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Preoperative systemic inflammatory markers in low- and high-grade gliomas: A retrospective analysis of 171 patients

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ABSTRACT

Purpose: Preoperative neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR) are recognized as prognostic markers of grade of gliomas. The aim of this study was to determine whether preoperative levels of NLR, PLR, and LMR differ between low- and high-grade gliomas.
Methods: Retrospective analysis of preoperative neutrophil, lymphocyte, monocyte, and platelet counts and NLR, PLR, and LMR were performed in 171 patients who underwent glioma surgery. The results were compared between low- and high-grade gliomas.
Results: Neutrophil count was significantly increased while lymphocyte count significantly decreased in high-grade gliomas (HGGs). NLR and PLR were significantly higher in HGGs but LMR was significantly reduced in HGGs. NLR and PLR correlated with glioma grade and only NLR showed highest accuracy predicting higher grade.
Conclusions: Levels of preoperative NLR value can help to evaluate disease progression and predict higher grade of glioma.

1. Introduction

Neuroepithelial tumors, namely gliomas, are the most common intracranial tumors accounting for almost 80% of malignant brain tumors. In high-grade gliomas (HGG), especially grade-IV gliomas, overall survival is short ranging from 12 to 15 months despite advanced treatment modalities [1]. Radiotherapy plus chemotherapy with temozolomide after surgery did not increase the survival rate, and we are still in our infancy for the treatment of gliomas.

The mechanism(s) behind the development and progression of gliomas has not been understood clearly, and thus effective treatment could not be introduced so far. Mounting evidence suggested that chronic inflammation could be associated with increased susceptibility for the development and progression of cancer [2], and inflammation is now accepted as one of the hallmarks of cancer [3]. Studies examining microenvironment of the tumor showed that tumor-associated macrophages and lymphocytes are deeply involved in tumor pathophysiology, and severity of inflammation may be correlated with grade of the tumor [4, 5]. Depending on these findings led researchers to think that local tumor inflammation can be detected systemically and a marker can be found and used for the early detection of tumor or tumor progression.

Elevated neutrophils and platelets and decreased monocyte blood counts before treatment have been demonstrated in patients with solid tumors, including prostatic cancer, colorectal cancer, lung cancer, and even grade-IV glioma [6, 7, 8, 9]. More importantly, the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte-ratio (PLR), and the lymphocyte-monocyte ratio (LMR) have been shown to be used as a marker for host inflammation. It has been shown that high peripheral blood NLR and PLR and low LMR were associated with a poor prognosis in solid tumors, such as esophageal, hepatic, thoracic, and colorectal tumors [7, 10, 11, 12]. Studies underlined that conducting peripheral blood analysis is always feasible and cost-effective, and thus suggested the use of the ratios mentioned above to predict outcome and develop a targeted treatment. Unfortunately, there is no useful marker for brain gliomas, and thus early detection is not possible.

Surprisingly, there has been a scarce number of studies focusing on blood inflammatory parameters, including NLR, PLR, and LMR, in gliomas, despite several published studies including other organ solid tumors. Most studies examined the predictive value of inflammatory ratios in grade-IV gliomas (glioblastoma multiforme-GBM) [9, 13, 14, 15, 16, 17]. and the common notion is that NLR can be used as a marker for grade-IV glioma progression, and NLR $\geq$4 was associated with a poor outcome and short survival in GBM. There have been only six reports which studied and compared inflammatory ratios (NLR, PLR, and LMR)

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between low-grade gliomas (LGGs) and HGGs [17, 18, 19, 20, 21, 22]. They stated that NLR and PLR were increased and LMR was decreased in HGGs and they were correlated with grade of gliomas. Furthermore, accumulated evidence indicates that an increased lymphocyte infiltration around the tumor is associated with better prognosis whereas increased neutrophils are associated with a poor prognosis, and targeted treatment decreasing the function of neutrophils may be beneficial [18, 23].

In this retrospective analysis, we wanted to show how levels of blood inflammatory markers, namely NLR, PLR, and LMR, change in our glioma patients and to see whether there is any difference between LGGs and HGGs. Our hypothesis is that lymphocyte and monocyte counts should be decreased and neutrophil count should be increased in HGGs compared to LGGs.

2. Materials and methods

2.1. Patients

Data of patients with newly diagnosed glioma, who were operated on between 2010 and 2017 by a single surgeon, was retrieved from the archive. Patients were included in this study depending on the following criteria: 1) glioma grading was verified by histopathology study; 2) no chemotherapy and radiotherapy before surgery; 3) patients without infectious diseases or extracranial tumor; 4) the presence of full blood count (FBC) before surgery; 5) completed informed consent. According to the selection criteria, 171 patients among 241 patients were selected, and all underwent resective surgery.

2.2. Data collection

Demographic, clinic, radiologic, and histopathological data were retrieved from the patient medical records. After hospitalization, blood samples were taken for FBC and other tests, including hepatic functions, serology, and electrolyte as standard preoperative work-up. Neutrophil (10^3 mm^3), lymphocyte (10^3 mm^3), platelet (10^3 mm^3), and monocyte (10^3 mm^3) counts were recorded. Preoperative NLR (quotient of an absolute number of the neutrophil count to lymphocyte count), PLR (quotient of an absolute number of platelet to lymphocyte count), and LMR (quotient of an absolute number of lymphocyte count to monocyte count) were calculated.

2.3. Statistical analysis

Statistical analysis was performed using SPSS version 22.0. Results were reported as mean ± standard deviation. Independent samples t-test and chi-square test were used for appropriate comparisons. Correlation analysis was judged by the Pearson correlation coefficient test. The area under the curve (AUC) of NLR, PLR, and LMR with the help of receiver-operator characteristics (ROC) curve analysis was used for diagnostic performance. A probability value (p-value) <0.05 was considered statistically significant.

2.4. Ethical approval

Our Local Ethics Committee informed that since this is a retrospective medical chart analysis, this study does not need ethical approval. This study contains no data disclosing patient identity.

3. Results

3.1. Demographic findings

The patient group in this study included 171 patients with a mean age of 38.7 years (ranged from 3 to 75 years). Females and males were 84 (49.1%) and 87 (50.9%), respectively, and no significant difference was found between the gender (χ^2 test; $p = 0.81$). Adults and children were 152 (88.9%) and 19 (11.1%), respectively, and statistical analysis was not performed due to a small number of children. Supratentorial location of glioma was 153 (89.5%), and the infratentorial location was 18 (10.5%). With respect to supratentorial location, 76 gliomas were (44.4%) right-sided whereas 77 gliomas (45%) were left-sided. In the infratentorial location, seven (4.1%) and two (1.2%) were in the right and left cerebellar regions, respectively. Nine (5.3%) gliomas were midline (within the fourth ventricle) region. Supra- and infratentorial right and left-sided gliomas were combined in each, and the difference was not significant (χ^2 test; $p = 0.75$) regarding the side of the location.

Histopathologic diagnosis with grading was as follows: grade-I in 14 (8.2%), grade-II in 81 (47.4%), grade-III in 27 (15.8%), and grade-IV in 49 (28.7%) patients. In order to get homogeneous groups, the histopathologic diagnosis was divided into LGGs (grade-I and II) and HGGs (grade-III and IV). Thus, in the LGG group, we had 95 (55.6%), and in the HGG group, we had 76 (44.4%) patients. There was no statistically significant difference between LGG and HGG groups (χ^2 test; $p = 0.14$).

3.2. Comparison of preoperative inflammatory markers within grades of glioma

Table 1 summarizes inflammatory markers in each grade of gliomas. According to the Table, there was a steady decrease in lymphocyte counts as the grade of glioma increased. However, there was a variation in the levels of monocytes and platelets among the grades. Neutrophil counts started to increase in grade-II and continued to increase to grade-IV, and the course of neutrophil count and NLR was similar. Likewise, platelet count and PLR showed a similar course. Monocyte count increased, and LMR decreased, in the HGG group.

Regarding neutrophil count, the differences were significant between grade-I and -IV ($p = 0.04$), grade-II and -III ($p = 0.005$), and grade-II and –IV ($p = 0.00001$). Lymphocyte counts showed a significant difference only between grade-II and -IV ($p = 0.04$). Comparisons between grade-I and II and grade-I and –IV showed significant differences ($p = 0.03$ and 0.02, respectively) regarding platelet counts. Increase in monocyte count was significantly different on comparing grade-II and –IV ($p = 0.02$).

Parallel to the increase in neutrophil count and a decrease in lymphocyte count in the HGG, comparisons of glioma grades with respect to NLR showed similar results. NLR showed significant difference between grade-I and –IV ($p = 0.00001$) and grade-II and –IV ($p = 0.00001$). The difference between grade-II and –IV for PLR was significant ($p = 0.01$). As expected from the monocyte count levels, LMR significantly decreased on comparing grade-II and –IV ($p = 0.002$).

Table 1
Preoperative inflammatory markers according to glioma grade.

Marker	Grade-I (n = 14)	Grade-II (n = 81)	Grade-III (n = 27)	Grade-IV (n = 49)
Neutrophils	5.29 ± 2.41	4.86 ± 1.72	6.32 ± 2.35	7.43 ± 3.65
Lymphocytes	2.36 ± 0.80	2.14 ± 0.68	1.96 ± 0.85	1.86 ± 0.85
Monocytes	0.72 ± 0.36	0.52 ± 0.16	0.57 ± 0.21	0.65 ± 0.35
Platelets	319.76 ± 119.43	262.33 ± 90.05	276.36 ± 76.0	256.86 ± 76.38
NLR	2.35 ± 1.16	2.25 ± 1.16	4.46 ± 5.44	4.86 ± 3.48
PLR	141.71 ± 51.48	130.38 ± 52.65	171.68 ± 104.04	160.16 ± 74.75
LMR	3.64 ± 1.29	4.39 ± 1.54	3.88 ± 1.79	3.45 ± 1.89

LMR: Lymphocyte-monocyte ratio; NLR: Neutrophil-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio.

Table 2
Preoperative inflammatory markers: high-grade *versus* low-grade gliomas.

Marker	LGG (n = 95)	HGG (n = 76)	*P* value
Neutrophils	4.92 ± 1.83	7.04 ± 3.27	0.00001*
Lymphocytes	2.17 ± 0.70	1.90 ± 0.85	0.02*
Monocytes	0.55 ± 0.21	0.62 ± 0.31	0.09
Platelets	270.79 ± 96.39	263.79 ± 76.32	0.6
NLR	2.44 ± 1.16	4.72 ± 4.25	0.00001*
PLR	132.05 ± 52.36	164.25 ± 85.79	0.005*
LMR	4.28 ± 1.52	3.60 ± 1.86	0.01*

HGG: High-grade glioma; LMR: Lymphocyte-monocyte ratio; LGG: Low-grade glioma; NLR: Neutrophil-lymphocyte ratio; LMR: Lymphocyte-monocyte ratio.
* Denotes statistically significant difference.

3.3. Comparison of inflammatory markers between LGG and HGG groups

Table 2 shows that neutrophil and monocyte counts increased whereas lymphocyte and platelet counts decreased in HGGs. However, only increase in neutrophil count, and a decrease in lymphocyte counts reached significant level; p = 0.00001 and 0.02, respectively. No significant differences were found regarding monocyte and platelet counts between LGGs and HGGs. In HGGs, NLR and PLR showed significant elevation (p = 0.00001 and 0.005, respectively), and LMR showed significant decrease (p = 0.01), compared to LGGs.

3.4. Correlation of preoperative inflammatory markers with glioma grade

Significant positive correlations were observed between NLR (r = 0.341, p = 0.00001), PLR (r = 0.177, p = 0.02), and glioma grade, but negative correlation was found between LMR (r = -0.173, p = 0.02) and tumor grade. Significant correlations were noted among the three inflammatory markers (Fig. 1a through c). A positive correlation was seen between NLR and PLR (r = 0.734, p = 0.00001), but negative correlations were observed between NLR and LMR (r = - 0.182, p = 0.01) and PLR and LMR (r = - 0.156, p = 0.04).

3.5. Diagnostic efficacy of preoperative inflammatory markers

Fig. 2a through c demonstrates the diagnostic value (ROC curves) of NLR, PLR, and LMR. As shown in Fig. 2, AUCs were found to be fair, poor, and poor for NLR, PLR, and LMR, respectively. The AUC was 0.72 (95% CI 0.64–0.79, p = 0.00001) for NLR, 0.61 (95% CI 0.52–0.70, p = 0.009) for PLR, and 0.62 (95% CI 0.54–0.71, p = 0.004) for LMR when LGG patients were tested against HGG patients. Depending on the ROC curve analysis, NLR demonstrated the highest accuracy in predicting HGG, followed by LMR and PLR. Because ROC curve analysis did not show excellent or good outcome for AUC, we did not designate a cutoff point for each ratio.

4. Discussion

For a neurosurgeon, it would be very practical to predict outcome and follow-up of operated patients with glioma depending on a peripheral blood marker. Using a biological marker from the peripheral blood analysis to predict glioma grade and survival would be easy and cost-effective compared to having magnetic resonance imaging (MRI), which is expensive. Blood screening tests for some other cancers [7, 8, 11, 12] have been identified and used successfully but, unfortunately, there has been no such test available for brain gliomas. Furthermore, it has been thought that it is difficult to have a marker for brain gliomas since the brain is the inflammation-privileged site.

Chronic inflammation is now accepted as one of the hallmarks for cancers [3]. It has been demonstrated that chronic inflammation can cause development and progression of cancers, and targeted treatment has been considered seriously in the literature [24]. Mounting evidence showed that a high NLR and PLR and low LMR are associated with some solid cancers, including gastrointestinal, prostate, and lung cancers, and NLR ≥ 4 shows poor prognosis and shorter survival [6, 7, 8]. Surprisingly studies including gliomas are limited, and the majority of them focused on only grade-IV gliomas, commonly known as GBM, the most aggressive glial tumor [9, 13, 14, 15, 16]. They studied several preoperative

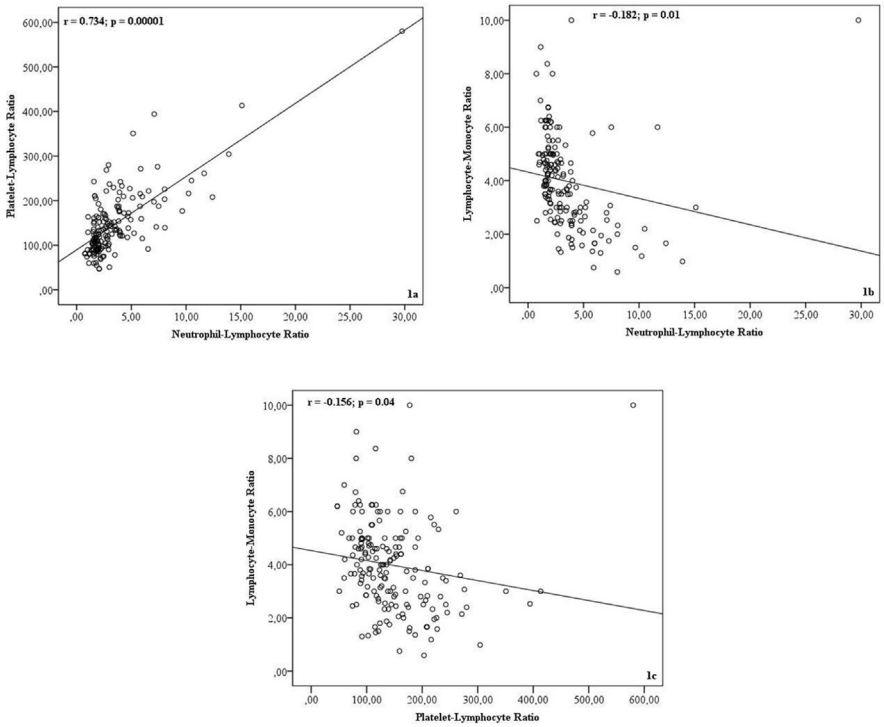

Fig. 1. A positive correlation was obtained between neutrophil-lymphocyte and platelet-lymphocyte ratios (a) but negative correlations were noted between neutrophil-lymphocyte and lymphocyte-monocyte ratios (b) and between platelet-lymphocyte and lymphocyte-monocyte ratios (c).

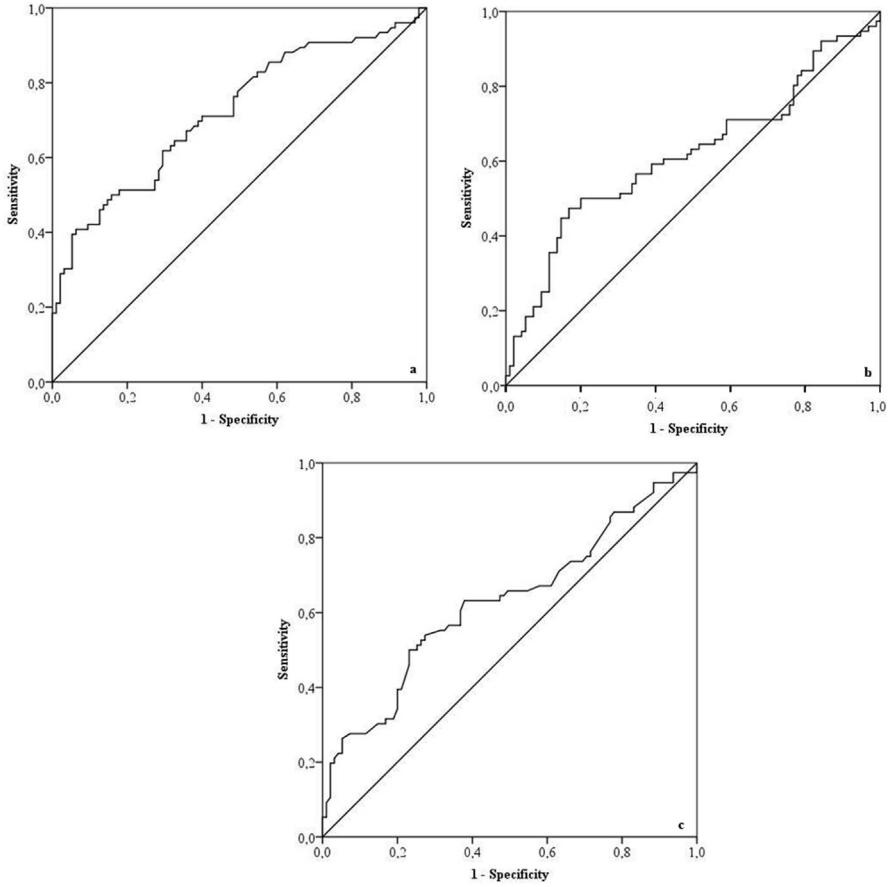

Fig. 2. ROC curve analyses for diagnostic efficacy of high-grade glioma regarding NLR (AUC is 0.72-fair; 95% CI 0.64–0.79, p = 0.00001) (a), PLR (AUC is 0.61-poor; 95% CI 0.52–0.70, p = 0.009) (b), and LMR (AUC is 0.62-poor; 95% CI 0.54–0.71, p = 0.004) (c).

inflammatory markers, such as NLR (most studied), PLR, LMR, and red cell distribution width (RDW). The common notion is that as the level of NLR or PLR increases or LMR decreases, the grade of glioma increases [17, 18, 19, 20, 21, 22]. Furthermore, a recent study suggested that LMR can be used for early detection of glioma since LMR has been shown to have the highest accuracy in predicting glioma and the best prognostic value was obtained with the combination of NLR + LMR [16].

Studies including gliomas have appeared in the literature over the last 5 years, and all are of retrospective nature. Studies comparing preoperative inflammatory markers between LGGs and HGGs have been published during the last 3 years, and the number is very limited [17, 18, 19, 20, 21, 22]. There have been only six studies which stratified patient groups into LGGs and HGGs and reported the differences regarding the levels of preoperative inflammatory markers [17, 18, 19, 20, 21, 22]. The first report was published in 2015 by Zadora et al. [18], and they pointed out that NLR could be used as a predictor of glioma grade. A cutoff point $\geq$2.5 for NLR can predict GBM. The second study was by Auezova et al. [19] which reported that NLR significantly increased in grade-IV gliomas compared to grades-I, II, and III, and a cutoff point $\geq$4 was a significant factor of poor prognosis. They found no correlation between NLR and PLR. Wiencke et al. [20] reported that NLR increased in GBM (grade-IV) compared to non-GBM gliomas, and high NLR was associated with increased risk of death. A recent study by Wilson et al. [21] included pediatric gliomas and found that neutrophil count was significantly lower in LGGs compared to HGGs, and the cutoff point for neutrophil count $\geq$3.36 would predict death at 2 years after surgery. Their study showed a higher level of NLR in HGGs compared to LGGs but failed to show a significant difference. They underlined that prediction of survival by using NLR might not be possible because AUC after ROC curve analysis was poor. Xu et al. [22] demonstrated that NLR and RDW were significantly higher in HGGs, and PLR was not associated with grade of gliomas. Furthermore, significant elevation of NLR and RDW was found in male HGG and female HGG, respectively, and PLR was not associated with glioma grade in both sexes. Red blood cell count, hemoglobin, PLR, mean platelet volume did not differ between LGG and HGG. The last study published in 2018 by Wang, et al [17] showed that NLR had the highest diagnostic value for distinguishing grade-IV glioma from grade-II to III gliomas and predicting the grade-IV IDH-1 wt molecular subtype.

Overall, common notion depending on the results from above-mentioned six studies [17, 18, 19, 20, 21, 22] is that NLR among the other preoperative inflammatory markers, including PLR, LMR or RDW, is the strongest marker that can be used as an index of the grade of gliomas and for the prediction of survival.

Depending on our study, we underlined that some of our results are in line, but some are in contrast to the above-mentioned studies. Similarly, we found that neutrophils and lymphocytes decreased and increased with an increase in grade of gliomas, respectively, and the differences were significant. NLR and PLR significantly increased, and LMR significantly decreased in HGGs. In contrast to Xu et al. [22] results, lymphocyte and neutrophil counts did prove to have significant differences between LGG and HGG indicating that elevated NLR was a reflection of lymphopenia. In contrast to some studies, NLR was significantly lowered in LGGs, and both NLR and PLR showed a positive correlation with the grade of gliomas. As reported by Zheng et al. [16], we found that LMR was negatively correlated with the grade of gliomas. Furthermore, NLR and PLR were positively correlated with each other. However, NLR/LMR and PLR/LMR showed a significant negative correlation, as expected. Our results in line with the current literature demonstrated that NLR had the highest diagnostic accuracy compared to PLR and LMR [17, 18, 19, 20, 21, 22].

5. Conclusion

Our study has shown that there is a correlation between the blood parameters, mainly NLR, but it has not shown anything other than that. Depending on our study and the limited number of studies published so far in the current literature regarding gliomas, the results should be evaluated carefully because we could not still have a common notion. Thus, future prospective studies with a larger patient population are needed in order to have a universally accepted inflammatory marker for a neurosurgeon to use and predict recurrence and survival of these devastating brain tumors.

5.1. Limitations

The present study had some limitations. The first is that this is a retrospective study that could cause some errors during data collection. Second, it would be better to show whether there is a correlation between the preoperative inflammatory markers studied and survival. Lastly, the cutoff point could not be calculated for NLR, PLR, and LMR for the prediction of glioma grades because of fair results obtained from ROC curve analysis, although some studies reported the cutoff points with almost similar values that we found in this study.

Declarations

Author contribution statement

Rahsan Kemerdere: Conceived and designed the experiments; Analyzed and interpreted the data.

Mehmet Yigit Akgun, Sureyya Toklu, Orkhan Alizada: Contributed reagents, materials, analysis tools or data.

Taner Tanriverdi: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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