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Correlation between preoperative inflammatory markers, Ki-67 and the pathological grade of glioma

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Abstract

To investigate the correlation between preoperative inflammatory markers, Ki-67 expression and the pathological grade of glioma, and to provide a reference for clinical prediction of glioma prognosis.

A total of 45 glioma patients who underwent surgery with complete clinical and pathological data were in our hospital from January 2012 to December 2018 were enrolled. Glioma was divided into WHO grade I to IV. Forty-five healthy health examiners with matched clinical characteristics were included to the control group. Blood routine tests were recorded at admission in both the glioma and control group. The ratio of neutrophil to lymphocyte cytometry (NLR), derived neutrophil to lymphocyte ratio (dNLR) (white blood cell count – neutrophil count to neutrophil count), platelet to lymphocyte ratio (PLR) and prognostic nutritional index (PNI, serum albumin content + 5 × lymphocyte count) were calculated. The expression of Ki-67 in glioma was detected by immunohistochemistry. The relationship between the above markers, Ki-67 expression and pathological grade of glioma was evaluated with receiver operating characteristics curve analysis and Spearman correlation test. The correlation between the markers and Ki-67 were also determined.

NLR, dNLR, PLR were increased in the glioma group ($P < .001$, $< .001$, .002), whereas red blood cell distribution width (RDW) was decreased ($P = .009$). All the glioma samples expressed Ki-67 with varying degree. Receiver operating characteristics curve analysis reveals NLR, dNLR, PLR, and RDW have significant discriminating ability in differentiating the glioma and control sample. NLR, PLR, PNI, and Ki-67 were significantly correlated with glioma pathology grade ($P = .023$, .006, .019, $< .05$), while dNLR and RDW were not associated with glioma grade. Finally, NLR and PLR were related to Ki-67 expression in glioma patients ($P = .002$, .022), while dNLR and RDW were not related to Ki-67 expression.

Preoperative inflammatory markers NLR, PLR, PNI, and postoperative Ki-67 expression are associated with pathological grade of glioma. Detection of these markers may aid in better prediction of glioma prognosis.

Abbreviations: AUC = area under the ROC curve, dNLR = derived neutrophil to lymphocyte ratio, IHC = immunohistochemistry, NLR = neutrophil to lymphocyte cytometry, PLR = platelet to lymphocyte ratio, PNI = prognostic nutritional index, RDW = red blood cell distribution width, ROC = receiver operating characteristics.

Keywords: glioma, Ki-67, neutrophil to lymphocyte cytometry, platelet to lymphocyte ratio, prognostic nutritional index, red blood cell distribution

1. Introduction

Glioma is the most common and aggressive primary tumor in the brain, accounting for 50%-60% of all intracranial tumors in adults.[1] Characterized by unclear boundaries, glioma is difficult to surgically remove completely. Glioma is clinically heterogeneous, with distinct response rate and outcome even for the same pathological grade.[2] The malignant degree, proliferative capacity, invasive ability, growth rate and prognosis of gliomas

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study is approved by the Ethics Committee of Affiliated Hospital of Yanbian University. Written informed consent was obtained.

Informed consent was obtained from all individual participants included in the study.

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The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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are related to the pathological grade. As glioma is often not detected until advanced stage, the overall prognosis is poor.

In recent years, studies evaluating systemic inflammatory markers in predicting the prognosis of patients with malignant tumors have gradually increased. Studies have shown that various inflammatory markers play a crucial role in the occurrence and development of tumors.[3–5] It has been reported preoperative inflammatory markers including granulocyte to lymphocyte ratio, derived neutrophil to lymphocyte ratio (dNLR) and prognostic nutritional index (PNI) are independent factors affecting the prognosis of malignant tumors such as gastric cancer, esophageal cancer and renal cell carcinoma.[6–8] Similarly, many inflammatory indicators such as peripheral blood neutrophils, platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte cytometry (NLR), dNLR, lymphocyte to monocyte ratio are reported to have a predictive effect on the prognosis of glioma,[3] but it remains unclear whether the inflammatory indicators are correlated with pathological grade of glioma.

Ki-67 is related to cell proliferation, differentiation, metastasis and apoptosis. Ki-67 is a non-nuclear protein that is expressed in proliferating nuclei. It is closely related to the cell cycle and mainly expresses in the S and G2 phases of cell cycle. With a relative short half-life, Ki-67 serves as a sensitive marker for proliferation of tumor cells. It has been demonstrated that Ki-67 is positively correlated with the malignant degree of glioma,[9] yet the relationship between Ki-67 and prognosis of glioma remains largely unknown.

In this study, we evaluated the associations of certain biomarkers including NLR, dNLR, PLR, red blood cell distribution (RDW), PNI and Ki-67 with pathological grade of glioma, and further infer their prognostic value in clinical practice.

2. Materials and methods

2.1. Case collection

In this retrospective study, 45 patients with glioma who underwent neurosurgical resection at Yanbian University Hospital between January 2012 and December 2018 were enrolled. Patients were eligible if they had not received chemotherapy and presented with no sign of severe infection. Patients were excluded if they developed other tumours, recurrent glioma, autoimmune diseases, and other diseases that would affect inflammation markers. Pathological and clinical data were collected and reviewed by expert physicians. Glioma was graded according to the 2016 WHO Central Nervous System Tumor Classification Standard. 45 health examination participants with matched age, sex, initial diseases without glioma were enrolled to the control group. The study was approved by ethics review board of the hospital. Written consent was obtained from the patients.

2.2. Method

2.2.1. Blood test. We collected peripheral blood from the patients and performed blood routine test. In particular, counts of white blood cells, neutrophils, lymphocytes, platelet, RDW, and serum albumin content, NLR, PLR, and PNI were measured or calculated. Inflammatory markers were recorded in healthy control group as well.

2.2.2. Immunohistochemistry. Tumors were obtained during surgery and processed for Ki-67 immunohistochemistry (IHC) study. All lesions were fixed in 10% formalin, embedded in paraffin, and sliced into 4 to 5 μm thick. Subsequently, IHC procedures were conducted as follows: antigen retrieval with Tris base buffer, quenching of endogenous peroxidase activity, incubation with anti-Ki-67 antibody (Affbiotech Corporation) for 12 hours at 4°C, secondary antibody incubation for 1 hour at room temperature, revelation with DAB detection kit. Finally, Ki-67 positive cells were counted in 5 visual field under the microscope and the Ki-67 positive index was calculated.

2.2.3. Statistical analysis. Statistical analysis was performed using SPSS 25.0 and GraphPad Prism 8.0. The measurement data were tested by the one-sample Kolmogorov–Smirnov test for normality. The normally distributed data were expressed as mean ± standard deviation, whereas the non-normal distributed data were represented by the median and interquartile range. The data of the normal distribution were compared between the 2 groups using the independent sample *t* test method. The data that did not conform to the normal distribution were compared using the Mann–Whitney *U* test. Using the receiver operating characteristic (ROC) curve, the optimal threshold values of NLR, dNLR, PLR, RDW, and PNI in the glioma patient group and the control group were obtained, and the patients were divided into 2 groups according to the optimal cut-off value. The relationship between NLR, dNLR, PLR, RDW, and PNI and glioma WHO grading was analyzed by chi-square test or Fisher exact probability method. The significance level was determined as $\alpha=0.05$, and *P*-value of $<.05$ was considered to be statistically significant.

3. Results

3.1. Pathology of glioma

Of the 45 cases of glioma enrolled in the study, 10, 14, 12, and 9 were categorized as WHO I, WHO II, WHO III, and WHO IV glioma, respectively (Table 1). Higher grade of glioma was associated with overexpression of Ki-67 as measured by IHC (Fig. 1).

3.2. ROC curves analysis of biomarkers

To evaluate inflammatory state of glioma, we compared NLR, dNLR, PLR, and RDW between glioma and control group. NLR, dNLR, and PLR showed significant elevation in glioma compared to the control group, whereas RDW was lower in the glioma group, indicative of the relationship between inflammation and pathology of glioma (Table 2).

We further investigated the clinical values of these markers in glioma by conducting ROC curves analysis. NLR, dNLR, PLR, RDW all showed robust separability in distinguishing glioma and control patients, among which dNLR and NLR outperformed PLR and RDW with area under the ROC curve (AUC) of 0.933

Table 1

WHO classification.

Glioma	Cases	Proportion
WHO I	10	22.2%
WHO II	14	31.1%
WHO III	12	26.7%
WHO IV	9	20.0%

WHO 2016 Central Nervous Tumor Classification.

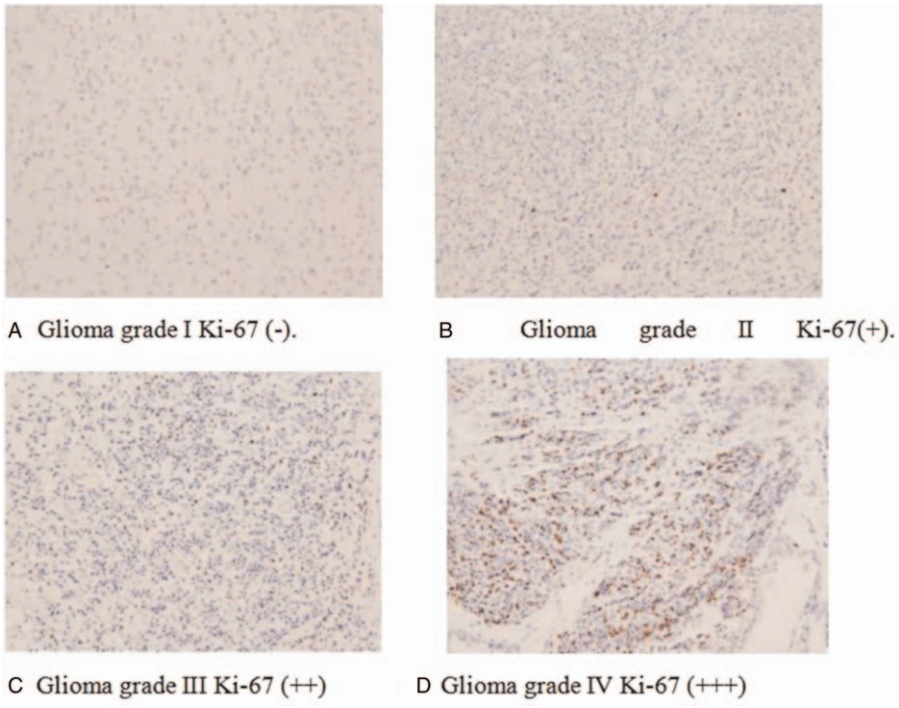

Figure 1. Immunohistochemistry staining of Ki-67 in glioma of different pathological grades.

($P < .001$) and 0.889 ($P < .01$), respectively. PLR and RDW showed comparable separability with AUC of 0.689 ($P < .01$) and 0.682 ($P < .01$) (Fig. 2A). The optimal cutpoints for ROC curves of NLR, dNLR, PLR, and RDW were calculated as 1.90, 0.398, 129.42, and 41.69, respectively. In addition, ROC curve of PNI was plotted, which indicated that PNI had similar discriminating ability as PLR and RDW with AUC of 0.732 ($P < .001$) and an optimal cutpoint at 57.47 (Fig. 2B).

3.3. The relationship between preoperative biomarkers and glioma pathlogical grade

We evaluated the independence between the preoperative biomarkers and pathological grade of glioma with Spearman correlation analysis based on the optimal cutpoints of ROC curves. NlR, PLR, and PNI were significantly correlated with glioma pathological grade with *P*-values of .023, .006, and .019, respectively, indicative of the roles of inflammation in glioma advance. In contrast, dNLR and RDW were independent of glioma pathological grade (Table 3). Additionally, there was significant correlation between Ki-67 and glioma glioma pathological grade ($P < .05$) (Table 3).

Table 2

Comparison of 2 groups of inflammation markers.

Inflammation markers	Glioma group	Control group	*P*
NLR	3.49 (2.19–4.82)	1.54 (1.13–1.95)	<.001
dNLR	2.17 (1.29–2.96)	0.08 (0.06–0.09)	<.001
PLR	139.78 (96.59–205.84)	101.79 (85.64–123.25)	.002
RDW	42.32 ± 3.68	44.16 ± 2.78	.009

dNLR = derived neutrophil to lymphocyte ratio, NLR = neutrophil to lymphocyte cytometry, PLR = platelet to lymphocyte ratio, RDW = red blood cell distribution width. Normal distribution data is expressed as mean ± standard deviation, and non-normal distribution data is expressed as median (interquartile range).

3.4. Ki-67 expression and preoperative inflammation markers

Relationships between preoperative biomarkers and Ki-67 were evaluated with Spearman correlation analysis as previously. Among NLR, dNLR, PLR, and RDW, NLR ($P = .002$) and PLR ($P = .022$) were significantly correlated with Ki-67 in the glioma patients (Table 4).

4. Discussion

Glioma is the most common intracranial tumor and ranks second among children with malignancies. One of the most crucial features of glioma is its aggressive growth, which makes the prognosis of glioma extremely poor. At present, the therapeutic treatment of glioma still relies on surgical approach. However, it is still a major problem to completely remove the tumor without damaging the normal brain function. Therefore, the current research in prognostic factors is of great significance for the development of personalized treatment options for glioma patients. Studies have shown that the inflammatory response has a certain relationship with tumors.[5,7,10] Inflammation partly constitutes the tumor microenvironment, and changes in inflammatory cells in the systemic circulation affect the process of tumor development, progression, and metastasis.[8–9] Peripheral blood cells can interact with tumor cells, promote tumor cell growth, tumor angiogenesis, migration and invasion, and inhibit apoptosis.[11–12] In vivo immune inflammatory response is closely related to the prognosis of a variety of malignant tumors, and is therefore used for prognosis prediction.[13–14] Consistently,

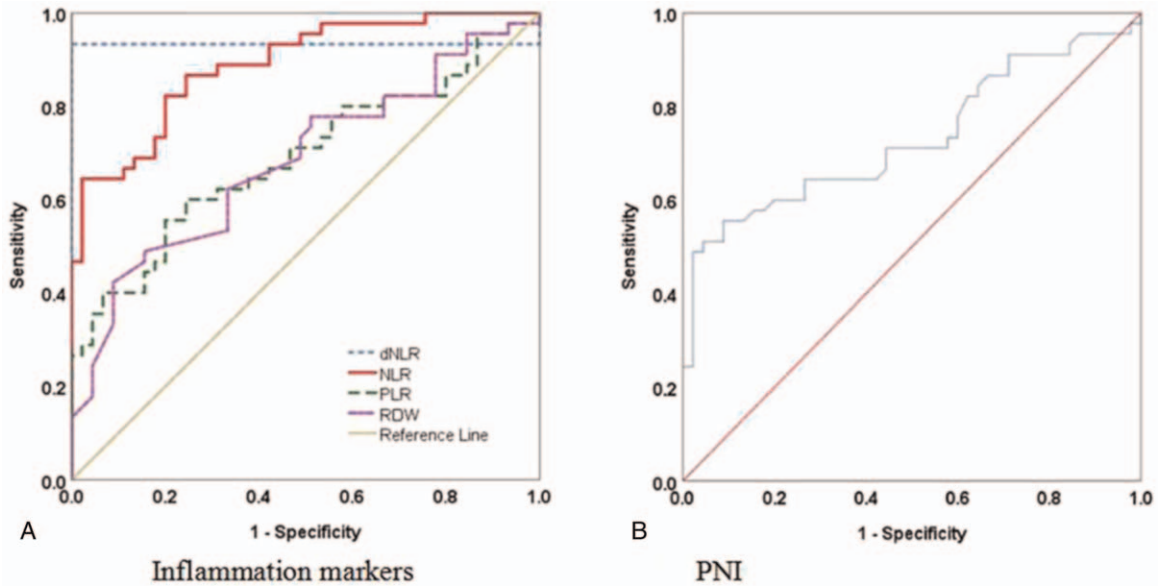

Figure 2. ROC curves of inflammation markers and PNI. dNLR = derived neutrophil to lymphocyte ratio, NLR = neutrophil to lymphocyte cytometry, PLR = platelet to lymphocyte ratio, PNI = prognostic nutritional index, RDW = red blood cell distribution width, ROC = receiver operating characteristics.

studies have identified many inflammatory factors capable of predicting the outcome of glioma, such as peripheral blood neutrophil count, PLR, NLR, dNLR, lymphocyte to monocyte ratio, and PNI.[15–17]

In this study, we sought to evaluate the relationships between preoperative inflammation markers and pathological grading of glioma. Our results suggest a positive correlation between NLR and WHO grade of glioma, while no correlation was observed

Table 3

Relationship between biomarkers and glioma pathological grade.

Biomarkers	Internal	WHO I + WHO II	WHO III + WHO IV	Total	*P*
NLR	<1.90	6 (25.0)	0 (0.0)	6 (13.3)	.023
	≥1.90	18 (75.0)	21 (100.0)	39 (86.7)	
dNLR	<0.398	1 (4.2)	2 (9.5)	3 (6.7)	.592
	≥0.398	23 (95.8)	19 (90.5)	42 (93.3)	
PLR	<129.42	15 (62.5)	4 (19.0)	19 (42.2)	.006
	≥129.42	9 (37.5)	17 (81.0)	26 (57.8)	
RDW	<41.67	12 (50.0)	10 (47.6)	22 (48.9)	.873
	≥41.67	12 (50.0)	11 (52.4)	23 (51.1)	
PNI	<57.47	10 (41.7)	16 (76.2)	26 (57.8)	.019
	≥57.47	14 (58.3)	5 (23.8)	19 (42.2)	
Ki-67	Weak positive	12 (75.0)	4 (25.0)	16 (35.5)	
	Positive	11 (73.3)	4 (16.7)	15 (33.3)	<.05
	Strong positive	1 (7.1)	13 (92.9)	14 (31.2)	

Numbers in parenthesis indicate percentage.
dNLR = derived neutrophil to lymphocyte ratio, NLR = neutrophil to lymphocyte cytometry, PLR = platelet to lymphocyte ratio, PNI = prognostic nutritional index, RDW = red blood cell distribution width.

Table 4

Relationship between inflammation markers and Ki-67.

Inflammation markers	Internal	Weakly positive	Positive	Strong positive	Total	*P*
NLR	<1.90	6 (37.5)	0 (0.0)	0 (0.0)	6 (13.3)	.002
	≥1.90	10 (62.5)	15 (100.0)	14 (100.0)	39 (86.7)	
dNLR	<0.398	2 (12.5)	0 (0.0)	1 (7.1)	3 (6.7)	.636
	≥0.398	14 (87.5)	15 (100.0)	13 (92.9)	42 (93.3)	
PLR	<129.42	6 (37.5)	0 (0.0)	4 (28.6)	10 (22.2)	.022
	≥129.42	10 (62.5)	15 (100.0)	10 (71.4)	35 (77.8)	
RDW	<41.67	7 (43.8)	6 (40.0)	9 (64.3)	22 (48.9)	.373
	≥41.67	9 (56.3)	9 (60.0)	5 (35.7)	25 (51.1)	

Ki-67 intensity was categorized as weak positive, positive, and strong positive according to immunohistochemistry studies. Numbers in parenthesis indicate percentage.
dNLR = derived neutrophil to lymphocyte ratio, NLR = neutrophil to lymphocyte cytometry, PLR = platelet to lymphocyte ratio, RDW = red blood cell distribution width.

between dNLR and the grading of glioma. Many studies have shown that NLR is closely related to the prognosis of various malignancies. The increase of NLRs mainly reflects an increase of neutrophils or a decrease in lymphocytes.[18] Studies have shown that neutrophils in human peripheral blood can infiltrate around the tumor, which plays an important role in the growth of tumor blood vessels. Neutrophils produce vascular elastase and endothelial growth factor in the immune microenvironment surrounding the tumor, providing an environment for tumor growth and development. At the same time, cytokines such as tumor necrosis factor and interleukin family are also secreted by neutrophils, which accelerate the division and differentiation of tumor cells through different pathways. On the other hand, CD4+ T helper lymphocytes play an essential role in antitumor response of the immune system. The reduction of lymphocytes in the peripheral blood suggests that the cellular antitumor immunity is reduced, thereby providing a relatively stable environment for the growth and migration of tumor cells. NLR represents a relatively balanced state of neutrophils and lymphocytes, and the increase of NLR reflects the advantages of tumor promoting effects over tumor inhibiting effect, leading to growth of the tumor. Our results reveal essential roles of cancer immunity in development of glioma and prognostic implication of NLR in glioma.

PLR has been shown to have a predictive function for the prognosis of many malignant tumors, such as rectal cancer, kidney cancer, liver cancer and gastric cancer. Like NLR, it has different sensitivities and specificities in different tumors. However, the use of this index to assess the prognosis of glioma patients is scarce, but the application of PLR for prognosis assessment of other tumors was reported.[19] In this study, PLR was positively correlated with pathological grade of glioma. The results of this group are the in line with other studies. The elevation of PLT also causes the tumor patient to be in a hypercoagulable state, slowing down the blood flow, leading to more immune cells or inflammatory cells accumulating in the peritumoral, continuously promoting the growth of tumor blood vessels, thereby promoting the occurrence and development of tumors. This study identifies PLR as a biomarker of grading of glioma and supports its use in prognosis prediction.

RDW, which serves as an important indicator for the heterogeneity of red blood cell volume in the peripheral blood, is clinically used to detect certain hematologic diseases such as anemia. After several years of research, experts have found that it is related to a variety of malignant tumors. It is believed that its elevation has a certain correlation with the poor prognosis of patients with multiple malignant tumors. Some experts have found by retrospective research that it can be used as an indicator to distinguish benign and malignant tumors. Our study failed to demonstrate significant relationship between RDW and glioma pathological grade, which requires more studies to confirm.

PNI was widely used clinically at the outset to estimate the preoperative nutritional status of patients undergoing elective surgery and the level of surgical risk, and to have a role in predicting postoperative complications.[20–22] It was extended to the field of oncology. Nozoe et al found that patients with high PNI had a significantly longer survival time than patients with lower PNI in esophageal cancer. In light of this finding, we analyzed PNI in glioma. In this study, PNI was positively correlated with glioma grade, consistent with the findings of other researches. We speculate PNI elevation indicates high exhaustion of glioma that leads to decrease of serum albumin.

Lastly, this article also analyzed the expression level of Ki67 in glioma by IHC. Our results show that Ki-67 was expressed in all the gliomas and it is significantly related to pathological grade of glioma, which is consistent with previous studies. Interestingly, correlation between Ki-67 and NLR, PLR were observed, suggesting potential biological link between inflammation and Ki-67 in glioma, but more studies are needed to confirm the hypothesis.

In summary, the inflammatory markers NLR, PLR, PNI, and Ki-67 are clinically simple and readily available indicators that is closely related to the grading of glioma. In contrast, no significant relationship was found between the malignancy degree of glioma and PLR, RDW. It should be noted that this study was performed on a small sample size, and therefore further studies on sufficiently more clinical samples are still needed to confirm the reliability of the conclusion. This study sheds light in implementing these indicators for evaluating prognosis of glioma under the concept of personized medicine.

Author contributions

Conceptualization: Junchen Zhang.
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Formal analysis: Guangda Xu.
Funding acquisition: Guangda Xu.
Investigation: Guangda Xu.
Methodology: Guangda Xu.
Project administration: Guangda Xu.
Validation: Guangda Xu, Junchen Zhang.
Visualization: Guangda Xu, Junchen Zhang.
Writing – original draft: Guangda Xu, Chengxue Li, Yanguo Wang, Jinan Ma.
Writing – review & editing: Guangda Xu, Chengxue Li, Yanguo Wang, Jinan Ma, Junchen Zhang.

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