

The Diagnostic Value of Preoperative Hematology Makers in the Classification and Molecular Subtypes of Newly Diagnosed High-Grade Gliomas

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Abstract

Objective

The purpose of our study is to explore the diagnostic value of the single and combined hematological maker for the classification and isocitrate dehydrogenase (IDH)-1/2 mutations molecular subtypes of high-grade gliomas (HGGs).

Methods

A total of 354 newly diagnosed HGGs patients were included in this study. Firstly, we compared the levels of hematology indicators in the classification and molecular subtypes of HGGs. Next, the correlation between the levels of hematology indicators with basic clinical features was analyzed. Finally, the diagnostic value of the single and combined hematology indicator for identifying the classification and molecular subtypes from HGGs was performed.

Results

The level of fibrinogen (FIB) was higher in higher grade gliomas and glioblastoma multiforme IDH wild type (GBM IDH-wt). Nutrition-related indicators such as serum albumin (ALB), albumin/globulin ratio (AGR), and prognostic nutrition index (PNI) were negatively correlated with age, whereas FIB was positively associated with age. Compared with women, men with GBM had significantly higher AGR and lower serum globulin (GLOB). We found that the best single and combined indicator for identifying GBM and GBM IDH-wt from HGGs were FIB [0.595 (0.519–0.672) and 0.615 (0.546–0.684)] and age + FIB [0.712 (0.642–0.783) and 0.726 (0.662–0.791)], respectively.

Conclusions

Preoperative hematological indicators have high diagnostic value for GBM and GBM IDH-wt from HGGs, especially FIB combined age.

Introduction

High-grade gliomas (HGGs) are the most common and lethal primary type of brain tumors, presenting one of the highest rates of occurrence within the tumors of the central nervous system (CNS), defined as Grade III (G3) and IV (G4) gliomas or glioblastoma multiforme (GBM) according to the 2016 World Health Organization (WHO) classification of CNS tumors^{1,2}. HGGs individual therapies greatly vary across identifying the glioma grade and isocitrate dehydrogenase (IDH)-1/2 mutations molecular subtypes confirmed by pathology after surgery^{3,4}. Currently, the grade and IDH molecular subtypes of HGGs are

determined by surgery or biopsy, which is invasive and traumatic to the human body. Therefore, it is necessary to establish a noninvasive method for the diagnosis of HGGs classification and IDH molecular subtypes.

At present, a large number of studies had shown that hematological indexes related to inflammation, coagulation, and nutrition had obviously predictive value in the prognosis of tumors⁵⁻⁷. Meanwhile, hematology related indicators had been demonstrated to be provided with remarkable predictive value for the prognosis of gliomas, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR)⁸, fibrinogen (FIB), prognostic nutrition index (PNI) and albumin-to-globulin ratio (AGR)⁹, etc. In addition, the different levels of hematological indicators had significant diagnostic value for gliomas^{10, 11}. Nevertheless, the current researches showed that the diagnostic value of hematological indicators had not yet fully included all indicators, and little is known about the grading diagnosis of HGGs.

In the present study, our goal is to identify the grade and IDH molecular subtypes of newly diagnosed HGGs based on preoperative hematological indicators related to inflammation, coagulation, and nutrition. Moreover, we also explored the correlation between these hematological indicators and basic clinical characteristics, and compared the levels of hematological indicators between HGGs of different grade and IDH molecular subtypes. We have also established the receiver operating characteristic (ROC) curve analysis to determine the best diagnostic indicators for HGGs classification and IDH molecular subtypes.

Clinical Materials And Methods

Patients

The retrospective study included patients who were confirmed with histologically as newly diagnosed G3 and G4 gliomas from January 2017 to December 2018 in the First Affiliated Hospital of Zhengzhou University. Approval for this study was acquired by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, and informed consent was obtained from all subjects or, if subjects are under 18, from a parent and/or legal guardian, based on the Declaration of Helsinki. The following inclusion criteria were used: 1) patients with G3 and G4 gliomas confirmed by histopathology; 2) patients with complete data of blood routine, biochemical, and coagulation results; 3) patients with IDH mutations results of histopathology; 4) patients without previous malignancy or second primary tumors. The exclusion criteria were as follows: 1) patients who had clinical evidence of liver disease, acute infection, or chronic active inflammatory diseases; 2) patients who had autoimmune diseases, hematological disorders, or anticoagulation treatment; 3) patients who had no complete hematology results; 4) patients who had previous anti-tumor treatment before admission. According to the above inclusion and exclusion criteria, 354 patients were included in the study, eventually.

Data collection

The baseline characteristics of all enrolled HGGs patients came from the electronic medical record system of the First Affiliated Hospital of Zhengzhou University. Basic clinical information was collected

including gender, age at diagnosis, preoperative Karnofsky performance status (pKPS) score, preoperative epilepsy (pEPI) status, histopathological grade, IDH mutation status, and hematology indexes, such as fibrinogen (FIB, g/L), serum albumin (ALB, g/L), serum globulin (GLOB, g/L). All blood sample tests were completed by the Clinical Laboratory of the First Affiliated Hospital of Zhengzhou University within 2 hours after collection. The related composite indexes were calculated as follows: NLR = absolute neutrophil counts/absolute lymphocyte counts ratio; PLR = absolute platelet counts/absolute lymphocyte counts ratio; MLR = absolute monocyte counts/ absolute lymphocyte counts ratio; AGR = serum albumin/serum globulin ratio; and PNI = albumin (g/L) + 5*total lymphocyte count ($10^9/L$)⁹.

Statistical Analysis

The unpaired t-test was used to compare two groups of continuous variables, and the comparison of categorical variables was performed with the Chi-square test. Multi-group comparisons were evaluated by one-way analysis of variance (one-way ANOVA), and the least significant difference t-test (LSD-t) was used for Post Hoc Multiple Comparisons. The correlation between the hematology markers and clinical features was judged by the Pearson correlation coefficient for continuous variables and the unpaired t-test. To identify the diagnostic value of the hematology markers and their combinations, the ROC analysis was used to acquire the area under the curve (AUC). The categorical variables and continuous variables were shown as frequency (percentage) and mean \pm standard deviation (SD), respectively. A 2-tailed P value of < 0.05 was considered to indicate statistical significance. All statistical analysis and drawing figures were performed using SPSS (version 24.0) and GraphPad Prism (version 6.01).

Results

Clinical Characteristics

There were 354 HGGs patients included in this retrospective study according to the inclusion and exclusion criteria. Table 1 summarized detailed demographic information of the research subjects. Overall, 59 (16.7%) were G3 and 295 (93.3%) were G4 of the 354 patients, respectively. All clinical features were not statistically significant ($p > 0.05$) except for IDH ($p < 0.001$), age ($p < 0.001$) and FIB ($p = 0.034$). IDH mutations tended to occur in G3 and the elderly population was more susceptible to GBM. Moreover, the level of FIB was higher in G4 compared with G3. There were 27 (45.8%) women and 32 (54.2%) men in G3 and 128 (43.4%) women and 167 (56.6%) men in G4. The existence of preoperative epilepsy (ex-pEPI) and pKPS ≤ 70 were 13 (22.0%) and 30 (50.8%) in G3 vs 46 (15.6%) and 147 (49.8%) in G4. The mean \pm SD of age, PLR, NLR, LMR, FIB, ALB, GLOB, AGR, PNI were 45.24 ± 13.36 (range 4–77), 138.26 ± 79.69 , 2.79 ± 2.24 , 0.28 ± 0.10 , 2.84 ± 0.65 , 42.14 ± 2.66 , 23.68 ± 3.82 , 1.83 ± 0.33 , 51.82 ± 4.90 and 53.76 ± 13.32 (range 9–78), 137.18 ± 66.27 , 3.46 ± 2.98 , 0.30 ± 0.16 , 3.08 ± 0.83 , 42.14 ± 3.66 , 24.49 ± 4.14 , 1.77 ± 0.35 , 50.85 ± 4.78 in G3 and G4, respectively.

Table 1
The Summary of Clinical Characteristics of HGGs patients (n = 354)

Characteristic	G3 (n = 59,16.7%)	G4/GBM (n = 295,83.3%)	P-value
gender			0.737
Female	27 (45.8%)	128 (43.4%)	
Male	32 (54.2%)	167 (56.6%)	
pEPI			0.226
wit-pEPI	46 (78.0%)	249 (84.4%)	
ex-pEPI	13 (22.0%)	46 (15.6%)	
pKPS			0.887
≤ 70	30 (50.8%)	147 (49.8%)	
>70	29 (49.2%)	148 (50.2%)	
IDH			0.000
IDH-wt	21 (35.6%)	273 (92.5%)	
IDH-mut	38 (64.4%)	22 (7.5%)	
age/years			0.000
mean ± SD	45.24 ± 13.36	53.76 ± 13.32	
range	4–77	9–78	
PLR	138.26 ± 79.69	137.18 ± 66.27	0.912
NLR	2.79 ± 2.24	3.46 ± 2.98	0.102
MLR	0.28 ± 0.10	0.30 ± 0.16	0.173
FIB	2.84 ± 0.65	3.08 ± 0.83	0.034
ALB	42.14 ± 2.66	42.14 ± 3.66	0.994
GLOB	23.68 ± 3.82	24.49 ± 4.14	0.165
AGR	1.83 ± 0.33	1.77 ± 0.35	0.257
PNI	51.82 ± 4.90	50.85 ± 4.78	0.159
wit-pEPI = without preoperative epilepsy status ; ex-pEPI = existence of preoperative epilepsy status; IDH-mut = IDH mutant type			

The Levels of Hematological Indicators were Different Among IDH Molecular Subtypes

To further understand the differences in the hematological indicators of IDH molecular subtypes, we divided patients into IDH wild type (IDH-wt) and IDH mutant type (IDH-mut) according to the IDH mutation status in the study. Compared with IDH-mut, the levels of NLR ($t = 2.315$, $p = 0.035$) and FIB ($t = 3.533$, $p < 0.001$) were both increased in IDH-wt (Fig. 1a, b; **Supplementary Table S1**). Furthermore, we further classified patients into four subgroups based on their IDH mutation status, including G3 IDH mutant type (G3 IDH-mut), G3 IDH wild type (G3 IDH-wt), G4 IDH mutant type (G4 IDH-mut), and G4 IDH wild type (G4 IDH-wt). The results showed that only FIB was statistically significant ($F = 4.160$, $p = 0.006$, Fig. 1c), and further analysis showed that the levels of FIB were increased in G4 IDH-wt, compared with G3 IDH-mut ($p = 0.003$) and G4 IDH-mut ($p = 0.040$) (**Supplementary Table S2**).

The Association of Hematological Indicators With Age, Gender, pEPI, and pKPS in G3 and G4

The results showed that ALB, AGR, PNI related to nutrition were negatively correlated with HGGs. Among them, ALB ($p < 0.000$), AGR ($p < 0.000$), and PNI ($p = 0.002$) were statistically significant in G4 (**Supplementary Figure S1f-h**), and only PNI ($p < 0.000$) was statistically significant in G3 (**Supplementary Figure S1d**). However, the coagulation-related FIB was positively correlated with G3 ($p = 0.430$) and G4 ($p = 0.003$) (**Supplementary Figure S1a, e**). Moreover, the inflammation-related PLR, NLR, and MLR were positively correlated with G3 but negatively correlated with G4, and they were not statistically significant (all $p > 0.05$, **Supplementary Table S3 and Table S4**).

Increased GLOB levels (25.54 ± 3.84 vs 23.69 ± 4.19 , $p < 0.000$) and decreased AGR levels (1.69 ± 0.28 vs 1.83 ± 0.38 , $p < 0.000$) were found in women, compared with men in G4 (**Supplementary Table S4**). It was worth noting that there had no significant difference in hematology indexes between pEPI and pKPS subgroups (all $p > 0.05$, **Supplementary Table S3 and Table S4**).

Evaluation of Diagnostic Efficacy of Hematological Indicators in Predicting Grade and IDH Molecular Subtypes of HGGs

To find out the diagnostic value of hematology indexes in distinguishing GBM and G4 IDH-wt from HGGs, the ROC curve was performed with single indexes and combined indexes, respectively. Firstly, a single indicator was used to predict GBM and G4 IDH-wt, and the FIB had the best diagnostic value in identifying GBM from HGGs [0.595 (0.519–0.672), $p = 0.021$] (Fig. 2a) and distinguishing G4 IDH-wt from other molecular subtypes [0.615 (0.546–0.684), $p = 0.002$] (Fig. 3a). Secondly, we combined the indicators for the ROC analysis, and the results showed that age + FIB, NLR + FIB, MLR + FIB, and FIB + PNI had the highest diagnostic value among the corresponding combinations (Fig. 2b,3b;2d-f,3d-f). Whether for GBM [0.712 (0.642–0.783), $p = 0.000$] (Fig. 2b) or G4 IDH-wt [0.726 (0.662–0.791), $p = 0.000$] (Fig. 3b), age + FIB was the best diagnostic index among all the combinations (Table 2). In addition, for the PLR combination group, PLR + FIB had a better diagnostic value for G4 IDH-wt [0.614 (0.545–0.683), $p = 0.002$] (Fig. 2c), but PLR + NLR had a higher diagnostic value for G4 [0.610 (0.530–0.689), $p = 0.008$] (Fig. 3c).

Table 2
The Predictive Value of Hematological Indicators in Distinguishing GBM and IDH
Molecular Subtypes from HGGs

Variable	G4/GBM		G4 IDH-wt	
	AUC (95%CI)	P-value	AUC (95%CI)	P-value
PLR	0.506 (0.427–0.585)	0.879	0.504 (0.435–0.573)	0.910
NLR	0.583 (0.504–0.662)	0.044	0.572 (0.502–0.642)	0.049
MLR	0.512 (0.438–0.586)	0.772	0.505 (0.439–0.572)	0.888
FIB	0.595 (0.519–0.672)	0.021	0.615 (0.546–0.684)	0.002
ALB	0.503 (0.431–0.575)	0.938	0.501 (0.433–0.568)	0.984
GLOB	0.542 (0.465–0.620)	0.303	0.524 (0.454–0.593)	0.517
AGR	0.544 (0.468–0.620)	0.285	0.536 (0.469–0.604)	0.320
PNI	0.525 (0.450–0.600)	0.552	0.519 (0.451–0.587)	0.605
age + PLR	0.702 (0.631–0.773)	0.000	0.722 (0.658–0.786)	0.000
age + NLR	0.711 (0.639–0.784)	0.000	0.723 (0.658–0.788)	0.000
age + MLR	0.709 (0.640–0.777)	0.000	0.720 (0.657–0.783)	0.000
age + FIB	0.712 (0.642–0.783)	0.000	0.726 (0.662–0.791)	0.000
age + ALB	0.700 (0.627–0.772)	0.000	0.707 (0.641–0.772)	0.000
age + GLOB	0.698 (0.629–0.767)	0.000	0.708 (0.645–0.771)	0.000
age + AGR	0.703 (0.634–0.772)	0.000	0.720 (0.657–0.783)	0.000
age + PNI	0.703 (0.634–0.773)	0.000	0.722 (0.658–0.785)	0.000
PLR + NLR	0.610 (0.530–0.689)	0.008	0.607 (0.538–0.677)	0.003
PLR + MLR	0.509 (0.435–0.584)	0.819	0.507 (0.441–0.574)	0.842
PLR + FIB	0.594 (0.518–0.670)	0.023	0.614 (0.545–0.683)	0.002
PLR + ALB	0.504 (0.426–0.582)	0.926	0.504 (0.435–0.573)	0.921
PLR + GLOB	0.539 (0.461–0.616)	0.349	0.522 (0.452–0.592)	0.547
PLR + AGR	0.535 (0.460–0.611)	0.389	0.533 (0.466–0.600)	0.364
PLR + PNI	0.528 (0.453–0.602)	0.504	0.520 (0.452–0.588)	0.589
NLR + MLR	0.569 (0.490–0.648)	0.096	0.559 (0.490–0.629)	0.105
NLR + FIB	0.604 (0.530–0.677)	0.012	0.618 (0.549–0.686)	0.001

Variable	G4/GBM		G4 IDH-wt	
	AUC (95%CI)	P-value	AUC (95%CI)	P-value
NLR + ALB	0.582 (0.503–0.661)	0.047	0.577 (0.506–0.647)	0.036
NLR + GLOB	0.578 (0.500-0.657)	0.058	0.559 (0.490–0.627)	0.108
NLR + AGR	0.580 (0.502–0.658)	0.053	0.568 (0.500-0.636)	0.063
NLR + PNI	0.561 (0.484–0.637)	0.141	0.552 (0.483–0.620)	0.157
MLR + FIB	0.600 (0.526–0.674)	0.015	0.615 (0.547–0.684)	0.002
MLR + ALB	0.515 (0.441–0.590)	0.708	0.506 (0.439–0.573)	0.864
MLR + GLOB	0.548 (0.472–0.625)	0.241	0.524 (0.455–0.592)	0.515
MLR + AGR	0.533 (0.458–0.609)	0.420	0.516 (0.449–0.584)	0.654
MLR + PNI	0.518 (0.444–0.593)	0.656	0.502 (0.434–0.569)	0.965
FIB + ALB	0.596 (0.519–0.672)	0.020	0.616 (0.547–0.686)	0.001
FIB + GLOB	0.593 (0.518–0.668)	0.024	0.603 (0.535–0.672)	0.005
FIB + AGR	0.595 (0.520–0.670)	0.022	0.611 (0.543–0.680)	0.002
FIB + PNI	0.612 (0.537–0.687)	0.007	0.623 (0.554–0.692)	0.001
ALB + GLOB	0.542 (0.465–0.620)	0.305	0.524 (0.454–0.593)	0.519
ALB + AGR	0.540 (0.462–0.618)	0.333	0.521 (0.450–0.591)	0.573
ALB + PNI	0.560 (0.482–0.639)	0.144	0.541 (0.472–0.610)	0.261
GLOB + AGR	0.545 (0.466–0.623)	0.279	0.525 (0.455–0.596)	0.488
GLOB + PNI	0.552 (0.475–0.629)	0.207	0.543 (0.475–0.611)	0.239
AGR + PNI	0.536 (0.461–0.610)	0.387	0.529 (0.461–0.596)	0.433

Discussion

Although the current pathological diagnosis of gliomas grading was the gold standard, it needed to be confirmed after surgery. For the diagnosis of HGGs grading, we need a method of preoperative prediction to guide surgical strategies and treatment more accurately. Previous studies had indicated that inflammation, including NLR, PLR, LMR, FIB, ALB, AGR and PNI had the predictive and diagnostic value for the grading and prognosis of gliomas^{8, 10–12}. Our research mainly analyzed the diagnostic value of preoperative hematological indicators related to inflammation, coagulation and nutrition in the classification and IDH molecular subtypes of HGGs. In addition, we explored their correlation with age,

gender, pEPI, pKPS in different grade of HGGs. Furthermore, we evaluated their levels in IDH molecular subtypes of HGGs and different grade of HGGs.

The results of this study showed that the higher grade gliomas had higher levels of NLR, MLR, FIB, ALB and GLOB, and lower levels of PLR, AGR and PNI, respectively. This result was consistent with the previous related studies^{11, 13}, and declared more severe inflammation and worse nutritional status were present in higher grade gliomas. However, they were not statistically significant in the different grade of HGGs except FIB, which was contrary to these researches^{11, 13}. The possible reason for this was that there were too few G3 gliomas included in this study. Only the levels of NLR and FIB were associated with IDH mutation groups, indicating that there was a link between inflammation and coagulation¹⁴. Furthermore, we further analyzed the relationship between hematological indicators and IDH mutation subgroups, and found that only FIB had a significant difference between G4 IDH-wt and G3 IDH-mut or G4 IDH-mut. Previous study had shown that the immune response of the tumor microenvironment was more susceptible to the modulation of IDH mutation status in lower-grade gliomas¹⁵. This result suggested that there may be a connection between systemic and local inflammation and coagulation and immune regulation.

In our study, the levels of FIB and GLOB were positively correlated with age, and the levels of ALB, AGR and PNI were negatively correlated in the HGGs classification. However, the inflammation indicators were oppositely correlated in the HGGs grading groups. The reason for this result was the levels of FIB may reflect the critical function of FIB in an inflammatory tumor microenvironment that favors tumor progression⁶. When comparing hematological indicators in gender, we found that NLR and FIB had higher levels in men. Moreover, the level of PNI had the same result, consistent with the previous study¹⁶. Different from other research results^{13, 17}, the levels of PLR in our research were opposite in this comparison. There was no significant difference in the levels of hematological indicators in the pKPS and pEPI subgroups.

In the analysis of the diagnostic value of hematological indicators, single and combined indicators were explored, respectively. The level of FIB had the highest diagnostic value among the 8 hematological indicators in distinguishing GBM and G4 IDH-wt from HGGs. Our results were different from studies that found that NLR was the best diagnostic indicator, and they studied the ability of hematological indicators in distinguish GBM and G4 IDH-wt from different diseases and three grade of gliomas^{11, 13}. In addition, as for combined indicators, age + PNI had the highest diagnostic value in the research of Wang et al¹³, however, the best combined diagnostic index was NLR + MLR in the study of Zheng et al¹¹. The difference from them was that our research distinguished GBM and G4 IDH-wt from HGGs, and age + FIB had the highest diagnostic value among all the combined indicators. It was worth noting that grade Ⅱ and grade Ⅲ gliomas were included in their study, respectively.

This mechanism was temporarily unclear between hematological indicators and the grade of gliomas. Previous studies had declared that immune suppression induced by neutrophils may promote the

progression of glioma, and some T lymphocyte subsets may inhibit it by inducing cytotoxic cell death and cytokine production^{18, 19}. Shao et al confirmed that platelet activation contributes to tumor angiogenesis, destroys extracellular matrix and releases adhesion molecules to promote cancer cell proliferation and metastasis, thus proving the importance of platelet activation in tumorigenesis²⁰. The correlation between nutritional indicators and cancer may be related to the antioxidant effect of albumin on carcinogens such as nitrosamines and aflatoxins, and the levels of GLOB may be related to the progression and metastasis of certain cancers^{21, 22}. Moreover, albumin reflected the state of systemic inflammation by down-regulating tumor necrosis factor alpha and interleukin 6²³. Plasma fibrinogen was an important factor in inflammation and cancer expression, and had been demonstrated in vitro studies playing an important role in tumor cell proliferation, epithelial-mesenchymal transition, invasion, angiogenesis and hematological dissemination of tumor cells²⁴⁻²⁶.

Our current research has some limitations. Firstly, this study may have a selection bias because it is a single center and retrospective analysis. Secondly, the sample size of the study included in this study was small, especially G3 gliomas, and grade \geq and grade \leq gliomas were not included. In addition, we did not have data for O6-methylguanine-DNA methyltransferase (MGMT) methylation status and telomerase reverse transcriptase (TERT) promoter status, both of which play an important role in patients with gliomas²⁷. Therefore, multi-center prospective studies, further molecular pathology experimental analyses, large sample researches of HGGs are required.

Conclusions

To sum up, the results of our research indicate that FIB plays an important role in the classification and IDH molecular subtypes of HGGs. FIB and age + FIB had the highest diagnostic value for distinguishing GBM and G4 IDH-wt from HGGs in single and combined blood indicators, respectively. Moreover, higher grade gliomas had lower levels of nutritional indicators.

Declarations

Availability of data and material

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

Authors' contributions

X.J.: conception, manuscript writing, data acquisition and analysis. X.W., F.Y., and Y.Z.: conception and critical review. Y.W. and S.W: data acquisition. All authors proofread and approved the manuscript.

Conflicts of interest/Competing interests The authors declare that there is no conflict of interest or competing interests.

Ethics approval Approval of the Ethical Committee from the First Affiliated Hospital of Zhengzhou University was taken for this retrospective study.

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Figures

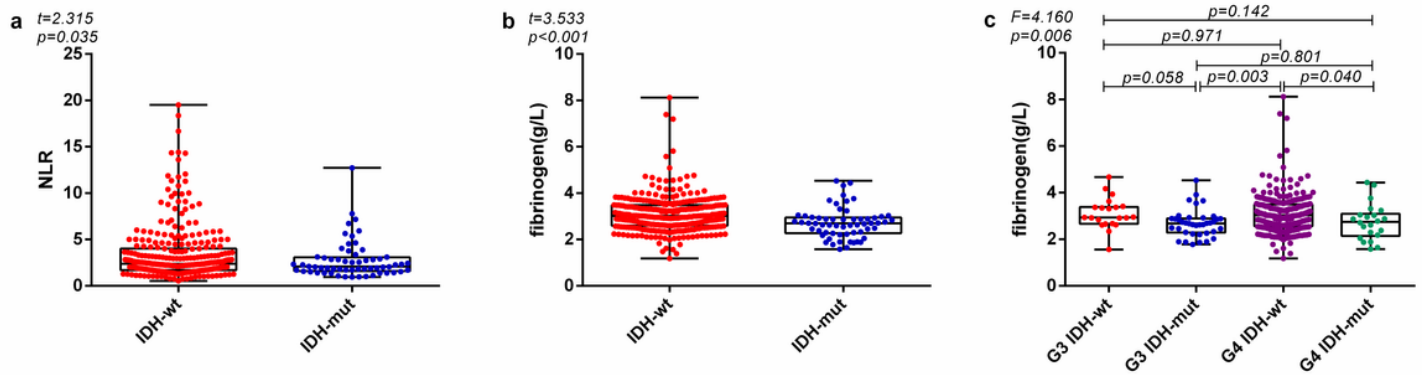


Figure 1

The comparison of hematology indexes in IDH groups and subgroups. (A)The comparison of NLR in different IDH groups; (B)The comparison of FIB in different IDH groups; (C)The comparison of FIB in different IDH subgroups.

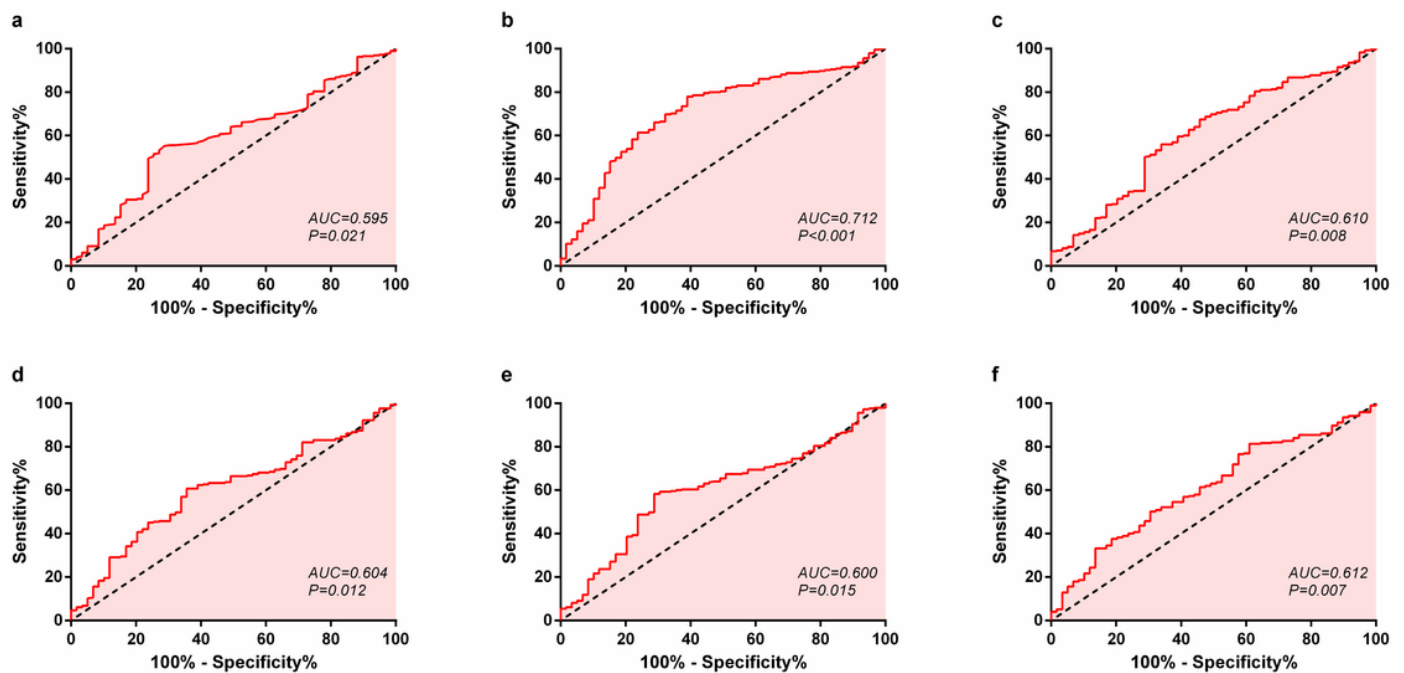


Figure 2

The diagnostic value of hematology indicators in distinguishing GBM from HGGs. the AUC of FIB(a), age+FIB(b), PLR+NLR(c), NLR+FIB(d), MLR+FIB(e), FIB+PNI(f).

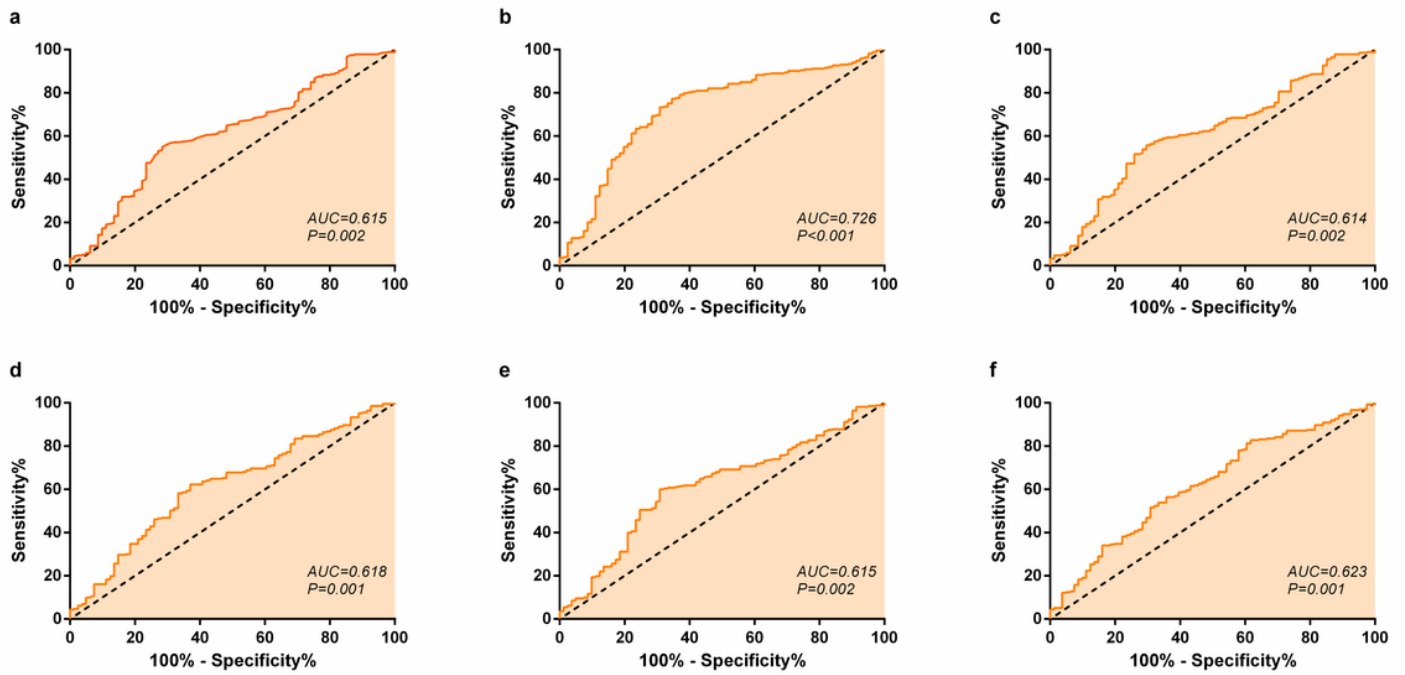


Figure 3

The diagnostic value of hematology indicators in distinguishing G4 IDH-wt from HGGs. the AUC of FIB(a), age+FIB(b), PLR+NLR(c), NLR+FIB(d), MLR+FIB(e), FIB+PNI(f).

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