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Prognostic value of preoperative neutrophil to lymphocyte ratio is superior to systemic immune inflammation index for survival in patients with Glioblastoma

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ABSTRACT

Objective: This study evaluated the prognostic value of preoperative neutrophil to lymphocyte ratio(NLR), platelet to lymphocyte ratio(PLR), and systemic immune inflammation index(SII) in patients with Glioblastoma (GBM).

Patients and methods: The peripheral blood indexes and other clinical data were obtained within 1 week before surgery. Receiving operating characteristics(ROC) curve was used to find the optimal cut-off value of NLR, SII and PLR, respectively. Kaplan-Meier (KM) analysis and cox proportional hazard models were used to assess the prognostic value of SII and other indexes.

Results: The optimal cut-off values for NLR, SII, PLR were 2.7, 718, 87, respectively. The high NLR group has a higher proportion of Ki67 expression than the low NLR group. KM survival curves revealed that patients with high NLR (> 2.7) or high SII (> 718) had worse overall survival. Multivariable Cox analysis revealed NLR, adjuvant therapy and age were prognostic factors for overall survival(OS). The AUC area (the area under the receiver operating characteristics curves) of the NLR was higher than the area of PLR or SII.

Conclusion: Preoperative NLR was superior to SII in prognostic value of patients with glioblastoma.

1. Introduction

Gliomas are the most common primary brain tumors in adults. And it involves in almost 80% of primary brain tumors [1]. In China, gliomas account for approximately 50% of the CNS malignant tumors [2]. Glioblastoma(GBM), the most malignant type of gliomas, the 5-years survival rate of GBM is only about 5% [3]. Some immune inflammatory indexes are associated with prognosis of patients with GBM,such as neutrophil-to-lymphocyte ratio(NLR) or platelet-to-lymphocyte ratio(PLR) [4,5]. An increased preoperative platelet count is correlated with worse survival in patients with GBM has been reported [6]. And platelet counts usually increases in patients with GBM within the months before diagnosis [7]. Recently, the systemic immune inflammation index(SII) which combines NLR and platelet, has emerged as a new inflammatory marker. SII has been shown to be associated with the prognosis of various tumors,such as esophageal squamous cell carcinoma and lung cancer [8,9]. A study shows that the value of SII of high-grade gliomas(HGG) is significantly higher than low-grade gliomas(LGG) [10]. In another study, elevated SII levels were present in high-grade gliomas group than that in low-grade gliomas group. But in multivariate analysis, SII was not closely related to OS of patients with gliomas [11]. However, whether SII is associated with the prognosis of patients with GBM has not been reported. The aim of our study is to reveal the prognostic value of SII in patients with GBM and to explore whether SII is superior to NLR or PLR in prognostic value.

2. Patients and methods

2.1. Study subjects

A total of 192 patients with GBM from Qianfoshan Hospital from January 2006 to July 2018 were retrospectively evaluated. The following eligibility criteria were considered in this article: first pathologically proven diagnosis of GBM, without previous anti-tumor therapies; no inflammation and no history of hematological or autoimmune disease; and no other primary tumors. All demographic and clinical

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data of the enrolled patients were collected from the electronic medical record system of Qianfoshan Hospital.Peripheral blood samples of the enrolled patients were collected within 1 week before surgery. The OS was defined as the time between the date of surgery and the date of death or the date of last follow-up. The index of SII was defined as platelet count × neutrophil count/lymphocyte count. NLR was calculated as absolute neutrophils count divided by absolute lymphocyte count. PLR was calculated as absolute platelet count divided by absolute lymphocyte count.

2.2. Statistical analysis

The Student's *t*-test was used for normally distributed data, and the Chi-square test was used to evaluate non-normally distributed data. Receiving operating characteristics(ROC) curve was used to find the optimal cut-off values of these three indexes. The OS of all the patients was estimated using Kaplan-Meier methods, and log-rank analysis was used to compare survival curves between different subgroups. Univariate and multivariate cox regression analysis was used to find prognostic factors for OS.And in multivariate regression analysis, the forward step-wise method was used to analyze prognostic factors. All the statistical tests were two sided, and $P < 0.05$ was considered statistically significant, and confidence intervals(CI) were calculated at the 95% level.All the data was analyzed using SPSS(version 22.0, IBM). Comparison of AUC areas among these indexes using MedCalc and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 192 patients (79 females and 113 males) with histologically confirmed GBM were enrolled in the present study (Table 1). The median follow-up was 57.5 months (range2-151months). And there were 104 cases received adjuvant therapy including radiotherapy or chemotherapy after surgery. According to the AUC curve, the optimal cut-off values for NLR, SII, PLR were 2.7,718 and 87, respectively ((sensitivity and specificity: 0.56 and 0.82 for NLR, 0.45 and 0.90 for SII, 0.844 and 0.51 for SII, respectively). According to the cut-off value of these indexes, all the cases were divided into the high and the low subgroup respectively (Table 1). No significant differences were found between the low and high subgroups in terms of age, sex, location, MGMT and IDH-1 status (Table 1). The high NLR group has a higher proportion of KI67 expression than the low NLR group ($P < 0.05$).

3.2. Kaplan-Meier analyses

The OS of patients was significantly longer in the low NLR group compared with that in the high NLR group ($P = 0.002$, Fig. 1A). Similarly, there was a significantly better OS in patients in low SII group than patients in high SII group ($P = 0.006$, Fig. 1B). However, there was no significant difference in OS between the PLR subgroups ($P = 0.057$, Fig. 1C).

3.3. Univariate and multivariate analysis

In univariate analysis, age, adjuvant therapy, NLR, SII were associated with OS of patients (Table 2). However, multivariate analysis revealed that only age, adjuvant therapy, NLR were significant prognostic factors for OS ($P < 0.05$).

3.4. Comparison of ROC curves of this three indexes

The prognostic value of each index was evaluated by comparing the AUC area (Fig. 2, Table 3).The AUC area was 0.683, 0.675, 0.656 for NLR, SII, PLR, respectively. The index of NLR had a higher AUC area than that of the index of SII or PLR.However, there were no statistical differences between the AUC areas of this three indexes (Table 3).

4. Discussion

GBM is a malignant tumor with poor prognosis.The 2-year survival rate for patients with GBM is only about 30% [12]. Previous studies show a strong linkage between inflammation and cancer [13]. NLR has been shown to be associated with the prognosis of various solid tumors,including GBM [13,14]. NLR was differed in the different grades of gliomas and were highest in patients with GBM [15]. NLR was correlated with gliomas grading and was an factor for survival of patients with GBM [16]. There was no significant difference on the IDH1 mutation statuses between the high NLR group and the low NLR group [16]. Wang et al showed that both preoperative NLR (cutoff value = 4) and PLR (cutoff value = 175) were prognostic indexes for patients with GBM.But there was no significant correlations between NLR or PLR and IDH-1 mutation statuses [5]. However, Han et al showed that only pre-

Table 1
Clinical and molecular characteristics in all the patients.

Variables	NLR		p	SII		p	PLR		P
	HIGH	LOW		HIGH	LOW		HIGH	LOW	
Age(year)	55.01 ± 13.53	51.85 ± 14.09	0.118	55.57 ± 13.46	51.95 ± 14.02	0.084	54.49 ± 13.51	49.54 ± 14.52	0.231
Sex									
female	32	47	0.380	25	54	0.300	60	19	0.799
male	53	60		44	69		84	29	
Adjuvant therapy									
yes	43	61	0.375	36	68	0.678	79	25	0.738
no	42	46		33	55		65	23	
Location									
left	44	49	0.700	36	57	0.568	71	22	0.500
right	37	53		31	59		65	25	
bilateral	4	5		2	7		8	1	
Ki-67									
< 30%	14	33	0.014	12	35	0.244	32	15	0.110
≥30%	34	30		23	41		52	12	
MGMT									
methylation	16	21	0.540	13	24	0.801	14	10	0.472
unmethylation	10	18		9	19		10	11	
IDH-1									
mutant	14	24	0.587	12	26	0.889	26	12	0.878
wild-type	13	17		9	21		20	10	

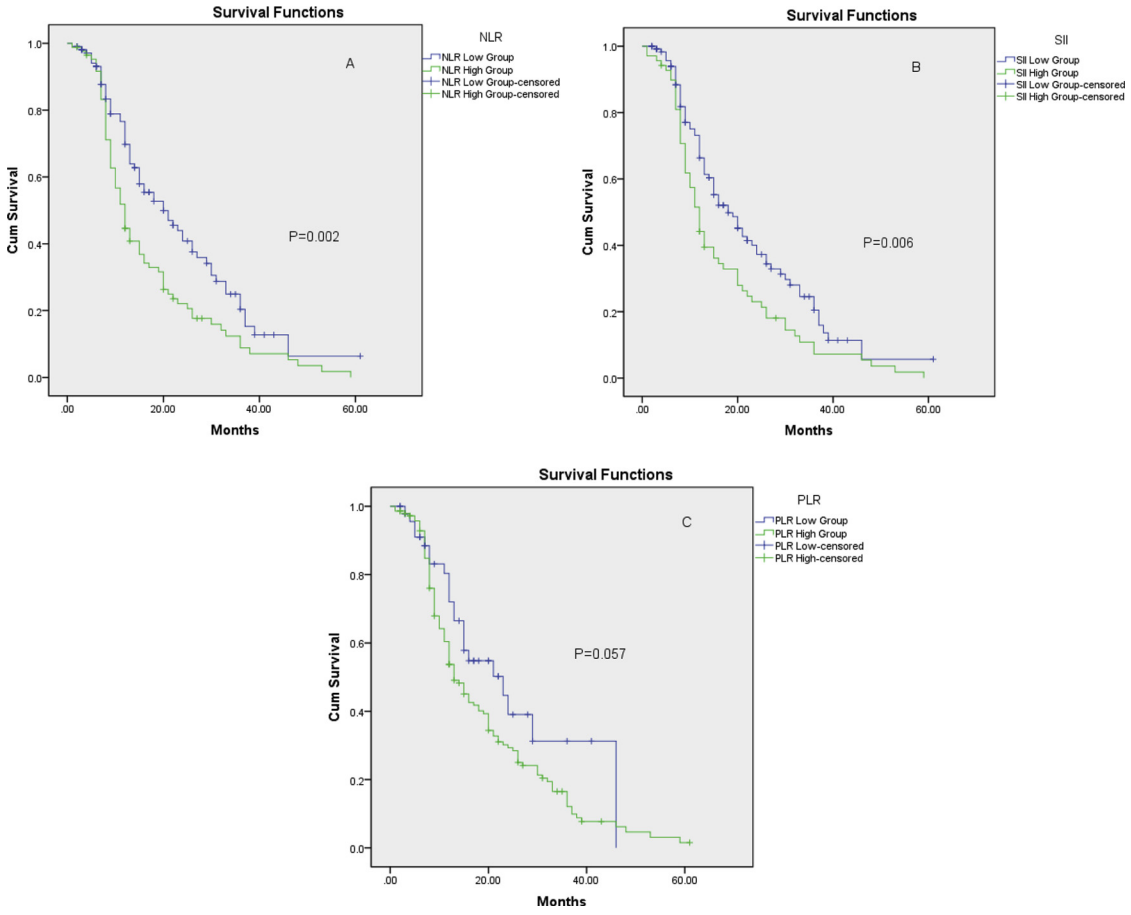

Fig. 1. Kaplan-Meier survival curves for OS in all the patients (A)NLR; (B) SII; (C)PLR.

Table 2
Univariate and Multivariate analyses of OS for all patients.

Variables	Univariate			Multivariate		
	HR	95 % CI	P value	HR	95 % CI	P value
Age (≥60 vs <60)	1.783	1.264–2.515	0.001	0.622	0.440–0.881	0.007
Sex(male vs female)	1.051	0.751–1.472	0.770			
Location						
Left						
Right	2.726	1.155–6.438	0.022			
Bilateral	2.230	0.942–5.275	0.068			
Adjuvant therapy(yes vs no)	0.555	0.394–0.781	0.001	2.492	1.065–5.833	0.035
NLR (>2.7 vs ≤2.7)	1.650	1.182–2.304	0.003	0.637	0.454–0.894	0.009
PLR(>87 vs ≤87)	1.531	0.969–2.419	0.068			
SII(>718 vs ≤718)	1.570	1.124–2.193	0.008			

treatment NLR (cutoff value = 4) was a prognostic index for patients with GBM. Pre-treatment PLR (cutoff value = 135) was not significantly correlated with OS in multivariate analyses.This article also showed that pre-treatment NLR was superior to PLR as a predictor of survival in patients with GBM. And in this study, NLR was not correlate with MGMT promoter methylation status [4]. Our study showed that NLR was not correlate with MGMT promoter methylation statuses or IDH-1 statuses (Table 1). Liang et al demonstrated that SII can be used in predicting gliomas grading.And Liang also showed the high-SII group had a significantly higher Ki-67 index than that of the low-SII group [10]. Kaya et al showed that only NLR was significantly correlated with OS in multivariate cox analysis. PLR was not a a predictor of OS [14]. PLR was not a a predictor for OS in multivariable cox analysis in our article (Table 2). Xu et al demonstrated that male patients with high grade gliomas had significantly higher NLR and SII than male patients with low grade gliomas. Xu also showed NLR, PLR, SII were not prognostic indicators in multivariate regression analysis [11]. Lopes et al showed that there was no significant correlations of NLR or PLR with OS for patients with GBM in multivariate analysis. However, preoperative NLR correlated with worse progression-free survival (PFS). Moreover, tumor location, systemic therapy and preoperative KPS were prognostic indicators for OS in patients with GBM [17].

The mechanisms of the prognostic value of these inflammatory indexes remains unclear in GBM.A recent study showed that elevated NLR was significantly associated with high neutrophils infiltration and low CD3 + T-cell infiltration into tissue [4]. Previous study showed that neutrophils infiltration can stimulate tumor angiogenesis and metastasis [18]. And there is a positive correlation between grade and the extent of neutrophil infiltration in gliomas [19]. In addition, increased of neutrophils will promotes tumor progression and treatment

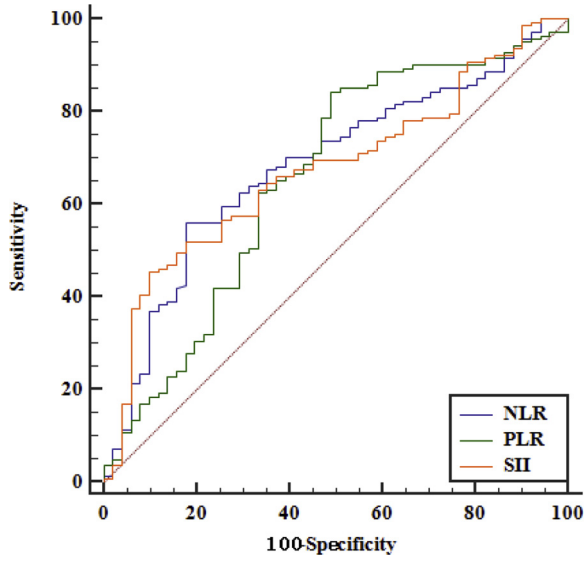

Fig. 2. Comparisons of the AUC areas of these index for OS.

Table 3
Comparison of AUC area for OS prediction.

Variables	AUC area	Z	P value
NLR vs SII	0.683vs 0.675	0.380	0.704
NLR vs PLR	0.683 vs 0.656	0.527	0.598
SII vs PLR	0.675 vs 0.656	0.444	0.657

resistance [20]. The tumor infiltrating lymphocytes, which regulatory T cells in the micro-environment, may suppress immune responses [21]. Platelets that released various growth factors including vascular endothelial growth factor(VEGF) and platelet derived growth factor (PDGF) to promote tumor growth and migration [22]. Our study found the high NLR group has a higher proportion of Ki-67 expression ratio, and Ki-67 is a nuclear protein that is correlated with cellular proliferation and survive time in patients with gliomas [23].

In the present study, we assessed the prognostic value of NLR, PLR and SII in GBM, taking into account IDH, MGMT, ki-67 status. Our article showed that NLR may serve as prognostic markers for patients with GBM.NLR is superior to SII or PLR in prognostic value for patients with GBM. However, this article has some limitations.First, it is a retrospective study and has a limited number of patients. Second, it is a single center study.Therefore, larger sample studies still need to be performed to confirm these findings.

5. Conclusions

The results of this study suggest that preoperative NLR was superior to SII in prognostic value of patients with GBM. These results should be carefully evaluated in future prospective studies.

Conflict of interest

The authors declare no conflicts of interest.

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