Original Article

Predictive Value of Blood Markers in Nonfunctional Pituitary Adenomas using Artificial Neural Network

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Abstract

Background: Nonfunctioning pituitary adenomas (NFPAs) are the most common pituitary tumors and although they do not secrete hormones, they can have systemic effects. These tumors affect the function of other organs in the body by exerting pressure on the pituitary gland. There are differences between biomarkers NFPAs compared to healthy people. This study was conducted to show blood marker changes in adenomas compared to healthy people.

Materials and Methods: This article compared the blood markers of NFPAs with healthy individuals retrospectively. The difference between blood markers in the two groups was statistically investigated where the predictive value of blood markers in the differentiation of the two groups was determined. An artificial neural network was also designed using the blood markers with its accuracy and predictive value determined.

Results: A total of 96 NFPAs (nonfunctional pituitary adenoma) and 96 healthy individuals were evaluated. There was statistically a significant difference and positive correlation in platelet to lymphocyte ratio, neutrophil to lymphocyte ratio, and derived neutrophil to lymphocyte ratio between NFPAs and healthy individuals. There was a significant and negative correlation between red blood cell (RBC), lymphocyte, and monocyte between the two groups. RBC as an independent factor was associated with NFPAs. In this study, the artificial neural network was able to differentiate between NFPTs cases and healthy individuals with an accuracy of 81.2%.

Conclusion: There are differences between blood markers in NFPAs relative to healthy people and the artificial neural network can accurately differentiate between them.

Keywords: Neural network, biomarkers, erythrocyte count, neutrophils, lymphocytes, pituitary neoplasms

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Submitted: 23-Jun-2021; **Revised:** 06-Nov-2021; **Accepted:** 20-Dec-2021; **Published:** 28-Mar-2023

Introduction

Nonfunctioning pituitary adenomas (NFPAs) are the most common type of macro-adenomas whose prevalence is 7%–41.3%.[1-3] Adenomas are more common in females. NFPAs are usually diagnosed due to pituitary insufficiency and visual impairment.[4,5] These tumors do not have drug treatment and their standard treatment is operation. After an operation, the recurrence rate of nonfunctioning adenomas is high and long-term follow-up is required.[6,7]

Genetic studies and evaluations of multiple biomarkers have been performed on pituitary adenomas.[8] The histopathological examination has shown that higher levels of markers such as CD147, folate receptor alpha, and Ki67 were associated

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Website: www.advbiores.net

DOI: 10.4103/abr.abr_183_21

How to cite this article: Sayyadi S, Kashani HR, Jafari R, Azhari S, Salimi S, Komlakh K, *et al*. Predictive value of blood markers in nonfunctional pituitary adenomas using artificial neural network. Adv Biomed Res 2023;12:83.

with increased tumor growth and invasion.[9] Lower TGFBP II levels have revealed more aggression and higher Knosp.[10] The ENC1 gene is associated with increased tumor invasion and invasiveness.[11] Most of these immunohistochemical and genetic tests are performed on postoperative tissue samples after surgery.

Blood markers such as white blood cell (WBC), neutrophils, monocytes, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR) have shown significant changes in various studies in malignant tumors.[12-15] The difference between these markers has been shown among the brain tumors, especially in gliomas, and the role of some of these markers, such as NLR, has been demonstrated in prognosis.[16-19]

In this study, blood markers in NFPAs are examined and their differences between NFPAs and healthy individuals are identified. In addition to statistical analysis, the difference between blood markers in both groups is investigated through an artificial neural network.

Materials and Methods

This was a retrospective study performed using electronic records of newly diagnosed NFPAs cases admitted to Imam Hossein Hospital between October 2016 and October 2018. The research protocol was approved by the hospital's Ethics Committee Institute. Patients with NFPAs based on the WHO 2017 classification were enrolled in the study. Inclusion criteria included the following: (1) Pituitary adenoma larger than 10 mm that has undergone an operation. (2) Histopathologic report of pituitary adenoma (3) Normal pituitary hormone assays except for increased prolactin due to stalk effect (4) No history of malignancy, blood disorders, and chronic use of corticosteroids (5) No history of apoplexy and acute conditions leading to operation.

The data of 96 NFPAs and 96 healthy individuals who had referred for periodic tests and had no previous medical history were included in the study. Healthy individuals were selected in terms of age and sex similar to the patient cases. Demographic data and blood markers were recorded before surgery. SPSS (version 19.0, IBM, USA) software was used for statistical analysis. Kolmogorov-Smirnov test was used to determine the normal distribution of variables in different groups. *T*-test was used to evaluate the mean of quantitative variables with normal distribution, while the Mann–Whitney test was applied for nonquantitative variables or abnormal distribution. The relationship between blood markers and the tumor in normal distribution groups was tested using Pearson's correlation coefficient, while Spearman's correlation coefficient was used in nonnormal distribution groups. Univariate and multivariate logistic regression were used to examine the relationship between blood markers and the presence of a tumor. Receiver operating characteristic (ROC) plot and area under the curve (AUC) were employed to evaluate the predictive effect of blood markers on the differentiation of healthy people and NFPAs.

In this study, an artificial neural network was used to evaluate the predictive effect of blood markers in differentiating NFPAs from healthy individuals. Multilayer perceptron (MLP), a class of feedforward artificial neural network, was used according to the type of study data. The MLP has three layers: The input layer, the output layer, and one or more hidden layers. The training method in this network is backpropagation. In this method, the input and output data are given to the network and the network error is determined. Then, the new weights are changed in such a way that the average squares of the network error are minimized. Equation 1 shows the network error and Equation 2 indicates the mean square of error.

Equation 1: $E = O\text{-}O'$

O: Expected Output and O': *System Output*

Equation 2: $$MSE = \frac{1}{n}\sum_{i=1}^{n}(e)^2$$

MSE: Mean Squared Error and *n*: Number of samples

In this study, the K-fold cross-validation method with k = 10 was used to evaluate the model. In this method, the data set is first divided into k categories. MLP is trained with k-1 every time and is validated with 1 category. This procedure is repeated k times, where each data are used once for training and once for testing. Finally, the average validation is used as the final estimate.

The topology of the MLP was as follows: The number of nodes in the input layer was equal to the number of inputs and the number of nodes in the output layer was equal to the number of outputs and the MLP had a hidden layer with 6 nodes. In this study, the Min-Max Normalization method in the range of 0–1 was used for normalization.

Blood markers of healthy individuals and NFPAs were used as the input to the MLP artificial neural network. The output of the neural network was one of two categories: 0 (healthy people) or 1 (NFPAs). After the training, MLP receives the person's blood markers and determines whether a case is healthy or NFPAs. The performance of the network was assessed at this stage, with the specifications of the artificial neural network determined further.

Results

A total of 109 patients with newly diagnosed NFPAs who had undergone operation were enrolled in the study. Among the patients, 13 people were excluded from the study for the following reasons: Apoplexy (6 cases), malignancy and history of chemotherapy (5 cases), long-term use of corticosteroids (2 cases). Data were collected on 96 healthy individuals, whose age- and sex-matched the NFPAs. As shown in Table 1, the mean age of the patients was 50.1 (25–72). Of the tumor cases, 54 (56.2%) were female and 42 (43.8%) were male. The mean WBC and neutrophils were higher in the

NFPAs than in healthy people, while other blood cells were lower in NFPAs than in healthy people.

Statistical analysis

Among the blood markers red blood cell (RBC) ($P < 0.001$), lymphocyte ($P < 0.041$) and monocyte ($P < 0.0.12$) were significantly different in the two groups; among the calculated blood markers NLR ($P < 0.013$), PLR ($P < 0.015$), derived neutrophil to lymphocyte ratio (dNLR) ($P < 0.014$) were significantly different between NFPAs and healthy cases. There was a positive correlation between NLR ($r = 302$), PLR ($r = 0.264$), as well as dNLR ($r = 0.301$) and NFPAs. The correlation between lymphocyte ($r = 0.201$), monocyte ($r = 0.194$), as well as RBC ($r = 0.394$) and tumor presence was negative. Univariate logistic regression test revealed a significant relationship between PLR ($P < 0.012$), NLR ($P < 0.025$), dNLR ($P < 0.028$), as well as RBC ($P < 0.001$), and presence of tumor. In multivariate logistic regression test, RBC was independently associated with NFPAs (odds ratio: 1.805; 95% confidence interval: 0.057–0474, $P = 0.001$).

Figure 1 shows the predictive value of blood markers with a positive relationship with NFPAs. PLR has the best AUC (0.653) but the predictive value of these markers is weak. As shown in Figure 2, the ROC plot reveals that between the blood markers with a negative relationship with NFPAs, RBC has the best AUC (0.728) and the predictive value of lymphocytes and monocytes is poor.

Artificial neural network

In this study, blood markers of 192 people including 96 NFPAs and 96 healthy individuals were used as a data set. Blood markers were used as MLP input for each person including RBC, WBC, neutrophil, lymphocyte, monocyte, platelet, NLR, LMR, PLR, and dNLR. Two classes 0 (healthy cases) and 1 (NFPAs) were used to determine the status of each case.

As shown in the confusion matrix in Figure 3, the network accuracy for differentiating a healthy person from the patient is 81.2%. In other words, out of 192 input samples, 156 cases were in the correct category, while 36 cases were in the wrong category.

Table 2 reports the specifications of the artificial neural network used in the study. The Recall parameter refers to the number of correct cases categorized by the network from one class to the number of cases present in the same class. In other words, Recall represents the number of examples in each class that is properly categorized. According to the results, Recall for

Table 1: Distribution of demographic characteristics and blood markers in healthy cases and patients with nonfunctioning pituitary adenomas tumour

Variables	Healthy	Adenoma	*P*
Age	50.1 (25-72)	49.3 (25-76)	
Sex			
Male	42	42	
Female	54	54	
RBC	4.78 (3.60-6.07)	4.29 (2.92-5.57)	0.001
WBC	6940 (4123-9821)	7523 (3126-12376)	0.92
Neutrophil	3876 (2043-6243)	4845 (1687-1108)	0.74
Lymphocyte	2320 (1252-5643)	2138 (638-5146)	0.041
Monocyte	423 (268-966)	366 (113-790)	0.012
NLR	1.66 (0.61-4.14)	3.47 (0.67-11.92)	0.013
LMR	6.62 (2.33-16.23)	6.31 (2.32-14.8)	0.56
PLR	102 (36-151)	137 (39-339)	0.015
dNLR	1.29 (0.522-2.86)	2.67 (0.534-13.49)	0.014
Platelet	246 (85-490)	244 (134-393)	0.17

RBC: Red blood cells, WBC: White blood cells, NLR: Neutrophil to lymphocyte ratio, dNLR: Derived NLR, LMR: Lymphocyte to monocyte ratio, PLR: Platelet to lymphocyte ratio

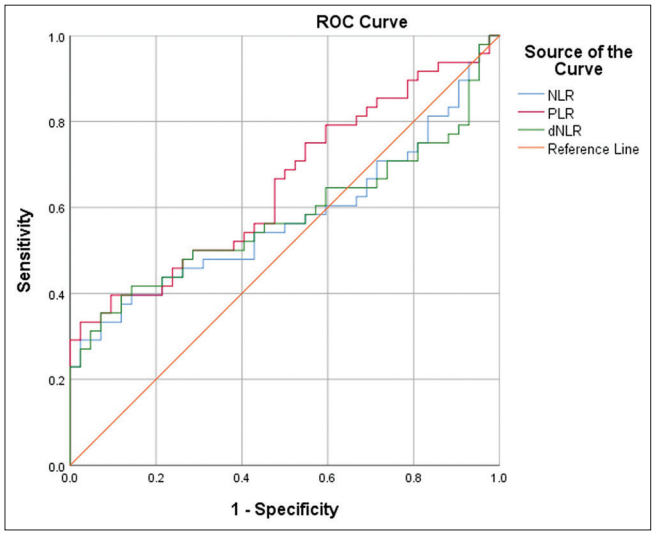

Figure 1: Receiver operating characteristic curve demonstrates the predictive value of blood markers in differentiation between healthy and adenoma cases. The area under the curve of the markers are as follows: Neutrophil to lymphocyte ratio = 0.574, platelet to lymphocyte ratio = 0.653, derived neutrophil to lymphocyte = 0.577

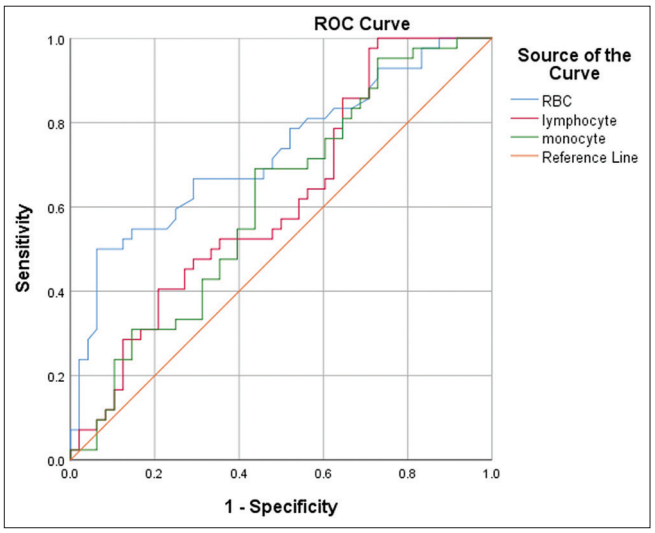

Figure 2: Receiver operating characteristic curve demonstrates the predictive value of blood markers in differentiation between healthy and adenoma cases. The area under the curve of the markers are as follows: Red blood cell = 0.728, lymphocyte = 0.617, monocyte = 0.612

class 1 (Recall^1) is equal to 0.785, which indicates the proper efficiency of the system in class 1. Recall for class 0 (Recall^0) is 0.75, which shows that 75% of healthy people are properly categorized. Comparison of Recall^0 and Recall^1 shows that the MLP function designed in this study was better for Class 1.

Precision refers to correct cases of a class, to all cases of that class, and shows the MLP output performance. The Precision^0 value is 0.857, which indicates the proper performance of MLP in diagnosing a healthy person. The Precision^1 value is 0.778, indicating that MLP correctly classified 77.8% of NFPAs. Comparing Precision^0 and Precision^1, the network output is more reliable for class 0 or healthy people, while MLP performs well in NFPAs.

F_Measure uses both Recall and Precision parameters simultaneously and is a good measure of the quality of the MLP performance. F_Measure can have values between 0 and 1. Comparison of F_Measure^0 and F_Measure^1 reveals a similar network performance in both classes (F_Measure^0 = 0.8 and F_Measure^1 = 0.82).

Matthews Correlation Coefficient (MCC) is a measure of the relationship between the values observed in a class and the predicted value of that class. The MCC gives a number between −1 and 1, where the value of +1 indicates an accurate and error-free as well as value of 0, indicates a random forecast, and a value of-1, indicates a complete mismatch between the predicted and observed cases. The MCC value of the designed MLP is 0.63 and it indicates that the results are not random.

Figure 4 shows the ROC plot related to the performance of the artificial neural network. The AUC of the artificial neural network is 0.784 which represents the acceptable predictive value of the artificial neural network in this study.

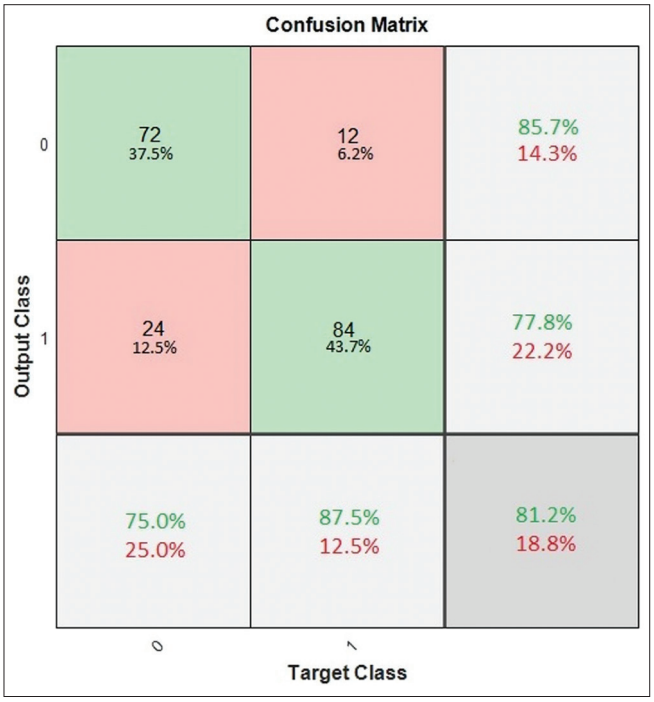

Figure 3: Confusion matrix of artificial neural network

Discussion

Various biomarkers have been studied in patients with nonfunctioning pituitary adenomas. CD34, CD105 are biomarkers for endothelial cell proliferation that are associated with the growth and invasion of adenomas.[20,21] Mitochondrial dysfunction and cell-cycle dysregulation, are more common in NFPAs.[22] Some biomarkers such as CHGA and CLU is used as a therapeutic target and markers of tumor invasion.[23] Folate receptor alpha biomarker is associated with increased tumor growth and invasion and TGF beta RII is associated with slower tumor growth.[9,24] Some biomarkers such as CD147 are associated with a worse prognosis.[25] Claudin and the ENC1 gene are signs of adenomas invasion.[26]

Blood markers are used in tumors of different areas of the body as biomarkers for predicting tumor malignancy and determining disease prognosis.[27-29] Blood markers have also been used to predict the histopathology of brain tumors such as glioma and meningioma.[18,19,30] Higher NLR is associated with higher tumor grade whose role has also been shown in predicting the prognosis of gliomas.[17,31,32] Various studies

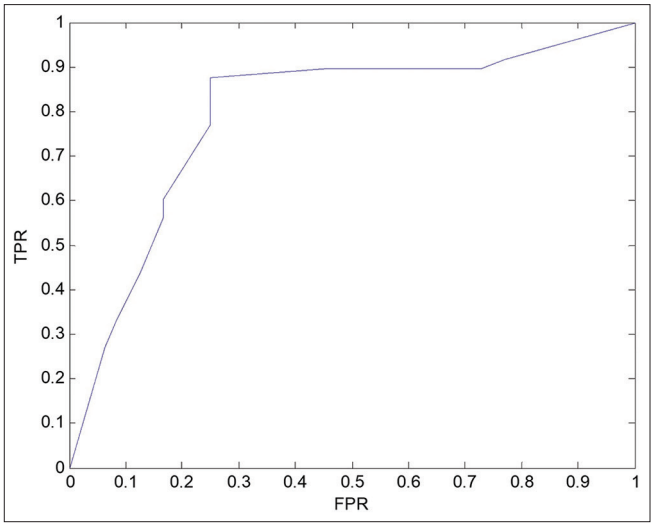

Figure 4: Artificial neural network receiver operating characteristic curve. False positive rate; true positive rate

Table 2: Specifications of artificial neural network designed to determine the nonfunctioning pituitary adenomas

Recall^0	Recall^1	Precision^0	Precision^1	F_Measure^0	F_Measure^1	MCC	AUC
0.75	0.785	0.857	0.778	0.8	0.82	0.63	0.784

0≤F_Measure ≤1, −1≤MCC≤+1. MCC: Matthews correlation coefficient, AUC: Area under the curve

have indicated that there is a positive correlation between NLR, dNLR, PLR, and tumor grade and a negative correlation between LMR and glioma malignancy.[17,30] Significant changes between blood markers have been shown in different grades of meningiomas where the artificial neural network can distinguish between benign and malignant meningiomas with acceptable accuracy.[19]

Having reviewed the literature, this is the first study to examine changes in blood markers in patients with NFPAs. This study revealed that there was a positive relationship between NLR, PLR, dNLR, and the presence of NFPAs and a negative relationship between RBC, lymphocyte, monocyte, and tumor. Multivariate logistic regression test displayed RBC as an independent factor related to the NFPAs. In studies of blood markers in tumors in different areas, RBC was not statistically significant, which can be due to a different mechanism of changes in blood markers in NFPAs than the tumors in other parts of the body.

The artificial neural network used in this study differentiated between healthy cases and NFPAs using blood markers with an accuracy of 81.2%. According to the AUC = 0.784 and MCC = 0.63, the performance of MLP is acceptable and reliable.

The study showed that blood markers were significantly different in NFPAs than in healthy cases, especially when using an artificial neural network. Changes in blood markers in malignant tumors are caused by the effects of inflammatory released mediators on bone marrow.[16,30] Significant changes in blood markers in NFPAs may be due to systemic effects of NFPAs. Although this study has been performed on NFPAs with normal hormone assays, unmeasurable and indefinite changes in hormones may be the cause of changes in blood markers. Local growth and invasion of the tumor may also play a role. In this study, there was a significant difference in RBC between the two groups, which is different from studies of blood markers in tumors in other areas. The difference in RBC levels can indicate a different mechanism for the changes in blood markers in NFPAs.

This study showed the systemic effect of NFPAs on bone marrow and changes in blood markers. Other variables such as tumor size, tumor radiological characteristics, tumor invasion to the surrounding tissue (Knosp grade), and clinical signs of the patient were not used, indicating the study limitation. Using other biomarkers associated with NFPAs and blood markers at the same time can produce more accurate results.

In this study, the size of the tumor was not examined and very large tumors can cause hormonal changes by pressure on the pituitary gland, but in this study, cases that had changes in pituitary hormones were excluded from the study. Study using multiple factors affecting pituitary adenomas (in addition to blood markers) can provide better and more specific results. Blood markers and other influencing factors in pituitary adenomas also can be used to evaluate the outcome and recurrence of tumor in the other studies.

Conclusion

Blood markers are significantly different in NFPAs compared to healthy individuals, and the artificial neural network can distinguish between the two groups with good accuracy (81.2%).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Szwagrzyk E. Visual disorders in pituitary adenoma and their treatment. Folia Med Cracov 1964;6:101-42.
2. Al-Dahmani K, Mohammad S, Imran F, Theriault C, Doucette S, Zwicker D, *et al.* Sellar masses: An epidemiological study. Can J Neurol Sci 2016;43:291-7.
3. Davis JR, Farrell WE, Clayton RN. Pituitary tumours. Reproduction 2001;121:363-71.
4. Pelsma IC, Verstegen MJ, de Vries F, Notting IC, Broekman ML, van Furth WR, *et al.* Quality of care evaluation in non-functioning pituitary adenoma with chiasm compression: Visual outcomes and timing of intervention clinical recommendations based on a systematic literature review and cohort study. Pituitary 2020;23:417-29.
5. Iwasaki Y. Pathophysiology and clinical features of non-functioning pituitary adenoma. Nihon Rinsho 2011;69 Suppl 2:138-41.
6. Lee MH, Lee JH, Seol HJ, Lee JI, Kim JH, Kong DS, *et al.* Clinical concerns about recurrence of non-functioning pituitary adenoma. Brain Tumor Res Treat 2016;4:1-7.
7. Ferrante E, Ferraroni M, Castrignanò T, Menicatti L, Anagni M, Reimondo G, *et al.* Non-functioning pituitary adenoma database: A useful resource to improve the clinical management of pituitary tumors. Eur J Endocrinol 2006;155:823-9.
8. Aydin B, Arga KY. Co-expression network analysis elucidated a core module in association with prognosis of non-functioning non-invasive human pituitary adenoma. Front Endocrinol (Lausanne) 2019;10:361.
9. Liu X, Ma S, Yao Y, Li G, Feng M, Deng K, *et al.* Differential expression of folate receptor alpha in pituitary adenomas and its relationship to tumor behavior. Neurosurgery 2012;70:1274-80.
10. Liu X, Ma L, Wang Z, Ye J, Liu X, Jiang G, *et al.* Expression and clinical significance of doublecortin (DCX) in pituitary adenoma. Bull Cancer 2019;106:1080-5.
11. Feng J, Hong L, Wu Y, Li C, Wan H, Li G, *et al.* Identification of a subtype-specific ENC1 gene related to invasiveness in human pituitary null cell adenoma and oncocytomas. J Neurooncol 2014;119:307-15.
12. Abe S, Kawai K, Nozawa H, Hata K, Kiyomatsu T, Morikawa T, *et al.* LMR predicts outcome in patients after preoperative chemoradiotherapy for stage II-III rectal cancer. J Surg Res 2018;222:122-31.
13. Wang J, Gao K, Lei W, Dong L, Xuan Q, Feng M, *et al.* Lymphocyte-to-monocyte ratio is associated with prognosis of diffuse large B-cell lymphoma: Correlation with CD163 positive M2 type tumor-associated macrophages, not PD-1 positive tumor-infiltrating lymphocytes. Oncotarget 2017;8:5414-25.
14. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, *et al.* Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with Non-Small Cell Lung Cancer (NSCLC) treated with nivolumab. Lung Cancer 2017;111:176-81.
15. Asaoka T, Miyamoto A, Maeda S, Tsujie M, Hama N, Yamamoto K, *et al.* Prognostic impact of preoperative NLR and CA19-9 in pancreatic cancer. Pancreatology 2016;16:434-40.
16. Ashwath KG, Aggarwal A, Praneeth K, Singla N, Gupta K. Neutrophil-to-lymphocyte ratio: Can it be used as an adjunct tool to predict histopathological grade of brain tumor? J Neurosci Rural Pract 2019;10:648-52.

17. Wang ZL, Zhang CB, Liu YQ, Wang Z, Jiang T. Peripheral blood test provides a practical method for glioma evaluation and prognosis prediction. CNS Neurosci Ther 2019;25:876-83.
18. Zheng SH, Huang JL, Chen M, Wang BL, Ou QS, Huang SY. Diagnostic value of preoperative inflammatory markers in patients with glioma: A multicenter cohort study. J Neurosurg 2018;129:583-92.
19. Khayat Kashani HR, Azhari S, Nayebaghayee H, Salimi S, Mohammadi HR. Prediction value of preoperative findings on meningioma grading using artificial neural network. Clin Neurol Neurosurg 2020;196:105947.
20. Rotondo F, Sharma S, Scheithauer BW, Horvath E, Syro LV, Cusimano M, *et al.* Endoglin and CD-34 immunoreactivity in the assessment of microvessel density in normal pituitary and adenoma subtypes. Neoplasma 2010;57:590-3.
21. Miao Y, Zong M, Jiang T, Yuan X, Guan S, Wang Y, *et al.* A comparative analysis of ESM-1 and vascular endothelial cell marker (CD34/CD105) expression on pituitary adenoma invasion. Pituitary 2016;19:194-201.
22. Zhan X, Desiderio DM. Signaling pathway networks mined from human pituitary adenoma proteomics data. BMC Med Genomics 2010;3:13.
23. Yu SY, Hong LC, Feng J, Wu YT, Zhang YZ. Integrative proteomics and transcriptomics identify novel invasive-related biomarkers of non-functioning pituitary adenomas. Tumour Biol 2016;37:8923-30.
24. Gu YH, Feng YG. Down-regulation of TGF-β RII expression is correlated with tumor growth and invasion in non-functioning pituitary adenomas. J Clin Neurosci 2018;47:264-8.
25. Qu X, Yang W, Jiang M, Han T, Han L, Qu Y, *et al.* CD147 expression in pituitary adenomas and its significance for clinical outcome. Hum Pathol 2010;41:1165-71.
26. Hong L, Wu Y, Feng J, Yu S, Li C, Wu Y, *et al.* Overexpression of the cell adhesion molecule claudin-9 is associated with invasion in pituitary oncocytomas. Hum Pathol 2014;45:2423-9.
27. Bao Y, Yang M, Jin C, Hou S, Shi B, Shi J, *et al.* Preoperative hematologic inflammatory markers as prognostic factors in patients with glioma. World Neurosurg 2018;119:e710-6.
28. Feng F, Tian Y, Liu S, Zheng G, Liu Z, Xu G, *et al.* Combination of PLR, MLR, MWR, and tumor size could significantly increase the prognostic value for gastrointestinal stromal tumors. Medicine (Baltimore) 2016;95:e3248.
29. Cananzi FC, Minerva EM, Samà L, Ruspi L, Sicoli F, Conti L, *et al.* Preoperative monocyte-to-lymphocyte ratio predicts recurrence in gastrointestinal stromal tumors. J Surg Oncol 2019;119:12-20.
30. Wang J, Xiao W, Chen W, Hu Y. Prognostic significance of preoperative neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with glioma. EXCLI J 2018;17:505-12.
31. He ZQ, Duan H, Lin FH, Zhang J, Chen YS, Zhang GH, *et al.* Pretreatment neutrophil-to-lymphocyte ratio plus albumin-to-gamma-glutamyl transferase ratio predict the diagnosis of grade III glioma. Ann Transl Med 2019;7:623.
32. Wang PF, Meng Z, Song HW, Yao K, Duan ZJ, Yu CJ, *et al.* Preoperative changes in hematological markers and predictors of glioma grade and survival. Front Pharmacol 2018;9:886.