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The preoperative neutrophil-to-lymphocyte ratio predictive value for survival in patients with brain metastasis

O valor do índice neutrófilo-linfócito como preditor de sobrevida em pacientes com metástases cerebrais

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Abstract

Background The neutrophil-to-lymphocyte (NLR), monocyte-to-lymphocyte (MLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) have been previously studied as predictors of survival in different malignancies.

Objective The aim of this study was to evaluate the predictive value of these hematologic inflammatory biomarkers for patients with brain metastases (BM).

Methods We reviewed a consecutive cohort of patients at Instituto do Cancer do Estado de São Paulo (ICESP-FMUSP) from 2011 to 2016 with ≥ 1 BM treated primarily by surgical resection. The primary outcome was 1-year survival. We optimized the NLR, MLR, PLR, and RDW cutoff values, preserving robustness and avoiding overestimation of effect size.

Results A total of 200 patients (mean age 56.1 years; 55.0% female) met inclusion criteria. Gross-total resection was achieved in 89.0%. The median (quartiles) preoperative and postoperative KPS scores were 60 (50–80) and 80 (60–90), respectively. Preoperative NLR was significantly associated with survival (HR 2.66, 95% CI: 1.17–6.01, $p = 0.019$). A NLR cutoff value of 3.83 displayed the most significant survival curve split.

Conclusions Preoperative NLR is an independent predictor of survival in newly diagnosed BM. We propose a cutoff value of 3.83 for preoperative NLR testing may be clinically useful as predictor of poor survival in this population. The wide accessibility

Keywords
- Brain Neoplasms
- Survival Analysis
- Biomarkers

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of the NLR favors its inclusion in clinical decision-making processes for BM management.

Resumo

Antecedentes Os neutrófilos para linfócitos (NLR), monócitos para linfócitos (MLR), proporção de plaquetas para linfócitos (PLR) e largura de distribuição de glóbulos vermelhos (RDW) foram previamente estudados como preditores de sobrevivência em diferentes malignidades.

Objetivo O objetivo deste estudo foi avaliar o valor preditivo desses biomarcadores inflamatórios hematológicos para pacientes com metástases cerebrais (MB).

Métodos Nós revisamos uma coorte consecutiva de pacientes no Instituto do Câncer do Estado de São Paulo (ICESP-FMUSP) de 2011 a 2016 com $\geq$ 1 MB tratados principalmente por ressecção cirúrgica. O desfecho primário foi a sobrevida em 1 ano. Otimizamos os valores de corte de NLR, MLR, PLR e RDW, preservando a robustez e evitando superestimação do tamanho do efeito.

Resultados Um total de 200 pacientes (idade média de 56,1 anos; 55,0% mulheres) preencheram os critérios de inclusão. A ressecção grosseira total foi obtida em 89,0%. A mediana (quartis) dos escores KPS pré-operatório e pós-operatório foram 60 (50–80) e 80 (60–90), respectivamente. O NLR pré-operatório foi significativamente associado à sobrevida (HR 2,66, IC 95%: 1,17–6,01, $p = 0{,}019$). Um valor de corte de NLR de 3,83 exibiu a divisão da curva de sobrevivência mais significativa.

Conclusões O NLR pré-operatório é um preditor independente de sobrevida em MBs recém-diagnosticados. Propomos que um valor de corte de 3,83 para o teste de NLR pré-operatório pode ser clinicamente útil como preditor de baixa sobrevida nesta população. A ampla acessibilidade do NLR favorece sua inclusão nos processos de tomada de decisão clínica para o gerenciamento de BM.

Palavras-chave
- Neoplasias Encefálicas
- Análise de Sobrevida
- Biomarcadores

INTRODUCTION

Brain metastasis (BM) are the most common malignant intracranial tumors, and their incidence continues to rise over time. Advances in oncologic treatments and supportive care provides patients with longer survival to the point of developing brain metastases in end-stage disease.[1] Treatment of BM ranges from supportive care to multimodal strategies considering surgery, fractioned radiotherapy, whole brain radiotherapy, stereotactic radiosurgery, or chemotherapy. Treatment decisions are based on primary tumor site, metastatic tumor characteristics, and patient performance status. Determining the most suitable treatment option based on the patient prognosis can be challenging.[2]

Cancer is a disease state associated with marked systemic inflammation.[3] Previous studies have demonstrated that elevated levels of inflammatory biomarkers can be associated with cancer progression and recurrence of solid tumors.[4] For example, the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and red blood cell distribution width (RDW) have shown promise as predictors of cancer survival in several different malignant diseases.[5–9]

The use of validated prognostic tools can greatly aid clinicians in creating patient-centered treatment plans. While the NLR, MLR, PLR, and RDW have demonstrated efficacy as prognostic factors in many malignancy states, few studies have evaluated their performance specifically for patients with BM.[6] This study aims to fill this gap by examining the relationship between these biomarkers and patient outcomes in a prospective cohort.

METHODS

This report adheres to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) statement. Although the STARD was developed for diagnostic accuracy studies, it also provides a useful framework for reporting other studies evaluating the performance of other clinical tests, including prognostic studies.[10]

Study design and patient selection

We retrospectively reviewed a database of 200 patients recruited prospectively and consecutively for a recent diagnosis of BM, and primarily treated with surgical resection between August 2010 and July 2016 at the Instituto do Câncer do Estado de São Paulo of the Faculdade de Medicina of the Universidade de São Paulo (ICESP-FMUSP).

Patients were included in this study if they met the following criteria: 1) adult patients ($\geq$ 18 years old); 2) at least one BM treated by surgical resection; and 3) did not receive any treatment for BM before surgery. One patient had

a limited surgical resection (< 50%) which was considered as an open biopsy. After surgical resection, patients were referred for adjuvant therapy after multidisciplinary evaluation. The patients were prospectively followed up and underwent magnetic resonance imaging (MRI) every 4 months for a maximum follow-up period of 60 months, or until death. Follow-up was lost on 16 patients, for whom the date of the last appointment was considered for analysis.

Data collection and hematologic variables

Patients' epidemiological and clinical information were collected from an electronic database, and their performance status was assessed using the American Society of Anesthesiologists (ASA) and the Karnofsky performance status (KPS) classifications. The graded prognostic assessment (GPA) oncologic prognostic score was used to adjust for risk. The primary outcome of interest was 1-year survival.

Blood samples were collected no more than 30 days before surgery in ethylenediaminetetraacetic acid (EDTA), and the complete blood count (CBC) was processed using an automated hematology analyzer. The NLR, MLR, and PLR were respectively calculated by dividing the absolute neutrophil, monocyte, and platelet counts, respectively, by the absolute lymphocyte count. The RDW was provided by the hematology analyzer.

Statistical analysis

Categorical variables were presented as relative and absolute frequencies. Normally distributed continuous data were presented as mean and standard deviation (SD), or median and quartiles, as appropriate and indicated. The normality assumption was assessed by skewness and kurtosis values, as well as graphical methods for each variable.

For the outcome of 1-year survival, potential categorical predictors were identified using the Kaplan-Meier method, using the logrank (Mantel-Cox) test for the comparison of the survival functions. Continuous variables were analyzed through a univariate Cox regression. Variables with a univariate *p*-value less than 0.10 were included in a multivariate Cox regression model, and the results were presented as hazard ratios (HR), with 95% confidence intervals (CI). The change-in-estimate criterion strategy was also employed as a sensitivity analysis while not changing the direction or effect size of the relationship between the hematological parameters and the outcome. The hematological parameter was then included in the regression model as a continuous variable. The proportionality and linearity assumptions were verified using graphical methods and the Schoenfeld and Martingale residuals, respectively. Since age, preoperative KPS, and the number of BM lesions are considered in the GPA score, these variables were not considered for inclusion in the multivariate models.

The cutoff values for the NLR, MLR, PLR, and RDW are not well established for solid cancers, although recent studies have suggested thresholds of NLR < 4[9] and PLR < 150.[10] We built separate multivariate regression models to assess the predictive performance of each of these biomarkers as continuous or categorical variables. Afterwards, we refined the cut-off determination directed at the survival outcome, as proposed by Budczies et al.[11] A Cox proportional hazard model was fitted to the dichotomized hematological and survival parameters. The survival analysis was performed using the functions *coxph* and *survfit* from the R package *survival*.[12] The optimal cutoff was defined as the point with the most significant (logrank test) split. Differences in survival were calculated from the mean survival times in the good and poor prognosis groups. Mean survival times were estimated from the area under the Kaplan-Meier curve using the maximum time that occurs in the data as the uniform time endpoint. To assess the robustness of the cutoff value and avoid overestimation of effect size, the HR, including 95% CI, was plotted against all possible cutoff values. A wider range of cutoff values demonstrating significance would indicate more robust findings.

Significance was tested through two-tailed tests at a significance level of $p < 0.05$ for all analyses. All analyses were conducted with the R (R Foundation for Statistical Computing, Vienna, Austria), version 3.5.2. The sample size was based on the available data, and no a priori power calculations were performed.

RESULTS

A total of 200 patients (mean age 56.1 ± 12.6 years, 55% female) met the eligibility criteria and were included in the analysis (►**Table 1**). The most common presenting malignancies were non-small cell lung cancer (NSCLC) (33.0%), breast cancer (18.0%), and cancers of the gastrointestinal tract (13.5%). A single BM was diagnosed in 52% of patients, three or more lesions in 30.5% during initial diagnosis, and carcinomatous meningitis in 10%. The performance status assessment by different scales is illustrated in ►**Table 1**.

All patients underwent surgical treatment; 89% underwent gross total resection, and 20.5% underwent en bloc resection. Adjuvant radiotherapy was administered to 63% of the patients. There were no intraoperative deaths; however, 3 patients died in the first postoperative week, and 7.5% died within 4 weeks. The median postoperative KPS score was 80 (quartiles 60–90), which was significantly improved from the preoperative score ($p < 0.001$). During follow-up, progression of primary disease was the most common cause of death. A total 131 patients died within the first year.

In the univariate survival analysis, GPA, ASA, preoperative hemoglobin, tumor location, laterality, radiotherapy, postoperative KPS, and recurrence were potential predictors. Thus, these variables were included in the adjusted models to assess the predictive performance for each blood-based parameter (►**Table 2**). The NLR was significantly associated with 1-year outcome (HR 2.19, 95% CI 1.13–4.25, $p = 0.021$), while the MLR was not (HR 2.05, 95% CI: 0.98–4.26, $p = 0.055$). In a multivariate model including all blood-based biomarkers concurrently, we opted to not include the MLR due to a high correlation with the NLR ($r = 0.626$, $p < 0.001$). In this model, only the NLR maintained significance (HR 2.66, 95% CI: 1.17–6.01, $p = 0.019$) (►**Figure 1**).

Table 1 Sample characteristics and univariate survival analysis

Variables		Total ($n = 200$)	Death at 1-year		*p*-value*
			No (n = 69)	Yes (n = 131)	
Age (years)		56.1 ± 12.6	54.5 ± 12.8	56.9 ± 12.6	0.196
Female		110 (55.0)	42 (60.9)	68 (51.9)	0.138
Synchronous presentation		72 (36.0)	19 (27.5)	53 (40.5)	0.260
Compartment	Infratentorial	54 (27.0)	20 (29.0)	34 (26.0)	0.814
	Supratentorial	137 (68.5)	46 (66.7)	91 (69.5)	
	Both	9 (4.5)	3 (4.3)	6 (4.6)	
Laterality	Right	62 (31.0)	30 (43.5)	32 (24.4)	0.034
	Left	60 (30.0)	19 (27.5)	41 (31.3)	
	Both	78 (39.0)	20 (29.0)	58 (44.3)	
Eloquent brain areas		55 (27.5)	13 (18.8)	42 (32.1)	0.005
Number of BM		1 (1–3)	1 (1–3)	2 (1 -3)	0.32
ASA		2 (2–3)	2 (2–3)	2 (2–3)	< 0.001
KPS	Preoperative	60 (50–80)	70 (60–80)	60 (50–70)	< 0.001
	Postoperative	80 (60–90)	90 (80–100)	70 (50–90)	< 0.001
GPA		1.5 (1–2)	2 (1–2.5)	1.5 (1–2)	0.001
ECOG		2 (1–3)	2 (1–3)	3 (1–4)	< 0.001
Number of resected BM		1 (1–1)	1 (1–1)	1 (1–1)	0.757
Extent of resection	Biopsy	1 (0.5)	0 (0.0)	1 (0.8)	0.069
	Partial	21 (10.5)	4 (5.8)	17 (13.0)	
	Gross total	178 (89.0)	65 (94.2)	113 (86.3)	
En bloc resection		41 (20.5)	17 (24.6)	24 (18.3)	0.471
Radiotherapy		126 (63.0)	57 (82.6)	69 (52.78)	< 0.001
Whole-brain		89 (44.5)	33 (47.8)	56 (42.7)	
RS/FSR (surgical bed)		40 (20.0)	25 (36.2)	15 (11.5)	
RS/FSR (concurrent BM)		14 (7.0)	8 (11.6)	6 (4.6)	

Abbreviations: ASA, American Society of Anesthesiologists; BM, brain metastasis; GPA, graded prognostic assessment; KPS, Karnofsky performance status; ECOG, Eastern Cooperative Oncology Group; RS/FRS, Radiosurgery/Fractionated Stereotactic Radiotherapy.
Notes: Categorical variables are presented as *n* (%). Continuous variables are presented as median and quartiles, except for age (mean ± standard deviation). *Survival analysis.

Table 2 Multivariate survival analysis

Blood-based parameter[a]	Models with one blood-based parameter at a time[b]		Model with all parameters[c]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
RDW-CV	1.66 (0.08–33.55)	0.741	0.15 (0.0–4.97)	0.285
NLR	2.19 (1.13–4.25)	0.021	2.66 (1.17–6.01)	0.019
MLR	2.05 (0.98–4.26)	0.055	–	–
PLR	1.68 (0.76–3.7)	0.198	0.7 (0.26–1.92)	0.492

Abbreviations: CI, confidence interval; HR, hazard ratios; MLR, monocyte-to-lymphocyte; NLR, neutrophil-to-lymphocyte; PLR, platelet-to-lymphocyte ratio; RDW-CV, red-cell distribution width coefficient of variation.
Notes: [a]All parameters were log-transformed for distribution normalization, except for hemoglobin. All of them were inserted on the models as continuous variables; [b]All models adjusted for GPA (age, preoperative KPS, number of CNS metastases, and presence of extracranial metastases), ASA, preoperative hemoglobin, eloquence of the affected area, laterality, radiotherapy, postoperative KPS, and recurrence; [c]Model adjusted for GPA (age, preoperative KPS, number of CNS metastases, and presence of extracranial metastases), ASA, preoperative hemoglobin, eloquence of the affected area, laterality, radiotherapy, postoperative KPS, and recurrence, besides the parameters on the table (hemoglobin, RDW-CV, NLR, and PLR). Finally, the MLR was not included due to high correlation with NLR.

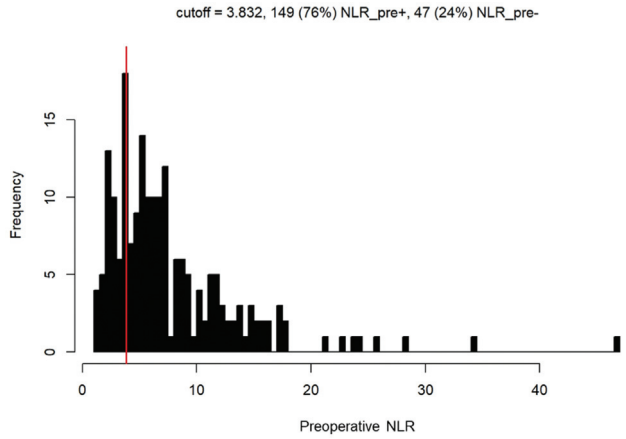

Figure 1 Neutrophil-to-lymphocyte ratio (NLR) histogram. Vertical line: optimal cutoff 3.832.

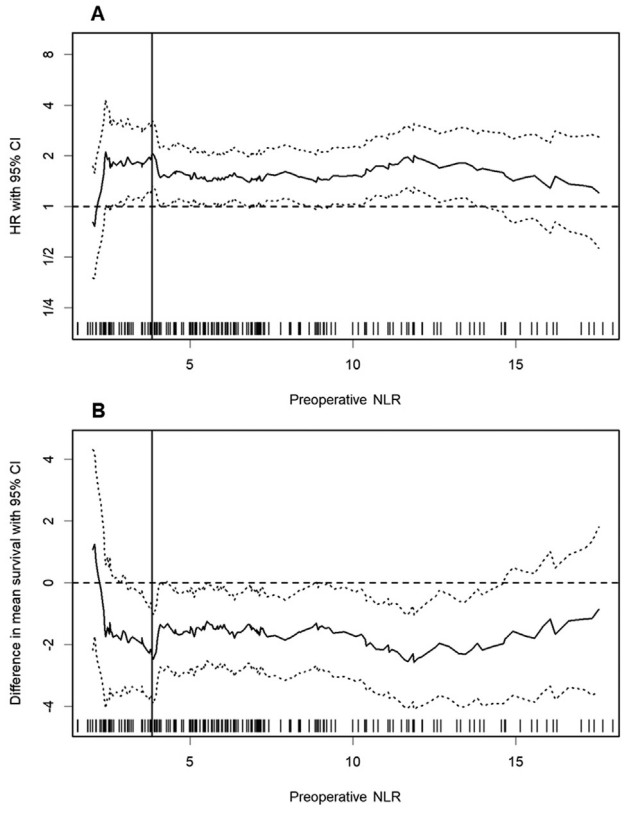

Figure 2 (**A**) Hazard ratios (HR) and 95% confidence intervals (CI) according to preoperative NLR cutoff; (**B**) Difference in mean survival (months) and 95% CI according to preoperative NLR cutoff. A total 132 of 171 possible cutoffs (77.2%) were significant. Vertical line: optimal cutoff 3.832.

►**Figure 2** presents the analyses aimed at determining the optimal NLR cutoff value. The HR and differences in mean survival times (months) are each plotted against each possible preoperative NLR cutoff. A total 132 of 171 possible cutoffs (77.2%) were significant—the larger the range of significant cutoff values, the more robust the finding. In our series, the optimal NLR cutoff value, based on HR and differences in mean survival, was 3.832. We compared the survival curves and effect sizes according to preoperative

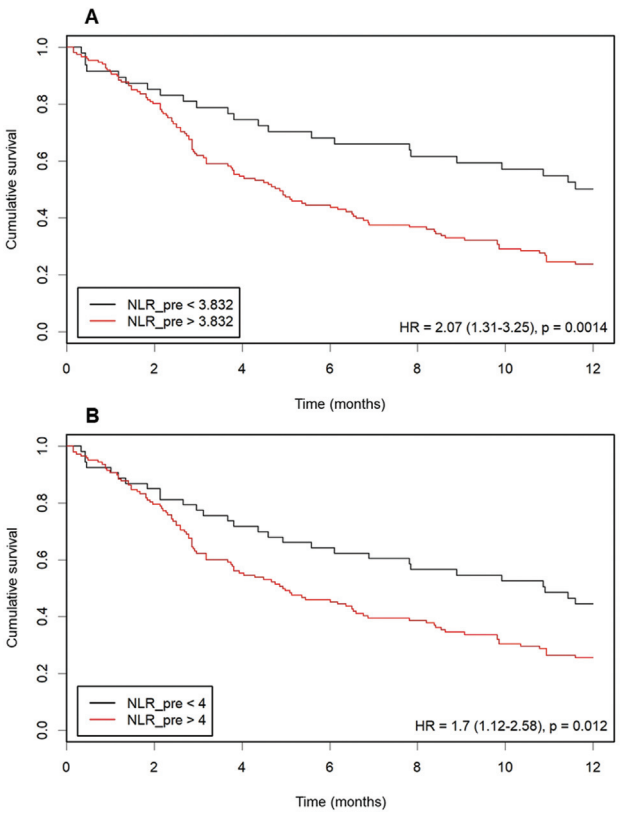

Figure 3 Survival curves and effect sizes (HR and CI) according to preoperative NLR cutoff (**A**: cutoff 3.832; **B**: cutoff 4.0).

NLR cutoff values for solid tumors, as suggested by Templeton et al.,[9,15] and our suggested optimal cutoff value. Both presented significant results in survival analysis; however, our value showed a higher HR = 2.07 (1.31–3.25; $p = 0.0014$) (►**Figure 3**).

DISCUSSION

The results of this study demonstrated a significant association between preoperative NLR levels and patient survival at 1-year after surgery for BM. Of all the hematologic inflammatory markers we analyzed, only the preoperative NLR was found to be an independent predictor of survival in our adjusted models. More specifically, shorter survival time after surgical resection of BM can be expected for patients with a preoperative NLR > 3.83.

These findings align with previous works testing the clinical utility of similar cutoff values for inflammatory biomarkers. The NLR has been used as a predictor of late recurrence, treatment response and poor prognosis in different solid cancers.[5,8] Templenton et al.[9,13] conducted a systematic review of 100 studies ($n = 40{,}559$ patients) that included different solid tumors and suggested a NLR cutoff of 4.0 for overall survival (OS). While the biological processes underlying these findings are not fully understood, there is some evidence of a tumor-promoting effect of neutrophils during metastasis progression by an increasing number of metastatic initiating cancer cells. Notably, Wculek and Malanchi[14] showed that neutrophil depletion in lungs

reduced local metastasis on a breast cancer experimental model.

The other hematologic biomarkers tested in our study did not perform as well as the NLR. The prognostic role of the PLR is hypothesized on increased host inflammatory response with higher secretion of thrombopoietic cytokines, such as IL-6. Platelet recruitment and activation is involved in the process of tumor growth and angiogenesis. There seems to exist a correlation between thrombocytosis and shorter survival time in different solid tumors, in addition to recent findings of higher PLR scores for metastatic patients compared with locoregional disease.[8,10,15,16]

Several biological events related to the cancer activity might implicate in high RDW levels. Higher levels of inflammatory cytokines are associated with increased metabolic activity, increased cellular proliferation, and, consequently, higher RDW rates. Furthermore, the RDW is directly related to the individual nutritional status.[7,17] Generalized hypovitaminosis (iron, folate, vitamin B12) in patients with advanced and uncontrolled cancers is an alternative hypothesis that could explain the role of the RDW as a prognosis predictor.[5,17] Consistent results of PLR and RDW as outcome predictors are related to advanced-stage cancers or uncontrolled systemic disease. Although brain metastasis is a hallmark of cancer disease progression, the majority of patients in this study had a good performance status preoperatively, possibly suggesting there was adequate control of the disease before brain metastasis detection. Therefore, we hypothesize that neither the PLR nor RDW were sensitive enough for significant results in this clinical setting.

The incidence of BM from solid cancers has been paradoxically rising due to improvements in diagnostic methods, increased availability of neuroimaging, and advances in systemic treatment.[1,7] The BM represents the end stage of a cancer disease; prognosis should be carefully considered for decision-making on additional treatments at this point. The decision on whether to treat a BM is challenging in neuro-oncology, as it represents not only a tumor with mass effect, but also a systemic uncontrolled disease in progression that must be considered for individualized decision. Currently, the decision to treat is based on patients' performance status, the number and size of tumors, and treatment responsiveness of the primary cancer.[1,18] New biomarkers are under investigation to support decision-making in this setting. Several blood-based biomarkers have been proposed for gliomas with promising results.[10,13,19–22] Our results promote the use of preoperative NLR in decision-making, and its contribution for prognostic predictive models for brain metastasis.

Other studies have analyzed the hematologic prognostic markers based on recent insights on cancer-immune system interactions. The NLR, PLR, and RDW were tested in several types of metastatic tumors, as well as in different brain tumors. Starzer et al.[23] addressed the role of systemic inflammation on cancer progression. In their retrospective analysis with more than one thousand patients, lower NLR, PLR, and MLR were associated with longer OS in patients with BM. Mitsuya et al.[6] used the cutoff of NLR $>$ 5 with promising results in a retrospective analysis with 105 BM patients. Cacho-Diaz et al.[24] applied the NLR cutoff $>$ 4.5, with significant correlation with mortality in those patients as well. Both studies have included only patients with uncontrolled primary cancer and high systemic inflammation. Some authors hypothesized that the involvement of the brain, as a critical and sensitive organ, is the main trigger of the systemic inflammation process that might influence the OS. Marini et al.[25] studied predictive factors on OS in patients with glioblastoma—a primary brain cancer with very low risk of distant metastasis. In this study, the NLR $>$ 4 cutoff was significantly related to worse OS in multivariate analysis, similar to other studies with BM.

Our study has several limitations that should be considered when interpreting the results. First, the study included patients with BM from different primary tumors; this was not included as a covariate in our models, given the limited sample size of the cohort. Second, our analyses did not consider the varying doses of corticosteroids that patients received, although this may have had effects on hematologic parameters. Third, we only included patients without any prior treatment for BM (radiotherapy/radiosurgery, immunotherapy etc.). While this was done to reduce treatment confounding effects, we recognize it limits the external validity of the study and favors the proof of concept. However, our study has a representative sample of patients with cancer and BM, and proposes an accessible test for treatment decision making in patients with BMs.

In conclusion, our analyses demonstrated that the preoperative NLR is associated with 1-year survival outcomes after surgery for BM, and may be an important predictor of survival, irrespective of primary cancer site. These findings further support the trend of considering serum inflammatory markers in oncologic treatment decisions. Given the complexity of this disease and its burden on patients, clinicians are tasked with carefully formulating robust treatment plans. Although additional validation studies are warranted, we believe the low cost and accessibility of accessing the NLR distribution rates favors its utility as a prognostic aide when making decisions for the management of BM. Future studies should continue to explore and validate the use of other biomarkers as prognostic factors in metastatic diseases.

Authors' Contributions

HP, IN, VY, DS, MT, EF, WP: conception and design; HP: patients' recruitment; HP, IN, AS, VY, BF: data collection; VY, AS, DS: data analysis and interpretation; HP, VY, IN, AS: drafting the manuscript for important intellectual content; HP, IN, VY, DS, AS, CD, MT, EF, WP: text review. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors have no conflict of interest to declare.

References

1 Soffietti R, Abacioglu U, Baumert B, et al. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). Neuro-oncol 2017;19(02):162–174

2 Picarelli H, Oliveira ML, Marta GN, Solla DJF, Teixeira MJ, Figueiredo EG. Mortality, Morbidity, and Prognostic Factors in the Surgical Resection of Brain Metastases: A Contemporary Cohort Study. J Neurol Surg A Cent Eur Neurosurg 2020;81(04):279–289
3 Karki R, Man SM, Kanneganti TD. Inflammasomes and Cancer. Cancer Immunol Res 2017;5(02):94–99
4 Acharyya S, Massague J. Arresting supporters: targeting neutrophils in metastasis. Cell Res 2016;26(03):273–274
5 Auezova R, Ryskeldiev N, Doskaliyev A, et al. Association of preoperative levels of selected blood inflammatory markers with prognosis in gliomas. OncoTargets Ther 2016;9:6111–6117
6 Mitsuya K, Nakasu Y, Kurakane T, Hayashi N, Harada H, Nozaki K. Elevated preoperative neutrophil-to-lymphocyte ratio as a predictor of worse survival after resection in patients with brain metastasis. J Neurosurg 2017;127(02):433–437
7 Pierscianek D, Ahmadipour Y, Oppong MD, et al. Blood-Based Biomarkers in High Grade Gliomas: a Systematic Review. Mol Neurobiol 2019;56(09):6071–6079
8 Sanchez-Salcedo P, de-Torres JP, Martinez-Urbistondo D, et al. The neutrophil to lymphocyte and platelet to lymphocyte ratios as biomarkers for lung cancer development. Lung Cancer 2016; 97:28–34
9 Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst 2014;106(06):dju124
10 Diem S, Schmid S, Krapf M, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 2017;111(July):176–181
11 Budczies J, Klauschen F, Sinn BV, et al. Cutoff Finder: a comprehensive and straightforward Web application enabling rapid biomarker cutoff optimization. PLoS One 2012;7(12):e51862
12 Therneau T. Survival: survival analysiš, including penalised likelihood. In: 2011
13 Yoshida D, Minami K, Sugiyama M, et al. Prognostic Impact of the Neutrophil-to-Lymphocyte Ratio in Stage I-II Rectal Cancer Patients. J Surg Res 2020;245:281–287
14 Wculek SK, Malanchi I. Neutrophils support lung colonization of metastasis-initiating breast cancer cells. Nature 2015;528 (7582):413–417
15 Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23 (07):1204–1212
16 Dudani S, Marginean H, Tang PA, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictive and prognostic markers in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation. BMC Cancer 2019;19(01):664
17 Hu L, Li M, Ding Y, et al. Prognostic value of RDW in cancers: a systematic review and meta-analysis. Oncotarget 2017;8(09): 16027–16035
18 Arvold ND, Lee EQ, Mehta MP, et al. Updates in the management of brain metastases. Neuro-oncol 2016;18(08):1043–1065
19 Loubersac T, Nguile-Makao M, Pouliot F, Fradet V, Toren P. Neutrophil-to-lymphocyte Ratio as a Predictive Marker of Response to Abiraterone Acetate: A Retrospective Analysis of the COU302 Study. Eur Urol Oncol 2020;3(03):298–305
20 Moon G, Noh H, Cho IJ, Lee JI, Han A. Prediction of late recurrence in patients with breast cancer: elevated neutrophil to lymphocyte ratio (NLR) at 5 years after diagnosis and late recurrence. Breast Cancer 2020;27(01):54–61
21 Ohno R, Kawamoto R, Kanamoto M, et al. Neutrophil to Lymphocyte Ratio is a Predictive Factor of Malignant Potential for Intraductal Papillary Mucinous Neoplasms of the pancreas. Biomark Insights 2019;14:1177271919851505
22 Yang S, Zhao K, Ding X, Jiang H, Lu H. Prognostic significance of hematological markers for patients with nasopharyngeal carcinoma: A meta-analysis. J Cancer 2019;10(11):2568–2577
23 Starzer AM, Steindl A, Mair MJ, et al. Systemic inflammation scores correlate with survival prognosis in patients with newly diagnosed brain metastases. Br J Cancer 2021;124(07): 1294–1300
24 Cacho-Díaz B, Spínola-Maroño H, Prado-Peredo JMY, et al. Prognostic utility of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for cancer patients with brain metastasis. Med Res Arch 2020;8(05):
25 Marini A, Dobran M, Aiudi D, Pesaresi A, di Somma LGM, Iacoangeli M. Pre-operative hematological markers as predictive factors for overall survival and progression free survival in glioblastomas. Clin Neurol Neurosurg 2020;197:106162

