Observational Study

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Association between systemic immune-inflammation index (SII) and survival outcome in patients with primary glioblastoma

Chao Yang, MD[a], Zhi-Qiang Li, MD[a], Jie Wang, MD[a,b,*]

Abstract

The purpose was to evaluate the prognostic value of systemic immune-inflammation index (SII) in glioblastoma patients. A total of 100 patients were retrospectively analyzed. We performed Kaplan–Meier and Cox regression analyses to determine the prognostic significance of SII. A nomogram was constructed by incorporating independent prognostic variables. The predictive accuracies of nomograms were evaluated by Harrell concordance index (c-index) and receiver operating characteristic curve analysis; the clinical benefit was evaluated by decision curve analysis. A high SII (>510.8×10^9 cells/L) (hazard ratio = 1.672, P = .034) and neutrophil count (>3.9×10^9 cells/L) (hazard ratio = 1.923, P = .009) were independently related with poor outcome in glioblastoma patients based on Cox analysis. The nomogram incorporating SII showed a good predictive accuracy (c-index = 0.866). Preoperative SII and neutrophil count are potential prognostic biomarkers for overall survival in glioblastoma patients and the nomogram model that integrated the SII may be used to facilitate a comprehensive preoperative survival evaluation.

Abbreviations: GBM = glioblastoma, IDH = isocitrate dehydrogenase, KPS = Karnofsky performance status, MGMT = O6-methylguanine-DNA methyltransferase, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, SII = systemic immune-inflammation index.

Keywords: glioblastoma, nomogram, prognosis, survival, systemic immune-inflammation index

1. Introduction

Glioblastoma (GBM) is the most common malignant tumor type in the central nerve system (CNS).[1] The outcome of patients with GBM remains poor, although great advances had been achieved in recent years, including maximum safe resection, chemoradiotherapy and tumor-treating fields.[2,3] Therefore, it is necessary to identify effective biomarkers with diagnostic or prognostic value in patients with GBM. Molecular biomarkers, such as isocitrate dehydrogenase 1 (IDH 1) and O6-methylguanine-DNA methyltransferase (MGMT) were firstly introduced to the classification and evaluation of prognosis in patients with GBM in 2016 revision World Health Organization classification of CNS tumors, which deepened our understanding of genome biology and prognosis in glioma and the prognostic value of molecular markers in patients with glioma had been demonstrated.[4] However, disadvantages in cost and complex test technology had limited their widespread application, moreover, these molecular markers can only be obtained postoperatively. Discovering and creating biomarkers with effectiveness and low cost is required to accomplish this goal that determine which patients should be treated (prognostic biomarkers) and which treatment is most likely to be effective (predictive biomarkers).

A biologic link between chronic inflammation and cancer risk has long been appreciated.[5] The existence of hematological peripheral inflammatory markers, which could be easily obtained from blood tests routinely, has been investigated as a prognostic factor in a number of types of malignant tumors.[6–8] Neutrophil, lymphocyte and platelet were the most common cell types in peripheral blood and the levels of them were associated with the body's immune inflammation status. The prognostic significance of blood cells and their corresponding ratios, like neutrophil-to-lymphocyte ratio (NLR),[9] lymphocyte-to-monocyte ratio [10] and systemic immune-inflammation index (SII)[11] had been identified in various types of cancers. NLR had been reported to correlate with survival outcome in many cancers, including breast cancer,[12] colorectal cancer,[13] prostate cancer,[14] renal cell carcinoma,[8] and gliomas.[9] SII, a novel inflammatory biomarker calculated by the following formula: platelet count × neutrophil count/lymphocyte count, has been reported to be associated with worse survival in many patients with malignant tumors, including breast cancer,[15] hepatocellular carcinoma[16] and glioma.[17] A recent study reported that a higher SII predicted a worse outcome in glioblastoma patients.[18] However, the prognostic role of SII in patients with GBM is still controversial and the numbers of relevant studies are small.

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The authors have no conflicts of interest to disclose.

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

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Nomograms are commonly used tools in oncology and provide an estimated numerical prognosis for each individual patient by integrating diverse prognostic and determinant variables.

The purpose of the present study was to explore the independent prognostic significance of SII in patients with GBM and a nomogram model was constructed to predict survival probability.

2. Materials and methods

2.1. Study cohort

From January 2016 to June 2020, we incorporated a total of 100 adult GBM patients.

1.2.1. Inclusion criteria were as follows.

(i) Age at diagnosis was over 18 years.
(ii) All the diagnosis were pathologically confirmed; and.
(iii) Data of clinical characteristics and preoperative peripheral blood routine examination can be obtained.

2.2.1. Exclusion criteria were as follows.

(i) Patients receiving preoperative radiotherapy and/or chemotherapy (including corticosteroids).
(ii) Patients accompanied with a prior history of malignant tumor
(iii) Recurrent GBM; or.
(iv) Patients endured perioperative death.

All procedures follow the Helsinki Declaration.[19] The end date of follow-up was September 31, 2021.

2.2. Ethics approval

The present study had gained approval from the Ethics Committee of Zhongnan Hospital of Wuhan University (No. 2019048).

2.3. Data collection

We collected data concerning demographic and clinical features, clinical outcome, including sex, age, locations of tumor, the characteristics of IDH1 mutation and MGMT promoter methylation, preoperative Karnofsky performance status (KPS), the extent of resection [gross total resection (GTR) = 100%, subtotal resection (STR) < 100%], and complete postoperative chemoradiotherapy regimen. Preoperative data of RDW and platelets count were also reviewed. Using these data, the SII was calculated (platelet × neutrophil/lymphocyte count). Overall survival (OS) was determined as the range between the operation and death with all cause or the endpoint of the last follow-up. Follow-up was conducted by outpatient or cellphone.

2.4. Statistical analysis

The normal distribution of continuous variables is expressed as mean ± standard deviation, and the non-normal distribution is expressed as median and interquartile range (IQR) and analyzed by nonparametric tests or t tests. Categorical variables are described as frequency (percentages) and compared between groups using chi-square tests. The best cutoffs of prognostic markers were obtained through X-tile using minimum *P* value method. (version3.6.1), or receiver operating characteristic curve. Kaplan–Meier survival curves were performed and were analyzed by the log-rank test (R survminer package) to assess the prognostic value of hematological markers. Independent prognostic significance of these markers was evaluated by univariate as well as multivariate Cox proportional hazard regression analyses (R survival package). Variables with independent value were included to establish nomograms to predict the survival rates at 2 years using R rms package. The predictive accuracies of nomograms were evaluated by Harrell concordance index (c-index). All the statistical analysis was performed with R software (version 4.0.2; Institute for Statistics and Mathematics, Vienna, Austria). *P* values were 2-sided and a *P* value of < .05 defined statistical significance.

3. Results

3.1. Clinical characteristics

The demographic characteristics of all the incorporated patients were shown in Table 1. 100 patients (40 females and 60 males) were included in our study, with a mean age of 57.1 years. In patients with GBM, STR was performed in 58.0% patients, and 59.0% received standard chemoradiotherapy regimen postoperatively. The number of patients with IDH1 mutation or MGMT methylation were 4 (4.0%) and 57 (57.0%), respectively.

3.2. Association between hematological indices and OS in GBM patients

Using X-tile software, the optimal cut off value for each peripheral marker were determined. As shown in Figure 1 and Figure S1, Supplemental Digital Content, http://links.lww.com/MD/I520, the cut off values for white blood cell (WBC), neutrophil, lymphocyte, platelet and SII were 6.7, 3.9, 1.9, 258 and 510.8 (10^9 cells/L) respectively. Subsequently, based on the cut-off value of every individual marker, the patients were divided into 2 groups. Survival analysis showed that among the GBM, a higher WBC (*P* = .006), neutrophil (*P* < .001) and SII (*P* < .001) had a worse outcome, whereas those with a higher lymphocyte (*P* = .028) had a better OS (Fig. 2 and Fig. 3). There was no significant association between platelet count with OS (*P* = .074) (Fig. 3). SII (*P* = .034) and neutrophil (*P* = .009) remained independent prognostic significance based on univariate and multivariate analysis in addition to age, KPS, postoperative chemoradiotherapy, and the extent of tumor resection (Table 2). Univariate analysis showed that the WBC and lymphocyte count were significant variables associated with OS, but multivariate analysis did not corroborate this finding.

3.3. Nomograms for predicting OS in GBM patients

According to multivariate regression analysis, a few independent prognostic markers were determined, including age, KPS, standard postoperative chemoradiotherapy, extent of resection and SII. Nomogram was constructed to assess the importance of these variables to predict the 2-year survival probability in patients with GBM (Fig. 4A). In the nomogram, KPS contributed most to the outcome, followed by age, chemoradiotherapy, resection of tumor and SII. The c-index of the nomogram was 0.866. The bootstrapped calibration plot of the nomogram performed well with the ideal model (Fig. 4B). Time-dependent receiver operating characteristic curve analysis also indicated that the nomogram had a high value of area under the curve (area under curve = 0.752) (Fig. 4C). Furthermore, decision curve analysis showed that the nomogram was clinically useful and had better discriminative ability (Fig. 4D).

4. Discussion

Many biological systems and disease processes are closely associated with inflammation, including cancer initiation and progression.[20] There was a correlation between peripheral inflammation status and overall survival in cancer patients,

Table 1

Clinical and pathological characteristics of patients.

Characteristic	SII ≤ 510.8	SII > 510.8	*P* value
n	47	53	
Sex, n (%)			.130
Female	23 (23%)	17 (17%)	
Male	24 (24%)	36 (36%)	
Location, n (%)			.682
Frontal	13 (13%)	13 (13%)	
Multiple	8 (8%)	11 (11%)	
Other	7 (7%)	12 (12%)	
Parietal	7 (7%)	4 (4%)	
Temporal	12 (12%)	13 (13%)	
KPS, n (%)			.001
>60	38 (38%)	25 (25%)	
≤60	9 (9%)	28 (28%)	
Chemoradiotherapy, n (%)			.002
No	11 (11%)	30 (30%)	
Yes	36 (36%)	23 (23%)	
Resection, n (%)			< .001
GTR	29 (29%)	13 (13%)	
STR	18 (18%)	40 (40%)	
IDH1, n (%)			.339
Wildtype	44 (44%)	52 (52%)	
Mutant type	3 (3%)	1 (1%)	
MGMT, n (%)			.774
Yes	28 (28%)	29 (29%)	
No	19 (19%)	24 (24%)	
Age, mean ± SD	57.43 ± 11.02	56.75 ± 11.74	.770

GTR = gross total resection, IDH = isocitrate dehydrogenase, KPS = Karnofsky performance status, MGMT = O^6-methylguanine-DNA methyltransferase, SII = systemic immune-inflammation index, STR = subtotal resection.

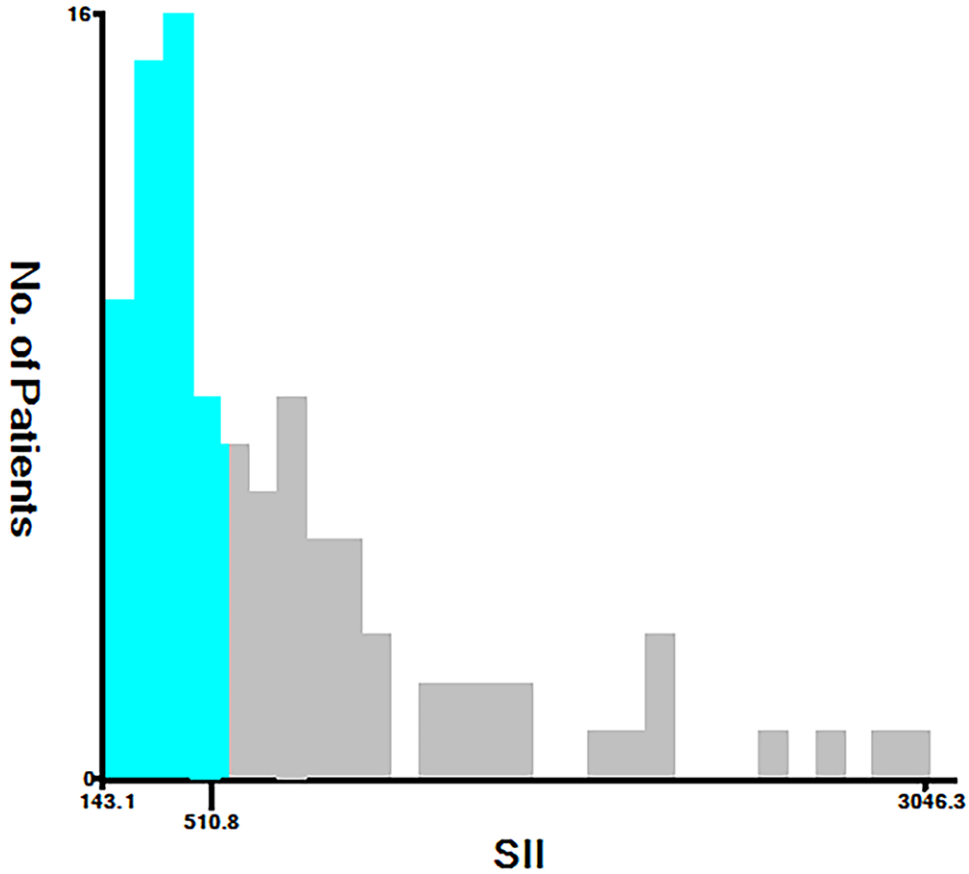

Figure 1. Cut off of SII in patients with glioblastoma. SII = systemic immune-inflammation index.

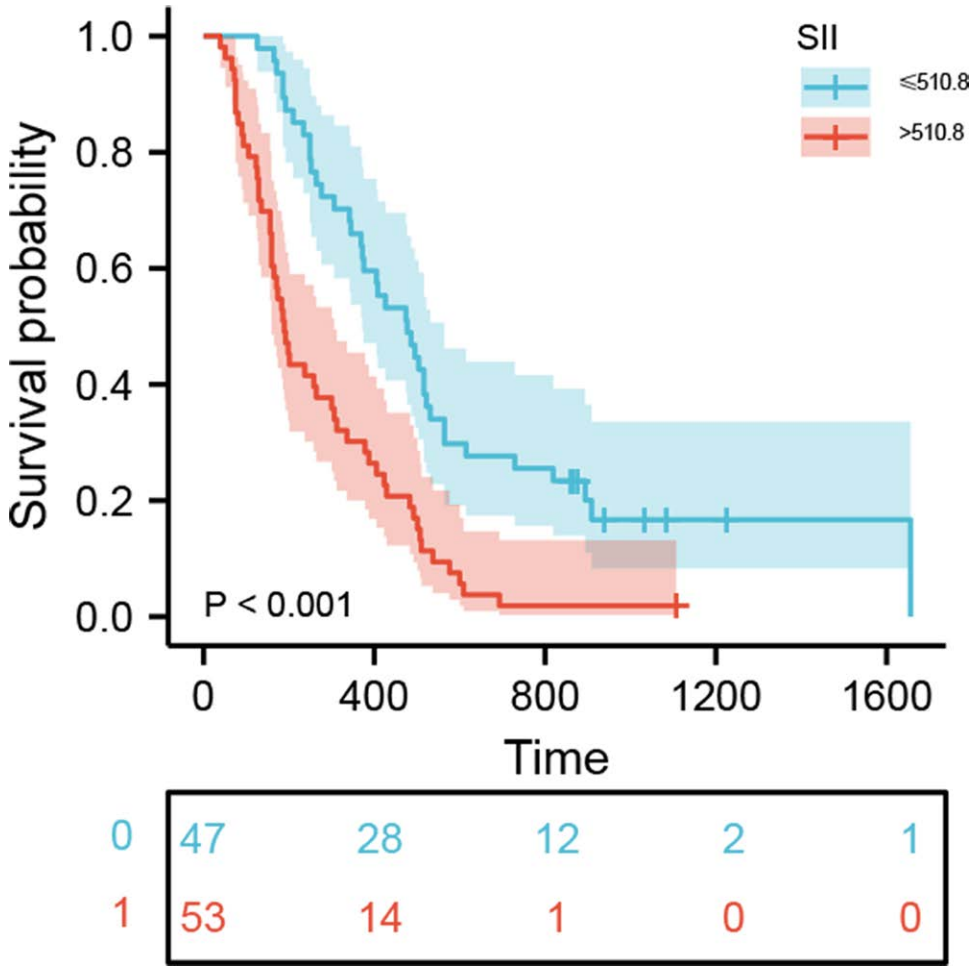

Figure 2. Kaplan–Meier survival curves of GBM patients based on the cutoff values of SII. GBM = glioblastoma, SII = systemic immune-inflammation index.

including those with gliomas. In the present study, we found that a higher value of SII and neutrophil significantly correlated with worse outcome in patients with GBM and a nomogram integrating SII had a better predictive accuracy and discrimination for estimating OS.

Systemic inflammatory reactions, including thrombocytosis, leukocytosis, neutrophilia or lymphocytopenia, have recently gained attention as indicators of poor prognosis or predictors of poorer treatment response in cancer patients. In line with these studies, our present study also identified the independent prognostic value of neutrophil in patients with GBM, however, there was no significant association between lymphocyte or platelet count with OS.

Previous studies have showed the significance of higher SII in predicting higher grade or stage and worse outcome in many kinds of cancers.[21] Lei et al[22] demonstrated that SII can be used as a predictor of higher pathological grade in young premenopausal endometrial cancer patients. The prognostic value of SII had also been identified in various types of cancers, including hepatocellular carcinoma[16] for the first time, small cell lung cancer[7] and glioma.[18] However, a study by Ylmaz et al[17] reported that SII could not be used as an independent biomarker for both PFS and OS in patients with GBM.

The mechanisms by which NLR and lymphocyte-to-monocyte ratio affect prognosis have not been fully elucidated. Patients with malignant tumors often have neutrophil and relative lymphopenia, mainly due to overproduction of tumor-cell-derived granulocyte colony stimulating factor, it has the potential to transfer bone marrow hematopoiesis from the lymphocyte lineage to the granulocyte lineage.[23,24] Tumor growth factor β secreted by tumor cells, had the potential to induce the activation of neutrophils with a preneoplastic phenotype.[25] Activated neutrophils can produce and secrete various molecules, such as vascular endothelial growth factor[26] and matrix metalloproteinases[27] to promote tumor progression, metastasis, and angiogenesis. The levels of platelets often elevated in patients with malignant tumors and the elevated platelets may accelerate the proliferation, angiogenesis and dissemination of tumor cells through some released factors, like vascular endothelial growth factor and platelet-derived growth factor (PDGF).[28,29]

Oncology research has widely used nomograms as visual calculating scale models as they provide numerical estimates of clinical events in individuals.[30] Age, KPS, chemoradiotherapy, the extent of tumor resection, and SII were independent prognostic markers that were included as variables for nomograms in our current study based on multivariate analysis and the nomogram showed fairly good accuracy for prognostic prediction and clinical benefits.

There are also some limitations in our present study. First, the retrospective nature of our study may have led to selection bias. Second, we included a relatively small number of GBMs in this study. Therefore, prospective and well-designed studies with more samples are needed to clarify the results.

5. Conclusion

Preoperative SII and neutrophil count are potential prognostic biomarkers for OS in patients with GBM and nomogram

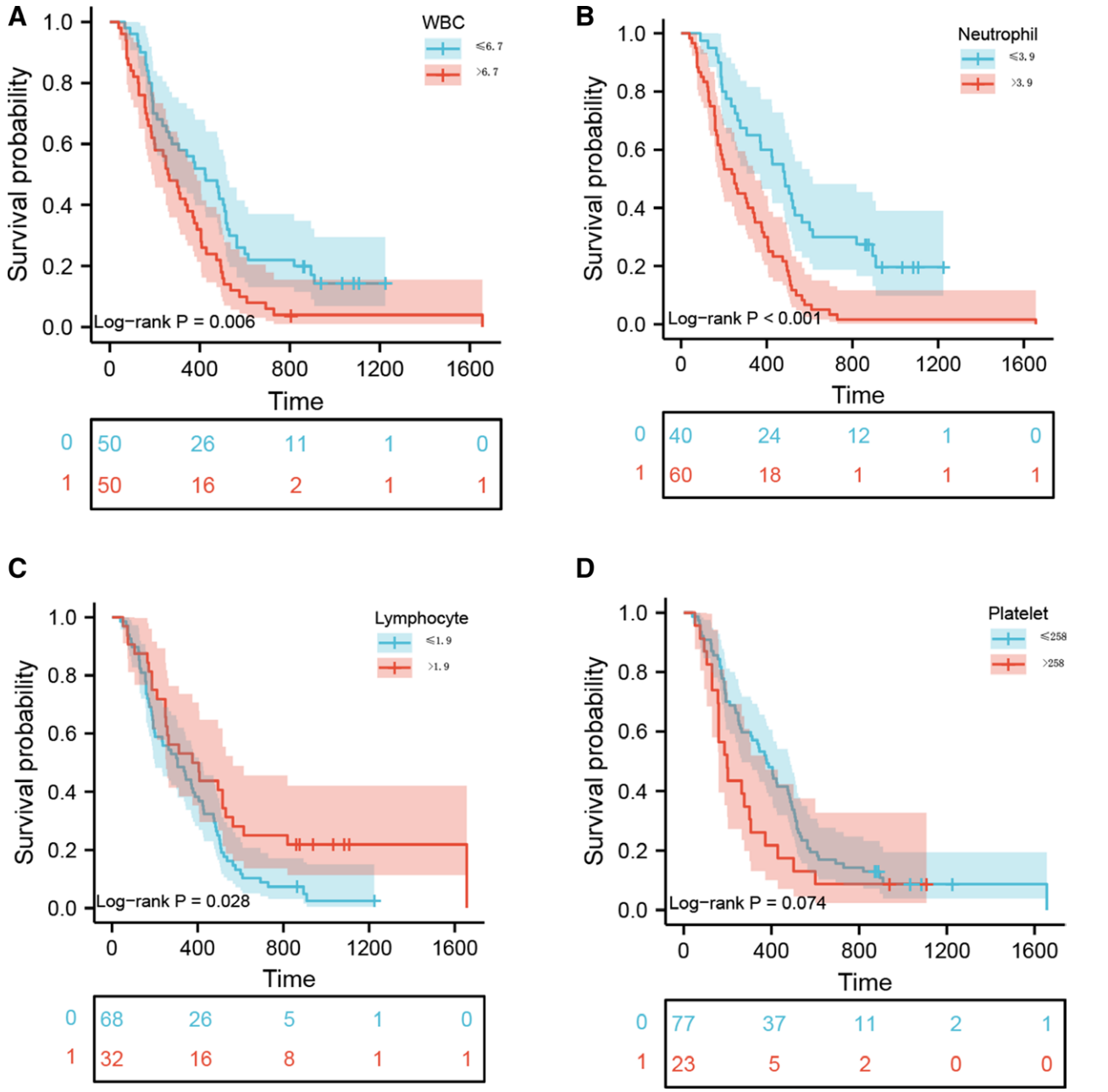

Figure 3. Kaplan–Meier survival curves of GBM patients based on the cutoff values of WBC (A), neutrophil (B), lymphocyte (C), and platelet (D). GBM = glioblastoma.

models that integrate the SII may be used to facilitate a comprehensive preoperative survival evaluation.

6. Contribution to the field statement

Peripheral inflammatory markers, such as systemic immune-inflammation index (SII), have been identified to be prognostic markers in various types of cancer. However, it is not yet known whether it is an independent biomarker for survival prediction in glioblastoma (GBM) patients. Therefore, we conducted this research to identify the prognostic value of SII in patients with GBM. According to our results, the preoperative SII and neutrophil count may serve as prognostic predictors of OS in GBM patients. Besides, nomograms based on multivariate analyses are established as well to provide a numerical and individualized estimation for OS in patients with GBM. As there are few robust, easily testable markers for prognosis in GBM, using these peripheral inflammatory markers that can be easily assessed in the preoperative peripheral blood has the potential to open new avenues to improve patient outcomes. To our knowledge, this is the first comprehensive study to establish nomograms based on SII to predict a numerical survival in GBM.

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Author contributions

Conceptualization: Chao Yang.
Data curation: Chao Yang, Jie Wang.

Table 2

Univariate and multivariate analyses of OS in GBM cohorts.

Characteristics	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Sex (female/male)	1.009 (0.661–1.540)	.967		
Age (>57/≤57)	1.027 (1.006–1.048)	.011	1.022 (1.002–1.042)	.032
Location	1.078 (0.934–1.244)	.306		
KPS (>60/≤60)	0.883 (0.862–0.905)	<.001	0.910 (0.885–0.936)	<.001
Chemoradiotherapy(yes/no)	0.098 (0.054–0.176)	<.001	0.448 (0.219–0.917)	.028
Resection (GTR/STR)	0.174 (0.107–0.282)	<.001	0.474 (0.259–0.869)	.016
IDH1 (mutant/wild)	0.771 (0.282–2.106)	.612		
MGMT (yes/no)	0.713 (0.467–1.088)	.117		
WBC (>6.7/≤6.7)	1.798(1.179–2.742)	.006	1.267(0.798–2.014)	.316
Neutrophil (>3.9/≤3.9)	2.536(1.614–3.984)	<.001	1.923(1.181–3.131)	.009
Lymphocyte (>1.9/≤1.9)	0.597(0.374–0.952)	.030	0.688(0.419–1.131)	.141
PLT (>258/≤258)	1.564(0.956–2.559)	.075	1.377(0.807–2.348)	.241
SII (>510.8/≤510.8)	2.625 (1.706–4.040)	<.001	1.672 (1.039–2.690)	.034

CI = confidence interval, GTR = gross total resection, HR = hazard ratio, IDH = isocitrate dehydrogenase, KPS = Karnofsky performance status, MGMT = O^6-methylguanine-DNA methyltransferase, OS = overall survival, SII = systemic immune-inflammation index, STR = subtotal resection.

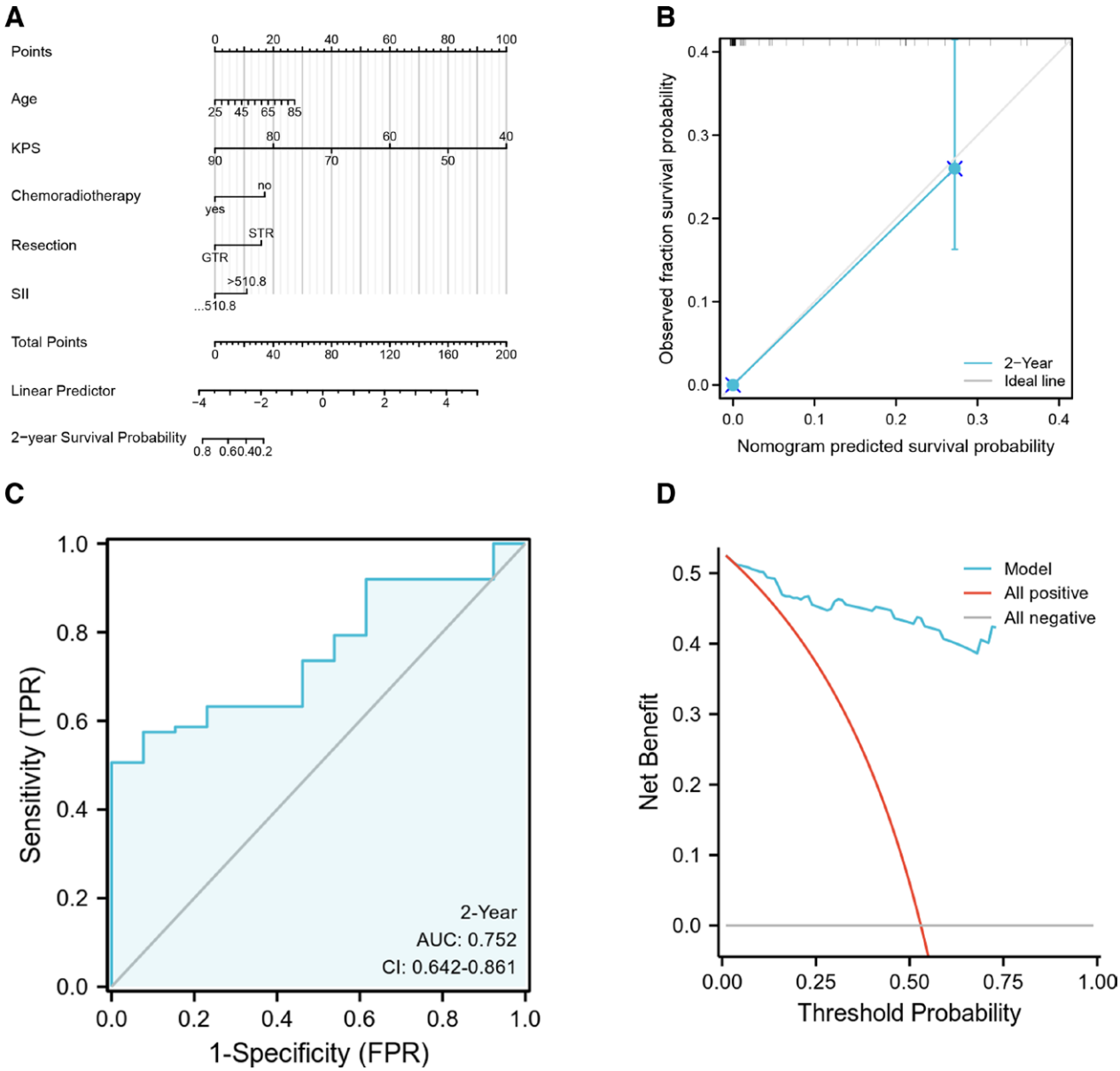

Figure 4. In the nomogram (A), each variable was assigned a different score as shown on the highest scale, and the total score for all variables yielded a numerical prediction of 2-year survival, with higher scores leading to worse prognosis. In the calibration curve (B), the dotted line represents the ideal prediction and the full red line represents the performance of the nomogram. (C) Time-dependent ROC curve analysis of SII for predicting OS in GBM patients. (D) Decision curve analysis of SII for predicting OS in GBM patients. GBM = glioblastoma, ROC = Receiver operating characteristic curve, SII = systemic immune-inflammation index.

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Writing – review & editing: Jie Wang.

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