

Preoperative Systemic Inflammatory Markers in Different Brain Pathologies: An Analysis of 140 Patients

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ABSTRACT

AIM: To analyze preoperative inflammatory markers including neutrophil, lymphocyte and platelet counts and neutrophil to lymphocyte (NLR) and platelet to lymphocyte (PLR) ratios in a group of patients with different brain pathologies and healthy controls.

MATERIAL and METHODS: Above mentioned preoperative inflammatory markers were analyzed in a total of 140 patients included 39 with temporal lobe epilepsy, 37 with glioblastoma multiforme, 32 with grade-I meningioma and 32 with intracranial metastasis. Healthy controls included 30 subjects. The levels were compared between each patient group and between patients and controls.

RESULTS: Significant higher neutrophil, platelet counts, NLR and PLR were found in glioma, meningioma and metastasis patients compared to epilepsy ($p < 0.05$). On the other hand lymphocyte counts were significantly lower than epilepsy ($p < 0.05$). PLR > 120.78 was suggestive of metastasis rather than GBM.

CONCLUSION: Preoperative inflammatory markers increase in different brain pathologies and metastasis show striking changes. PLR can have diagnostic value in differentiating metastasis from GBM.

KEYWORDS: Inflammatory marker, Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio.

ABBREVIATIONS: **AUC:** Area under the curve, **CBC:** Complete blood count, **GBM:** Glioblastoma multiforme, **HGG:** High grade glioma, **LMR:** Lymphocyte to monocyte ratio, **NLR:** Neutrophil to lymphocyte ratio, **PLR:** Platelet to lymphocyte ratio, **ROC:** Receiver operating curve, **TLE-HS:** Temporal lobe epilepsy-hippocampal sclerosis

INTRODUCTION

Inflammation has been proven to be one of the crucial causes of development and progression of several pathological entities, including brain tumors and epilepsy (3,8). It is now considered one of the hallmarks of cancer, and targeted treatment has been a matter of discussion over the last several years. Lymphocyte infiltration has been clearly demonstrated in the microenvironment around brain tumors and epileptogenic areas, and the host inflammatory response is characterized by changes in the levels of neutrophils,

lymphocytes, and platelets (6). Studies have demonstrated that changes in the blood levels of preoperative inflammatory markers, such as the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR), which can be obtained from a simple complete blood count (CBC) analysis, can provide insight into tumor progression (2,11).

The common notion is that a higher NLR is the most accurate prognostic parameter for solid tumor progression: the higher the NLR, the poorer the outcome. However, the preoperative



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systemic inflammatory markers mentioned above have been mostly studied in solid tumors, such as prostate (5), or gastrointestinal tumors (9), and there are only a limited number of studies in neurosurgical patients. Finding a biomarker with improved sensitivity and specificity is necessary in patients undergoing operation for solid tumors such as glioma or meningioma. Since obtaining peripheral blood before surgery is easy and inexpensive, the NLR, PLR, and LMR are attractive candidates, but it is necessary to further assess their usefulness in brain tumors.

The aim of the present study was to describe differences in the levels of several preoperative inflammatory markers among patients with temporal lobe epilepsy with hippocampal sclerosis (TLE-HS), glioblastoma multiforme (GBM), meningioma (grade I), intracranial metastasis, and healthy controls.

■ MATERIAL and METHODS

Study Population

The medical records of patients newly diagnosed with TLE-HS, GBM, meningioma, or metastasis at two hospitals were collected and analyzed. Patients analyzed in this study were selected according to the following criteria: 1) GBM, grade I meningioma, or histologically proven metastasis according to the World Health Organization criteria, or TLE-HS histologically proven according to the International League Against Epilepsy criteria; 2) no prior chemotherapy or radiotherapy; 3) no hematological disease or infection; 4) complete data related to CBC; and 5) informed consent. A total of 140 patients were analyzed: 39 patients with TLE-HS, 37 with GBM, 32 with grade I meningioma, and 32 with intracranial metastasis. For the controls, we reviewed the records of 30 healthy patients who had undergone their annual health check. Our local ethics committee informed us that this retrospective data analysis does not need approval since this study did not include any data disclosing the patients' identities.

Data Collection

Demographic, clinical, radiological, and histopathological data were retrieved from the patient medical records. After hospitalization, blood samples were taken for CBC and other tests, including hepatic function, serology, and electrolytes, as standard preoperative work-up. Neutrophil ($10^3/\text{mm}^3$), lymphocyte ($10^3/\text{mm}^3$), and platelet ($10^3/\text{mm}^3$) counts were recorded. The preoperative NLR (the absolute neutrophil count divided by the absolute lymphocyte count) and PLR (the absolute platelet count divided by the absolute lymphocyte count) were calculated.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0. Initially, the Kolmogorov-Smirnov test was performed to determine whether the variables were distributed normally. All data in this study were not subject to normal distribution, so non-parametric Mann-Whitney U-test was used for comparisons between groups. Receiver operating characteristic curve analysis was performed to determine

the area under the curve (AUC) for the NLR and PLR, which were used to determine diagnostic performance regarding GBM and metastasis. A probability value (p value) < 0.05 was considered statistically significant.

■ RESULTS

Study Population

A total of 170 subjects were finally analyzed in this study. There were 39 patients with TLE-HS, 37 with GBM, 32 with meningioma, 32 with metastasis, and 30 healthy controls. The TLE-HS group included 22 men (56.4%) and 17 women (43.6%), with a mean age of 25.53 ± 10.99 years. All patients underwent epilepsy surgery and were diagnosed with HS. The glioma group consisted of 21 men (56.8%) and 16 women (43.2%), with a mean age of 56.16 ± 16.45 years. All were histopathologically diagnosed with grade IV glioma (GBM). The meningioma group had 13 men (40.6%) and 19 women (59.4%), with a mean age of 57.50 ± 12.39 years. All were diagnosed with grade I meningioma after surgery. The intracranial supratentorial metastasis group consisted of 21 men (65.6%) and 11 women (34.4%), with a mean age of 56.09 ± 9.41 years. The last group was the control group, which included 16 healthy men (53.3%) and 14 healthy women (46.7%), with a mean age of 32 ± 10.8 years.

Comparison of Preoperative Inflammatory Markers Between Groups

Table I shows a summary of the statistical analysis of preoperative inflammatory markers among the groups. As shown in Table I, there were significantly higher preoperative neutrophil counts and NLRs in the GBM, meningioma, and metastasis groups than in the control group. The PLRs in the GBM and metastasis groups were significantly higher than that in the control group. On the other hand, the lymphocyte counts were significantly lower in the GBM, meningioma, and metastasis groups than in the control group. Surprisingly, none of the parameters showed a significant difference between the TLE-HS and control groups. Neutrophil counts, the NLR, and the PLR were significantly higher in the GBM, meningioma, and metastasis groups than in the TLE-HS group. The metastasis group also had a significantly higher PLR compared to the GBM and meningioma groups. Again, surprisingly, there was no significant difference in platelet counts between the patient groups. A significantly lower lymphocyte count was found in the GBM, meningioma, and metastasis groups compared to the TLE-HS group.

Diagnostic efficacy was evaluated between the GBM and metastasis groups using the NLR and PLR (Figure 1 for the NLR and -2 for the PLR). The AUCs were 0.59 (95% confidence interval [CI] 0.46-0.73, $p = 0.17$) for the NLR and 0.66 (95% CI 0.53-0.79, $p = 0.06$) for the PLR. The cut-off point for the NLR was 2.63 with 71% sensitivity and 44% specificity. The cut-off point for the PLR was 120.78 with 84% sensitivity and 48% specificity. Our findings suggested that the PLR showed significantly better efficacy (diagnostic value) than the NLR in differentiating GBM from metastasis before surgery.

■ DISCUSSION

It has been well established that TLE, intracranial tumors such as glioma, and intracranial metastasis are closely correlated with chronic inflammation (3,8). The current literature underlines the role of systemic inflammatory markers, such as a high NLR and PLR and a low LMR, for detecting, staging,

and monitoring solid cancers, such as colorectal and prostate tumors (5,9). Unfortunately, little is known about their use in intracranial pathologies. A limited number of studies found that a high NLR and PLR are correlated with glioma grade and can be used as biomarkers of disease monitoring (2,7,11). Over the last 5 years, mounting evidence has indicated that an elevated NLR is associated with poor survival in patients with

Table I: Statistical Summary of Preoperative Inflammatory Markers in the Groups

Parameters	Neutrophils	Lymphocytes	Platelets	NLR	PLR
TLE	4.02 ± 2.0	2.27 ± 0.8	235.8 ± 69.4	1.92 ± 1.1	110.7 ± 41.7
GBM	6.28 ± 2.2*	1.90 ± 0.9*	252.1 ± 76.5	4.12 ± 2.5*	151.3 ± 61.6*
Mgm	6.48 ± 3.6*	2.0 ± 1.3*	230.6 ± 51.2*	4.81 ± 4.4*	150.2 ± 71.4
Met	7.23 ± 3.6*	1.63 ± 0.7*	275.3 ± 90.6	5.88 ± 4.8*	203.2 ± 105.5*
Control	4.11 ± 0.8	2.36 ± 0.5	269.1 ± 61.2	1.81 ± 0.5	119.0 ± 35.3

Statistical comparisons

TLE/GBM	0.00001	0.03	NS	0.00001	0.007
TLE/Mgm	0.001	0.03	NS	0.001	0.02
TLE/Met	0.00001	0.002	NS	0.00001	0.00001
GBM/Mgm	NS	NS	NS	NS	NS
GBM/Met	NS	NS	NS	NS	0.01
Mgm/Met	NS	NS	NS	NS	0.03

Values are given as mean ± standard deviation.

* p < 0.05, compared to healthy controls.

GBM: Glioblastoma Multiforme, **Met:** Metastasis, **Mgm:** Meningioma, **NLR:** Neutrophil-lymphocyte ratio, **NS:** Not significant, **PLR:** Platelet-lymphocyte ratio.

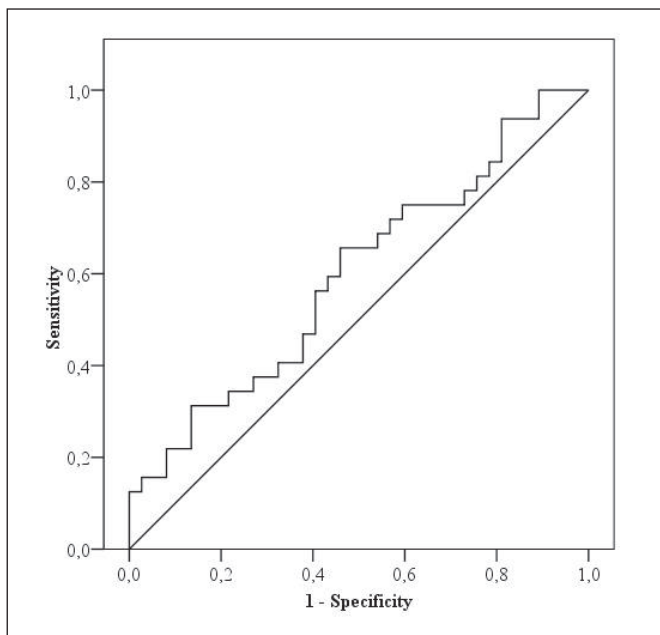


Figure 1: Diagnostic efficacy of NLR for differentiating GBM from metastasis. The AUC is 0.59 (95 % CI 0.46-0.73) and p = 0.17.

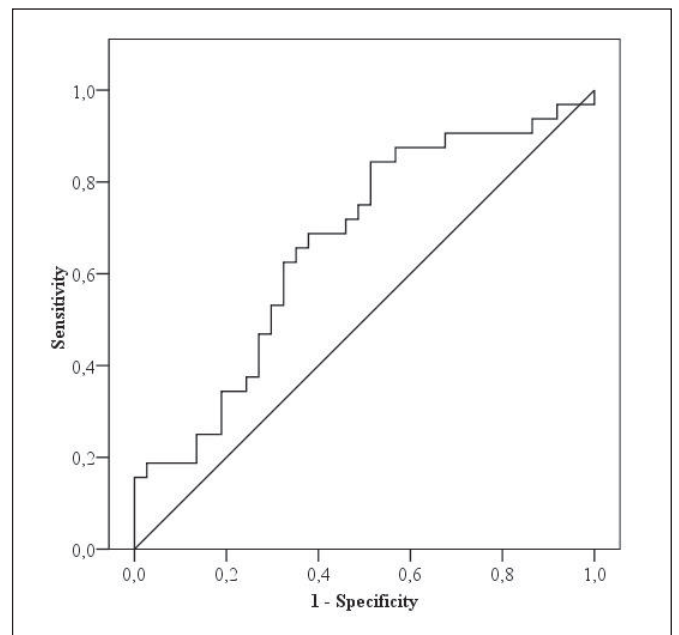


Figure 2: Diagnostic efficacy of PLR for differentiating GBM from metastasis. The AUC is 0.66 (95 % CI 0.53-0.79) and p = 0.06.

high grade glioma (HGG), and, moreover, an NLR > 4 prior to second surgery in patients with HGG is a poor prognostic factor (7). In addition to the NLR, which is the most studied parameter in intracranial malignancies, use of the PLR and LMR as prognostic markers has also been examined. A higher PLR and a lower LMR have been shown to be associated with poor outcomes in patients with HGG (11). A recent study underlined that a high NLR demonstrated the highest accuracy in predicting GBM over other intracranial pathologies, such as meningiomas, acoustic neuromas, and non-lesional epilepsy, and healthy subjects (11). Moreover, the authors found that using a combination of the NLR and the LMR may be a useful marker for GBM diagnosis and in differentiating GBM from meningioma or acoustic neuroma (11).

Studies regarding preoperative inflammatory markers have focused mainly on gliomas, and only one report analyzed preoperative inflammatory markers in different intracranial pathologies (11). Some of our results supported the study by Zheng et al. (11), in that the preoperative serum neutrophil and lymphocyte counts were found to be significantly higher and lower, respectively, in patients with GBM, meningioma, and metastasis than in healthy controls. The NLR was significantly higher in patients with these pathologies. Higher neutrophil counts and lower lymphocyte counts suggest neutrophil-dependent inflammatory reactions and decreased lymphocyte-dependent anti-tumor immune response (1,10,11). As expected, the TLE group was not significantly different from the healthy controls with regard to any of the preoperative inflammatory markers. This finding was expected because inflammation is not as severe in TLE as in glioma or metastasis. One of the most striking findings in the current study was that inflammatory reactions were more severe in patients with metastasis compared to patients with TLE, meningioma, and GBM. The highest neutrophil counts, platelet counts, NLR, and PLR and the lowest lymphocytes counts were found in patients with metastasis. These findings were expected because patients with intracranial metastasis have primary tumors such as lung or breast. However, no significant difference was found between patients with metastasis and those with meningioma with respect to neutrophil counts, lymphocyte counts, platelet counts, or the NLR, which was unexpected and contrary to results in the current literature (11). This may be due to the fact that we included a smaller number of patients in each group. In this study we especially wondered whether the NLR or PLR have diagnostic value in differentiating metastasis from GBM or vice versa. Neurosurgeons sometimes have difficulty differentiating GBM from metastasis using current neuroimaging studies, such as magnetic resonance imaging (MRI), prior to surgery. It has been clearly demonstrated that even advanced MRI provides only 50% to 80% diagnostic specificity for differential diagnosis of GBM from metastasis (4). Therefore, the preoperative NLR or PLR can provide additional information to aid in the differential diagnosis of GBM from metastasis. In this study, we focused on the difference between GBM and metastasis regarding the NLR and PLR. Our results demonstrated that the PLR, but not the NLR, may be a useful marker for differentiating GBM

from metastasis before surgery. The AUC was 0.66 with a p value of 0.06, and the cut-off point was found to be 120.78. Although the numbers of patients with GBM and metastasis in this study were small, the test sensitivity and specificity were found to be 84% and 48%, respectively. We strongly encourage future studies with a larger cohort of patients with GBM and metastasis to analyze the diagnostic accuracy of these ratios.

■ LIMITATIONS

There are several limitations to this study. First, this is a retrospective data analysis, and some bias may have occurred during data retrieval. Second, our sample consisted of a relatively small number of patients, and future studies with a larger cohort of patients are needed to confirm our results.

■ CONCLUSIONS

We demonstrated that a higher preoperative PLR could be used as a biomarker in differentiating GBM from intracranial metastasis, although the test showed high sensitivity (84%) and low specificity (48%). We believe that future studies with a larger patient sample may increase the test specificity. Our findings showed that a PLR > 120.78 could indicate metastasis rather than GBM.

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