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Pretreatment neutrophil-lymphocyte ratio has prognosis value in breast cancer patients

A relação neutrófilo-linfócito pré-tratamento tem valor prognóstico em pacientes com câncer de mama

La relación neutrófilos-linfocitos previa al tratamiento tiene valor pronóstico en pacientes con cáncer de mama

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Abstract
Objectives: This study aimed to determine the prognostic value of the pretreatment inflammatory indexes neutrophil-lymphocyte ratio, lymphocyte-monocyte ratio, and platelet-lymphocyte ratio in breast cancer. Methods: A retrospective cohort of patients with breast cancer receiving treatment at a specialized cancer hospital were collected from 2016. Pretreatment complete blood cell counts were evaluated to assess inflammatory indexes. The outcome variable was 5-year overall survival. Kaplan-Meier curves, log-rank test, and Cox regression (hazard ratio; 95% confidence interval) were used. Results: A total of 312 women (mean age 51.9 years; histopathological grade II 61.6%; tumor stage III 50.0%) were included in the study. Of these, 169 (54.2%) died within 5 years, the majority of whom had neutrophil-lymphocyte ratio ≥ 2.5 (62.5%; p= 0.002), histopathological grades II and III (60.4%; p= 0.024), more advanced tumor stages (87.7%; p<0.001), and significantly lower overall survival. Neutrophil-lymphocyte ratio ≥ 2.5 (hazard ratio, 1.53; 95% CI, 1.11-2.11) was an independent prognostic factor for overall survival. In addition, histopathological grades II (hazard ratio, 3.53; 95% confidence interval, 1.29-9.68) and III stage (hazard ratio, 2.50; 95% confidence interval, 1.45-4.34) and stage IV (hazard ratio, 6.07; 95% confidence interval, 3.43-10.73) demonstrated predictive power. Conclusion: Pretreatment neutrophil-lymphocyte ratio was considered a useful predictor of overall survival in breast cancer.
Keywords: Breast cancer; Inflammation; Biomarkers; Prognosis; Survival.

Resumo
Objetivos: Este estudo teve como objetivo determinar o valor prognóstico dos índices inflamatórios pré-tratamento relação neutrófilo-linfócito, relação linfócito-monócito e relação plaqueta-linfócito no câncer de mama. Métodos:

Uma coorte retrospectiva de pacientes com câncer de mama em tratamento em um hospital especializado em câncer foi coletada a partir de 2016. Hemogramas completos pré-tratamento foram avaliados para avaliar os índices inflamatórios. A variável de desfecho foi a sobrevida global em 5 anos. Curvas de Kaplan-Meier, teste de log-rank e regressão de Cox (hazard ratio; intervalo de confiança de 95%) foram usados. Resultados: Um total de 312 mulheres (idade média de 51,9 anos; grau histopatológico II 61,6%; estágio do tumor III 50,0%) foram incluídas no estudo. Destes, 169 (54,2%) morreram em 5 anos, a maioria com relação neutrófilo-linfócito ≥ 2,5 (62,5%; p= 0,002), graus histopatológicos II e III (60,4%; p= 0,024), tumores mais avançados (87,7%; p<0,001) e sobrevida global significativamente menor. Razão neutrófilos-linfócitos ≥ 2,5 (hazard ratio, 1,53; IC 95%, 1,11-2,11) foi um fator prognóstico independente para a sobrevida global. Além disso, os graus histopatológicos II (hazard ratio, 3,53; intervalo de confiança de 95%, 1,29-9,68) e estágio III (hazard ratio, 2,50; intervalo de confiança de 95%, 1,45-4,34) e estágio IV (hazard ratio, 6,07; 95% intervalo de confiança, 3,43-10,73) demonstrou poder preditivo. Conclusão: A relação neutrófilos-linfócitos pré-tratamento foi considerada um preditor útil de sobrevida global no câncer de mama.
Palavras-chave: Câncer de mama; Inflamação; Biomarcadores; Prognóstico; Sobrevida.

Resumen
Objetivos: Este estudio tuvo como objetivo determinar el valor pronóstico de los índices inflamatorios previos al tratamiento, la relación neutrófilos-linfocitos, la relación linfocitos-monocitos y la relación plaquetas-linfocitos en el cáncer de mama. Métodos: Se recopiló una cohorte retrospectiva de pacientes con cáncer de mama que recibieron tratamiento en un hospital oncológico especializado a partir de 2016. Se evaluaron los hemogramas completos previos al tratamiento para evaluar los índices inflamatorios. La variable de resultado fue la supervivencia global a los 5 años. Se utilizaron curvas de Kaplan-Meier, log-rank test y regresión de Cox (hazard ratio; intervalo de confianza del 95%). Resultados: Se incluyeron en el estudio un total de 312 mujeres (edad media 51,9 años; grado histopatológico II 61,6%; estadio tumoral III 50,0%). De estos, 169 (54,2%) fallecieron dentro de los 5 años, la mayoría con cociente neutrófilo-linfocito ≥ 2,5 (62,5%; p= 0,002), grados histopatológicos II y III (60,4%; p= 0,024), tumor más avanzado (87,7%; p<0,001), y una supervivencia global significativamente menor. La relación neutrófilos-linfocitos ≥ 2,5 (cociente de riesgos instantáneos, 1,53; IC del 95 %, 1,11-2,11) fue un factor pronóstico independiente para la supervivencia global. Además, los grados histopatológicos II (razón de riesgo, 3,53; intervalo de confianza del 95 %, 1,29-9,68) y estadio III (razón de riesgo, 2,50; intervalo de confianza del 95 %, 1,45-4,34) y estadio IV (razón de riesgo, 6,07; 95 % intervalo de confianza, 3.43-10.73) demostró poder predictivo. Conclusión: la proporción de neutrófilos-linfocitos antes del tratamiento se consideró un predictor útil de la supervivencia global en el cáncer de mama.
Palabras clave: Cáncer de mama; Inflamación; Biomarcadores; Pronóstico; Supervivencia.

1. Introduction

The overall survival (OS) of patients with breast cancer is on the rise in developed countries, but demonstrates great global disparity. Five-year survival rates of 76.9% and 75.2% have been reported for the periods from 2005 to 2009 and 2010 to 2014, respectively (Allemani *et al*., 2018). Longer OS in breast cancer is primarily related to earlier diagnosis and treatment. Consequently, lower mortality rates are found in patients diagnosed at the initial stages of the disease (Ethier *et al*., 2017).

Several clinical, therapeutic, and sociodemographic factors have shown prognostic value in patients with breast cancer (Ethier *et al*., 2017; Marín Hernández *et al*., 2018; Guo *et al*., 2019; Wiegert *et al*., 2020). According to Ayala (2019), the factors with the greatest prognostic value for these patients are the stage of the disease, the characteristics of the tumor, treatments received, age, race, and economic status. Nonetheless, the identification of simple and objective prognostic factors remains a challenge in clinical practice (Geng *et al*., 2018). In this context, biomarkers of systemic inflammatory response could be helpful as they are easily tested at low cost.

There is ample evidence of the role of systemic inflammation in tumor progression and metastasis (De Giorgi *et al*., 2019; Huszno *et al*., 2020; Zhang *et al*., 2020). Accordingly, patients with advanced-stage disease have an increased inflammatory response caused by increased levels of inflammatory cytokines induced by the solid tumor, as well as the release of pro-angiogenic factors (Ethier *et al*., 2017; Duan *et al*., 2018; Cao *et al*., 2020; Chen *et al*., 2020). Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte- monocyte ratio (LMR) have been studied as factors associated with a worse prognosis in several types of tumors, including in the breast (Guo *et al*., 2019; De Giorgi *et al*., 2019; Duan *et al*.,

2018; Cao *et al*., 2020; Zhang *et al*., 2017; Cho *et al*., 2018; Gago-Dominguez *et al*., 2020). A point of note is that these biomarkers can vary considerably in response to anticancer treatment.

In addition, at the present moment, few studies have evaluated the prognostic power of NLR, PLR, and LMR at the pre-treatment phase of breast cancer. Thus, this study aimed to determine the prognostic value of these inflammatory pretreatment indexes in patients with breast cancer receiving treatment at a specialized cancer hospital.

2. Methodology

2.1 Study design and patients

This retrospective cohort study was carried out with women with breast cancer treated at a national Brazilian reference hospital for cancer treatment between February and November 2016. The eligibility criteria were: age ≥ 18 years; diagnosis of breast cancer confirmed by histopathological analysis; no previous anti-cancer treatment; laboratory data available in electronic records. The exclusion criteria were: presence of a pre-existing hematological disease; infection, fever, or other inflammatory diseases prior to treatment; incomplete clinical data.

The original study protocol was approved by the ethics committee Research Ethics Committee of the National Cancer Institute (CEP-INCA) (CAAE: 51310915.7.0000.5274) and all the participants read and signed an informed consent form.

2.2 Data collection

This study is part of a larger study. For this proposal, the following data, which predated the patients' cancer treatment, were extracted from their electronic medical records by one trained researcher: age (years), presence of comorbidities (diabetes mellitus and systemic arterial hypertension), histopathological type (invasive ductal carcinoma or invasive lobular carcinoma or others) and histopathological grade (well-differentiated [I] or moderately differentiated [II] or poorly differentiated [III]) and tumor stage (early stage [I and II] or locally advanced [III] or with distant metastasis [IV]).

In addition, routine laboratory data were collected, including absolute lymphocyte count, absolute neutrophil count, absolute monocyte count, and platelets. These values were then used to calculate the pretreatment baseline NLR, LMR, and PLR.

For the present study, the duration of follow-up was calculated from the date of diagnosis to the date of death from any cause. All the patients who were alive after the end of follow-up (5 years) were censored for the survival analysis. The latest follow-up of this study was in May 2020.

2.3 Statistical analysis

Statistical analysis was performed using Stata 13.1 (Stata Corp., College Station, Texas, USA). Statistical significance was set at $p < 0.05$.

The Kolmogorov-Smirnov test was used to assess the distribution of variables. Continuous numerical variables were described as means ± standard deviation (SD) or medians with interquartile range (IQR, 25th and 75th percentiles), according to distribution and normality. Categorical variables were described as absolute frequencies (n) and relative frequencies (%). Proportions were compared using the chi-squared test, means were compared using Student's t-test, and medians were compared using the corresponding non-parametric test, the Mann-Whitney U test.

Biomarker values were expressed as percentiles (1st, 5th, 10th, 15th, 25th, 50th, 75th, 90th, 95th, and 99th), and their medians were compared against death within 5 years. A receiver-operating characteristic curve (ROC) was constructed to determine the optimal NLR cutoff points related to death within 5 years (the only inflammatory index with a statistically significant association with death according to the Mann-Whitney U test).

All the variables for which p < 0.20 in the analyses of the comparisons between groups (Mann-Whitney U tests, Student's t test, and chi-square test) were selected for the survival analyses. Kaplan-Meier curves and the log-rank test were used to verify the difference in survival probability between the groups. Additionally, the Cox proportional hazards model was used, taking the hazard ratio (HR) and its respective 95% confidence interval (CI) as the effect measure. The stepwise selection method was used, in which variables with p values < 0.05 in the bivariate regression models were included in the final model.

3. Results

A total of 312 patients were included in this study. All the patients were female, with a mean age of 51.9 (± 12.7) years and a predominance of tumor stage III (50.0%). One hundred and sixty-nine (54.2%) of them died within 5 years, the majority of whom had histopathological grade II (p = 0.030) and tumor stage IV (p <0.001) (Table 1).

Table 1. Demographic and clinical characteristics of women with breast cancer according to the occurrence of death within 5 years (n = 312).

Variables	Total N (%)	Death within 5 years		p-value
		No n = 143 (45.8%)	Yes n = 169 (54,2%)	
Age (years)[a]	51.9 (12.7)	50.6 (13.2)	53.0 (12.2)	0.125
Age < 60 years[b]				
Yes	235 (75.3%)	107 (45.5%)	128 (54.5%)	0.852
No	77 (24.7%)	36 (46.7%)	41 (53.3%)	
Histological type [b]				
IDC	274 (87.8%)	127 (46.3%)	147 (53.7%)	0.603
ILC	23 (7.4%)	11 (47.8%)	12 (52.2%)	
Others	15 (4.8%)	5 (33.3%)	10 (66.7%)	
Histological grade[c]				
1	16 (5.4%)	12 (75.0%)	4 (25.0%)	**0.030**
2	183 (61.6%)	84 (45.9%)	99 (54.1%)	
3	98 (33.0%)	38 (39.6%)	60 (60.4%)	
Histopathological grade[c]				
I+II	57 (23.4%)	41 (71.9%)	16 (28.1%)	**<0.001**
III	122 (50.0%)	53 (43.4%)	69 (56.6%)	
IV	65 (26.6%)	8 (12.3%)	57 (87.7%)	
SAH[b]				
No	169(54.2%)	80 (47.3%)	89 (52.7%)	0.562
Yes	143(45.8%)	63 (44.1%)	80 (55.9%)	
DM[b]				
No	251 (80.4%)	114 (45.4%)	134 (54.6%)	0.765
Yes	61 (19.6%)	29 (47.5%)	32 (52.5%)	

Note: n = number of observations; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; SAH = systemic arterial hypertension; DM = diabetes mellitus.
[a]Mean (standard deviation)/Student's t-test);
[b]Number of observations (frequency) / Chi-square test for proportions;
[c]Variables with missing data;
P-values in bold indicate statistical significance (< 0.050). Source: Authors.

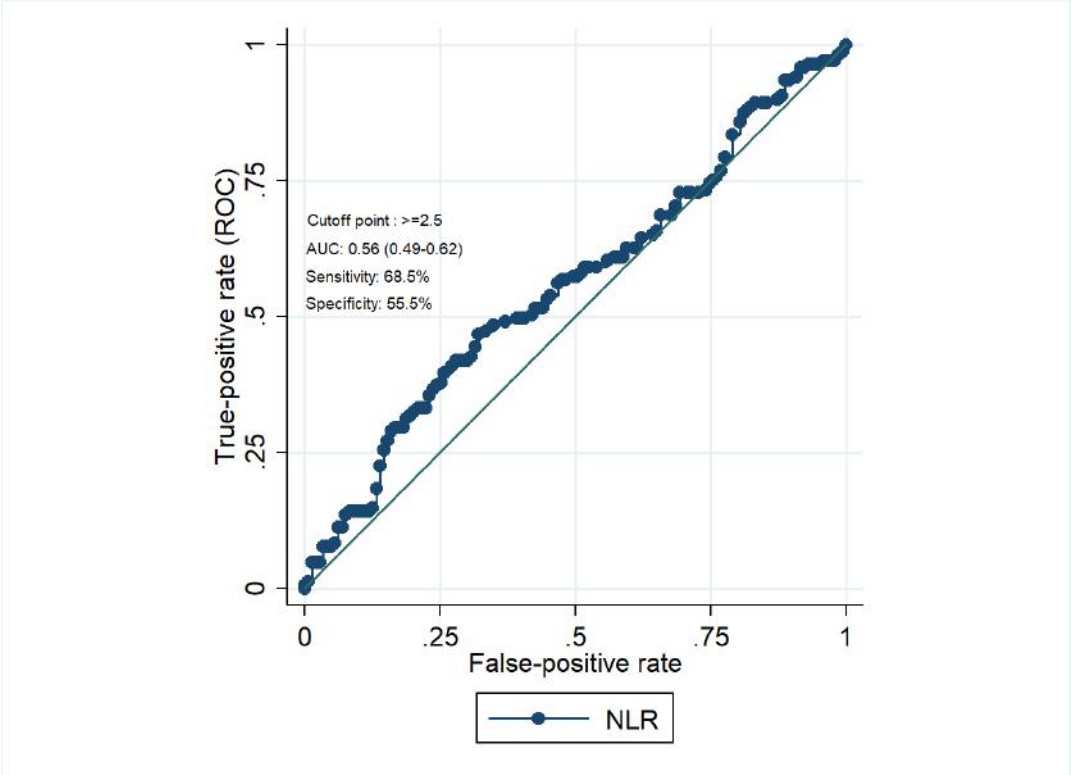
The median NRL was 2.1 (IQR, 1.6-3.2) and was significantly higher in the patients who died (p = 0.049), while the LMR, and PLR showed no statistically significant difference (Table 2). According to the ROC analysis, the optimal cutoff point for NLR was ≥ 2.5 for 5-year mortality (area under the ROC, 0.56 [95% CI, 0.49, 0.62]) (Figure 1).

Table 2. Percentile description of laboratory markers in women with breast cancer (n = 312).

Variables	Total									Death within 5 years		p-value[a]
	P1	P5	P10	P25	P50	P75	P90	P95	P99	No n=143 (45,8%)	Yes n=169 (54,2%)	
NLR	0.8	1.0	1.1	1.6	2.1	3.2	5.5	7.0	16.9	2.0	2.2	**0.049**
PLR	43.0	62.2	76.0	94.0	123.2	181.0	266.4	298.5	598.2	11.9	12.9	0.079
LMR	0.9	1.5	2.0	2.9	3.9	5.2	6.5	7.6	10.7	3.9	3.8	0.245
Neutrophil (mmL/³)	1774	2321	2815	3556	4699	6096	8216	10026	16220	4361	4766	0.188
Lymphocyte (mmL/³)	74	311	464	794	1221	1701	2383	2854	3708	1/250	1208	0.094
Monocyte (mmL/³)	185	290	338	451	541	682	844	960	1260	539	542	0.535
Platelet (mmL/³)	124000	167000	187000	218000	266000	324000	392000	484000	636000	263000	273000	0.392
Leukocyte (mmL/³)	4110	4800	5130	6400	7805	9595	11900	13700	18000	7700	7920	0.668

Note: n = number of observations; P = percentile; NLR = neutrophil-lymphocyte ratio; PLR = platelet-lymphocyte ratio; LMR = lymphocyte-monocyte ratio; Hb = hemoglobin
[a]p-value refers to the Mann-Whitney U test for differences in medians between groups.
P-values in bold indicate statistical significance (< 0.050). Source: Authors.

Figure 1: Receiver-operating characteristic curve-to-neutrophil-lymphocyte ratio as a predictor of death in 5 years in breast cancer patients.



Note: AUC = area under the curve; ROC = Receiver-operating characteristic; NLR = neutrophil-lymphocyte ratio. Source: Authors.

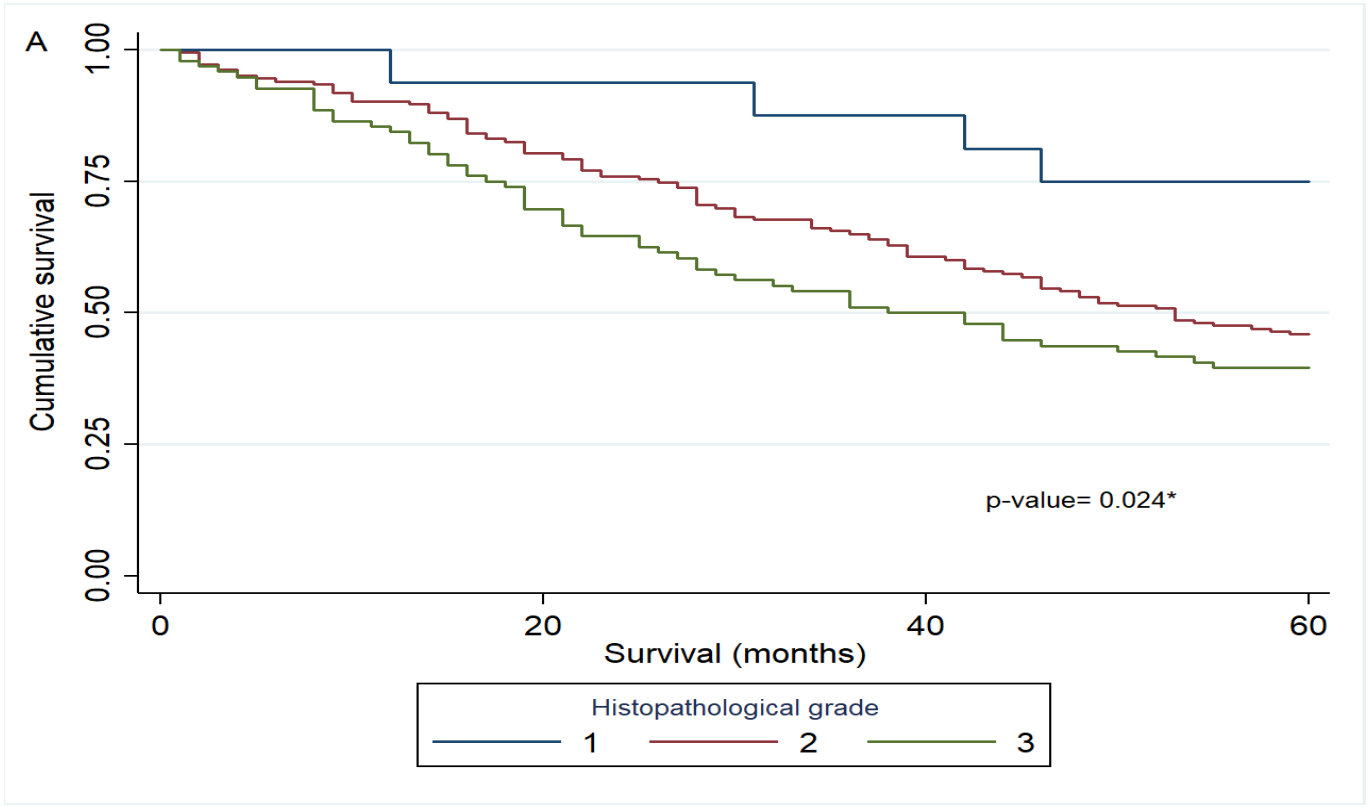
The median OS was 52 (IQR, 22-60) months. Patients with NLR < 2.5 had a median OS of 60 (IQR, 28-60) months, while those whose NLR ≥ 2.5 had a median OS of 35 (IQR, 14-60) months (p = 0.002). In addition, the patients with higher histopathological grades (p = 0.024) and more advanced tumor stage (p < 0.001) had significantly shorter OS (Table 3 and Figure 2).

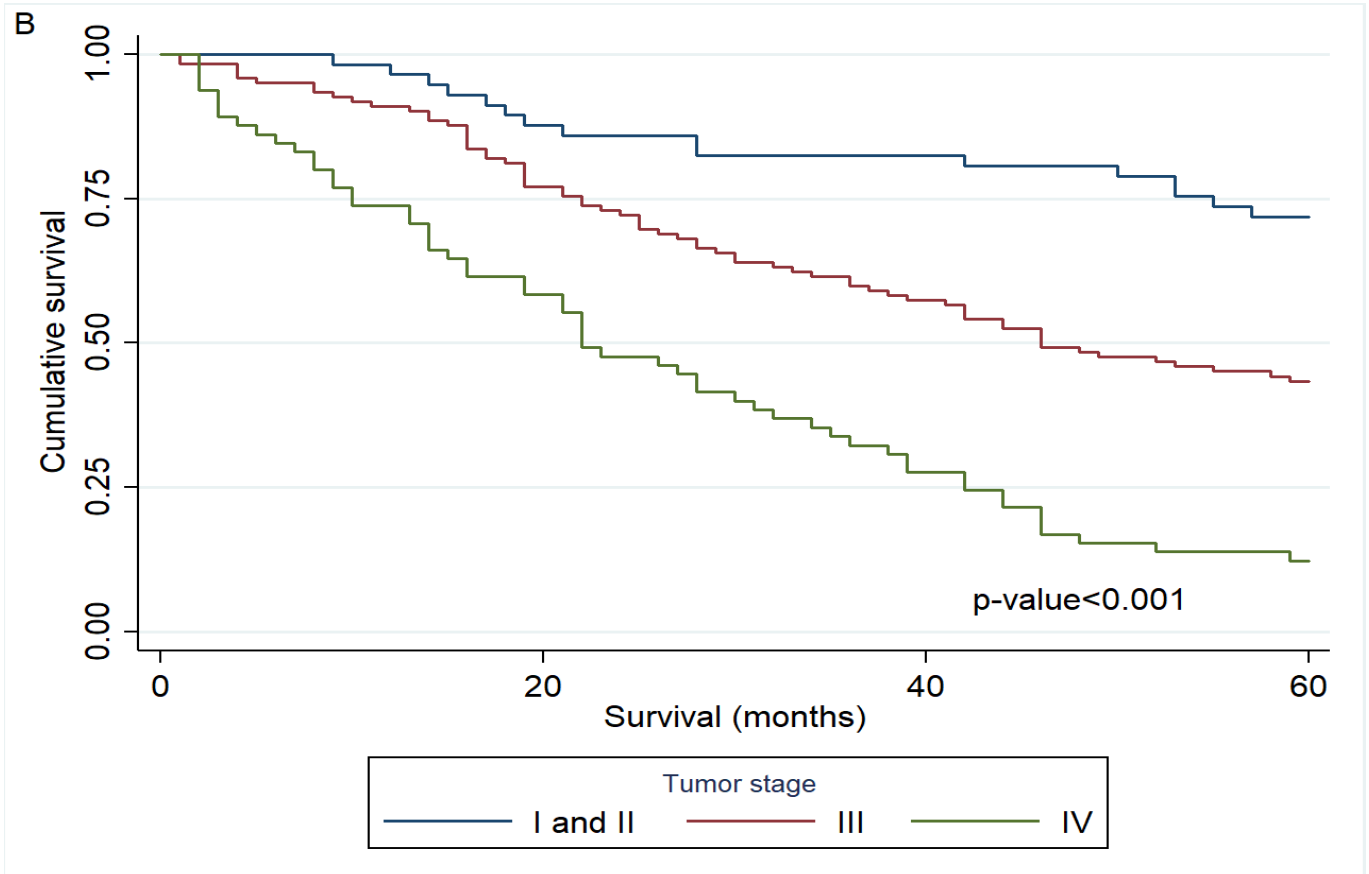
Table 3: Overall survival (OS) of women with breast cancer (n = 312).

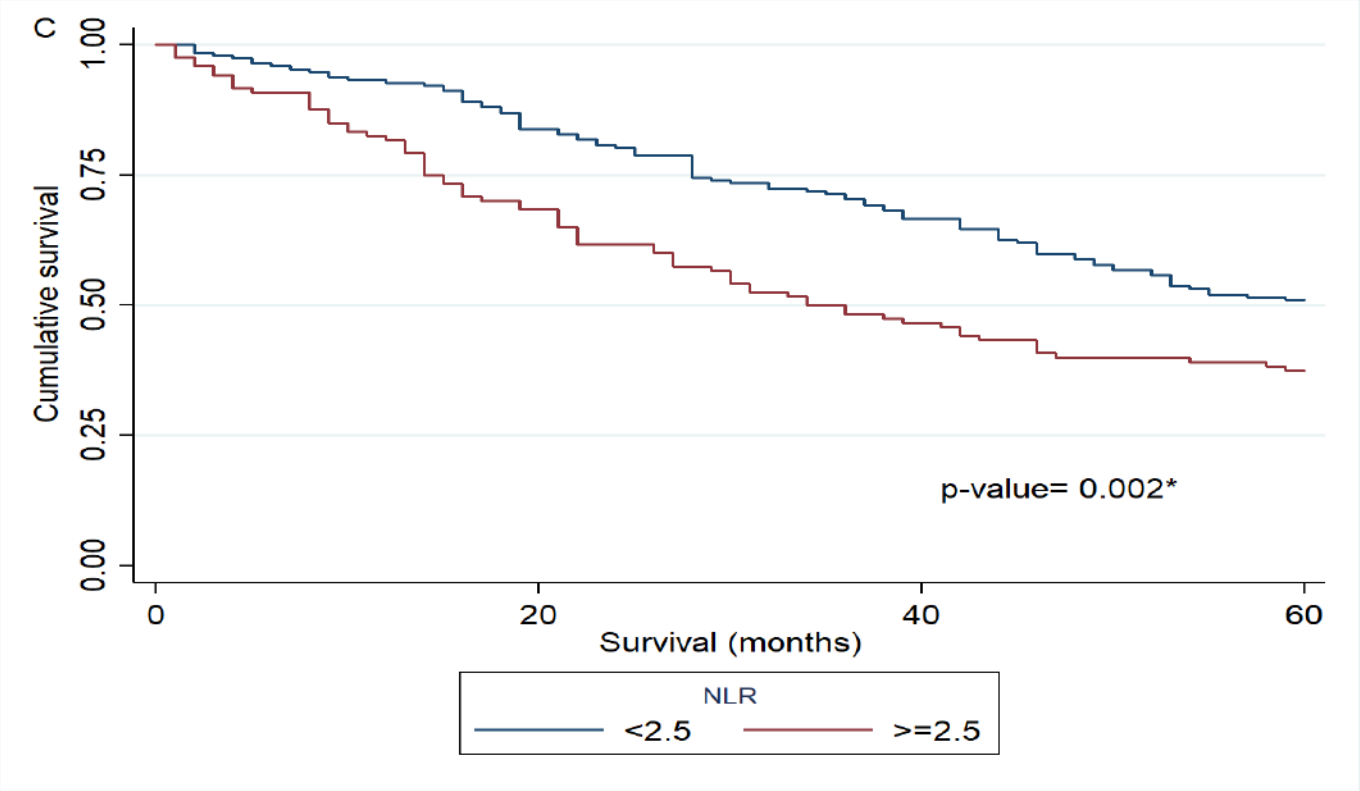
Variables	Events (%)	OS	
		Median /IQR (months)	p-value[a]
NLR ≥ 2.5			
No	49.0	60 (28-60)	**0.002**
Yes	62.5	35 (14-60)	
Histological grade			
1	25.0	60 (53-60)	**0.024**
2	54.1	53 (26-60)	
3	60.4	40 (17-60)	
Histopathological grade [b]			
I+II	28.1	60 (55-60)	**<0.001**
III	56.6	46 (22-60)	
IV	87.7	22 (10-42)	

Note: IIQ = interquartile range; NLR = neutrophil-lymphocyte ratio
[a]p-value refers to the log-rank test for differences in median survival between groups.
p-values in bold indicate statistical significance (< 0.050). Source: Authors.

Figure 2: Survival curves of patients with breast cancer according to (A) histopathological grade, (B) tumor stage, and (C) NLR.







Note: NLR = neutrophil-lymphocyte ratio.
*p-value refers to log-rank test. Source: Authors.

The multivariate Cox regression model demonstrated that NRL ≥ 2.5 (HR, 1.53; 95% CI, 1.11, 2.11) was an independent prognostic factor for 5-year mortality, as were histopathological grades II (HR, 3.53; 95% CI, 1.29, 9.68) and III (HR, 2.50; 95% CI, 1.45-4.34) and tumor stage IV (HR, 6.07; 95% CI, 3.43-10.73) (**Table 4**).

Table 4: Predictors of 5-year overall survival (OS) in women with breast cancer (n = 312).

Variables	Gross		Adjusted	
	HR (95% CI)	p-value*	HR (95% CI)	p-value*
Histological grade				
1	1.00		1.00	
2	2.68 (0.99-7.29)	0.053	3.53 (1.29-9.68)	**0.014**
3	3.44 (1.25-9.48)	**0.017**	4.15 (1.49-11.52)	**0.006**
Histopathological grade [b]				
I+II	1.00		1.00	
III	2.54 (1.47-4.39)	**0.001**	2.50 (1.45-4.34)	**0.001**
IV	6.09 (3.48-10.67)	**<0.001**	6.07 (3.43-10.73)	**<0.001**
NLR ≥ 2.5				
No	1.00		1.00	
Yes	1.62 (1.20-2.20)	**0.002**	1.53 (1.11-2.11)	**0.009**

Note: CI = confidence interval; HR = hazard ratio; NLR = neutrophil-lymphocyte ratio
Bold characters indicate significant differences (< 0.050).
*p-value refers to Cox regression. Source: Authors.

4. Discussion

In this study, female pretreatment breast cancer patients at a specialized cancer hospital were studied retrospectively. The results indicate that NRL is an independent prognostic factor for this group, alongside recognized prognostic factors such as higher histological grade and more advanced tumor stage. The final regression model confirms the independent predictive power of each of these three variables (eg, NLR can be considered a prognostic factor independent of the patient's clinical staging). These findings highlight indicate that NRL – a simple and objective factor – can help to identify women with a worse prognosis before they start their cancer treatment trajectory, enabling the design of a supportive care plan.

More than half of the patients evaluated died within five years of follow-up. Among them, there were higher proportions of patients with histopathological grade 3 and clinical tumor stage IV, in addition to high NRL. Allemani (2018) demonstrated that the probability of 5-year survival in women with breast cancer was greater than 90.0% among North American and Australian women and 40.0% among South African women. This could be explained by the fact that in low-income countries, more than 60% of women are only diagnosed when the disease has reached an advanced stage (tumor stages III and IV) (Jedy-Agba *et al*., 2018). In developed countries such as the United States, only 6% of women have evidence of distant metastasis at the time of (DeSantis *et al*., 2019).

Our results corroborate the study by Höfelmann (2014) carried out with 170 Brazilian women with breast cancer, which demonstrated that the risk of mortality (HR, 17.1; 95% CI, 2.17, 135.05) was higher in the patients at stages III and IV. Another study with data from a cohort of 269 women with breast cancer in French Guiana reported that the presence of distant metastases was associated with an increased risk of death (HR, 20.78; 95% CI, 7.72, 55.89) (Roué *et al*., 2016). Regarding histological grade, the more undifferentiated the cells, the more distant their characteristics are from normal ones. Thus, grades 2 and 3 are considered worse prognostic factors (Rakha *et al*., 2008; Singh *et al*., 2018). The results of Ayala (2019) showed that in 471 women with breast cancer, the presence of lymphatic invasion, increased age, and advanced stage of the disease were predictors of a worse prognosis. In the study conducted by Freitas Júnior (2017), the factors that associated with the worst prognosis were axillary lymph nodes, histological grade, progesterone receptor, positive HER 2, cancer stage, and disease extension.

In addition to recognized prognostic factors such as tumor stage and histological grade, our results show NRL to be a significant prognostic marker. Several studies in the literature have addressed inflammation and cytokine production in different types and stages of cancer. Neutrophils are responsible for inflammatory and immune response and influence tumor development, progression, and metastasis through factors such as neutrophil elastase, matrix metalloproteinase - 9 (MMP - 9), nuclear factor - κB (NF - kB), vascular endothelial growth factor (VEGF), and interleukin-8 (IL-8) (Chen *et al*., 2020). However, neutropenia can also be the result of elevated granulopoiesis and therefore may not be an adverse sign for cancer progression. However, evidence of the harmful effect of circulating neutrophils and elevated NLR on prognosis and survival in several types of tumors, with the exception of gastric cancer, seems consistent in the literature (Gago-Dominguez *et al*., 2020).

Our results showed that patients with LNR < 2.5 survived almost twice as long as others with a significantly higher risk of death within 5 years. One explanation could be the fact that systemic inflammatory response is associated with the progression and severity of the disease and therefore a worse prognosis (Shalapour & Karin, 2015).

Divergent cutoff points have been reported in the literature (Zhang *et al*., 2020). In a meta-analysis conducted by Wei (2016) with preoperative patients, which included 12 studies, the high cutoff for NRL associated with OS ranged from 2 to 4. In a study by Wariss (2017) with 2374 female patients in pre-treatment, the NRL cutoff point for OS was > 5.00 (HR, 1.66; CI 95%, 1.08, 2. 55; p = 0.021). This is greater than the cutoff points described in other meta-analyses.

Ethier (2017) based on the results of a meta-analysis with 15 studies totaling 8,563 breast cancer patients, found that most of the selected articles (n =13) considered a cutoff point of > 3.0 for NRL (HR, 2.56; 95% CI, 1.96, 3.35) for analyses of

OS, and > 2.5 (n = 10) for analyses of disease-free survival. According to the meta-analysis conducted by Duan (2018) of 20 studies, with a total of 9,837 patients in the preoperative period, high NRL value (cutoff points from 2 to 3.3) was associated with an increased risk of mortality (HR, 2.45; 95% CI, 1.69, 3.54, p = < 0.001). In a study by Cho (2018), the optimal cutoff point for NRL in 661 breast cancer patients was > 1.3 (AUC, 0.58; sensitivity, 80.6; specificity 36.7), while De Giorgi (2019) found NRL ≥ 3.0 (AUC, 0.58; sensitivity, 53.6; specificity, 59.8) to be the optimal cutoff in a study of 516 patients with breast cancer. In another meta-analysis with 14,264 breast cancer patients, the NRL cutoff points ranged from 1.35 to 3.0 (HR, 1.78; 95% CI, 1.49, 2.13) (Guo *et al*., 2019).

In a study by Cao (2020) with 906 preoperative, pretreatment breast cancer patients, the NRL cutoff point was > 2.2 (AUC, 0.829; 95% CI, 0.792, 0.866; sensitivity, 95.4%; specificity, 61.7%). In a study by Kim (2020) of 533 pretreatment breast cancer patients, the NRL cutoff point was > 1.82 for overall survival (AUC, 0.601; 95% CI, 0.520, 0.681; sensitivity, 64.2%; specificity, 52.1%), in contrast to several studies, demonstrating that NRL after initial treatment better reflects prognosis than NRL at time of diagnosis.

Some of these values differ from those found in our study, which can be explained by the intrinsic variability between the populations studied, histological types and stages, and systemic and individual responses. However, it is worth emphasizing that the accuracy of these studies is similar to that of our results, which makes us reflect on whether values lower than NRL 3 may be more appropriate for assessing survival in these patients.

Some limitations of this study include its retrospective and cross-sectional nature, not permitting the evaluation of variations of NRL over time. Future research is needed to determine whether the prognosis varies after this period. Also, the sample size did not allow the sample to be stratified into subgroups, as found in some studies in the literature.

5. Conclusion

Our results corroborate those of various studies, finding that in addition to recognized prognostic factors such as histological grade and tumor stage, NRL is a useful prognostic indicator for breast cancer. Few studies have been published, particularly based on data from middle-income countries, on NLR as a predictive and/or prognostic factor in the pretreatment phase of breast cancer.

References

Allemani, C., Matsuda, T., Di Carlo, V., Harewood, R., Matz, M., Nikšić, M., Bonaventure, A., Valkov, M., Johnson, C. J., Estève, J., Ogunbiyi, O. J., Azevedo E Silva, G., Chen, W. Q., Eser, S., Engholm, G., Stiller, C. A., Monnereau, A., Woods, R. R., Visser, O., Lim, G. H., … CONCORD Working Group (2018). Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet (London, England)*, *391*(10125), 1023–1075. https://doi.org/10.1016/S0140-6736(17)33326-3

Ayala, A., Anjos, J., Cassol, G. A., & Höfelmann, D. A. (2019). Sobrevida em 10 anos em mulheres com câncer de mama: coorte história de 2000-2014 [Survival rate of 10 years among women with breast cancer: a historic cohort from 2000-2014]. *Ciencia & saude coletiva*, *24*(4), 1537–1550. https://doi.org/10.1590/1413-81232018244.16722017

Cao, X., Zhou, Y., Mao, F., Lin, Y., & Sun, Q. (2020). Combination of preoperative fibrinogen concentration and neutrophil-to-lymphocyte ratio for prediction of the prognosis of patients with resectable breast cancer. *Oncology letters*, *20*(5), 200. https://doi.org/10.3892/ol.2020.12061

Chen, L., Kong, X., Wang, Z., Wang, X., Fang, Y., & Wang, J. (2020). Pre-treatment systemic immune-inflammation index is a useful prognostic indicator in patients with breast cancer undergoing neoadjuvant chemotherapy. *Journal of cellular and molecular medicine*, *24*(5), 2993–3021. https://doi.org/10.1111/jcmm.14934

Cho, U., Park, H. S., Im, S. Y., Yoo, C. Y., Jung, J. H., Suh, Y. J., & Choi, H. J. (2018). Prognostic value of systemic inflammatory markers and development of a nomogram in breast cancer. *PloS one*, *13*(7), e0200936. https://doi.org/10.1371/journal.pone.0200936

De Giorgi, U., Mego, M., Scarpi, E., Giordano, A., Giuliano, M., Valero, V., Alvarez, R. H., Ueno, N. T., Cristofanilli, M., & Reuben, J. M. (2019). Association between circulating tumor cells and peripheral blood monocytes in metastatic breast cancer. *Therapeutic advances in medical oncology*, *11*, 1758835919866065. https://doi.org/10.1177/1758835919866065

DeSantis, C. E., Ma, J., Gaudet, M. M., Newman, L. A., Miller, K. D., Goding Sauer, A., Jemal, A., & Siegel, R. L. (2019). Breast cancer statistics, 2019. *CA: a cancer journal for clinicians*, *69*(6), 438–451. https://doi.org/10.3322/caac.21583

Duan, J., Pan, L., & Yang, M. (2018). Preoperative elevated neutrophil-to-lymphocyte ratio (NLR) and derived NLR are associated with poor prognosis in patients with breast cancer: A meta-analysis. *Medicine*, *97*(49), e13340. https://doi.org/10.1097/MD.0000000000013340

Ethier, J. L., Desautels, D., Templeton, A., Shah, P. S., & Amir, E. (2017). Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. *Breast cancer research : BCR*, *19*(1), 2. https://doi.org/10.1186/s13058-016-0794-1

Freitas, R., Júnior, Nunes, R. D., Martins, E., Curado, M. P., Freitas, N., Soares, L. R., & Oliveira, J. C. (2017). Prognostic factors and overall survival of breast cancer in the city of Goiania, Brazil: a population-based study. *Revista do Colegio Brasileiro de Cirurgioes*, *44*(5), 435–443. https://doi.org/10.1590/0100-69912017005003

Gago-Dominguez, M., Matabuena, M., Redondo, C. M., Patel, S. P., Carracedo, A., Ponte, S. M., Martínez, M. E., & Castelao, J. E. (2020). Neutrophil to lymphocyte ratio and breast cancer risk: analysis by subtype and potential interactions. *Scientific reports*, *10*(1), 13203. https://doi.org/10.1038/s41598-020-70077-z

Geng, S. K., Fu, S. M., Fu, Y. P., & Zhang, H. W. (2018). Neutrophil to lymphocyte ratio is a prognostic factor for disease free survival in patients with breast cancer underwent curative resection. *Medicine*, *97*(35), e11898. https://doi.org/10.1097/MD.0000000000011898

Guo, W., Lu, X., Liu, Q., Zhang, T., Li, P., Qiao, W., & Deng, M. (2019). Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for breast cancer patients: An updated meta-analysis of 17079 individuals. *Cancer medicine*, *8*(9), 4135–4148. https://doi.org/10.1002/cam4.2281

Höfelmann, D. A., Anjos, J. C. D., & Ayala, A. L. (2014). Sobrevida em dez anos e fatores prognósticos em mulheres com câncer de mama em Joinville, Santa Catarina, Brasil. *Ciência & Saúde Coletiva*, *19*, 1813-1824. https://doi.org/10.1590/1413-81232014196.03062013

Huszno, J., Kołosza, Z., Mrochem-Kwarciak, J., & Zajusz, A. (2020). Prognostic Value of the Neutrophil-Lymphocyte, Platelet-Lymphocyte, and Monocyte-Lymphocyte Ratios in Male Breast Cancer Patients. *Oncology*, *98*(7), 487–492. https://doi.org/10.1159/000505627

Jedy-Agba, E., McCormack, V., Adebamowo, C., & Dos-Santos-Silva, I. (2016). Stage at diagnosis of breast cancer in sub-Saharan Africa: a systematic review and meta-analysis. *The Lancet. Global health*, *4*(12), e923–e935. https://doi.org/10.1016/S2214-109X(16)30259-5

Kim, J. Y., Jung, E. J., Kim, J. M., Lee, H. S., Kwag, S. J., Park, J. H., Park, T., Jeong, S. H., Jeong, C. Y., & Ju, Y. T. (2020). Dynamic changes of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio predicts breast cancer prognosis. *BMC cancer*, *20*(1), 1206. https://doi.org/10.1186/s12885-020-07700-9

Marín Hernández, C., Piñero Madrona, A., Gil Vázquez, P. J., Galindo Fernández, P. J., Ruiz Merino, G., Alonso Romero, J. L., & Parrilla Paricio, P. (2018). Usefulness of lymphocyte-to-monocyte, neutrophil-to-monocyte and neutrophil-to-lymphocyte ratios as prognostic markers in breast cancer patients treated with neoadjuvant chemotherapy. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*, *20*(4), 476–483. https://doi.org/10.1007/s12094-017-1732-0

Rakha, E. A., El-Sayed, M. E., Menon, S., Green, A. R., Lee, A. H., & Ellis, I. O. (2008). Histologic grading is an independent prognostic factor in invasive lobular carcinoma of the breast. *Breast cancer research and treatment*, *111*(1), 121–127. https://doi.org/10.1007/s10549-007-9768-4

Roué, T., Labbé, S., Belliardo, S., Plenet, J., Douine, M., & Nacher, M. (2016). Predictive Factors of the Survival of Women With Invasive Breast Cancer in French Guiana: The Burden of Health Inequalities. *Clinical breast cancer*, *16*(4), e113–e118. https://doi.org/10.1016/j.clbc.2016.02.017

Shalapour, S., & Karin, M. (2015). Immunity, inflammation, and cancer: an eternal fight between good and evil. *The Journal of clinical investigation*, *125*(9), 3347–3355. https://doi.org/10.1172/JCI80007

Singh, K., He, X., Kalife, E. T., Ehdaivand, S., Wang, Y., & Sung, C. J. (2018). Relationship of histologic grade and histologic subtype with oncotype Dx recurrence score; retrospective review of 863 breast cancer oncotype Dx results. *Breast cancer research and treatment*, *168*(1), 29–34. https://doi.org/10.1007/s10549-017-4619-4

Wariss, B. R., de Souza Abrahão, K., de Aguiar, S. S., Bergmann, A., & Thuler, L. (2017). Effectiveness of four inflammatory markers in predicting prognosis in 2374 women with breast cancer. *Maturitas*, *101*, 51–56. https://doi.org/10.1016/j.maturitas.2017.04.015

Wei, B., Yao, M., Xing, C., Wang, W., Yao, J., Hong, Y., Liu, Y., & Fu, P. (2016). The neutrophil lymphocyte ratio is associated with breast cancer prognosis: an updated systematic review and meta-analysis. *OncoTargets and therapy*, *9*, 5567–5575. https://doi.org/10.2147/OTT.S108419

Wiegert, E., de Oliveira, L. C., Calixto-Lima, L., Mota E Silva Lopes, M., & Peres, W. (2020). Cancer cachexia: Comparing diagnostic criteria in patients with incurable cancer. *Nutrition (Burbank, Los Angeles County, Calif.)*, *79-80*, 110945. https://doi.org/10.1016/j.nut.2020.110945

Zhang, M., Huang, X. Z., Song, Y. X., Gao, P., Sun, J. X., & Wang, Z. N. (2017). High Platelet-to-Lymphocyte Ratio Predicts Poor Prognosis and Clinicopathological Characteristics in Patients with Breast Cancer: A Meta-Analysis. *BioMed research international*, *2017*, 9503025. https://doi.org/10.1155/2017/9503025

Zhang, W., Shen, Y., Huang, H., Pan, S., Jiang, J., Chen, W., Zhang, T., Zhang, C., & Ni, C. (2020). A Rosetta Stone for Breast Cancer: Prognostic Value and Dynamic Regulation of Neutrophil in Tumor Microenvironment. *Frontiers in immunology*, *11*, 1779. https://doi.org/10.3389/fimmu.2020.01779