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Neutrophil/lymphocyte and platelet/lymphocyte ratio and outcome after first chemotherapy of patients with breast cancer in a city of Minas Gerais

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Abstract

Aim. To evaluate the factors associated with the pre and post-first chemotherapy inflammatory response in cancer patients, by determining the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) in the breast cancer population in Barbacena, and to verify their contribution to the observed outcome. **Methods.** Retrospective study, including 152 breast cancer patients in a reference hospital in Barbacena, MG, between 2016 and 2021. The results of complete peripheral blood counts before any therapeutic procedure (baseline blood count- surgery, radiotherapy, or chemotherapy) were collected, as well as follow-up exams. Additionally, data regarding the outcome of the first treatment and/or date of disease progression or death were also collected. The NLR was obtained by the ratio of the absolute neutrophil count to the absolute lymphocyte count. The PLR was calculated by dividing the absolute number of platelets by the absolute number of lymphocytes. The median NLR and PLR were calculated, and the data were processed using JASP statistical software v. 16.4.0. **Results.** It was observed that both alterations in NLR and PLR were predictors of outcome, with patients showing higher NLR (p = 0.034) and PLR (p = 0.043) in the post-first cycle of treatment blood count for disease progression or death. The effect size for both relationships was 0.218. **Conclusion.** NLR and PLR are useful as predictors of post-first treatment outcome in breast cancer patients.

Key words. Breast cancer; Lymphocytes; platelets; Neutrophils; Prognosis.

Razão neutrófilo/linfócito e plaquetas/linfócito e desfecho pós primeira quimioterapia de pacientes com câncer de mama em uma cidade de Minas Gerais

Resumo

Objetivo. Avaliar os fatores associados à resposta inflamatória pré e pós primeira quimioterapia em pacientes oncológicos, por meio da determinação da razão de neutrófilos para linfócitos (RNL) e a razão de plaquetas para linfócitos (RPL) na população com câncer de mama em Barbacena e verificar se essas contribuem para o desfecho observado. **Métodos.** Estudo retrospectivo, incluindo 152 pacientes com câncer de mama referenciados ao hospital Ibiapaba CEBAMS, em Barbacena, MG, entre os anos de 2016 a 2021. Os resultados de hemogramas completo periférico anterior a qualquer procedimento terapêutico (hemograma basal- cirurgia, radioterapia ou quimioterapia) foram coletados; bem como os exames de acompanhamento. Além disso, foram também coletados os dados relativos ao resultado do primeiro tratamento e/ou data da progressão da doença ou óbito. A RNL foi obtida pela razão entre a contagem absoluta de neutrófilos e a contagem absoluta de linfócitos. A RPL foi calculada dividindo o número absoluto de plaquetas pelo número absoluto de linfócitos. Foi calculada a mediana de RNL e RPL e os dados foram processados em software estatístico Jasp v. 16.4.0. **Resultados**. Observou-se que ambas as alterações no RNL e no RPL foram preditoras de desfecho, com pacientes de progressão ou óbito com maior RNL (p = 0,034) e RPL (p = 0,043) no hemograma pós primeiro ciclo de tratamento. O tamanho de efeito para ambas as relações foi 0,218. **Conclusão.** Conforme esperado, a RNL e a RPL foram úteis como preditoras de desfecho pós primeiro tratamento em pacientes com câncer de mama.

Palavras-chave. Câncer de mama; Linfócitos; Plaquetas; Neutrófilos; Prognóstico.

Introduction

Breast cancer is currently the second most diagnosed cancer in the world[1], with an estimated 2.3 million new cases per year, and it is also the second most common cancer in Brazil[2]. Despite improvements in survival rates in recent years due to better screening techniques, which allow for early-stage diagnosis and more accurate treatment methods, it remains the fourth cancer-related mortality worldwide and the third in Brazil[1,2,3].

Although the immune system plays an important role in the response to cancer, with the ability to develop antitumor responses that contribute to the eradication of tumors, it can also significantly participate in its progression and development, influencing initiation, growth, malignant transformation, invasion, and metastasis, impacting various stages of tumorigenesis. Moreover, the tumor immune environment is one of the factors that can affect the response to cancer therapy, influencing the prognosis[4,5,6,7].

Neutrophils infiltrated in tumors have different functions, acting both as antitumor and tumor-promoting agents. Antitumor neutrophils exert their role through antibody-dependent cytotoxicity; production of hypochlorous acid (HOCl), nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), and reactive oxygen species (ROS) leading to direct tumor cell death; inhibition of tumor suppressors like interleukin-17 (IL-17), among others. On the other hand, the pro-tumor function is carried out through the production of chemokines such as CCL2 and CCL17, which recruit cells and promote an immunosuppressive environment; by stimulating tumor angiogenesis through the release of matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF), essential for tumor cell migration and formation of a metastatic niche; production of neutrophil extracellular traps (NETs) that escort circulating tumor cells and promote cancer metastasis, in addition to being associated with hypercoagulability; and the release of substances such as elastin, IL-6, IL-1β, among others[8].

Evidence shows that neutrophils and other components of the inflammatory response are crucial in oncogenesis and metastasis of breast cancer. One way to analyze the inflammatory response of patients is through the calculation of the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), defined by the absolute neutrophil count divided by the absolute lymphocyte count and the absolute platelet count divided by the absolute lymphocyte count, respectively. Some studies suggest that an NLR higher than the median cutoff in various neoplasms may indicate a poorer prognosis with a decrease in overall survival. Conversely, patients with a decrease in NLR during treatment may experience increased survival, as a lower ratio between these parameters indicates a reduced inflammation context, leading to a better treatment[9] response. In breast cancer, the NLR has been extensively studied as a marker of the systemic inflammatory response in the development and progression of the disease, with its elevation being widely associated with a poorer prognosis[10]. The PLR has also been studied as a marker of the inflammatory response in various diseases, including cancer[11]. Both measures are relatively low-cost, which increases their accessibility[5,6]. Studies related to the influence of NLR and PLR and patient prognosis in different populations are useful for guiding and individualizing therapeutic planning, thereby improving therapeutic outcomes.

Thus, seeking additional information, this study evaluated the inflammatory response, through the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), in breast cancer patients in Barbacena, and its contribution to the observed outcome.

Methods

Study Type and Population

This is a retrospective study based on the review of medical records of breast cancer patients referred to Hospital Ibiapaba CEBAMS in Barbacena, Minas Gerais, between 2016 and 2021.

The hospital studied is a regional reference for cancer care, covering 14 municipalities: Alfredo Vasconcelos, Antônio Carlos, Alto Rio Doce, Capela Nova, Carandaí, Cipotânea, Desterro do Melo, Ibertioga, Paiva, Ressaquinha, Santa Bárbara do Tugúrio, Santana do Garambéu, Santa Rita do Ibitipoca, and Senhora dos Remédios.

Data Collection

The medical records were selected non-randomly, at random. Between 2016 and 2021, 401 new cases of breast cancer were treated at Hospital Ibiapaba. Based on this number, it was determined necessary to evaluate 152 medical records, considering a sampling error of 5%, 95% confidence, and a more homogeneous distribution of data.

Variables recorded included sex and age at diagnosis, tumor pathology report variables, including tumor size and type, surgery performed, as well as staging according to the 8th edition[12] of TNM. The results of complete peripheral blood counts were evaluated at two points in time: the first before any therapeutic procedure (baseline blood count – surgery, radiotherapy, or chemotherapy) and the second after the first cycle of chemotherapy. Additionally, data related to the outcome of the first treatment and/or date of disease progression or death were collected for outcome definition purposes. Medical records of patients lacking data for at least one of the two blood counts, patients with recurrence, or those who had previously undergone chemotherapy for another primary tumor were excluded.

The research protocol was approved by the Research Ethics Committee, with approval number 4.972.650.

Analysis of Results

Data were recorded in a Microsoft Excel spreadsheet. The NLR was obtained by the ratio of the absolute neutrophil count to the absolute lymphocyte count. The PLR was calculated by dividing the absolute number of platelets by the absolute number of lymphocytes. For patients who had both blood count results, dynamic changes in NLR and PLR were determined by subtracting the pre-therapy NLR and PLR results from the post-first cycle of chemotherapy results. Data were processed using JASP statistical software v. 16.4.0.

Absolute and relative frequency tables were produced in a row-by-column format. The Shapiro-Wilk test was used to verify the normality assumption of quantitative variables. Means and standard deviations were calculated for parametric variables, and medians and interquartile ranges for non-parametric variables.

Student's t-test or Mann-Whitney test for independent samples was performed to investigate the extent to which blood count parameters, NLR, and PLR differed between observed patient outcomes. One-way analysis of variance (ANOVA) with Welch's correction, in the occurrence of variance heterogeneity, was used to assess whether there were differences in blood count results

between sociodemographic and clinical variable groups. In all tests, data normality was assessed using the Shapiro-Wilk test, and the homogeneity of variance assumption was assessed using Levene's test. Additionally, the relationship between sociodemographic and clinical variables was verified by the Chi-square test.

Differences with $p < 0.05$ were considered significant. For variables that showed significant differences between groups, the effect size was calculated using Cohen's d, considered low when < 0.5, moderate when between 0.5 and 0.7, and high when greater than 0.7.

Results

A total of 181 medical records were analyzed to obtain the required 152, with a higher prevalence of females (98.7%), individuals over 60 years old (43.4%) with a mean age of 58.5 years, "married" marital status (46%), and "literate" educational level (46.7%).

The clinical data of the included patients are presented in Table 1. It is observed that the most common histopathological classification at diagnosis was G2 (59.9%), with a wide diversity in staging, with IIA (29.6%) and invasive ductal type being the most prevalent (77.6%). Regarding treatment data, the most frequent modality was chemotherapy, with the treatment regimen including doxorubicin, cyclophosphamide, and paclitaxel being the most used. Regarding outcome, the majority of patients were still under follow-up at the time of data analysis (86.8%).

The data from pre-therapy blood counts (HemG_01) and after the first cycle of chemotherapy (HemG_02) of the included patients are presented in Table 2. Regarding pre-treatment blood counts, there were 61 valid tests containing hematocrit, 63 containing hemoglobin, and 62 containing both leukocytes, neutrophils, lymphocytes, and platelets, with respective medians of 4.47 million/mm^3, 13.2 g/dL, 6830, 3825, 2135, 2135, and 256500/mm^3. Regarding blood counts after the first cycle of chemotherapy, there were 116 valid tests containing hematocrit, hemoglobin, leukocytes, neutrophils, and lymphocytes, and 114 containing platelets, with respective medians of 4.420, 12.700, 5630.000, 3118.000, 1688.000, and 266500.000.

The analysis of outcome results - follow-up (S) or progression or death (P/O) according to HemG_01 and HemG_02 results was performed using the Mann-Whitney t-test, and the results are presented in Table 3. The relationship between the number of platelets and lymphocytes from the pre-therapy blood count (RPL_01) and the absolute number of lymphocytes from the blood count after the first cycle of therapy (Linfo_02) was significantly lower ($p < 0.05$) in patients under follow-up compared to those with progression or death. The effect size for these two relationships was low, 0.207 for RPL_01 and 0.159 for Linfo_02.

For patients who had both blood count results, the influence of dynamic changes in NLR and PLR on the observed outcome was evaluated by subtracting HemG_01 and HemG_02 results. It was observed that both alterations in NLR and PLR were predictors of outcome, with patients with progression or death having higher NLR ($p = 0.034$) and PLR ($p = 0.043$) in the second blood count. The effect size for both relationships was also low:-0.218. Additionally, the relationship between age and dynamic changes in NLR and PLR was evaluated, and no significant relationship was found between them (Table. 4).

Table 1. Clinical data of breast cancer patients treated in Barbacena between 2016 and 2021 and included in the present study (n = 152).

Histopathological Classification	N	%
G1	12	7.9
G2	91	59.9
G3	24	15.8
Gx	15	9.9
Not informed	10	6.5
Staging		
0	2	1.3
IA	26	17.1
IB	2	1.3
IIA	45	29.6
IIB	28	18.4
IIIA	20	13.1
IIIB	10	6.6
IIIC	1	0.6
IV	17	11.1
Not informed	1	0.6
Histological Type		
Invasive Ductal	118	77.6
Ductal Carcinoma in Situ	18	11.9
Invasive Lobular	10	6.6
Others	6	4.0
Treatment Line		
Surgery and Chemotherapy	20	13
Surgery Chemotherapy and Hormone Therapy	6	3.9
Hormone Therapy	10	6.5
Chemotherapy	40	26.3
Chemotherapy and Surgery	10	6.5
Chemotherapy, Radiotherapy. and Hormone Therapy	16	10.6
Other combinations	48	31.9
Not informed	2	1.3
Chemotherapy		
Doxorubicin Cyclophosphamide and Paclitaxel	67	44.1
Cyclophosphamide 5FU and MTX	8	5.2
Docetaxel and Cyclophosphamide	12	7.9
Tamoxifen	8	5.2
Others	37	24.6
Not Informed	20	13
Outcome after first Chemotherapy		
Follow-up	133	87.5
Progression	4	2.6
Death	13	8.6
Not Informed	2	1,3

Finally, the frequency of outcomes according to age, type of breast cancer, histological classification, and clinical staging was analyzed using the Chi-square test. Only clinical staging showed a relationship with the outcome, with progression or death being more frequent in advanced stages, above IIIB ($p < 0.001$).

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Table 2. Pre-therapy and post-first cycle of chemotherapy hemograms of breast cancer patients treated in Barbacena between 2016 and 2021 and included in the present study (n = 152).

	Red blood cells (millions/mm³)	Hemoglobin (g/dL)	Leukocytes (/mm³)	Neutrophils (/mm³)	Lymphocytes (/mm3)	Platelets (/mm3)
HemG-01						
Valid exams	61	63	62	62	62	62
Median	4.470	13.200	6830	3825	2135	256500
Mean	4.495	13.214	6836	4058	2102	258354
Standard Deviation	0.482	1.341	2176	1929	675	54213
Shapiro-Wilk p-value	0.584	0.010	<.001	<.001	0,028	0,294
Minimum	3.350	8.800	2310	1294	696	162000
Maximum	5.510	15.500	16180	14416	4281	389000
HemG-02						
Valid exams	116	116	116	116	116	114
Median	4.420	12.700	5630	3118	1688	266500
Mean	4.348	12.658	5939	3580	1817	268374
Standard Deviation	0.442	1.212	2483	2047	776	86695
Shapiro-Wilk p-value	0.013	0.018	<.001	<.001	<.001	0.070
Minimum	2.820	8.000	1300	364	322	6760
Maximum	5.270	14.900	16930	14729	4889	591000

*Caption: HemG-01- blood count 1; HemG-02- blood count 2.

Table 3. Relationship between pre-therapy (01) and post-first cycle of chemotherapy (02) blood count parameters of breast cancer patients treated in Barbacena between 2016 and 2021 and included in the present study (n = 152).

	Grup	N	Mean	Standard deviation	p	Effect Size
Hm_01	S	52	4.500	0.481		
	P/O	9	4.468	0.518	0.911	
Hb_01	S	54	13.200	1.378	0.937	
	P/O	9	13.300	1.163		
Leuco_01	S	53	6728	1841	0.624	
	P/O	9	7474	3679		
Neutro_01	S	53	3892	1442	0.369	
	P/O	9	5035	3688		
Linfo_01	S	53	2159	662.035	0.231	
	P/O	9	1767	692.682		
Pq_01	S	53	252679	52492	0.080	
	P/O	9	291777	55042		
RNL_01	S	53	1.919	0.772	0.194	
	P/O	9	4.144	6.231		
RPL_01	S	53	122.993	41.718	**0.016**	**0.207**
	P/O	9	196.021	93.699		
Hm_02	S	101	4.357	0.451	0.434	
	P/O	15	4.289	0.379		
Hb_02	S	101	12.672	1.238	0.521	
	P/O	15	12.560	1.057		
Leuco_02	S	101	5775	2363	0.058	
	P/O	15	7040	3042		
Neutro_02	S	101	3500	2009	0.222	
	P/O	15	4116	2286		
Linfo_02	S	101	1.742	688.377	**0.032**	**0.159**
	P/O	15	2.323	1.119		
Pq_02	S	99	263259	86963	0.057	
	P/O	15	302133	79504		
RNL_02	S	101	2.348	1.848	0.567	
	P/O	15	2.083	1.312		
RPL_02	S	101	173.664	113.577	0.363	
	P/O	15	171.911	129.304		

* Legend: Hm – red blood cells; Hb – hemoglobin; Leuko – leukocytes; Neutro – neutrophils; Lymph – lymphocytes; Pq – platelets; NLR- neutrophil/lymphocyte ratio; RPL - platelet/lymphocyte ratio; S- follow-up; P/O- progression or death.

Table 4. Relationship between the dynamic change in NLR and PLR and the outcome of breast cancer patients treated in Barbacena between 2016 and 2021 and included in the present study (n = 152).

	Group	N	Average	Standard Deviation	p	Effect size
RNL01 - RNL02	S	51	-0.382	1.789	0.034	0.218
	P/O	8	2.285	5.412		
RPL01 - RPL02	S	51	-49.997	131.029	0.043	0.218
	P/O	8	38.207	94.682		

* Legend: NLR- neutrophil/lymphocyte ratio; PLR- platelet/lymphocyte ratio; S- follow-up; P/O- progression or death.

Discussion

In this study, the relationship between NLR and PLR measured at two time points - pre and post-first cycle of chemotherapy - and the prognosis of patients with breast cancer was evaluated. It was observed that pre-therapy PLR was increased in patients who experienced disease progression or death. However, the effect size was low (0.207). A cross-sectional study involving 288 patients, analyzing inflammatory biomarkers and complete pathological response in breast cancer patients treated with neoadjuvant chemotherapy, found that complete pathological response was significantly higher in the low PLR group compared to the high PLR group. Therefore, breast cancer patients with a low platelet-to-lymphocyte ratio treated with neoadjuvant chemotherapy achieved a higher complete pathological response, regardless of the molecular subtype of the primary[13] tumor. Another study evaluating PLR in 177 breast cancer patients treated with neoadjuvant chemotherapy showed that the group with lower PLR had a higher rate of complete pathological response, had a higher disease-free survival, and overall survival compared to the high PLR group, concluding that in breast cancer patients treated with neoadjuvant chemotherapy, a low PLR indicated high sensitivity to chemotherapy, suggesting that PLR could serve as a predictive marker of the therapeutic effect of neoadjuvant chemotherapy, although the effect size regarding complete pathological response was low, observed in 67 patients, accounting for 37.9% of the sample[14].

A study conducted with 102 patients diagnosed with inflammatory breast cancer revealed that high NLR or PLR was associated with reduced overall survival and disease-free survival in this type of non-metastatic[15] cancer.

In the present study, NLR measured at both time points showed no relation with the observed outcome, and the absolute number of lymphocytes after the first cycle of chemotherapy was increased in patients with disease progression or death, also with a low effect size. A retrospective cohort study including 312 patients was conducted, evaluating complete pre-treatment blood counts to assess inflammatory indices of breast cancer patients, with the 5-year survival as the outcome variable. It observed that pre-treatment NLR was considered a useful predictor of overall survival in breast[16] cancer. A retrospective analysis of 862 invasive breast cancer patients treated with neoadjuvant chemotherapy, of which 151 patients were included, and analyzed the ratio of absolute neutrophil count to lymphocyte count in peripheral blood, and the complete pathological response to neoadjuvant chemotherapy showed that pre-treatment NLR can provide additional information on the likelihood of achieving a complete pathological response to neoadjuvant[17] chemotherapy.

A meta-analysis conducted with 15 studies, including 8,563 breast cancer patients and exploring the association of NLR with overall survival or disease-free survival, revealed that high NLR is associated with worse overall survival and disease-free survival, with a greater effect in estrogen receptor-negative or HER2-negative[10] disease. In a study analyzing 204 meta-analyses of 86 studies investigating the association between NLR or tumor-associated neutrophils and cancer outcomes, it was observed that 29% of the meta-analyses presented strong or highly suggestive evidence that high NLR is associated with worse outcomes. However, when considering effect size, significance, and biases, only 9% of the studies provided strong evidence. The authors evaluated that, although promising results, additional studies are required for the formation of robust evidence, identification of causality, and determination of the clinical validity of the measure[18].

The analysis of dynamic changes in NLR and PLR demonstrated that both changes in NLR and PLR were predictive of outcome, with patients with disease progression or death having higher NLR ($p = 0.034$) and PLR ($p = 0.043$) in the second blood count. The effect size for both relationships was 0.218. This result is corroborated by the current literature, although no study evaluating short-term dynamic changes has been published and studies do not provide effect size calculation, which would be useful for comparative purposes. A study conducted with 600 triple-negative breast cancer patients, evaluating NLR at four different treatment time points (before surgery, before chemotherapy, before radiotherapy, and 1 year after surgery), observed that NLR increased in the disease progression group from before surgery or radiotherapy to 1 year after surgery, confirming that changes in NLR may reflect the prognosis of triple-negative[19] breast cancer patients. Furthermore, another study conducted with 533 breast cancer patients demonstrated that persistently elevated NLR and PLR after initial treatment have significantly worse prognosis in terms of late[20] metastasis.

As strengths of the present study, it is noteworthy that patients were treated at a reference center in the region, with standardized approach and the same care team. Limitations included retrospective data collection, heterogeneity of breast cancers and treatments of included patients, and incomplete data for some patients, reducing the analyzed sample and preventing stratified analyses. Additionally, the reduced number of patients in the progression/death group may have contributed to the low effect size observed for statistically significant parameters. The absence of effect size data in the literature prevented comparative analysis of the relevance of the findings. Prospective studies should be conducted for confirmation and further analysis of the findings.

Conclusion

The results of this study suggest that pre-therapy PLR and changes in NLR and PLR from pre-treatment to post-first cycle are useful in predicting post-first chemotherapy outcome in breast cancer patients, corroborating findings from the literature and presenting, in an unprecedented way, short-term dynamic changes as a possible prognostic marker.

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Authors' Contributions

PBP conceived the original idea, analyzed and interpreted the results, and critically reviewed the final manuscript; AVV, CGMO, TMMA, TFRL were responsible for data collection and tabulation, and manuscript writing.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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