Research Article

Diagnostic Significance of Pre-Treatment Prognostic Nutritional Index, Platelet/Albumin Ratio and Red Cell Distribution Width in Patients with Differentiated Glioblastoma from Brain Metastasis

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Abstract

Objectives: Due to a lack of similar research, this retrospective analysis of patients indicated the blood parameters of pre-treatment inflammatory markers to assess the diagnostic accuracy of the protein nutritional index (PNI), platelet albumin ratio (PAR) and red cell distribution width (RDW) in patients with brain metastasis (BM) and glioblastome multiforme (GBM).

Methods: Clinical and laboratory data were retrospectively collected from a group of 244 patients and randomly divided into GBM (142 patients) and BM (102 patients). PNI, PAR and RDW values were calculated 3 weeks before from a chosen pre-treatment modality (preoperative or pre-radiotherapy).

Results: The neutrophil and trombocyte counts were higher, while the lymphocyte count was lower in patients with GBM and BM. A lower PNI value (p=0.019), higher PAR value (p=0.027) and higher RDW value (p=0.008) were independent diagnostic factors for brain metastasis. Although both PNI and PAR were diagnostically accurate, RDW had proven the highest accuracy of them all.

Conclusion: Our study shows that the retrospective analysis provided a robust and independent diganostic value for pretreatment. The RDW ≥14.3%, PNI ≤ 49.1%, and Plt/alb ≥ 61.6 ratios also support this diagnostic index for differentiating between GBM and BM.

Keywords: Platelet albumin ratio, red cell distribution width, brain metastasis and glioblastome multiforme

Brain metastases(BM) are the most common central nervous system neoplasm in adults and can be found in 10–40% of patients with cancer.[1] The average life expectancy of patients with multifocal metastases undergoing whole-brain radiation therapy (WBRT) is 4–6 months. Patients with oligometastases treated with stereotactic radiosurgery and/or fractionated stereotactic radiotherapy (SRS/SRT) have an estimated survival of 12 months or more.[2–4] Grade 4 gliomas (glioblastoma multiforme, GBM) make up the majority of central nervous system (CNS) tumours.

GBM, with an incidence of approximately 3.5/100,000 per year and a five-year overall survival (OS), ranges from 1% to 19% with age.[5]

Occasionally, GBM is solitary and BM are multifocal tumours. Similar symptoms (dizziness, headache, vertigo, vision, auditory deficit, neuro cognitive detoriation, etc.) and similar radiological images (surrounding edema, peripheral contrast increase, central necrosis, etc.) can be difficult to distinguish from each other.[6] A definitive diagnosis currently can be made by histopathological studies with tumour tissue obtained by resection or biopsy, whereas neuroimaging (CT or MRI), molecular markers and laboratory tests are used to evaluate response to treatment, staging and recurrence.[7] Patients undergoing multi-modality treatment (chemotherapy and radiotherapy following aggressive surgery) experience an extremely poor clinical outcome due to the highly proliferative and aggressive nature of the tumour, and the prognosis of glioma remains poor.[8]

Numerous studies have indicated that systemic inflammation and malnutrition promote tumour progression, which is an important prognostic factor with glioma and brain metastasis. However, the role of those peripheral inflammatory indicators in gliomas remains unclear and controversial. Some markers showed high inflammatory factors, such as the prognostic nutrition index (PNI), red cell distribution with (RDW) and the platelet albumin ratio (PAR) which can be easily determined from blood tests.

Increased plasma albumin levels in patients with GBM have been associated with favorable clinical outcomes.[9] Lymphocytes infiltrating the tumour by inducing cytotoxic cell death and inhibiting tumour proliferation and migration secretes cytokines such as IFN-γ and TNF-α, which play a crucial role in triggering immunity for preventing distant metastasis.[10] PNI is calculated by multiplying the albumin level and the lymphocyte count. It has been shown in previous studies of gliomas to be a predictive and prognostic factor.[11]

An elevated platelet count is considered to be an indicator of a poor chance of cancer survival. Platelets protect circulating tumour cells (CTCs) from immune responses by producing adenine nucleotides and TGF-β that stimulate the epithelial-mesenchymal transition, cell proliferation and metastasis as part of the tumour microenvironment.[12, 13]

The prognostic effect of the PAR ratio has been shown in cancers such as diffuse large cell lymphoma,[14] nasopharyngeal carcinoma,[15] esophagus cancer[16] and pancreatic cancer.[17]

The RDW reflects the value of variation in size (anisocytosis) of circulating red cells, closely related to chronic inflammation and chronic disease.[18] A high RDW is associated with

a poor overall survival of GBM patients.[19, 20] Preoperative RDW has been found to be associated with high mortality in metastatic brain tumour surgery.[18]

Therefore, we hypothesised about the diagnostic factors that differentiate the BM and GBM disease course. This study evaluated the pre-treatment blood parameters with a comprehensive database of 102 brain metastasis and 142 GBM patients treated in Adana City Hospital.

Methods

Study Population

We retrospectively studied patients who were newly diagnosed with GBM and patients who were diagnosed for BM between 2015 and 2021. Inclusion criteria were as follows: patients without infectious and haematological diseases who did not undergo surgery before for GBM or a primary cancer with pre-existing metastases and did not receive radiotherapy to the brain. All GBM patients underwent resective surgery and postoperative radiotherapy plus temozolomide treatment. For BM patients, resective surgery was performed, and some of them underwent radiotherapy after resection. On the other hand, radiotherapy treatment was recommended for those who could not undergo surgery. The study was conducted according to the guidelines of the Declaration of Helsinki.

Data Collection

The patients' clinical, histopathological and radiological data, including their age, sex, primary cancer, and Eastern Cooperative Oncology Group (ECOG) performance, were recorded. Complete blood cell counts and some biochemistry parameters were assessed as a standard preoperative or preradiotherapy work-up. Albumin (ALB), total lymphocyte counts (TLC), platelet (PLT) counts and RDW counts were analyzed. PNI is calculated as serum ALB (g/L) C 5 × TLC (109/L). PAR is considered as a quotient of the absolute number of PLT counts (109/L)/ALB (g/dl). Preoperative markers, such as PNI(≤ 49.1% vs. > 49.1%), PLT/ALB (< 61.6% vs. ≥ 61.6%) and RDW (< 14.3% vs. ≥14.3%), were dichotomised with defined normal-range values.

Statistical Analysis

The conformity of continuous variables to normal distribution was examined by visual (histogram) and analytical methods (Kolmogorov-Smirnov). In the descriptive analysis, mean and standard deviations were used for normally distributed variables, while median and interquartile range values were given for non-normally distributed variables. An independent group t-test was used to compare normally distributed numerical variables. The Mann Whitney U

test was used to compare the numerical values that did not show normal distribution. The Chi-square or Fisher Exact tests were used to compare categorical variables. The diagnostic decision-making of RDW, PNI and PLT/ALB values was analysed using an ROC curve analysis. The analyses were performed using SPSS Version 20.0 software for evaluation, and a p value of <0.05 was accepted for statistical significance.

Results

This study included 102 patients with BM (64% men, 36% women) and 142 patients with GBM (59% men, 41% women). Their demographics are shown in Table 1. The median age at the onset of treatment was 60 (range 30–93) years for BM and 64 (range 21-93) years for GBM. Patients with multiple brain metastases received WBRT treatment. Patients with oligo metastases received surgery with or without radiotherapy or direct SRS treatment. Patients with GBM planned operations. After surgery, adjuvant concurrent chemoradiotherapy and systemic chemotherapy was administered on GBM patients. The receiver operating characteristic curve showed a cutoff value of ≤ 49.1 as a marker of PNI for diagnostic brain metastasis (p 0.019) with a sensitivity of 58.4% and specificity of 57.8%. The area under the curve was 0.59 (Fig. 1). The receiver operating characteristic curve showed a cutoff value of ≥ 61.6 as a marker of PAR for diagnostic brain metastasis (p=0.027) with a sensitivity of 60.0% and specificity of 50.0%. The area under the curve was 0.59 (Fig. 2). The receiver operating characteristic curve showed a cutoff value of ≥ 14.3 as a marker of RDW for diagnostic brain metastasis (p=0.008) with a sensitivity of 60.0% and specificity of 60.0%. The area under the curve was 0.60 (Fig. 3)

Table 1. Patients Demographics

	BM n=102	GBM n=142	p
Age-median (min-max)	60.0 (30.0-93.0)	64.0 (21.0-93.0)	0.488
Sex			
Female	37	57	0.540
Male	65	85	
Neutrophil	5422±1262	5514±1457	0.600
Lymphocyte	1634±728.8	1682±639.7	0.582
Trombocyte (min-max)	253.5 (141-452)	243.5 (137-433)	0.116
Albumin	3.9±0.6	4.1±0.4	0.006
RDW (min-max)	14.9(12.1-24.4)	14.0 (11.6-22.1)	0.008
PNI	47.1±8.1	49.6±5.5	0.012
PAR (min-max)	64.7 (38.0-164.8)	61.6 (35.4-107.6)	0.027

BM: brain metastasis; GBM: Glioblastome Multiforme; RDW: red cell distribution width; PNI: prognostic nutritional index; PAR: platelet to albumin ratio.

Discussion

Nutritional status, inflammatory status and immune function, as we know, are associated with malignant prognosis. A tumour's morphological, immunophenotypic, molecular
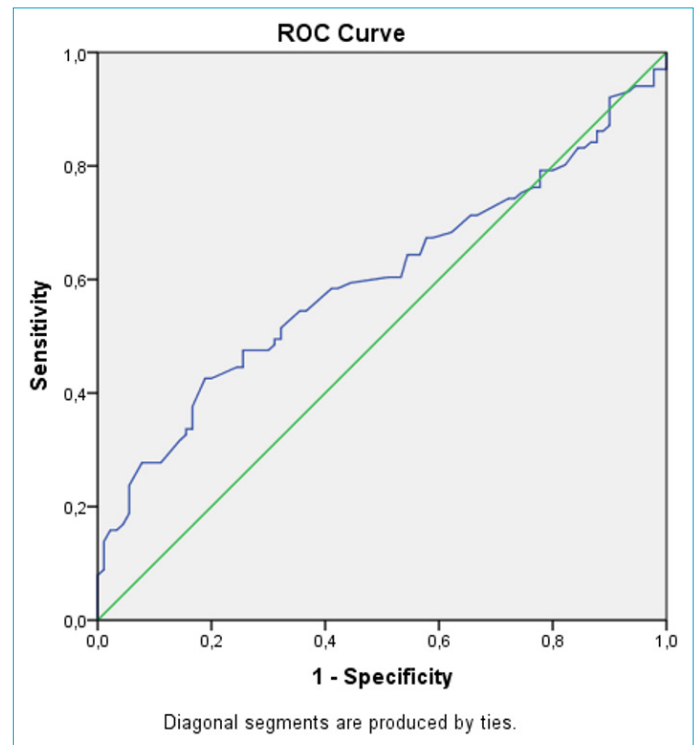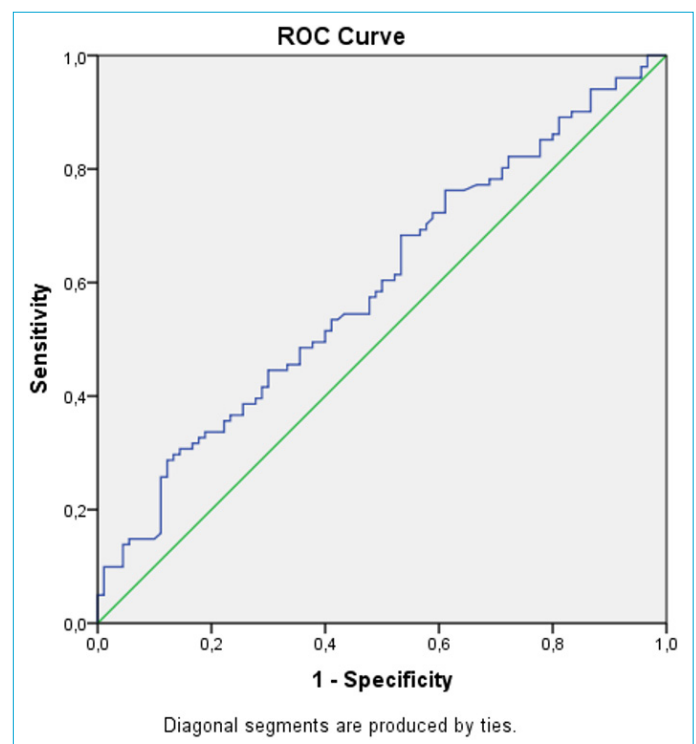

Figure 1. PNI ROC graphic.
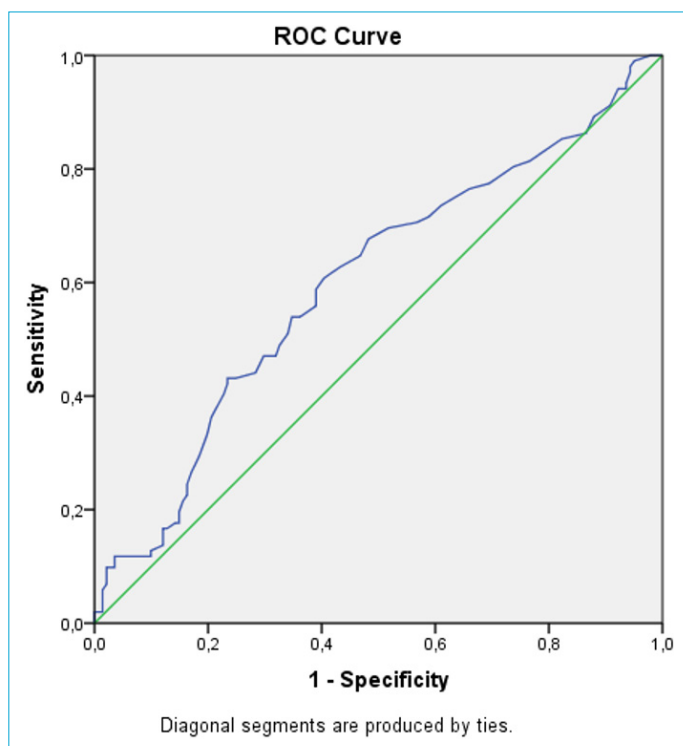

Figure 2. PAR ROC graphic.

Figure 3. RDW ROC graphic.

and genetic biomarker features are important to its diagnosis. Detection of molecular and genetic markers is often difficult to do in some developing countries because doing so requires costly and highly technical approaches. It is important to determine the diagnostic serum biomarkers in GBM and BM patients.[21] PNI, PAR, RDW are simple, economical and effective parameters that can be easily calculated from laboratory tests.

Serum albumin levels indicate the nutritional status and activation of chronic inflammation, which is an important component of PNI.[22] Lymphocytes, is another component of PNI and has an important role in cell-mediated immunity on GBM.[23]

All previous studies investigating the relationship between the PNI and prognosis of GBM have focused solely on the impact of reported preoperative PNI and inconsistent results in OS.[21,24]

Postoperatively high PNI also showed improved OS and perioperative changes in PNI provides additional important information for prognostic prediction in GBM patients.[25]

The decision to resection the brains of metastatic patients must be made urgently but carefully because surgery can potentially cause morbidity and mortality. The increased level of neutrophils suppresses the cytolytic activity of lymphocytes and activated T cells.[26,27] The value of PNI has to be indirectly decreased. Lymphopenia suppresses immunity in many types of cancer and is proven to be associated

with poor prognosis.[28] Based on our database, PNI is best to differentiate between GBM and BM, with a PNI less than 41.9 being in favor of BM.

Platelets, which play critical roles in cancer pathogenesis, protect circulating tumour cells (CTCs) with epithelial-mesenchymal transition and tumour cell extravasation by producing TGF-β and adenine nucleotides.

Activated platelets can cause phenotypic changes in cancer cells that promote their metastasis and angiogenesis. [29,30] Thrombocytosis increases cancer cells' aggressiveness and shields them from the immune system. It is also associated with poor prognosis in lung, breast, gastric, renal, pancreatic and glial cancers.[31-35] A decrease in platelet levels was considered a favorable biomarker in some studies and an unfavorable prognostic predictor in others.[36,37]

Albumin is associated with host immune-nutritional status, which is a biomarker of cancer-related malnutrition. Malnutrition is strongly related to tumour growth and metastasis.[38] A systemic inflammatory response with the release of IL-6 by Kupffer cells inhibits albumin synthesis.[39] Hypoalbuminemia is the cornerstone of malnutrition. It also indicates cancer-related cachexia and malfunctioning of the immune system.[40]

A high pre-treatment PAR is an indicator of poor survival chances in large lung carcinomas,[41] advanced pancreatic cancer treated with chemoradiotherapy,[42] advanced nasopharyngeal cancers treated with chemoradiotherapy[43] and curative surgery followed by preoperative adjuvant chemotherapy for esophageal cancer.[44] Our study aims to use the preoperative PAR ratio in the differential diagnosis of GBM and BM. According to our study results, a PAR higher than 61.6 supports the possibility of metastasis.

Anemia, including GBM, is known to decrease the overall survival chances in many different types of cancer, possibly by increasing tumour aggressiveness.[45] RDW is an anemia marker and high values of it in cancer patients is an indicator of a proinflammatory state. RDW elevation boosts other inflammation markers, such as IL-6, tumour necrosis factor-α, CRP and other different cytokines that can influence the biological characteristic of the tumour cell.[46,47] Anemia can also have a potentially hypoxic effect (free radicals formation, increase in HIF-1α (hypoxia-inducible factor1α), triggering a VEGF signalling pathway, etc.) in GBM. Thus, tumour invasiveness results in a poorer prognosis.[48]

RDW <14% is a prognostic factor related to decreased overall survival (GBM, lung, esophageal carcinoma, multiple myeloma, etc.).[46] Some studies recommend that a high RDW can be changed throughout dieting, using nutritional supplements and partaking in exercise therapy.[49] Another study investigated a metastatic brain tumour prognosis

which preoperative RDW ≥13.2 is significantly associated with high mortality in metastatic brain tumour surgery.[50] Our data showed that increased RDW in BM may be due to more inflammatiory reactions or a greater hypoxic effect than GBM .

This study had several limitations: a single institution, retrospective data collection, small sample size and using a single ethnic group in Turkey biased the study towards a homogeneus group. First ,the type of operation (gross total resection (GTR), subtotal resection (STR), extent of resection), tumour residual volume and molecular biomarkers (IDH mutant/wild type tumours, etc.) are needed for subgroup analysis. Second, inflammatory and nutritional statuses are easily affected by diseases, medications, nutritional supplements, diet and exercise.

Wide accessibility, ease of determination, reliability, cost efficiency and affordability of the tests differentiate BM and GBM from each other. Our study suggests that novel prognostic inflammatory markers PNI, PAR and RDW could be used to distinguish GBM and BM. However, this conclusion needs to be validated in a large-scale study to properly determine the contribution of these parameters in relation to the prognosis.

Disclosures

Ethics Committee Approval: This study started after obtaining ethics approval from the Turkish Republic Ministry of Health, Health Sciences University Adana Numune Training and Research Hospital Scientific Research Evaluation Commission. (Date of Approval: 10.02.2022; Decision Number: 1775).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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