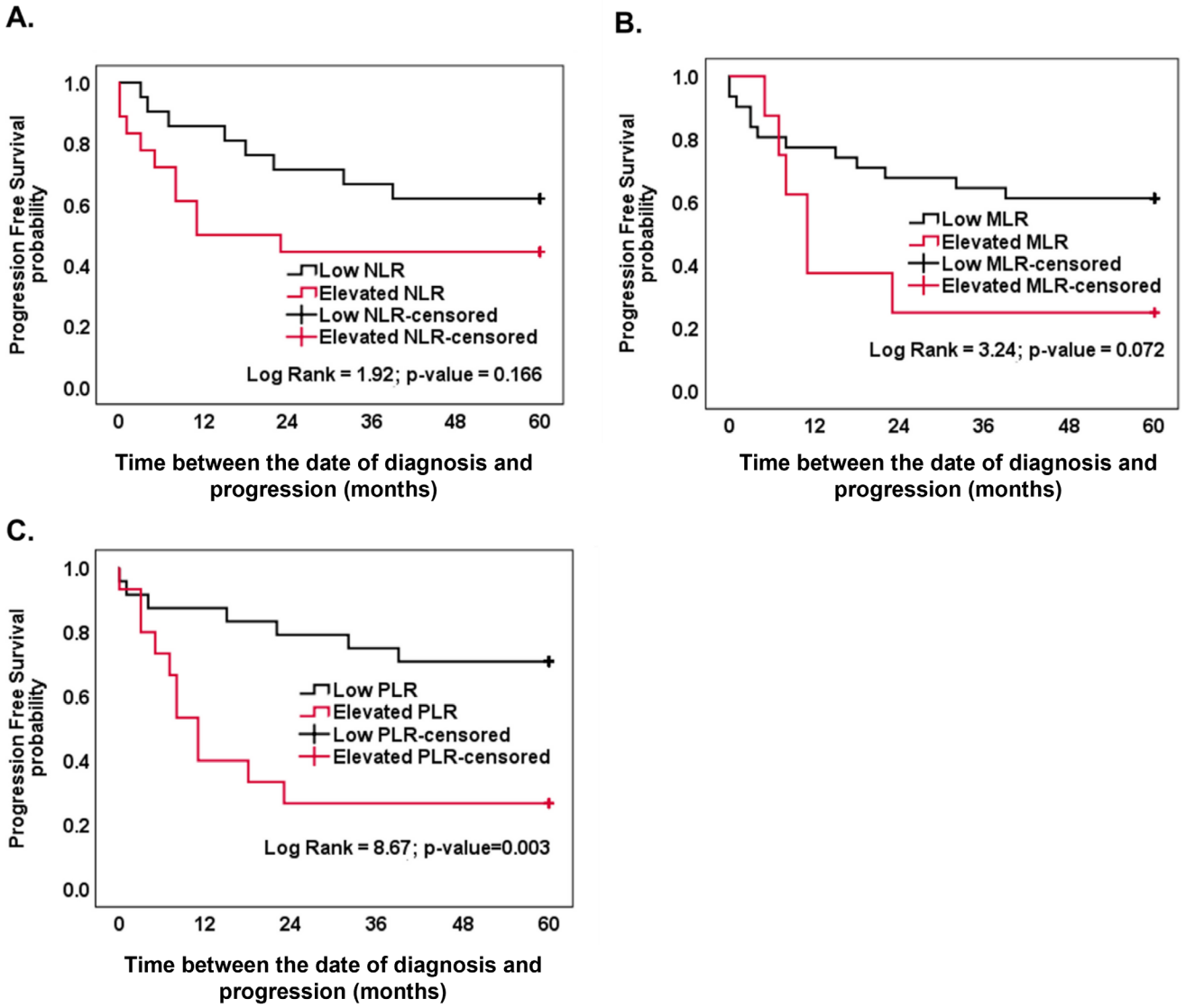
(A) Median overall survival was 54.95 months in the patients in the low neutrophil/lymphocyte ratio group and 38.55 months in the high neutrophil/lymphocyte ratio group. (B) Median overall survival was 51.1 months in the patients in the low monocyte/lymphocyte ratio group and 34.6 months in the patients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