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Diagnostic Utility of Pre-Intervention Inflammatory Markers in Patients with Glioma Vs Brain Metastasis

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Abstract

Glioma and brain metastatic tumors are the most common neoplasms encountered in the central nervous system (CNS) and continue to be the major cause for mortality and morbidity. Histological examination of tumor tissue through biopsy or resection serves as a definitive diagnosis of glioma and brain metastasis, whereas contrast tomography (CT) and magnetic resonance imaging (MRI) are supplemental tests for disease staging and treatment response monitoring. However, these are expensive and collecting specimens for histopathological studies are invasive.

Currently, studies have shown that cancer cells and the immune system have interaction in several steps in tumorigenesis hence involvement of the inflammatory markers. Tumors have a tumor microenvironment (TME) which contains not only cancer cells but also noncancerous cell types including endothelial cells, pericytes, fibroblasts, and immune cells such as neutrophils, lymphocyte, monocytes and platelets. [1] Thus, studies investigated the relationship of these cells to other tumors with note that preoperative or pre-intervention levels of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) are new markers for diagnosis and predicting prognosis of tumors [2, 3, 4, 5].

This study focuses on the diagnostic utility of pre-intervention inflammatory markers in comparing glioma and brain metastasis. This is a retrospective study of patients admitted in Jose R. Reyes Memorial Medical Center from January 2016 to December 2022. There were 91 patients included, 47 were diagnosed with glioma while 44 were diagnosed with brain metastasis. Statistical analysis based on quartile values of the inflammatory markers yielded significant difference among patients with glioma and brain metastasis. NLR cut-off value at <3.95 has the highest specificity at 88.64% and sensitivity at 34.04% in glioma patients. PLR cut off value at <12.47 has the highest specificity at 90.91% and sensitivity at 38.30% in glioma patients. Hence, low NLR and PLR favors the diagnosis of glioma while high NLR and PLR favors the diagnosis of brain metastasis.

Keywords: Pre-Intervention Inflammatory Marker, Glioma, Brain Metastasis

Introduction

Glioma and brain metastatic tumors are the most common neoplasms encountered in the central nervous system (CNS) and continue to be the major cause for mortality and morbidity. Gliomas are primary brain tumors, accounting for 80% of CNS tumors that originate from glial cells such as astrocytes, oligodendrocytes and ependymal cells from which histologically these tumors are being graded while brain metastatic tumors originate from tumors of lung, breast, melanoma, kidney and gastrointestinal tract. [6] A challenge remains in differentiating these two entities since symptoms of both tumors are the same, presenting as focal neurologic deficits, headache or seizures and imaging studies may show similar findings of hypodense focus on computed tomography (CT) or hyperintense focus on T2 weighted magnetic resonance imaging (MRI) suggestive of vasogenic edema and both entities may also present as multiple lesions on imaging, making it more difficult to distinguish glioma from brain metastasis. [7]

Currently, histological examination of tumor tissue obtained through biopsy or resection serves as the standard procedure for definitive diagnosis of glioma and brain metastasis, whereas CT and MRI are supplemental procedures for disease staging and treatment response monitoring. [8] However, both the histopathological and neuroimaging tests are expensive and collecting

specimens for histopathological studies may cause neurological tissue damage. Moreover, unlike other cancer types such as breast or prostate cancer, brain neoplasms have had no sensitive or specific serum marker that can be used for their detection, disease staging, treatment response monitoring and prognosis. Thus, the need for a minimally invasive, affordable and readily available biomarker may help clinicians distinguish gliomas from brain metastases.

In recent years, studies have shown that systemic cellular inflammatory markers can be non-invasive biomarkers for glioma diagnosis and prognosis. A number of studies suggest that preoperative levels of Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), and Lymphocyte-Monocyte Ratio (LMR) are new markers for diagnosis and predicting prognosis of gliomas. [2, 3, 4, 5] Studies also have shown interaction of cancer cells and the immune system that are crucially involved in several steps in tumorigenesis which explain the changes in the above-mentioned inflammatory markers. [1]

To date, there are no studies looking into the diagnostic utility of these pre-inflammatory markers in differentiating gliomas versus brain metastases. Hence the primary objective of this study is to determine the diagnostic utility of pre-intervention inflammatory markers in patients diagnosed with glioma and brain metastasis. This study would specifically compare the pre-intervention inflammatory markers of patients with glioma and brain metastasis and compute the specificity and sensitivity of the pre-inflammatory markers in patients diagnosed with glioma vs brain metastasis, and determine the prognostic utility of the pre-intervention inflammatory markers in patients with glioma vs brain metastasis.

This study is relevant in developing countries such as the Philippines particularly in the areas where there is unavailability of high technology diagnostic tools to compare brain tumors. The complete blood count (CBC) is one the basic tests for almost all patients and it is readily available, accessible, and less invasive. By knowing the diagnostic utility using the pre-inflammatory markers, the result may act as a biomarker, a marker for treatments response, a prognosticating marker or an important source in the advances of prevention and treatment of brain tumor.

Methodology

Data was collected through chart review of adult patients (>18 years old) admitted in Dr. Jose R. Reyes Memorial Medical Center, Philippines and diagnosed with glioma and brain metastasis from January 2016 to December 2021. Data collected include the patient demographic, final diagnosis, relevant clinical, radiologic and histopathological data. Furthermore, data on pre-intervention CBC was collected particularly the white blood cell (WBC), neutrophil, lymphocyte, monocyte and platelet count. Pre-intervention NLR (quotient of an absolute number of the neutrophil count to lymphocyte count), PLR (quotient of an absolute number of platelets to lymphocyte count), and LMR (quotient of an absolute number of lymphocyte count to monocyte count) were calculated and analyzed. Fig 1 shows the research framework of this study.

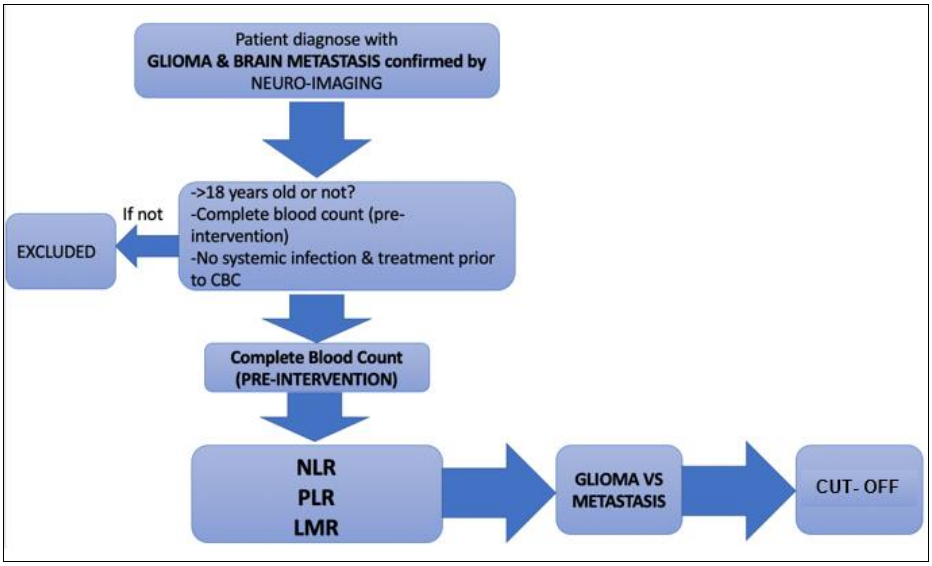

Fig 1: Research framework

Excluded in the study were patients who were treated with steroid or anti-inflammatory drugs prior to first CBC test, patients who showed signs of active infection, bleeding, autoimmune or hematological disorders, hyper or hypothyroidism, as well as uncontrolled hypertension and uncontrolled diabetes, which affect leukocyte (subtypes) counts or function and patients who had undergone chemotherapy or radiation therapy prior to first CBC.

Statistical Data Analysis

All the data retrieved were analyzed using Statistical Package for Social Sciences (SPSS version 24.0). Descriptive statistics was used to compute the general characteristics of the subjects. Independent sample t-test and chi-square test were used for appropriate comparisons and were reported as mean with standard deviation for numerical data, and percentages for nominal data. Correlation was analyzed using the Pearson correlation coefficient test. Specificity and sensitivity were computed and diagnostic cut-offs of NLR, PLR and LMR in comparison with glioma and brain metastasis were identified. The statistical significance was determined if the p- value is <0.05.

Results

Between January 2016 to December, 2021, a total of 217 patients were included. A total of 126 (58%) were excluded and only 91 (42%) patients were included in the study. Patients who were excluded had history of other infectious disease such as pneumonia and others had treatment with steroids, antibiotics or had undergone chemotherapy and radiotherapy. Among the 91 patients, 47 (52%) were diagnosed with glioma while 44 (48%) were diagnosed with brain metastasis. Glioma patients include both high- or low-grade glioma while brain metastasis patients include patients with lung, cervical, breast, rectal and ovarian cancer with lung Cancer having most of the metastasis noted among 38 (86%) patients. However, six patients (14%) under brain metastasis are of unknown cause since some of the patients deteriorated and had not completed the metastatic work up (Table 1). There were 37 (41%) males and 54 (59%) females and among age groups there were 66 (73%) patients under 31-60 years old, 14 (15%) patients under 18-30 years old while 11 (12%) patients under 60-90 years old (Table 1).

Table 1: Demographics of patients diagnosed with glioma and brain metastasis included in the study, n=91

Glioma vs Metastasis	Number of patients
Diagnosed with glioma	47
Diagnosed with brain metastasis (Known cause)	38
Diagnosed with brain metastasis (Unknown cause)	6
Sex	
Number of Male	37
Number of Female	54
Age	
18-30	14
31-60	66
60-90	11

Table 2 shows the mean values of the pre-intervention inflammatory markers among patients with glioma compared to patients with brain metastasis. Among the complete blood count values, WBC (18.37 ± 25.42, p-value 0.0141), neutrophils (78.34± 12.28, p-value 0.920), monocytes (6.33± 2.37, p-value 0.822) and platelets (289.09 ± 84.11, p-value 0.091) have higher mean values in brain metastasis while lymphocyte (12.23 ± 6.55, p-value 0.092) value was higher in glioma. Ratio of the values from complete blood count particularly that of neutrophil, lymphocyte, monocyte and platelet were computed. NLR and PLR were high in patients with brain metastasis with average of 10.34± 9.81 (p-value 0.255) and 35.43± 30.18 (p-value 0.125). LMR was high in patients with glioma with an average of 2.73 ±2.26 (p-value 0.105). Comparing the NLR, PLR and LMR between glioma and brain metastasis yielded no significant difference with p- values of 0.255, 0.125 and 0.105 respectively.

Table 2: Average values with standard deviation of the pre-intervention inflammatory markers of patients with glioma vs brain metastasis

Marker	Metastasis (n=44)	Glioma (n=47)	p-value
White Blood Cells	18.37 ± 25.42	12.52 ± 5.07	0.141
Neutrophils	78.34 ± 12.28	78.1 ± 10.83	0.920
Monocytes	6.33 ± 2.37	6.22 ± 2.28	0.822
Lymphocytes	12.23 ± 6.55	15.2 ± 9.83	0.092
Platelets	289.09 ± 84.11	254.79 ± 106.61	0.091
NLR	10.34 ± 9.81	8.3 ± 6.76	0.255
PLR	35.43 ± 30.18	25.95 ± 27.98	0.125
LMR	2.09 ± 1.38	2.73 ± 2.26	0.105

Sub-analysis of the pre-inflammatory markers were made by dividing the mean scores of the markers into quartiles. Table 3 shows the number of cases with pre-intervention inflammatory markers in quartile and comparison of the values using chi-square test to determine p-values among patients with glioma vs brain metastasis in addition, sensitivity and specificity where computed. NLR quartile values yielded significant difference in the number of cases at Quartile 1 (glioma 34% vs brain metastasis 11.4% with p-value of 0.012). NLR cut-off value at <3.95 has the highest specificity at 88.64% and sensitivity at 34.04% in glioma patients. PLR quartile values yielded significant difference at Quartile 1 (glioma 38.3% vs brain metastasis 9.1% with p-value of <0.01). PLR cut off value at <12.47 has the highest specificity at 90.91% and sensitivity at 38.30% in glioma patients. LMR quartile values yielded no significant difference in all quartiles.

Table 3: Comparison of the sensitivity and specificity of pre-intervention inflammatory markers in quartile among patients with glioma vs brain metastasis

Marker	Cut-off	Glioma	Metastasis	p-value	Sensitivity	Specificity
NLR						
Quartile 1	*< 3.95*	16 (34%)	5 (11.4%)	0.012	34.04 (20.86 - 49.31)	88.64 (75.44 - 96.21)
Quartile 2	*3.96 - 6.93*	24 (51.1%)	21 (47.7%)	0.379	51.06 (36.06 - 62.92)	52.27 (36.69 - 67.54)
Quartile 3	*6.94 - 11.03*	37 (78.7%)	31 (70.5%)	0.601	78.72 (64.34 - 89.30)	29.55 (16.76 - 45.20)
Quartile 4	*11.04 - 43.55*	47 (100%)	44 (100%)	0.379	99.8 (97.82 - 100.00)	2.27 (0.06 - 10.02)
PLR						
Quartile 1	*< 12.47*	18 (38.3%)	4 (9.1%)	<0.01	38.30 (24.51 - 53.62)	90.91 (78.33 - 97.47)
Quartile 2	*12.48 - 21.58*	26 (55.3%)	20 (45.5%)	0.178	55.32 (40.12 - 69.83)	54.55 (38.85 - 69.61)
Quartile 3	*21.59 - 32.11*	36 (76.6%)	32 (72.7%)	0.341	76.60 (61.97 - 87.70)	27.27 (14.96 - 42.79)
Quartile 4	*32.12 - 168.52*	47 (100%)	44 (100%)	0.875	99.3 (97.42 - 100.00)	2.19 (0.11 - 12.42)
LMR						
Quartile 1	*< 1.37*	10 (21.3%)	13 (29.5%)	0.189	21.71 (10.14 - 33.89)	70.87 (53.86 - 85.74)
Quartile 2	*1.38 - 2.08*	20 (42.6%)	25 (56.8%)	0.385	42.55 (28.26 - 57.82)	43.18 (28.35 - 58.97)
Quartile 3	*2.09 - 2.82*	31 (66%)	37 (84.1%)	0.678	65.96 (50.69 - 79.14)	15.91 (6.64 - 30.07)
Quartile 4	*2.83 - 13.84*	47 (100%)	44 (100%)	0.571	99.45 (98.28 - 100.00)	1.28 (0.04 - 15.24)

Discussion

The above results showed a diagnostic utility of inflammatory markers in determining whether patient has glioma comparing to brain metastasis. Predictive of glioma were low values of NLR at <3.95 and PLR at <12.47. However, in brain metastasis, a high value of NLR at >3.95

and PLR at >12.47 were favored. These results are supported by studies that cancer cells and the immune system have interaction in several steps in tumorigenesis hence involvement of the inflammatory markers. Tumors also, have a tumor microenvironment (TME) which contains not only cancer cells but also noncancerous cell types including endothelial cells, pericytes, fibroblasts, and immune cells such as neutrophils, lymphocyte, monocytes and platelets. [1]

Neutrophils are among the first responders to inflammation promoting tissue repair however in chronic inflammation, they are continuously recruited to the site and drives release of serine proteases and formation of complex with platelet by binding to P-selectin enhancing prothrombotic state. This pathway or interaction may support our data regarding the high neutrophil and platelet count of patients with brain metastasis since metastatic diseases are chronic diseases with prothrombotic state. [9, 10] A high NLR and PLR maybe a suggestive of brain metastasis rather than a glioma.

Different inflammatory cytokines also initiate the inflammatory cascade. The initiation of the classical inflammatory response is marked by the localization and subsequent activation of blood circulating monocytes into M1 macrophage. The M1 macrophage are activated by cytokines produced by lymphocytes particularly T helper 1 cells (Th1). Since gliomas particularly the high-grade gliomas belong to tumor presenting with acute to subacute symptoms due to destructive lesion in the brain parenchyma prompting immediate consult, patient detection rate and work up were done earlier making lymphocyte count high compared to the other inflammatory marker. One type of lymphocyte, the (Th1) cell is important in recruiting macrophages promoting pro-inflammatory cytokines causing inflammation. [11] Thus, in glioma, high lymphocyte count may explain the low NLR and PLR observed in the study.

There were studies regarding the cut-off value of the different inflammatory markers in detecting glioma and brain metastasis but the studies did not compare the two and there were no definite cut-off values to brain metastasis since some studies only investigated metastasis from one organ source. [12, 13, 14, 15] For this study, the results showed the cut-off values for NLR is 3.95 and for PLR is 12.47 with a high specificity but low sensitivity.

The strengths of this study include the comparison of the pre-intervention inflammatory markers of both glioma and brain metastasis. This study also got the inflammatory markers prior to any treatment or in the absence of any conditions that can alter the CBC and TME of the patient.

We also acknowledge the limitations of the study since it did not differentiate and subdivide the different types of brain tumors and only focused on glioma and brain metastasis as a dichotomy. Furthermore, this study did not correlate the status of the patients and did not look into the post-intervention status of patients investigated.

Conclusion

This study showed that pre-intervention inflammatory markers play a role in tumorigenesis and maybe a helpful and less invasive tool in differentiating gliomas from brain metastasis. In this study, glioma and brain metastasis were compared since they are the most common brain tumors that may present with a diagnostic challenge since they both may have similar clinical and neuroimaging findings. In the absence of advancing technology and biopsy, clinicians may use these biomarkers as an adjunct test to support their diagnosis.

Recommendations

The authors recommend that the results of this study will be validated in future research. It is also recommended that future studies utilize a prospective study design in order to limit biases while collecting the data. The authors also recommend that in future studies, distinguishing the types of glioma as well as types of brain tumors can be done to properly delineate the pre-inflammatory factors involved. Lastly, correlation of the pre-inflammatory markers as well as survival rates of the patients can be explored.

Disclosure

The authors report no disclosures relevant to the manuscript.

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