Neutrophil/Lymphocyte Ratio Is an Independent Prognostic Factor in Elderly Patients with High-Grade Gliomas

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■ OBJECTIVE: **The present study was performed to investigate the prognostic role of the preoperative neutrophil/lymphocyte ratio (NLR) in elderly patients with high-grade glioma.**

■ METHODS: **We collected the data from elderly patients (age ≥65 years) who had been diagnosed with high-grade glioma in our hospital from December 2014 to January 2018. The preoperative NLR was evaluated in univariate and multivariate models to examine their effect on overall survival (OS).**

■ RESULTS: **The study included 135 elderly patients (World Health Organization grade III, $n = 22$; grade IV, $n = 113$) with a mean age 70.61 ± 4.60 years. The mean NLR was 3.98 ± 3.28. The optimal NLR cutoff for predicting OS was 3. Of the 135 patients, 65 (48.1%) had a baseline NLR of ≥3 and 70 (51.9%) a baseline NLR <3. For patients with an NLR of ≥3 and NLR <3, the mean OS was 9.6 months and 17.1 months, respectively. The results showed that age, gender, tumor location, preoperative Karnofsky performance scale score, extent of resection (EOR), and postoperative adjuvant therapy were not associated with the NLR. The tumor grade, neutrophil count, and lymphocyte count were significantly associated with the NLR ($P < 0.001$). On univariate analysis, tumor grade, preoperative Karnofsky performance scale score ≥80, EOR, frontal tumor, adjuvant radiotherapy plus temozolomide, NLR of ≥3, and lymphocyte count of ≥1.6 × 10^9/L were significantly associated with OS. On multivariate analysis, tumor grade, EOR, adjuvant radiotherapy plus temozolomide, NLR of ≥3, and lymphocyte count of ≥1.6 × 10^9/L were still associated with OS after excluded related parameters.**

■ CONCLUSIONS: **A high NLR was an unfavorable predictor of prognosis for elderly patients with high-grade glioma.**

INTRODUCTION

The neutrophil/lymphocyte ratio (NLR) is one of the markers of systemic inflammatory response and has been shown to be a poor prognostic factor for many malignancies, including colon, prostate, bladder, and gastric cancer.[1-4] Moreover, in a nononcology population, an increase in the NLR has a detrimental effect on the prognosis of community acquired pneumonia and coronary artery disease.[5,6] In recent years, some studies have demonstrated that the NLR is a poor prognosis marker for adult patients with glioblastoma multiforme (GBM), independent of other known prognostic factors.[7,8] However, the exact prognostic significance of the NLR in elderly patients with high-grade glioma has not yet been reported.

Key words
- Brain tumor
- Elderly patients
- Glioblastoma
- High-grade glioma
- Neutrophil/lymphocyte ratio
- NLR
- Prognostic factor

Abbreviations and Acronyms
CI: Confidence interval
EOR: Extent of resection
GBM: Glioblastoma multiforme
HR: Hazard ratio
KPS: Karnofsky performance scale
NLR: Neutrophil/lymphocyte ratio
OS: Overall survival
RT: Radiotherapy
TMZ: Temozolomide
WHO: World Health Organization

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The aging of the population has led to an increase in the incidence of glioma in the elderly, especially the most common subtype of GBM.[9] Data from many retrospective studies and meta-analyses have indicated that older patients with high-grade gliomas will have a worse prognosis than younger patients, especially elderly patients with GBM, possibly because of comorbidities and resistance to treatment, genetic aberrations, neurodegeneration, and/or age discrimination. Elderly patients constitute approximately one half of the patients with malignant glioma, and the prevalence of GBM increases with age. Age remains the most important prognostic factor for patients with GBM. One half of all patients with GBM will be aged ≥65 years at the diagnosis, and the incidence rate of GBM has been rapidly increasing in patients aged >65 years.[10] Despite aggressive treatment, the median survival of all patients with GBM has been only 12–15 months after the diagnosis. According to population-based studies, median survival was significantly reduced in older patients to only 4–5 months.[10] The prognostic factors that have been identified include age, molecular marker status, extent of surgical resection (EOR), and postoperative treatment options. The exact meaning of the NLR in elderly patients with high-grade glioma is unknown.

The primary aim of the present study was to assess the prognostic effects of the NLR in a clinically annotated cohort of elderly patients with high-grade glioma. We hypothesized that an elevated NLR would be associated with a poor prognosis in elderly patients with high-grade glioma.

METHODS

Patient Population

We collected data from 315 elderly patients (aged ≥65 years) with a diagnosis of high-grade glioma, including various primary and recurrent gliomas, in our hospital from December 2014 to January 2018. All the patients had undergone surgery. From these data, we focused on primary high-grade glioma cases in the elderly.

Elderly patients with diabetes, metabolic syndrome,[11] heart disease (i.e., acute coronary syndrome, rheumatic or congenital heart disease, cardiomyopathy), hypertension,[12] severe renal or hepatic insufficiency, other malignancies, inflammatory disease, or a history of acute infection within 3 months or who had used drugs that could significantly influence the NLR were excluded. To be included in the present study, the patients were required to have full blood count results available for analysis before surgery or other treatment. The neutrophil and lymphocyte counts were extracted from the full blood count. The NLR was calculated as the neutrophil count divided by the lymphocyte count using standard units. Finally, 135 elderly patients with a diagnosis of high-grade glioma were included in the present analysis.

Clinical Information

The medical records were also reviewed to extract clinical information, including gender, age, preoperative Karnofsky performance scale (KPS) score, EOR, tumor location, postoperative adjuvant therapy, World Health Organization (WHO) grade, NLR, neutrophil count, lymphocyte count, and overall survival (OS) data. From the assessment of the surgeon, EOR was classified as gross total resection (100% tumor resection), subtotal resection (90%–95%), partial resection (<90%), and biopsy. The tumor locations include frontal lobe, temporal lobe, parietal lobe,

Table 1. Clinical Patient Characteristics ($n = 135$)

Characteristic	*n* (%)
Age (years)	
Mean ± SD	70.61 ± 4.60
Range	65–91
Age group	
≥69 years	77 (57.0)
<69 years	58 (43.0)
Gender	
Male	89 (65.9)
Female	46 (34.1)
Tumor location	
Frontal lobe	57
Temporal lobe	52
Occipital lobe	30
Parietal lobe	14
Deep brain location	21
WHO grade	
III	22 (16.3)
IV	113 (83.7)
Preoperative KPS score	
≥80	88 (65.2)
<80	47 (34.8)
EOR	
GTR	23 (17.0)
STR	53 (39.3)
PR	57 (42.2)
Biopsy	2 (1.5)
Adjuvant therapy	
RT+TMZ	57 (42.2)
TMZ alone	22 (16.3)
RT alone	5 (3.7)
None	51 (37.8)
Neutrophil count ($\times 10^9$/L)*	4.87 ± 2.28
Lymphocyte ($\times 10^9$/L)*	1.50 ± 0.65
NLR*	3.98 ± 3.28

SD, standard deviation; WHO, World Health Organization; KPS, Karnofsky performance scale; EOR, extent of resection; GTR, gross total resection, STR, subtotal resection; PR, partial resection; RT, radiotherapy; TMZ, temozolomide; NLR, neutrophil/lymphocyte ratio.
*Data presented as mean ± standard deviation.

occipital lobe, and deep brain. Patients received radiotherapy (RT) plus concomitant and adjuvant temozolomide (TMZ), RT alone, TMZ alone, or no RT or chemotherapy.[13]

Histopathological Examination

All the specimens were pathologically examined in the pathology department of our hospital. The comprehensive diagnosis and WHO grade for all cases were determined using the 2016 WHO classification of tumors of the central nervous system.[14]

Statistical Analysis

Univariate and multivariate Cox proportional hazards models were constructed to investigate the influence of variables on OS. Gender, age, preoperative KPS score, EOR, tumor location, postoperative adjuvant therapy, tumor grade, NLR, neutrophil count, and lymphocyte count were included in the analysis. Statistical analysis was performed using SPSS Statistic, version 20 (IBM Corp., Armonk, New York, USA). The categorical variables were compared between the subgroups using the χ^2 test, and the continuous variables were compared using the t test. The OS curves were estimated using the Kaplan-Meier method and compared using log-rank test. Univariate and multivariate analyses were used to assess the influence of the NLR on OS. A 2-tailed P value of <0.05 was taken to indicate statistical significance. In the present study, we used the X-tile software (Yale University School of Medicine, New Haven, Connecticut, USA) to identify the optimal cutoff point for the NLR and other continuous variables. Using the NLR cutoff calculated using X-tile, the patients enrolled in the present study were classified into 2 groups.

RESULTS

Clinical Characteristics

The clinical characteristics of the 135 patients included in the present study are presented in Table 1. Of the 135 patients, 89 were men (65.9%) and 46 were women (34.1%), with a mean age of 70.61 ± 4.60 years (range, 65–91). According to the comprehensive diagnosis using the 2016 WHO classification, 113 patients (83.7%) had grade IV and 22 (16.3%) had grade III.[14] The preoperative KPS scores ranged from 30 to 100, with 88 patients (65.2%) having a score of ≥80. Regarding the EOR, 23 (17%), 53 (39.3%), 57 (42.2%), and 2 (1.5%) patients had undergone gross total resection, subtotal resection, partial resection, and biopsy, respectively. After surgery, 57 (42.2%), 22 (16.3%), and 5 (3.7%) patients had received combined RT and TMZ (RT+TMZ), TMZ alone, and RT alone, respectively. The remaining 51 patients (37.8%) did not receive any postoperative treatment. The most common location involved by tumor was the frontal lobe ($n = 57$), followed by the temporal lobe ($n = 52$), parietal lobe ($n = 14$), occipital lobe ($n = 30$), and deep brain ($n = 21$). The mean neutrophil and lymphocyte counts were 4.87 ± 2.28 $\times 10^9$/L and 1.50 ± 0.65 $\times 10^9$/L, respectively. The mean NLR was 3.98 ± 3.28. The optimal NLR cutoff for predicting the OS of elderly patients with high-grade glioma was 3 (Figure 1). Thus, the NLR was analyzed as a dichotomous variable with a cutpoint of ≥3. The relationship of some baseline parameters in the present study with an increased NLR level is shown in Table 2. We found that age, gender, tumor location, preoperative KPS score, EOR, and postoperative adjuvant therapy were not associated with the NLR level. However, tumor grade, neutrophil count, and lymphocyte count were significantly associated with the NLR ($P < 0.001$).

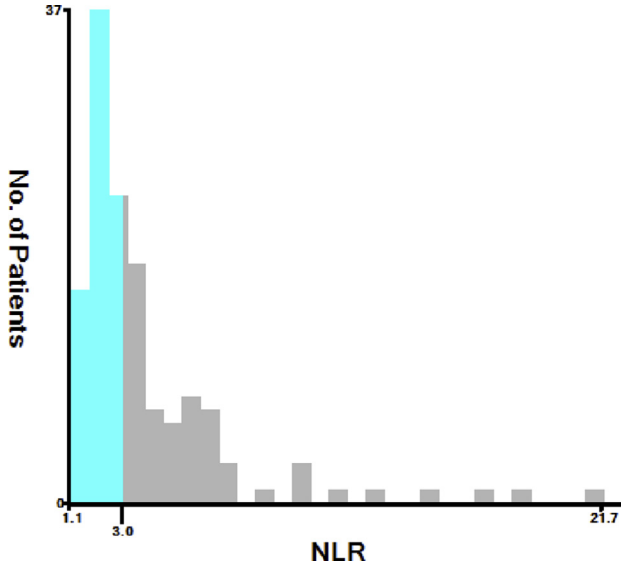

Figure 1. The cutpoint for the neutrophil/lymphocyte ratio (NLR) determined using X-tile software (Yale University School of Medicine).

NLR and Other Prognostic Factors on Univariate and Multivariate Analysis

At the last follow-up examination, 105 patients had died. The mean OS for all patients was 13.4 months (95% confidence interval [CI], 11.514–15.297). Of the 135 patients, 65 (48.1%) had had a baseline NLR of ≥3 and 70 (51.9%) a baseline NLR of <3. For patients with an NLR of ≥3 and those with an NLR of <3, the mean OS was 9.6 months and 17.1 months, respectively. On univariate analysis, tumor grade (hazard ratio [HR], 11.951; 95% CI, 3.779–37.798; $P < 0.001$), preoperative KPS score of ≥80 (HR, 0.667; 95% CI, 0.448–0.994; $P = 0.05$), EOR (HR, 1.685; 95% CI, 1.283–2.212; $P < 0.001$), frontal tumor (HR, 1.745; 95% CI, 1.164–2.165; $P = 0.006$), adjuvant RT+TMZ (HR, 0.483; 95% CI, 0.322–0.722; $P < 0.001$), NLR of ≥3 (HR, 2.298; 95% CI, 1.552–3.403; $P < 0.001$), lymphocyte count ≥1.6 $\times 10^9$/L (HR, 0.458; 95% CI, 0.302–0.649; $P < 0.001$) were significantly associated with OS (Table 3). On multivariate analysis, tumor grade (HR, 14.014; 95% CI, 3.938–49.871; $P < 0.001$), EOR (HR, 1.952; 95% CI, 1.286–2.962; $P = 0.002$), adjuvant RT+TMZ (HR, 0.579; 95% CI, 0.364–0.923; $P = 0.022$), NLR of ≥3 (HR, 1.712; 95% CI, 1.071–2.734; $P = 0.025$), and lymphocyte count ≥1.6 $\times 10^9$/L (HR, 0.608; 95% CI, 0.385–0.962; $P = 0.034$) were still associated with OS after exclusion of the related parameters. Of these, WHO grade IV, failure to complete adjuvant RT+TMZ, and NLR of ≥3 remained as independent prognostic indicators for a poor outcome. In addition, the neutrophil counts in isolation were not prognostic (Table 3).

Table 2. Assessment for Correlation Between Neutrophil/Lymphocyte Ratio and Other Prognostic Variables

Variable	NLR <3	NLR ≥3	*P* Value
Age (years)	70.70 ± 4.97	70.52 ± 4.20	0.824
Gender			
Male	45	45	
Female	25	20	
Tumor location			
Frontal lobe	32	25	0.394
Temporal lobe	23	33	0.035
Occipital lobe	19	11	0.154
Parietal lobe	8	6	0.676
Deep brain location	10	11	0.673
WHO grade			
III	20	2	
IV	50	63	
Preoperative KPS score			
≥80	47	41	
<80	23	24	
EOR			
GTR	14	9	0.342
STR	28	25	0.855
PR	26	31	0.215
Biopsy	1	1	0.958
Adjuvant therapy			
RT+TMZ	29	28	0.902
TMZ alone	15	7	0.094
RT alone	4	1	0.199
None	24	27	0.385
Neutrophil count ($\times 10^9$/L)	4.08±1.52	5.73±2.65	<0.001*
Lymphocyte count ($\times 10^9$/L)	1.92±0.57	1.06±0.37	<0.001*

Data presented as mean ± standard deviation or number of patients.
NLR, neutrophil/lymphocyte ratio; WHO, World Health Organization; KPS, Karnofsky performance scale; EOR, extent of resection; GTR, gross total resection, STR, subtotal resection; PR, partial resection; RT, radiotherapy; TMZ, temozolomide.
*$P < 0.05$.

DISCUSSION

In the present study, we retrospectively analyzed the prognostic effect of the NLR in 135 elderly patients with high-grade glioma treated in our hospital. Previous data suggested that the NLR should be analyzed as a dichotomous variable, an NLR of ≥4 versus an NLR <4 suggesting a poor prognosis.[7,8,15] However, in the present study, X-tile software (Yale University School of Medicine) was used to find the best cutpoint for the NLR. Our data showed that an NLR of ≥3 (relative to an NLR of <3) indicated a poor prognosis (Figure 1). The mean OS for the patients with an NLR of ≥3 was 9.6 months (P = 0.025), which was significantly shorter than the mean OS of 17.1 months for patients with an NLR <3 (Figure 2). This finding indicates the importance of host immunity in elderly patients with high-grade glioma and is consistent with the findings from studies of multiple other solid tumors, as discussed in our introduction section. Our finding is also consistent with the previously reported role of the NLR in adult patients with glioblastoma, although the cutpoint of NLR was 4 in those studies.[7,8] In previous reports, the NLR was an independent prognostic factor in adult patients with glioblastoma,[7,8,15] in line with the results in the present study of elderly patients with high-grade glioma. The NLR is a convenient, objective, and inexpensive test. Its use for elderly patients with high-grade glioma, however, will be somewhat complicated, because the NLR should be measured before surgery or other treatment because these interventions will lead to distortion of the value by increasing the neutrophil count.

Despite the known role an elevated NLR can play in cancer prognosis, the exact biological mechanism behind it remains to be fully elucidated. Barberis et al.[16] proposed the NLR as a marker of systemic inflammatory response, which promotes cancer cell proliferation by increasing the availability of growth factors, angiogenic factors, and other proneoplastic signaling molecules, thereby predicting for a worse prognosis. It has been reported that the effects of systemic inflammation on white blood cells was achieved by an increase in neutrophils, accompanied by a decrease in lymphocytes, which might result from the increased marginalization and apoptosis of lymphocytes.[17] Cell-mediated immunity declines or will even be lost by a decreased lymphocyte count.[18] In GBM and other cancers, tumor infiltrating lymphocytes were associated with a better prognosis, suggesting that both systemic and local indicators of antitumor reactions have prognostic value.[19,20] Therefore, research in this area might be enhanced by assessing the importance of various T-cell subsets, eosinophils, and C-reactive protein levels in patients with malignancies.[21] Such an analysis could help us better understand the importance of the various factors involved in the immune system of elderly patients with glioma for prognosis. Neutrophils are the most abundant circulating leukocytes and stand as early immune defense. Because leukocytes influence the function and phenotype of CD8-positive T cells, neutrophils could be a potential prognostic biomarker for patients with high-grade glioma.[22] However, in some reports, the neutrophil and lymphocyte counts in isolation were not prognostic when analyzed as categorical or continuous variables.[7] Also, although neutrophils have not been shown to be prognostic, lymphocytes were found to have prognostic significance in our data set. Furthermore, it has recently been reported that the preoperative NLR correlated with the histopathological grade of gliomas, with the highest level of neutrophils and the lowest level of lymphocyte observed in patients with GBM.[23,24] In our analysis, the increased NLR was related to the WHO grade (P < 0.001; Table 2), consistent with previous reports. It was probable that in several aggressive histologic types, the increase in the NLR was associated with the greater "activity" of the neoplasm and the consequent activation of various pathways.[25,26] Moreover, a positive correlation between

Table 3. Prognostic Effect of Variables on Overall Survival

			Univariate Analysis			Multivariate Analysis		
Variable	**Patients (*n*)**	**OS (%)**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Age (years)			1.315	0.881–1.961	0.175	1.369	0.840–2.229	0.207
≥69	77	12.4						
<69	58	14.7						
Gender			0.833	0.549–1.264	0.385	1.361	0.809–2.290	0.246
Male	89	12.8						
Female	46	13.9						
WHO grade			11.951	3.779–37.798	<0.001*	14.014	3.938–49.871	<0.001*
IV	113	10.9						
III	22	31.5						
Preoperative KPS score			0.667	0.448–0.994	0.05*	0.758	0.466–1.235	0.28
≥80	88	10.5						
<80	47	14.7						
EOR			1.685	1.283–2.212	<0.001*	1.952	1.286–2.962	0.002*
GTR	23	20						
STR	53	13.5						
PR	57	11						
Biopsy	2	1.3						
Tumor location								
Frontal lobe	57	17.1	1.745	1.164–2.165	0.006	0.908	0.493–1.672	0.757
Temporal lobe	52	12.3	0.808	0.549–1.191	0.281	NA	NA	NA
Occipital lobe	30	14.7	0.917	0.597–1.410	0.694	NA	NA	NA
Parietal lobe	14	13.1	1.119	0.608–2.059	0.718	NA	NA	NA
Deep brain location	21	9.5	0.631	0.382–1.045	0.088	NA	NA	NA
Adjuvant therapy								
RT+TMZ	57	17.2	0.483	0.322–0.722	<0.001*	0.579	0.364–0.923	0.022
TMZ alone	22	14.1	0.806	0.484–1.344	0.408	NA	NA	NA
RT alone	5	7.2	1.693	0.533–5.384	0.366	NA	NA	NA
None	51	12.9	1.046	0.799–1.562	0.827	NA	NA	NA
NLR			2.298	1.552–3.403	<0.001*	1.712	1.071–2.734	0.025*
≥3	65	9.6						
<3	70	17.1						
Neutrophil count ($\times 10^9$/L)			0.963	0.654–1.418	0.848	1.078	0.691–1.683	0.74
>4.45	68	14						
≤4.45	67	12.7						
Lymphocyte count ($\times 10^9$/L)			0.458	0.302–0.649	<0.001*	0.608	0.385–0.962	0.034*
≥1.6	55	18						
<1.6	80	10.4						

OS, overall survival; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; KPS, Karnofsky performance scale; EOR, extent of resection; GTR, gross total resection; STR, subtotal resection; PR, partial resection; NA, not applicable; RT, radiotherapy; TMZ, temozolomide; NLR, neutrophil/lymphocyte ratio.
*$P < 0.05$.

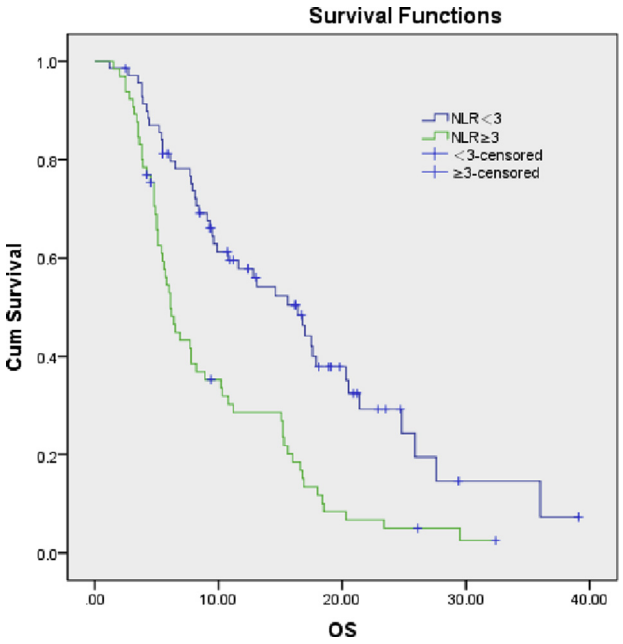

Figure 2. Kaplan-Meier curves for overall survival (OS) for patients with high versus low neutrophil/lymphocyte ratio (NLR). The mean OS for the cohort with an NLR of ≥3 was 9.6 months. The mean OS for the cohort with an NLR <3 was 17.1 months ($P < 0.001$).

the peripheral blood NLR levels and increased tumor neutrophil infiltration/decreased CD3-positive T-cell infiltration into glioblastoma was demonstrated recently.[8] However, the biochemical linkage between the NLR and gliomas has not been well established. Although the mechanism underlying the prognostic role of NLR in gliomas remains unclear, it has generally been regarded that the tumor-infiltrating lymphocytes could suppress the immune response.[27]

Our study had some important limitations. First, it was a single-center, retrospective study, and our results should be confirmed in an independent prospective cohort. Second, we did not have data on MGMT methylation status or TERT promoter status, both of which are known to have prognostic significance in elderly patients with glioma.[28,29] Third, unlike a randomized study, a selection bias regarding the decisions on the treatment strategy could have been present. The attending physician might have decided to deliver treatments plan after considering the patient's age, comorbidities, and wishes; thus, the treatment selection could have affected the survival outcomes.

CONCLUSION

The results from our study have indicated that a high NLR is an unfavorable predictor of prognosis for elderly patients with high-grade gliomas in our hospital. If the NLR is validated as an independent prognostic factor in other cohorts, it could be a useful addition to predicting the prognosis for elderly patients with high-grade gliomas. In the future, when a prognostic risk score has been created for elderly patients with high-grade glioma, the pretreatment NLR could be considered a candidate variable, given its ease of measurement.

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REFERENCES

1. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol*. 2005;91:181-184.
2. Keizman D, Gottfried M, Ish-Shalom M, et al. Pretreatment neutrophil-to-lymphocyte ratio in metastatic castration-resistant prostate cancer patients treated with ketoconazole: association with outcome and predictive nomogram. *Oncologist*. 2012;17:1508-1514.
3. Gondo T, Nakashima J, Ohno Y, et al. Prognostic value of neutrophil-to-lymphocyte ratio and establishment of novel preoperative risk stratification model in bladder cancer patients treated with radical cystectomy. *Urology*. 2012;79:1085-1091.
4. Deng Q, He B, Liu X, et al. Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. *J Transl Med*. 2015;13:66.
5. Arbel Y, Finkelstein A, Halkin A, et al. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. *Atherosclerosis*. 2012;225:456-460.
6. Curbelo J, Bueno SL, Galván-Román JM, et al. Inflammation biomarkers in blood as mortality predictors in community-acquired pneumonia admitted patients: importance of comparison with neutrophil count percentage or neutrophil-lymphocyte ratio. *PLoS One*. 2017;12:e0173947.
7. Bambury RM, Teo MY, Power DG, et al. The association of pre-treatment neutrophil to lymphocyte ratio with overall survival in patients with glioblastoma multiforme. *J Neurooncol*. 2013;114:149-154.
8. Han S, Liu Y, Li Q, Li Z, Hou H, Wu A. Pre-treatment neutrophil-to-lymphocyte ratio is associated with neutrophil and T-cell infiltration and predicts clinical outcome in patients with glioblastoma. *BMC Cancer*. 2015;15:617.
9. Tamura Y, Kato H, Oh A, et al. A study on the prescription status of metformin and DPP-4 inhibitors in patients with type 2 diabetes mellitus in Japan: an analysis of time trends by use of a health insurance administrative claims database. *Ther Res*. 2018;39:67-76.
10. Arvold ND, Reardon DA. Treatment options and outcomes for glioblastoma in the elderly patient. *Clin Interv Aging*. 2014;9:357-367.
11. Yasar Z, Buyuksirin M, Ucsular FD, et al. Is an elevated neutrophil-to-lymphocyte ratio a predictor of metabolic syndrome in patients with chronic obstructive pulmonary disease? *Eur Rev Med Pharmacol Sci*. 2015;19:956-962.
12. Belen E, Sungur A, Sungur MA, Erdoğan G. Increased neutrophil to lymphocyte ratio in patients with resistant hypertension. *J Clin Hypertens*. 2015;17:532-537.
13. Hau P, Bogdahn U. Maligne gliome—chemotherapie. *Onkologe*. 2004;10(suppl 1):S26-S29.
14. Toro-Moreno AC, Serna-Velez L, Gallego-González D, Jaramillo-Jaramillo LI, Martínez-Sánchez LM, Álvarez-Hernández LF. Tumores de sistema nervioso central en pediatría: presente y futuro del abordaje diagnóstico. *Rev Ecuatoriana Neurol*. 2017;26:283-288.
15. McNamara MG, Lwin Z, Jiang H, et al. Factors impacting survival following second surgery in patients with glioblastoma in the temozolomide treatment era, incorporating neutrophil/lymphocyte ratio and time to first progression. *J Neurooncol*. 2014;117:147-152.
16. Barberis I, Martini M, Iavarone F, Orsi A. Available influenza vaccines: immunization strategies,

history and new tools for fighting the disease. *J Prev Med Hyg*. 2016;57:E41-E46.

17. de Jager CPC, Wever PC, Gemen EFA, et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. *PLoS One*. 2012; 7:e46561.

18. Mirzaei R, Sarkar S, Dzikowski L, et al. Brain tumor-initiating cells export tenascin-C associated with exosomes to suppress T cell activity. *Oncoimmunology*. 2018;7:e1478647.

19. Murphy J, O'Sullivan GC, Lee G, et al. The inflammatory response within Dukes' B colorectal cancers: implications for progression of micrometastases and patient survival. *Am J Gastroenterol*. 2000;95:3607-3614.

20. Lohr J, Ratliff T, Huppertz A, et al. Effector T-cell infiltration positively impacts survival of glioblastoma patients and is impaired by tumor-derived TGF-β. *Clin Cancer Res*. 2011;17:4296-4308.

21. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med*. 2012;366: 925-931.

22. Lança T, Silva-Santos B. The split nature of tumor-infiltrating leukocytes: implications for cancer surveillance and immunotherapy. *Oncoimmunology*. 2012;1:717-725.

23. Lopes M, Carvalho B, Vaz R, Linhares P. Influence of neutrophil—lymphocyte ratio in prognosis of glioblastoma multiforme. *J Neurooncol*. 2018;136: 173-180.

24. Weng W, Chen X, Gong S, Guo L, Zhang X. Preoperative neutrophil—lymphocyte ratio correlated with glioma grading and glioblastoma survival. *Neurol Res*. 2018;40:917-922.

25. Gregory AD, Houghton AM. Tumor-associated neutrophils: new targets for cancer therapy. *Cancer Res*. 2011;71:2411-2416.

26. Mantovani A, Garlanda C, Allavena P. Molecular pathways and targets in cancer-related inflammation. *Ann Med*. 2010;42:161-170.

27. Wainwright DA, Sengupta S, Han Y, Lesniak MS. Thymus-derived rather than tumor-induced regulatory T cells predominate in brain tumors. *Neuro Oncol*. 2011;13:1308-1323.

28. Sasaki T, Fukai J, Kodama Y, et al. Characteristics and outcomes of elderly patients with diffuse gliomas: a multi-institutional cohort study by Kansai Molecular Diagnosis Network for CNS Tumors. *J Neurooncol*. 2018;140:329-339.

29. Gorlia T, van den Bent MJ, Hegi ME, et al. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. *Lancet Oncol*. 2008;9:29-38.

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