RESEARCH ARTICLE

Prognostic utility of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for cancer patients with brain metastasis

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Abstract

Introduction: In order to optimize clinical and therapeutic approaches for patients with brain metastasis (BM), prognostic markers need to be widely available and simple to execute.
Objective: Considering that a Complete-Blood-Count is usually obtained at the initial routine work-up of almost all oncologic patients, the aim of this study was to determine the utility of the neutrophil-to-lymphocyte-ratio (NLR) and the platelet-to-lymphocyte-ratio (PLR) as prognostic markers for BM.
Results: A total of 550 patients with systemic cancer were included. Median age at the time of cancer diagnosis was 49 years and median age at the time of BM was 51 years. Median follow-up time was 11.2 months. Employing NLR cutoff values at BM diagnosis, patients were divided into groups I to III (I: <3, II: 3–4.49, III: ≥4.5), and median overall survival (MOS) was calculated for each one (I: 20 months, II: 13.9 months, and III: 7.5 months). Groups divided by a PLR cutoff (I: 250, II: ≥250) also differed in MOS (13.9 vs. 9.3 months). After multivariable analysis, only NLR was a significant independent predictor of MOS [I vs. II: 1.5 Odds Ratio (OR); I vs. III: 1.9 OR], meaning that NLR obtained at the time of BM diagnosis was inversely associated with MOS.
Conclusion: The NLR, but not the PLR, is predictive of outcome in cancer patients with BM, therefore, NLR might serve as a complement to the already known prognostic scales.

Keywords: Survival; Prognosis; Platelet-to-Lymphocyte Ratio; Neutrophil-to-Lymphocyte Ratio; Brain Metastasis.

1. INTRODUCTION

Brain metastasis (BM) from systemic cancers are up to 10 times more frequent than primary Central Nervous System malignancies, this is probably due to better tools for early detection and better treatments for systemic cancer that have resulted in longer survival.[1] The most common primary tumors that metastasize to the brain are lung, breast, and skin cancers.[2,3] Approximately 60%–75% of these patients will present clinically significant symptoms.[4] Although BM are usually associated with a grim prognosis, opportune diagnosis and targeted therapies have shown to improve survival.[4]

In order to optimize clinical and therapeutic approaches,[5] prognostic scores employ distinctive prognostic markers, which are defined as "situation, condition or characteristic of a patient that can be use to estimate the chance of recovery from a disease or chance of the disease recurring".[6] For example, based on compelling evidence accrued over the past 2 decades that the inflammatory response contributes to cancer genesis, clinical presentation, and prognosis,[7] serum inflammatory markers such as C-reactive protein and albumin have been proposed as prognostic factors.[8] Similarly, the neutrophil-to-lymphocyte ratio (NLR) was first introduced in 2005 as a prognostic marker in patients with colorectal cancer.[9]

As a prognostic marker, NLR has several advantages, it is particularly quick, low-priced and wide available, considering that a complete blood count (CBC) is usually conducted at the initial routine work-up of almost all oncologic patients, however its use in prognosis of BM is not broadly reported. Several studies have also proposed that the platelet-to-lymphocyte ratio (PLR) may predict outcome, but it is less studied. Therefore, the aim of the current study is to assess the utility of the NLR and the PLR as prognostic indicators in BM patients.

2. MATERIAL AND METHODS

A computerized database was created from patients with brain metastases (BM) sent for neuro-oncology (NeOn) consultation at a single cancer referral center (Instituto Nacional de Cancerología, Mexico City), the information gathered was retrospectively analyzed. Data included were: age at cancer and BM diagnosis, gender, primary cancer site, Karnofsky performance score (KPS) at the time of BM diagnosis, recursive partitioning analysis (RPA), graded prognostic assessment (GPA) index, presence of absence of non-brain metastases, complete blood count (CBC) at the time or around the 7 days before or after the diagnosis of BM. From the CBC a neutrophil (Ne) to lymphocyte (Ly) and a platelet (Pla) to Ly ratio were calculated by dividing Ne/Ly and Pla/Ly.

Inclusion criteria were as follows: 1. Histologically confirmed cancer diagnosis; 2. BM confirmed by Magnetic Resonance Imaging (MRI); 3. Examination by the neuro-oncology service from May 2012 to June 2017; CBC available at the time of BM

diagnosis (± 1 week). Exclusion criteria were: primary Central Nervous System (CNS) cancer, steroid use and hematologic malignancies. For the purpose of the present study, gynecologic cancers included: ovarian, endometrial and cervix-uteri cancers; skin cancers included: melanoma and non-melanoma. Overall survival (OS) was calculated as the period between BM diagnosis and death in months. The Institutional Review Board and Ethics committees reviewed and accepted the study protocol (INCAN/CI/837/17). Written informed consent was not obtained from each participant. All procedures were in accordance with the 1964 Helsinki declaration and its later amendments.

Statistical analysis

Variables were presented as frequencies, percentages (%), or median with interquartile range (IQR) as appropriate. Groups were compared using chi-square or *t*-test. Survival was assessed by the Kaplan–Meier method and compared between groups by the log-rank test. Bivariable and multivariable comparisons of survival were performed using logistic regression models and results expressed as odds ratio (OR) with 95% confidence intervals (CI). Significance was set at a P value <0.05 for all tests.

Receiver operating characteristic (ROC) curves were constructed to identify NLR and PLR cutoff values for the outcome variables OS (vs. death) and 12-month survival (yes *vs*. no). Sensitivity (S) and specificity (ES) were calculated for each value, and Youden indexes (YI) obtained as follows: [A] For NLR, a YI of 0.26 for OS and 0.25 for 12-month survival with S of 76% and ES of 50% yielded a cutoff value of 2.85, and S of 65% and ES of 60% yielded a second cutoff value of 4.45. For better separation of individual patient values into groups, cutoffs were rounded off to 3 and 4.5. [B] For PLR, a YI of 0.21 for OS and 0.14 for 12-month survival with S of 52% and ES of 69% yielded a cutoff value of 231, and S of 48% and ES of 65% yielded a second cutoff value of 263. Given the proximity of these values, a single cutoff of 250 was used for stratification. **Figure 1** & **2** show the results of the ROC analysis.

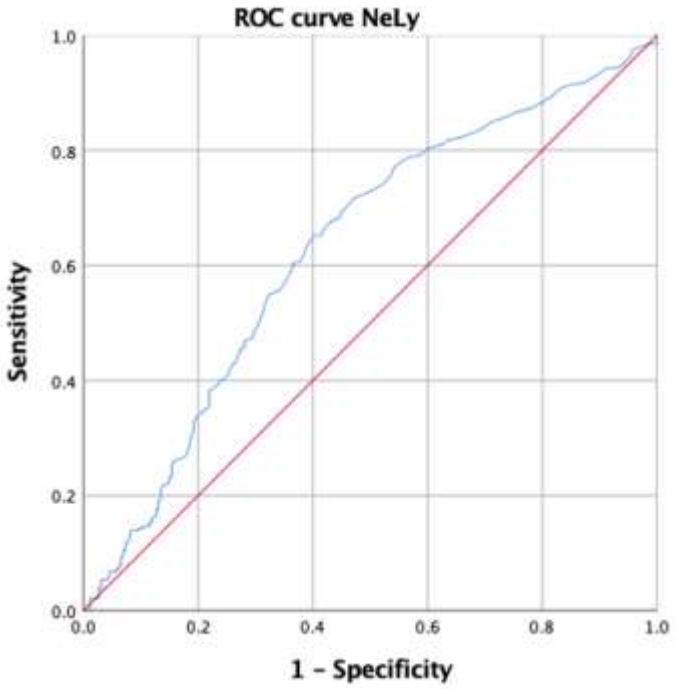

Figure 1. ROC curve for the Neutrophil-to-lymphocyte ratio. An area under the curve of 63% with a *p* value of <0.0001 was determined.

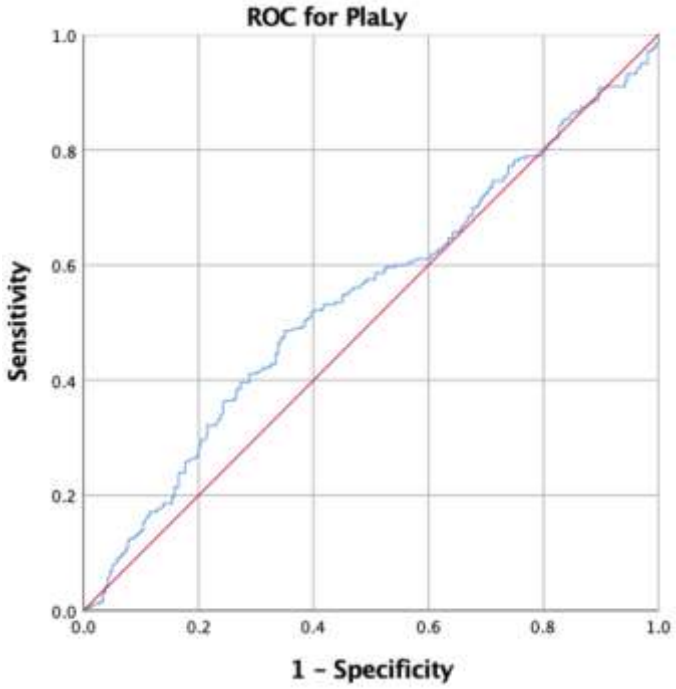

Figure 2. ROC curve for the Platelet-to-lymphocyte ratio. An area under the curve of 54% with a *p* value of 0.07 was determined.

3. RESULTS

A total of 567 patients were initially enrolled, 17 subsequently excluded because a CBC could not be found for the time of BM diagnosis. **Table 1** summarizes the general characteristics of the cohort. Median age at the time of cancer diagnosis was 49 years and median age at the time of BM was 51 years. Median follow-up time was 11.2 months (IQR 4.2–24.5 months). The majority of cases (403, 73%) were female. Breast was the most common primary cancer site (*n*=214). Breast cancer patients were further divided according to histologic characteristics into Luminal A (85/214, 40%), Luminal B (36, 17%), Human Epidermal Growth Factor Receptor 2 (HER2)-positive (45, 21%), Basal-like (47, 22%), and undetermined (3 cases). Lung was the second most common cancer site (*n*=135), of which 7% were small cell lung cancer and 93% were non-small cell lung cancer.

Table 1. General characteristics found in the 550 patients with brain metastasis.

Feature		n (%)
Median age	At cancer diagnosis [IQR]	49 [40–59]
	At BM diagnosis [IQR]	51 [42–61]
Gender	Female	403 (73)
	Male	147 (27)
Cancer site	Breast	214 (39)
	Lung	135 (25)
	Gynecologic	56 (10)
	Head and neck	29 (5)
	Sarcomas and soft tissue	3 (0.5)
	Thyroid	7 (1)
	Urologic	59 (11)
	Skin	20 (4)
	Gastrointestinal	16 (3)
	Other	11 (2)
KPS	<70	197 (36)
	≥70	353 (64)
RPA	I	29 (5)
	II	69 (13)
	III	452 (82)
GPASS	0-1	202 (37)
	1.5-2.5	296 (54)
	3	32 (6)
	3.5-4	20 (4)
Metastasis	Systemic activity	454 (83)
	Lung metastases	216 (39)
	Bone metastases	224 (41)
	Liver metastases	139 (25)
Median ratio	Neutrophil-to-lymphocyte [IQR]	4.6 [2.7–9.2]
	Platelet-to-lymphocyte [IQR]	228 [152–363]

IQR = Interquartile range, KPS = Karnofsky Performance Status, GPASS = General Practice Administration System for Scotland

Of the 550 patients, 123 (22%) were diagnosed with BM at the time of cancer diagnosis or led to the diagnosis of cancer, in 208 (38%) the diagnosis of BM was done during the first line of treatment, in 118 (22%) during the second line and in 101 (18%) during or after the third line of treatment. Median time from the diagnosis of cancer to the diagnosis of BM was 12.3 months (IQR 1.7-35.9 months). At the time of BM diagnosis, 454 (83%) had any form of systemic disease other than CNS, 216 (39%) had lung metastases, 224 (21%) bone metastases, and 139 (25%) liver disease. Brain metastases treatment included whole brain radiotherapy (WBRT) in 357 (65%), change in chemotherapy and WBRT in 61 (11%), Surgery followed by radiotherapy (RT) in 40 (7%), radiosurgery and WBRT in 12 (2%), Radiosurgery and chemotherapy in 4 (1%); 44 patients (8%) refused or were severely affected to receive any form of treatment.

Most patients had poor outcome scale scores, with 82% assigned RPA grade III, 37% a GPASS of 0–1, and 81% presenting with metastases outside the CNS. Both NLR and PLR were non-normally distributed, with median values of 4.6 and 228, respectively.

Median overall survival (MOS) was 11.5 months (95% CI 9.6–13.4 months). Survival according to NLR and PLR are presented in **Table 2** and **Figure 3**. MOS was longest in the NLR < 3 group, followed by the 3–4.5 group, and shortest in the > 4.5 group (p <0.0001). MOS was also longer for patients with PLR < 250 than for those with PLR > 250 (p = 0.005).

Table 2. Survival analysis of the 550 patients with brain metastasis.

Variable		**MOS, months (95% CI)** Total = 11.49 (9.6–13.4)	**Log Rank p**
Age at BM diagnosis	<50 years ≥50 years	11.5 (9.1–13.8) 11.5 (8.7–14.2)	0.22
Gender	Female Male	12.8 (10.9–14.6) 7.1 (5.0–9.3)	0.002
NLR	<3 3-4.49 >4.5	20 (14.3–25.6) 13.9 (10.9–16.) 7.5 (5.8–9.2)	<0.0001
NLR	<4.5 ≥4.5	16.9 (13.6–20.2) 7.5 (5.8–9.2)	<0.0001
PLR	<250 ≥250	13.9 (11.7–16.1) 9.3 (7.6–11.1)	0.005
KPS	<70 ≥70	5.3 (4.1–6.4) 15.6 (13.7–17.4)	<0.0001
RPA	I II III	Not reached 32 (20.4–45.1) 9.1 (7.5–10.7)	<0.0001
GPASS	0–1 1.5–2.5 3 3.5–4	6.4 (4.4–8.4) 13.8 (12.1–15.5) 14.5 (13.2–15.7) Not reached	<0.0001

Metastasis	Systemic	11.1 (9.3–12.9)	0.001
	Lung	9.3 (6.6–12.0)	0.08
	Bone	12.7 (10.1–15.3)	0.47
	Liver	8.6 (5.8–11.3)	0.006

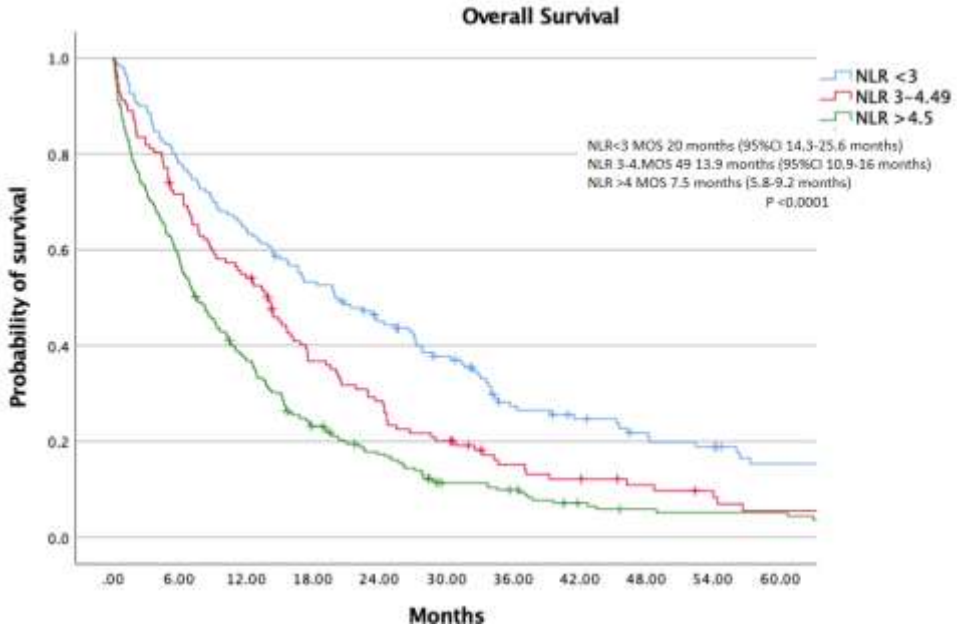

Figure 3. Kaplan-Meier curve for patients with brain metastases according to their Neutrophil-to-lymphocyte ratio.

A multiple regression model was constructed including NLR group, PLR group, age, sex, Karnofsky Performance Status (KPS), and presence of systemic, lung, and/or liver metastases to identify independent outcome predictors (**Table 3**). The NLR group was independently associated with prognosis (p <0.05) while the PLR group was not. Other variables that remained significant by multivariate analysis included age, KPS, and the presence of liver metastases. RPA and GPASS were not included in the multivariable analyses as they are already in use as prognostic scales.

Table 3. Bivariable and multivariable logistic regression analysis of the risk of death at 12 months.

Variable	**Bivariable OR (95% CI)**	***p* value**	**Multivariable OR (95% CI)**	***P value***
Female vs Male	1.6 (1.1-2.4)	0.01	1.5 (0.9-2.2)	0.05
Age <50 vs ≥50 years	1.06 (0.7-1.5)	0.7	-	-
KPS <70 vs ≥70	3.2 (2.2-4.6)	<0.0001	2.6 (1.7-3.8)	<0.0001
Systemic disease	0.9 (0.6-1.5)	0.8	-	-
Lung metastasis	0.8 (0.6-1.2)	0.4	-	-
Liver metastasis	0.8 (0.6-1.2)	0.3	-	-
Bone metastasis	1.3 (0.9-1.9)	0.08	-	-
NLR <4.5 vs ≥4.5	2.5 (1.8-3.6)	<0.0001	2.2 (1.4-3.3)	<0.0001
PLR <250/≥250	1.4 (1.0-2.0)	0.03	0.8 (0.5-1.4)	0.5

Regarding patients treated with steroids we made a subgroup and analyzed them. Median NLR in patients using steroids was 5 and 4.6 for those without steroids (p = 0.03). MOS of those who were taking steroids (n=107) was 14.5 months (95% CI 10.9-17.9 months) and for those without 10.5 months (95% CI 8.7-12.3 months) p = 0.20. Median NLR in patients with a concomitant infection (n=9) at the time of BM was 5.7 vs those without 4.6 (p = 0.54).

4. DISCUSSION

In this cohort of 550 patients with BM from systemic cancer, the NLR obtained at the time of BM diagnosis was inversely associated with MOS. Calculated cutoff values of 3 and 4.5 defined 3 prognostic groups. Group I with NLR <3 survived the longest (MOS of 20 months), group II (NLR 3–4.49) substantially decreased (MOS of 13.9 months), and group III (NLR >4.5) the shortest, with MOS of only 7.5 months (p<0.0001). Alternatively, the calculated PLR cutoff value of 250 was not associated with prognosis by multivariable analysis. As MOS of the whole cohort was 11.5 months, NLR <3 predicted substantially prolonged survival.

In recent years, there have been great advances in our understanding of the contributions of inflammation to cancer development (inflammation-associated cancer) and symptoms (cancer-associated inflammation). Neutrophils have been shown to promote tumor growth or expansion through the secretion of epidermal growth factor, transforming growth factor-beta (TGF-β1), and platelet-derived growth factor (PDGF). Peritumoral neutrophils promote metastases through effects on cancer cell migration, angiotropism, and the development of the premetastatic niche.[10] Lymphocytes initially provide protection against cancer cell proliferation and migration, as better prognosis has been found in lymphocyte rich (inflammatory) malignancies.[11] However, high NLR also indicates high levels of neutrophil-derived cytokines such as TGF-β, which are associated with tumor progression, angiogenesis, and peritumoral stroma formation determined by neutrophilia with relative lymphopenia.[12]

Platelets release PDGF, platelet factor 4 (PF4), and thrombospondin, growth factors implicated in tumor spread, tumor cell adhesion, invasion, and angiogenesis.[13] In chronic inflammatory conditions, proinflammatory mediators increase platelet formation and once activated, they can enhance tumor growth, dissemination, and angiogenesis.[14] An elevated PLR indicates activation of proinflammatory transcription factors, which in turn trigger the production of tumor growth-promoting cytokines such as tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6.[14]

There is substantial evidence for the prognostic utility NLR in multiple disorders, including insulin resistance,[15] Alzheimer disease,[16] acute coronary syndrome,[17] and acute pancreatitis,[18] while the clinical utility of PLR has been established in cardiovascular disease[19] and end-stage renal disease.[20] To our

knowledge, there are very few reports evaluating the utility of NLR or PLR for prognosis of BM.[21]

Previously reported cutoff values for the NLR are quite similar to our own. Two studies[14,22] with preoperative samples of glioma patients both set 4 as their cutoff value, while 2 others, one of general oncology patients before surgery[23] and another of melanoma patients with BM[24] both set their cutoff at 5, and all found significant prognostic efficacy. Still another determined a cutoff value of 6.[21] Given this variation across studies, we decided to calculate our own cutoff values.

A meta-analysis[25] confirmed that NLR has consistent significant value as a prognostic tool in systemic cancer. Pooled results also indicated that NLR is a better prognostic factor for patients with advanced cancer, although none of the included studies specified the presence of BM. Another meta-analysis[26] with over 40,000 patients found that a median NLR cutoff value of 4 was strongly predictive of cancer-specific survival, progression, and disease-free survival. Other studies with more than 25,000 advanced cancer patients found a median NLR cutoff value of 5,[12, 27-29] while a meta-analysis including gynecologic cancer patients found a cutoff value of 2.95[30] and another including urothelial cancer patients found cutoff values ranging from 2 to 5.[31] Based on these findings, some have proposed a continuous range instead of using a predetermined cutoff value.[10] Finally, a study by Young et al.[32] found that an NLR value > 4.95 predicted the presence of BM in non-small-cell lung cancer. Finally, a recent study, similar to ours, made on 66 non-small cell lung cancer patients with BM and treated with WBRT founded a NLR <5 (and a PD-L1 expression) as a prognostic marker.[33]

In contrast to NLR, there is much less evidence on the prognostic efficacy of the PLR. In glioma patients,[21] a cutoff value of 200 correlated with prognosis. A meta-analysis studying ovarian cancer patients found a worse prognosis in patients with PLR above 200,[34] and another meta-analysis of advanced cancer patients found that cutoff values ranging from 89.62 to 300 all had prognostic significance.[35] Yet another meta-analysis[36] including patients with colorectal, hepatocellular, gastroesophageal, ovarian, and pancreatic cancer found associations with outcome using cutoffs ranging from <150 to >300. Another meta-analysis[28] evaluated 12 studies with cutoffs ranging from 111.23 to 322, only 1 of which reported that a high PLR is associated with worse prognosis.

Several biases and limitations of the present study must be acknowledged. First, it was conducted at a single cancer referral center and only patients treated by the neuro-oncology unit were included, so there is some risk of selection bias; another limitation is that this study did not include other outcomes like progression free survival or quality of life; also, we must notice that recent improvement of chemotherapy may contribute to the survivals. To avoid information bias, all definitions were

established before data acquisition and had specific norms, and all data extraction and analyses were supervised by one of the authors (HSM). Nonetheless, this study is unique, as it includes a large series of patients with BM at the time of diagnosis, each cutoff level for NLR and the PLR was individually calculated, and the general characteristics of the patients included are presented in detail. Also, we should mention the fact that NLR is a very nonspecific marker and is subject to a number of biases from artificial elevation or depression, a number of conditions that could alter the CBC (like infection or hematologic malignancies) or transient changes not reliable to prognosis making.

5. CONCLUSION

The NLR, but not the PLR, is predictive of outcome in cancer patients with BM, therefore, NLR might serve as a complement to the already known prognostic scales.

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