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Neutrophil-to-lymphocyte ratio dynamics: prognostic value and potential for surveilling glioblastoma recurrence

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Abstract

Purpose Glioblastoma (GBM) is a challenging malignancy with a poor prognosis. While the neutrophil-to-lymphocyte ratio (NLR) is reported to correlate with the prognosis, the significance of changes in the NLR and its prognostic value in GBM remain unclear. This study aims to evaluate changes in the NLR and its predictive value for GBM prognosis and recurrence.

Methods The cohort included 69 newly-diagnosed GBM patients undergoing a standard treatment protocol. NLR was assessed at multiple time points. The dynamic change in NLR (dNLR), defined as the NLR at the point of interest (post-CCRT or post-Stupp) divided by the preoperative NLR, also was assessed. Univariate and multivariate COX regression analyses were conducted to assess the association between the NLR, dNLR and overall survival (OS) and progression-free survival (PFS).

Results Univariate analysis revealed that age at diagnosis ≥ 70 ($p = 0.019$) and post-Stupp dNLR ≥ 1.3 ($p = 0.006$) were significantly associated with shorter OS. Significant correlations were found between pre-operative KPS ≥ 60 ($p = 0.017$), gross total resection ($p = 0.042$), post-Stupp dNLR ≥ 1.3 ($p = 0.043$) and PFS. Multivariate analysis showed age at diagnosis ≥ 70, pre-operative KPS ≥ 60, post-Stupp NLR ≥ 5 and dNLR ≥ 1.3 were significantly associated with a shorter OS. Significant correlation was found between pre-operative KPS ≥ 60 and PFS.

Conclusion This study revealed that post-Stupp NLR ≥ 5 and dNLR ≥ 1.3 correlated significantly with a worse glioblastoma prognosis in OS, and dNLR might be more reliable. These two parameters are potentially surveilling markers for glioblastoma recurrence, however further studies are warranted.

Keywords Glioblastoma, Neutrophil–lymphocyte ratio, Dynamic NLR, Prognosis, Recurrence

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Introduction

The immune system plays an important role in modern treatments for malignancies, particularly the adaptive immune system [1]. Patients with glioblastoma, the most common and malignant primary brain tumor, are assumed to be immunosuppressed. Evidence includes decreased function of natural killer (NK) and T cells and high peripheral release of both TGF-β and prostaglandins [2]. Despite the immunosuppressed status, these patients are found to have elevated circulating neutrophil activity, which correlates with worse overall and progression-free survival in several malignancies [3]. The underlying pathophysiological mechanism remains unclear, but may be related to neutrophilia as an inflammatory response that inhibits the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, activated T cells, and natural killer cells. One of the most commonly accepted markers is the neutrophil-to-lymphocyte ratio (NLR) [4].

Several previous studies have provided valuable information regarding the relationship between NLR and a variety of outcomes [5–7]. Without a useful serum marker, the detection of recurrent glioblastoma currently relies solely on magnetic resonance imaging (MRI), which is not only expensive but also inconvenient in most medical settings. The NLR, which is easily obtained and inexpensive as well, has been reported to have prognostic value for glioblastoma. However, most studies have focused on the prognostic value at a given time point, most commonly the pre-operative NLR. Therefore, this study aims to investigate the change in the NLR to determine its value in detecting recurrent glioblastoma and predicting outcomes.

Materials and methods

Study design, data collection, and ethics

All data and clinical information used in this retrospective cohort study were collected from medical records. Ethical approval for this study was provided by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No. 104-2656B). This study was performed in line with the principles of the Declaration of Helsinki.

Inclusion and exclusion criteria

Patients who met the following criteria were included: (1) newly-diagnosed with glioblastoma based on the 2021 World Health Organization (WHO) criteria; (2) underwent surgery between Oct. 2011 and Dec. 2022 in Chang Gung Memorial Hospital; (3) underwent the standard protocol as described below. Patients meeting the following criteria were excluded: (1) age below 18; (2) received additional treatment other than the Stupp protocol, including immunotherapy, additional chemotherapy (nitroureas), target therapy (bevacizumab), or unknown regimen from clinical trials for fear of their potential influences on leukocyte distribution; (3) refused to complete the protocol for reasons other than undergoing a second operation for tumor recurrence (for instance, intolerable side effects; patients' or family's decision); (4) hemogram test not available or possibly influenced by steroid use or infection; (5) did not receive post-op MRI for evaluation of resection status and treatment response; (6) loss to follow-up within 2 years after surgery.

Treatment and surveillance protocol

As per the standard treatment and surveillance for high grade gliomas in our hospital, patients with newly-diagnosed glioblastoma underwent a post-operative MRI within 48 h for evaluation of resection status. Following the first surgery for tumor removal, patients received adjuvant concurrent chemoradiotherapy (CCRT) with radiotherapy for 2 gray (Gy) per daily fraction (Monday through Friday) over 6 weeks (total dosage, 60 Gy) and concurrent temozolomide (TMZ) 75 mg per square meter of body-surface area per day, 7 days per week. After receiving CCRT, patients received the standard Stupp protocol, with monthly adjuvant TMZ (aTMZ) for 6 cycles, consisting of 150–200 mg per square meter of body-surface area for the first 5 days of each 28-day cycle. Patients underwent MRI surveillance after the Stupp protocol and every 3 months afterwards for 1 year. The frequency of MRI surveillance varied after the first year, with most patients undergoing yearly follow-ups. If a recurrence was documented during follow-up, further treatment was discussed with the patient. The options included continuing monthly aTMZ, repeated surgery, and/or bi-weekly adjuvant bevacizumab, or surveillance only. A hemogram was conducted before the CCRT, within 1 month after completion of the CCRT, and within 1 month after each course of aTMZ.

Clinical variables and outcome assessment

Clinical information was collected retrospectively, including the age at diagnosis (cut-off value, 70 years), pre- and post-operative Karnofsky Performance Status (KPS) scores (cut-off value, 60), the extent of resection (EOR) and the Ki-67%. The cut-off age to define an elderly population differs among clinical studies, ranging between 60 and 75 years [8]. In this study, the cut-off value was set at 70 for the age at diagnosis to keep consistency with the critical Stupp trial [9, 10]. The cutoff value for KPS was set at 60 since the latest NCCN guideline suggested determining post-operative adjuvant therapy and treatment for elderly patients based on their performance status, which was defined as KPS ≥ 60 [11]. All the glioblastomas were IDH wildtype, according to the 2021 WHO classification of tumors of the central nervous system. MGMT methylation status was not available in all

patients, and was therefore not analyzed in this study. The EOR was classified as gross-total resection (GTR) (>99% resection), subtotal resection (STR) (90–99% resection), and partial resection (PR) (<90% resection) based on contrast-enhanced T1-weighted MRI. The overall survival (OS) was defined as the interval between the first pathology-proved diagnosis and the last follow-up or death. Progression-free survival (PFS) was defined as the interval from the first surgery until recurrence as determined by evidence on MRI surveillance.

The neutrophil/lymphocyte ratio (NLR) was defined as the absolute neutrophil count (ANC) divided by the absolute lymphocyte count (ALC). Hemogram measurement and analysis was conducted at two time points: post-CCRT and post-Stupp. The post-Stupp time point was defined as the hemogram obtained within 1 month after the last course of aTMZ. The dynamic change in NLR (dNLR) was defined as the NLR at the point of interest (post-CCRT or post-Stupp) divided by the pre-operative NLR. The cut-off value for ALC was set at 800 and 500 cells/μL, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, as grade 1 (1500–800 lymphocytes/μL), grade 2 (800–500 lymphocytes/μL) and grade 3 (500–200 lymphocytes/μL). For NLR and dNLR, the cut-off values were determined with the receiver operating characteristic (ROC) analysis, which were finally set as 1.3 and 5 respectively.

Statistical analysis

Differences for changes in leukocytes, ANCs, ALCs and NLRs were analyzed using the Wilcoxon signed rank test. Analysis of OS and PFS was conducted using univariate and multivariate Cox proportional hazards models. Variables would be introduced into the multivariate models for following reasons: (1) showing a potential statistical significance (p value ≤ 0.2) in the univariate analyses; (2) proved to be prognostic in previous studies; (3) of our interest (e.g. the hemogram parameters). Three multivariate models were performed. For the OS, model A analysis included age, pre-operative KPS, EOR, and post-Stupp ALC. Model B analysis included age, pre-operative KPS, EOR, and post-Stupp NLR. Model C analysis included age, pre-operative KPS, EOR, and post-Stupp dNLR. For the PFS, the other three multivariate analyses A–C were also performed, except that the variable "age at diagnosis" was removed, as it was neither proved to be prognostic for PFS in previous studies nor of our interest. All p-values were 2-sided, with significance set at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics (Version 29; IBM, Armonk, NY, USA).

Results

Patient population

A total of 525 patients were diagnosed with glioblastoma and underwent surgery for tumor resection between Jan. 2011 and Dec. 2022 in a single tertiary medical center. Of these patients, 456 were excluded for the following reasons: age < 18 years, 7 patients; underwent surgery for recurrent glioblastoma, 17 patients; enrolled in other clinical trials, 74 patients; did not receive the standard CCRT or monthly aTMZ, 137 patients; received treatments other than the standard protocol, 42 patients; did not have complete lab data or follow-up MRI, 101 patients; hemogram results were potentially confounded by steroid prescription or infection, 26 patients; lost to follow-up within 2 years after surgery, 52 patients. As a result, 69 patients were included in this study. The inclusion and exclusion flowchart is shown in Fig. 1. The summary of demographics and clinical characteristics for the included patients is shown in Table 1.

Changes in leukocyte counts

After the standard CCRT and Stupp protocol, the leukocyte counts, ANCs, and ALCs were lower than in pre-operative hemograms, while the NLR increased. Statistical significance was observed in the change in leukocyte counts, ANCs, and ALCs ($p < 0.001$) but not in the change in NLR ($p = 0.853$ and 0.071, respectively) (Fig. 2). The changes in leukocyte counts, ANCs, ALCs and NLR for each patient across the three timepoints were also presented (Fig. 3).

Overall survival (OS)

The risk factor analyses for OS were presented in Table 2 for continuous variables, and Table 3 for categorical variables. As shown in Table 3, univariate analysis revealed remarkable statistical significance between age at diagnosis ≥ 70 ($p = 0.019$), post-Stupp dNLR ($p = 0.006$) and OS. No statistical significance was found between the OS and several variables, including post-CCRT ALC ≥ 500 cells/μL ($p = 0.104$), and post-Stupp ALC ≥ 500 cells/μL ($p = 0.128$). Potential statistical significance was found between the OS and pre-operative KPS ≥ 60 ($p = 0.056$). The other variables showed no statistical significance, including the EOR, the post-operative KPS, the post-CCRT NLR, and the post-Stupp NLR. The survival plots according to ALC, NLR and dNLR were presented in Fig. 4A–C.

In the multivariate analyses, both the age at diagnosis ≥ 70 ($p = 0.005$, 0.001, and 0.007, respectively) and pre-operative KPS ≥ 60 ($p = 0.046$, 0.007, and 0.033, respectively) were significantly correlated with the overall survival in all 3 models. The EOR, either STR or GTR, showed no significant benefit in OS in all 3 models. Among hemogram variables, the post-Stupp ALC ≥ 500

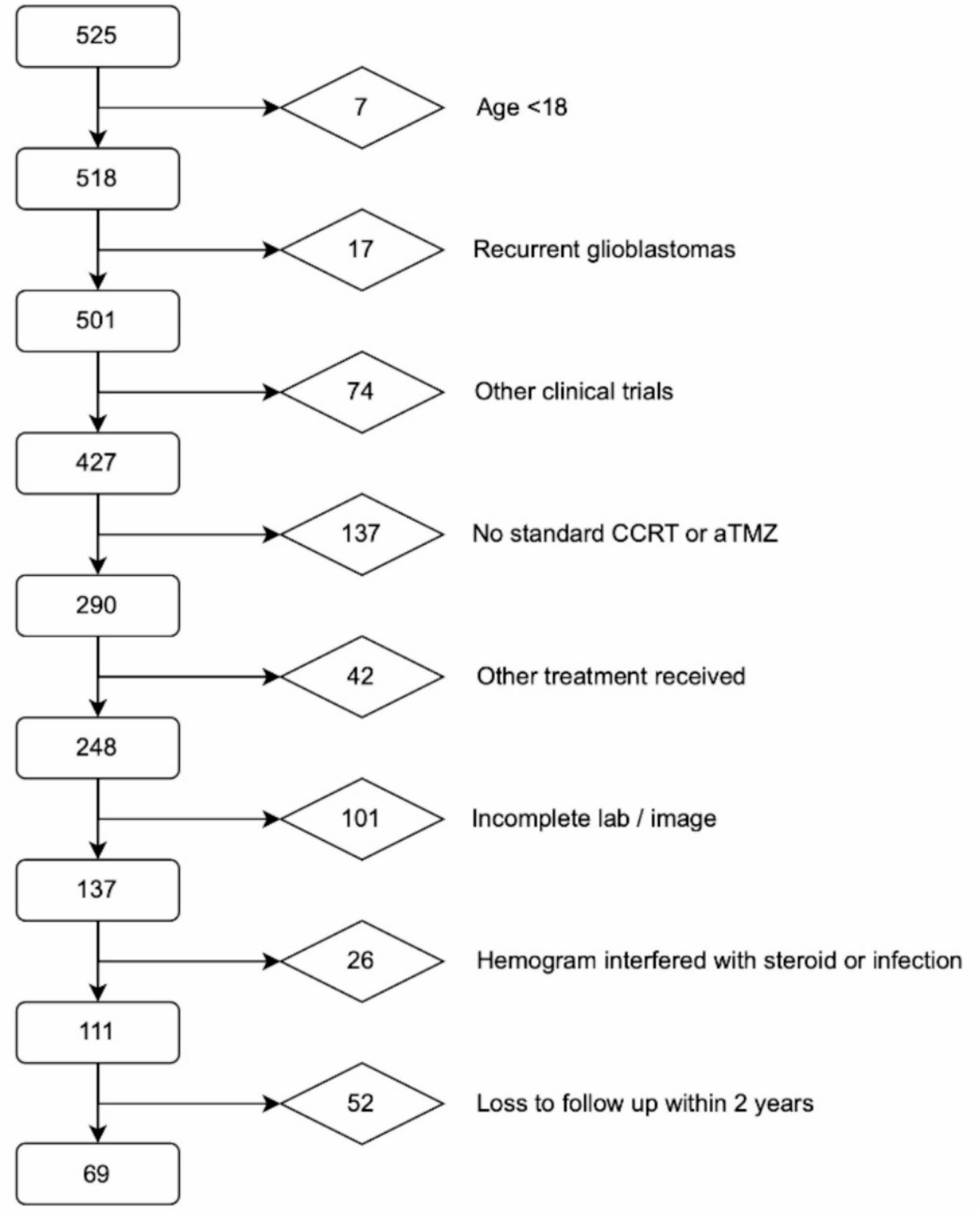

Fig. 1 The inclusion and exclusion flowchart for patient selection

Table 1 Summary of demographic and clinical characteristics of the included patients

	Median (SD) or number (%)
Age at diagnosis (year)	61.0 (12.9%)
	45 (65.2%)
Preoperative KPS	70 (14.3%)
Tumor location	
Lobar cerebral	64 (92.8%)
Cerebellar	2 (2.3%)
Central	6 (8.7%)
Multifocal	6 (8.7%)
Ki-67%	20 (21.5%)
Extent of resection	
GTR	33 (47.8%)
STR	25 (36.2%)
PR	11 (15.9%)
Hemogram (per μL)	
WBCs	8200 (2559.5)
Neutrophils	5565 (2278.6)
Lymphocytes	1692 (806.9)
Outcome	
Death	38 (55.1%)
Recurrence	64 (92.8%)
OS (month)	26 (17.3)
PFS (month)	9 (12.0)

KPS, Karnofsky performance status; GTR, gross total resection; STR, subtotal resection; PR, partial resection; WBC, white blood cell; OS, overall survival; PFS, progression free survival

cells/μL showed no significant prognostic values in our models. The post-Stupp NLR ≥ 5 and dNLR ≥ 1.3 both showed significant prognostic values ($p = 0.027$ and $p = 0.014$ respectively).

Progression-free survival (PFS)

The risk factor analyses for PFS were presented in Table 4 for continuous variables, and Table 5 for categorical variables. As shown in Table 5, univariate analysis found 3 variables that significantly correlated with PFS: pre-operative KPS ≥ 60, GTR status, and post-Stupp NLR ≥ 1.3 ($p = 0.017$, 0.042, and 0.043, respectively). No statistical significance was found between the PFS and the following 3 hemogram variables: post-CCRT ALC ≥ 500 cells/μL ($p = 0.184$), post-Stupp ALC ≥ 500 cells/μL ($p = 0.114$), and post-Stupp NLR ≥ 5 ($p = 0.087$). The other variables did not differ significantly, including the age at diagnosis, STR status, post-CCRT NLR ≥ 5, and post-CCRT dNLR ≥ 1.3. The survival plots according to ALC, NLR and dNLR are shown in Fig. 4D–F.

In the multivariate analyses, the GTR status did not show statistical correlation with the PFS in all 3 models ($p = 0.078$, 0.068, 0.105). Significant correlation between the pre-operative KPS ≥ 60 and PFS could be observed in all 3 models ($p = 0.034$, 0.015 and 0.038, respectively). The hemogram analysis revealed that neither the post-Stupp

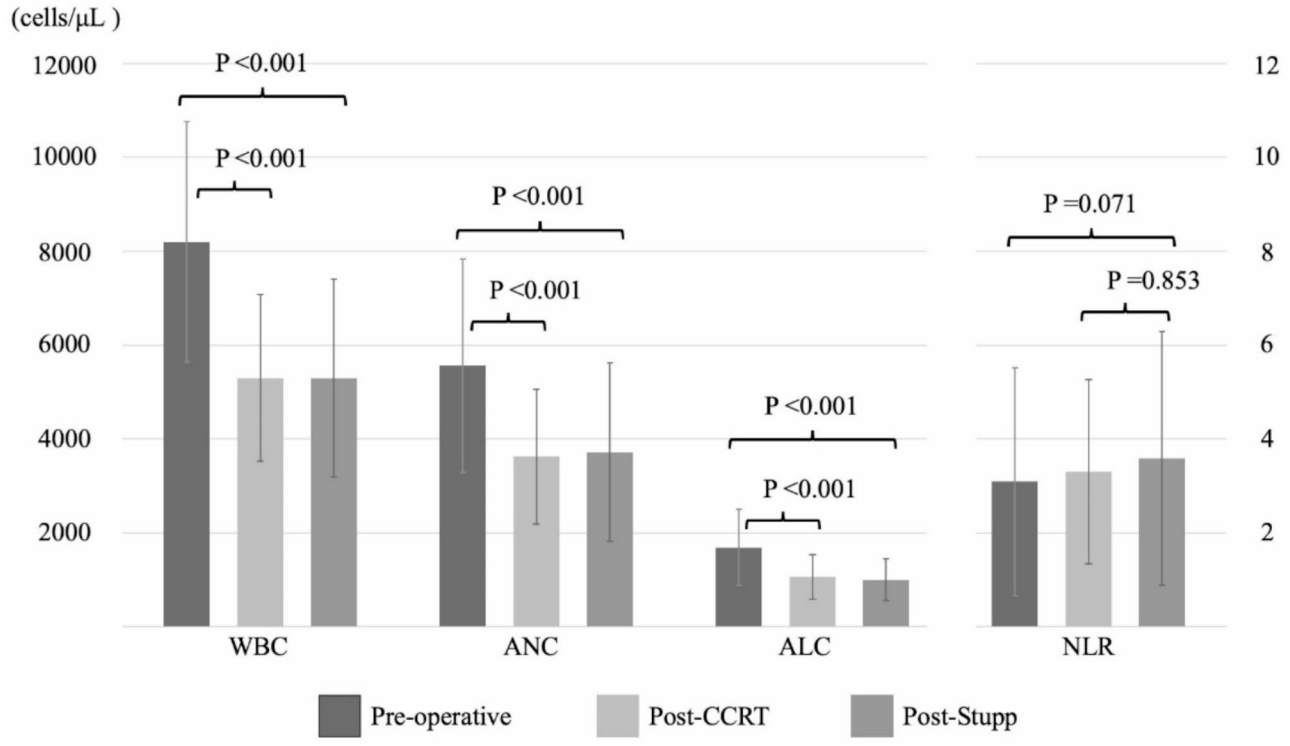

Fig. 2 Differences between pre-operative, post-CCRT, and post-Stupp hemograms, including leukocyte counts (WBC), absolute neutrophil counts (ANC), absolute lymphocyte counts (ALC), and the neutrophil-to-lymphocyte ratio (NLR). The analysis was performed with Wilcoxon signed rank test

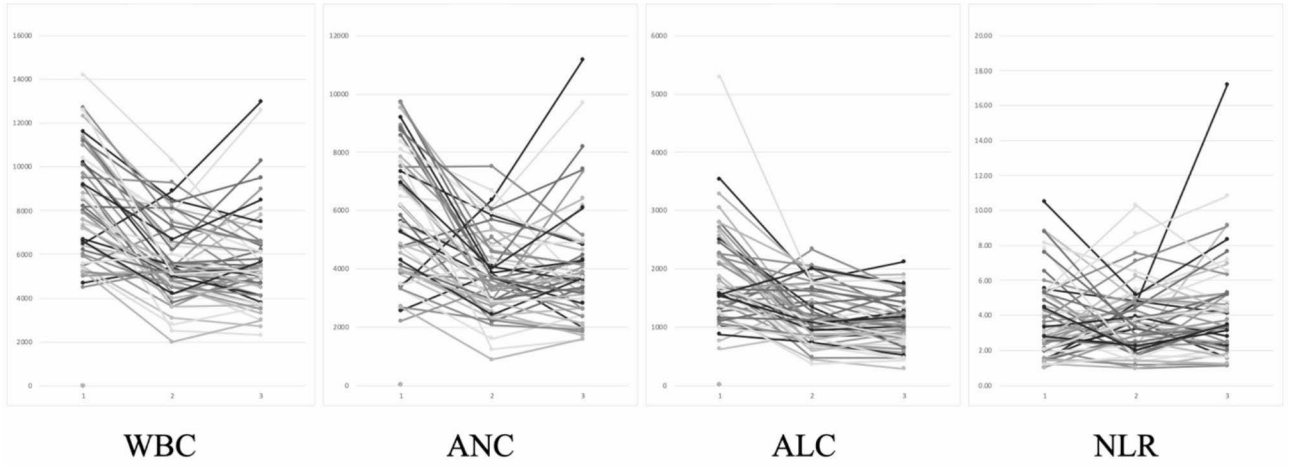

Fig. 3 Changes in leukocyte counts (WBC), absolute neutrophil counts (ANC), absolute lymphocyte counts (ALC), and the neutrophil-to-lymphocyte ratio (NLR) for each patient across three time points: pre-operative, post-CCRT, and post-Stupp

Table 2 Risk factor analysis for overall survival (OS), continuous variable

	HR	CI	*P* value
Age	1.016	0.990–1.042	0.235
KPS			
Pre-operative	0.978	0.956–1.002	0.069
Post-operative	0.994	0.976–1.011	0.467
ALC			
Pre-operative	1.000	1.000–1.001	0.535
Post-CCRT	1.000	0.999–1.001	0.859
Post-Stupp	1.000	0.999–1.001	0.508
NLR			
Pre-operative	0.960	0.836–1.104	0.569
Post-CCRT	0.979	0.799–1.200	0.840
Post-Stupp	1.040	0.945–1.145	0.421
dNLR			
Post-CCRT	0.995	0.568–1.741	0.986
Post-Stupp	1.000	0.849–1.177	0.999

HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; GTR, gross total resection; STR, subtotal resection; PR, partial resection; ALC, absolute lymphocyte count; CCRT, concurent chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; dNLR, the dynamic change of neutrophil-to-lymphocyte ratio

ALC, post-Stupp NLR ≥ 5, or post-Stupp dNLR ≥ 1.3 showed significant correlation with the PFS.

Cox proportional hazard models from a bootstrap resampling

The Cox model results from the bootstrap samples showed the similar adjusted hazard ratios and 95% confidence interval estimates for the categorical variables in NLR ≥ 5 (2.289 with 95% CI 1.056–4.937) and dNLR ≥ 1.3 (2.673 with 95% CI 1.268–6.079).

Discussion

Results interpretation and comparison with previous studies

We observed decreased WBC, ALC, and ANC and an increased NLR after the CCRT and standard Stupp protocol, as observed in a previous study [12]. The lack of significance in NLR could be attributed to the relatively small patient cohort. A previous study reports that this change in hemogram seems to remain at least for 1 year [13]. However, this suggestion needs confirmation by studies with complete lab data, longer follow-up times, and larger patient cohorts.

Of the 3 hemogram parameters investigated in this study (ALC, NLR and dNLR), the dNLR (cut-off value set at 1.3), showed the strongest prognostic value for both OS and PFS in univariate analyses. However, this finding was not reproduced in the multivariate model for PFS. This finding could be attributed to the strong interactive effect between the EOR and dNLR, since the p-value after removing EOR as a variable in model C was 0.091 for post-Stupp dNLR ≥ 1.3 (not shown in Tables). This finding also be explained by our hypothesis that the immunosuppression effect was alleviated after a larger proportion of the tumor was removed. At the same time, in the multivariate analyses, a post-Stupp NLR ≥ 5 showed significant prognostic value in predicting the OS ($p = 0.027$) but no prognostic value in predicting the PFS ($p = 0.086$).

While previous studies have reported the pre-operative NLR to be a prognostic factor for OS in gliomas, this finding was not reproduced in this study ($p = 0.569$, not presented in Tables) [14–16]. We propose that the post-Stupp NLR/dNLR might provide more information than the pre-operative NLR for the following reasons. First, the pre-operative NLR provides no information regarding the change in tumor burden or tumor microenvironment. Second, since CCRT and Stupp protocol have

Table 3 Risk factor analysis for overall survival (OS), categorical variable

	Univariate			Multivariate model A			Multivariate model B			Multivariate model C		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age (≥ 70 vs < 70 year)	1.571	1.144–4.465	0.019	3.109	1.397–6.920	0.005	4.018	1.740–9.276	0.001	3.03	1.352–6.789	0.007
Gender (female vs male)	0.702	0.346–1.427	0.329									
KPS (≥ 60 vs < 60)												
Pre-operative	0.44	0.189–1.022	0.056	0.386	0.152–0981	0.046	0.292	0.119–0716	0.007	0.382	0.157–0.927	0.033
Post-operative	0.71	0.276–1.831	0.479									
Resection												
PR	Reference group											
STR	0.714	0.271–1.878	0.494	1.073	0.377–3.050	0.895	1.119	0.390–3.210	0.834	1.254	0.425–3.701	0.682
GTR	0.672	0.264–1.710	0.404	0.738	0.287–1.899	0.529	0.736	0.285–1.899	0.526	1.039	0.387–2.792	0.94
ALC (≥ 500 vs < 500/μL)												
Pre-operative	N/A											
Post-CCRT	0.296	0.068–1.285	0.104									
Post-Stupp	0.438	0.152–1.267	0.128	0.586	0.184–1.873	0.368						
NLR (≥ 5 vs < 5)												
Preoperative	0.642	0.282–1.464	0.292									
Post-CCRT	1.188	0.409–3.446	0.752									
Post-Stupp	1.468	0.744–2.895	0.268				2.288	1.099–4.767	0.027			
dNLR (≥ 1.3 vs < 1.3)												
Post-CCRT	1.234	0.520–3.232	0.578									
Post-Stupp	2.491	1.301–4.770	0.006							2.387	1.191–4.783	0.014

HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; GTR, gross total resection; STR, subtotal resection; PR, partial resection; ALC, absolute lymphocyte count; CCRT, concurrent chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; dNLR, the dynamic change of neutrophil-to-lymphocyte ratio

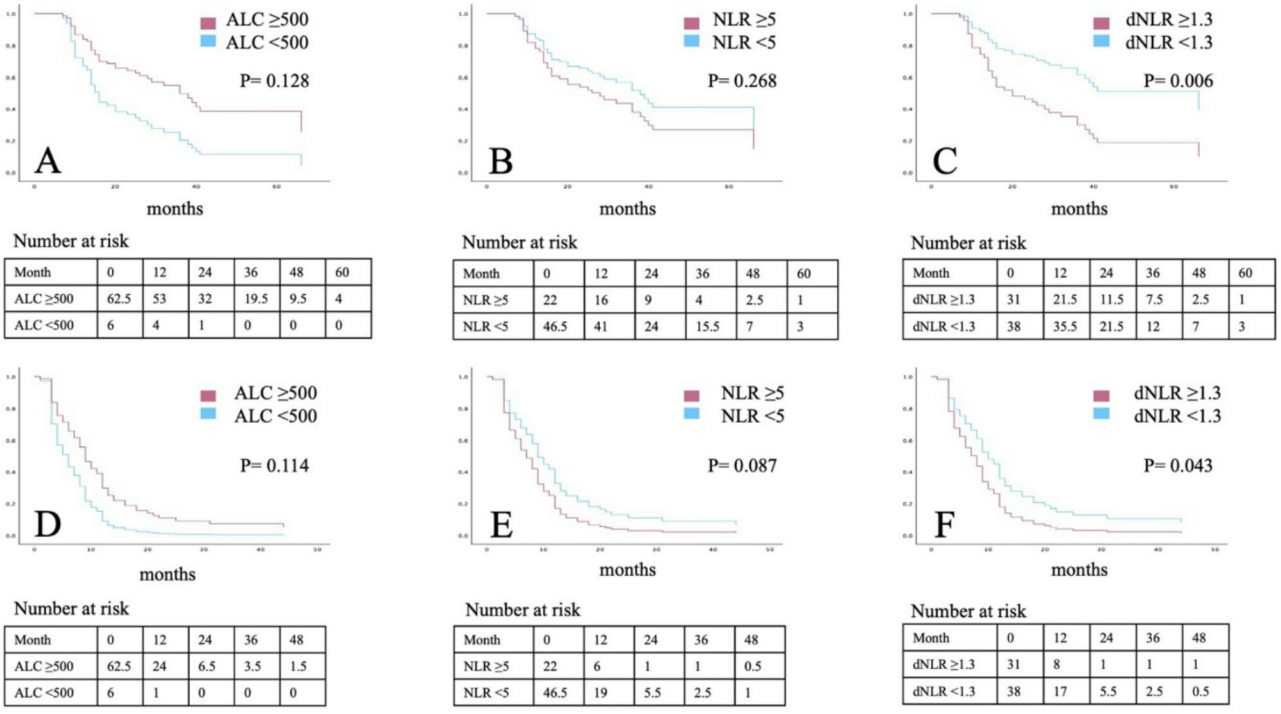

Fig. 4 Survival curves and risk tables based on post-Stupp hemograms. **A-C**. Survival curves for overall survival (OS); **D-F**. Survival curves for progression free survival (PFS)

Table 4 Risk factor analysis for progression free survival (PFS), continuous variable

	HR	CI	*P* value
Age	0.999	0.981–1.018	0.921
KPS			
Pre-operative	0.992	0.974–1.011	0.418
Post-operative	0.988	0.974–1.003	0.107
ALC			
Pre-operative	1.000	1.000–1.000	0.863
Post-CCRT	1.000	0.999–1.000	0.600
Post-Stupp	1.000	0.999–1.000	0.146
NLR			
Pre-operative	1.008	0.904–1.123	0.891
Post-CCRT	0.979	0.846–1.133	0.778
Post-Stupp	1.114	1.017–1.221	0.020
dNLR			
Post-CCRT	0.941	0.582–1.521	0.803
Post-Stupp	1.154	1.005–1.326	0.043

HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; GTR, gross total resection; STR, subtotal resection; PR, partial resection; ALC, absolute lymphocyte count; CCRT, concurent chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; dNLR, the dynamic change of neutrophil-to-lymphocyte ratio

been widely accepted as standard adjuvant treatments for high-grade gliomas, the prognosis depends primarily on the treatment, including a maximal safe margin of resection and completion of the standard treatment. Therefore, in our opinion, the prognostic value should be higher after the Stupp protocol.

Aside from the hemogram parameters, different prognostic factors of high grade glioma and glioblastoma were proposed from previous studies, including age, KPS, the EOR, molecular markers (MGMT methylation, IDH mutation, 1p/19q co-deletion, EGFR alteration, TERT promoter mutation, and etc.), and post-operative Stupp regimen [17–20]. In addition, several newer molecular markers (e.g., C5AR2, specific autophagy-related genes) also show potentially promising value [21]. In this study, all the glioblastomas were IDH-wildtype according to the 2021 WHO classification of tumors of the central nervous system. Other molecular markers were not available in all patients, especially in the early years, and therefore were not analyzed in this study.

Growing evidence has revealed a correlation between performance status and the glioblastoma survival (OS or PFS) [22–26]. Regarding OS, lower performance status clearly correlates with shorter OS due to the numerous subsequent medical issues resulting from a bedridden status, including aspiration pneumonia, poor nutrition, and bedsores. The shorter PFS might result from cognitive and functional decline following tumor recurrence. On the other hand, advances in cancer neuroscience suggest that nervous system–cancer interactions can regulate oncogenesis and the tumor microenvironment [27–29]. In this study, a pre-operative KPS ≥ 60 correlated with a longer OS and PFS and the protective effect was significant in all multivariate models (Tables 3 and 5),

Table 5 Risk factor analysis for progression free survival (PFS), categorical variable

	Univariate			Multivariate model A			Multivariate model B			Multivariate model C		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age (≥ 70 vs < 70 year)	1.13	0.639–1.999	0.674									
Gender (female vs male)	0.894	0.532–1.500	0.67									
KPS (≥ 60 vs < 60)												
Pre-operative	0.428	0.213–0.861	0.017	0.441	0.207–0.940	0.034	0.409	0.200–0.838	0.015	0.459	0.221–0.957	0.038
Post-operative	0.646	0.306–1.364	0.252									
Resection												
PR	Reference group											
STR	0.803	0.389–1.655	0.552	0.912	0.434–1.915	0.807	0.872	0.416–1.828	0.716	0.9	0.428–1.890	0.78
GTR	0.48	0.236–0.974	0.042	0.526	0.257–.076	0.078	0.512	0.250–1.050	0.068	0.55	0.267–1.134	0.105
ALC (≥ 500 vs < 500/μL)												
Pre-operative	N/A											
Post-CCRT	0.448	0.137–1.466	0.184									
Post-Stupp	0.499	0.211–1.182	0.114	0.804	0.318–2.031	0.644						
NLR (≥ 5 vs < 5)												
Preoperative	0.97	0.548–1.717	0.918									
Post-CCRT	1.14	0.534–2.437	0.734									
Post-Stupp	1.587	0.935–2.692	0.087				1.601	0.935–2.741	0.086			
dNLR (≥ 1.3 vs < 1.3)												
Post-CCRT	0.926		0.789									
Post-Stupp	1.677	1.017–2.767	0.043							1.358	0.800–2.305	0.257

HR, hazard ratio; CI, confidence interval; KPS, Karnofsky performance status; GTR, gross total resection; STR, subtotal resection; PR, partial resection; ALC, absolute lymphocyte count; CCRT, concurrent chemoradiotherapy; NLR, neutrophil-to-lymphocyte ratio; dNLR, the dynamic change of neutrophil-to-lymphocyte ratio

again highlighting the prognostic value of baseline performance status.

In this study, a trend was observed showing that a greater extent of resection resulted in a longer OS, though far from statistically significant. A longer PFS correlated with GTR status but not STR status. Although the optimal extent of resection for glioblastoma remains under debate, the growing consensus to date is to achieve a maximal safe margin of resection, which has shown benefits in both OS and PFS [30]. We attribute the lack of statistical significance in our study to the following factors. First, the surgery dates spanned more than a decade (2011–2022), during which time the concept of maximal safe resection has been established. In addition, intra-operative adjunct treatments have also been gradually applied as a regular practice, including 5-aminolevulinic acid (5-ALA), cortical mapping, intra-operative MRI, and the awake craniotomy in cooperation with a neurologist for intra-operative neurologic performance monitoring. Thus, earlier surgical procedures may have achieved maximal resection but at the expense of brain function, leading to impaired neurocognitive outcomes and performance status. Thus, extensive tumor resection for a better OS had little benefit for the patient.

Treatment-related lymphopenia

Previous studies have demonstrated the presence and importance of post-treatment lymphopenia [5, 13, 31]. Grossman et al. concluded that a low CD4 count 2 months after standard treatment with radiation therapy and TMZ is independently associated with shorter survival [13]. Kim et al. found that while leukopenia and neutropenia also occurred after standard treatment, these conditions recovered much earlier than lymphopenia [12]. This finding might explain the increase in NLR and dNLR after standard treatment. Several factors have been proposed to cause the observed post-treatment lymphopenia, including TMZ, radiation therapy, corticosteroid use, and even the progression to primary malignancy [32].

Neutrophils and the tumor microenvironment

Neutrophilia is associated with the presentation of malignancy, including glioblastoma [33]. Granulocyte colony-stimulating factor (G-CSF) secretion from tumor cells is one of the hypothetical causes [34]. G-CSF shifts bone marrow hematopoiesis toward the myeloid lineage and away from the lymphocyte lineage, thereby increasing neutrophil and decreasing lymphocyte counts [35, 36]. Neutrophilia also is thought to accelerate tumor growth through several tumor growth-promoting factors, including vascular endothelial growth factor, IL-6, IL-8, matrix metalloproteinases, and elastases [37–41]. By promoting angiogenesis and metastasis and suppressing adaptive immune responses, these factors exacerbate the progression and invasion of malignant cells. These findings were not only found in clinical practice, but also widely revealed in basic studies [42–45].

Although neutrophilia is related to elevated immune activity in some scenarios, malignancy-related neutrophilia actually causes immunosuppression, in part by the G-CSF-induced shift in hematopoiesis toward the myeloid lineage. In addition, neutrophils are reported to suppress the cytolytic activity of other immune cells, including cytotoxic T lymphocytes and natural killer (NK) cells. Other studies have reported the critical role of tumor-infiltrating lymphocytes and NK cells in treating cancer [33, 46, 47].

A vicious cycle establishes the TME, a systemic and local tumor-related inflammation that further promotes immunosuppression and malignancy progression. Thus, the shift in the hemopoietic lineage with resultant neutrophilia, lymphopenia, and increased NLR is thought to be an important laboratory presentation of immunosuppression and tumor progression [33, 47].

Tumor associated neutrophils

Despite reports that neutrophils promote malignancy, neutrophils also have been found to have antitumoral effects [47, 48]. During neutrophil polarization, tumor associated neutrophils (TANs) are polarized to anti-tumor (N1) or pro-tumor (N2) phenotypes, depending on the environment and the cytokines they are exposed to [46, 49]. Neutrophil polarization factors are often secreted by tumor cells themselves. In addition, TANs exhibit functional plasticity and the ability to undergo alternative activation upon different TME exposures [46, 50]. In fact, Gurrierit et al. reported the prognostic role of CD68 + macrophage and CD66b + neutrophils expressed in vascular/perivascular area in predicting median OS and PFS [51].

Advantages and disadvantages of NLR and dNLR

Although the NLR has been widely accepted as an independent factor for glioblastoma prognosis, few studies have investigated the changes in NLR. Instead, most studies have focused only on the NLR at a static time point, such as the preoperative NLR, and its prognostic value. Considering the complicated interactions between TANs and the TME, we believe the NLR is dynamic and reflects the present tumor burden in response to treatment. Here, we investigated the NLR and dNLR, analyzing the change in NLR relative to the pre-treatment status, at 2 time points: after the CCRT and after the standard Stupp protocol. While the post-Stupp NLR ≥ 5 showed no significant correlation with the OS or PFS, dNLR ≥ 1.3 was correlated significantly with a shorter OS and PFS in univariate analyses. Ma et al. also reported that changes in

the NLR, using the interval between preoperative and postoperative NLRs, correlated significantly with tumor recurrence [7]. However, the study included patients with glioblastoma and grade 2–4 gliomas.

Despite their significant correlation with glioblastoma prognosis, NLR and dNLR use in clinical practice still has some disadvantages. First, the hemogram results, particularly the distribution of leukocyte cell lineages, can be affected by many common factors other than tumor status. For instance, the NLR could be highly influenced by infection, steroid use, and chemotherapy. In this study, we tried to exclude confounding factors from infection and steroid use by careful chart review. Regarding chemotherapy, an observational study reports a decrease in NLR during the standard Stupp protocol compared to the preoperative and post-Stupp status [12]. However, no significant difference was observed in NLR between the CCRT or each monthly aTMZ. This finding further supports our conclusion that the NLR and dNLR can be used to predicting prognosis and even detect tumor recurrence.

Dynamic change in leukocyte count as a prognostic factor for glioblastoma and its potential for early detection of glioblastoma recurrence

Several studies have demonstrated the prognostic value of NLR for glioblastoma and glioma. To explain this hemogram finding, some studies emphasize the importance of increased neutrophil activity, while other favor the presence of lymphopenia [3, 5, 6, 12, 14, 52, 53]. These studies evaluated data at different timepoints, with most studies focusing on the pre-operative NLR. While several NLR cutoff values have been proposed, NLR > 4 has is most commonly proposed to be an independent prognostic factor for a worse outcome [16]. In our analysis, while a post-Stupp NLR ≥ 5 did not show a significant correlation with OS or PFS, a dNLR ≥ 1.3 was significantly associated with shorter OS and PFS in univariate analyses. Additionally, in the multivariate analysis, NLR ≥ 5 was found to be significantly correlated with OS ($p = 0.027$), which is consistent with previous reports [16]. Notably, dNLR remained strongly associated with OS ($p = 0.014$) in multivariate analysis. These findings highlight the potential importance of dNLR as a key prognostic marker for predicting outcomes and recurrence in GBM patients.

To date, no widely accepted biomarker had been identified for glioblastoma recurrence. Therefore, the only surveillance for tumor recurrence involves brain MRI, which is expensive and not always available in all medical settings. Considering the high recurrence rate of glioblastoma and the survival benefit from re-operation [54], more frequent surveillance for detecting recurrence could be beneficial.

To evaluate the correlation between dynamic changes in leukocyte count with tumor recurrence and its potential as a glioblastoma biomarker, we analyzed post-Stupp ALC, NLR, and dNLR for PFS using the Cox proportional hazard model. A post-Stupp dNLR ≥ 1.3 correlated significantly with a shorter PFS in univariate analysis. ALC ≥ 500 and NLR ≥ 5 also showed potential prognostic value, but without significance. This finding might reflect the importance of the post-treatment lymphocyte count, which is hypothesized to be the main leukocyte in treating malignancy and is the basis of current immunotherapy using peptide vaccines, adaptive T cells, or immune checkpoint inhibitors. Though still lacking strong evidence, emerging clinical immune biomarkers and promising treatment outcomes have been achieved [55–64].

Other potential systemic inflammatory markers

Several systemic inflammatory markers other than NLR have been reported and evaluated. A systemic review and meta-analysis reported that the red cell distribution width and prognostic nutritional index, but not the platelet/lymphocyte ratio or lymphocyte/monocyte ratio, are also independent factors for predicting the OS for patients with glioma [65]. One study reported NLR to be a better prognostic factor for glioblastoma than the platelet/lymphocyte ratio or systemic immune inflammation index [15]. Another recent meta-analysis supported the usefulness of NLR, platelet/lymphocyte ratio, systemic immune inflammation index and systemic inflammation response index as prognostic factors in patients with glioblastoma [66]. However, a larger prospective study with a long follow-up period has not yet been conducted.

Strengths and limitations

To our knowledge, this study is the first to investigate the use of dynamic changes in NLR for predicting glioblastoma prognosis, including the OS and PFS. Although only 69 patients were enrolled, Cox proportional hazard models with bootstrap resampling yielded consistent results, suggesting that an NLR ≥ 5 or dNLR ≥ 1.3 could serve as prognostic indicators for monitoring and predicting outcomes in glioblastoma patients. However, more cases should be enrolled to yield a more consistent result. This study has several limitations. First, although we excluded patients whose hemogram results might had been confounded by steroid use or major infection, other factors could potentially affect the distribution of hemograms and leukocyte counts, such as unreported trivial infection, anemia, nutritional status or concomitant medications affecting blood counts. Secondly, the molecular markers proved to show prognostic values, such as MGMT methylation [67, 68], which was not available in our patients. Instead of methylation status, we performed immunohistochemistry method to analyze the MGMT

protein expression level and therefore MGMT methylation status. The statistical results did not reveal any differences between both groups. In addition, this study was retrospective in design, with no pre-determined evaluation time point or cut-off value for the hemograms. The inconsistency in follow-up does exist, and prevent us from making a stronger conclusion. Due to these limitations in the study design, the results do not provide solid support for using the dNLR to detect the recurrence of glioblastoma. Nonetheless, using the values NLR ≥ 5 and dNLR ≥ 1.3 seems to be a potential clinical parameter. Considering the completely different features of the TAN phenotypes (N1 and N2), further studies could focus on the value of N2LR, which may better reflect the tumor-associated immunosuppression and tumor burden and would be less easily influenced by other medical conditions such as steroid use or infection. Hemogram analysis with a longer follow-up period is necessary to gather data regarding long-term surveillance. Studies with a prospective design enrolling more cases are warranted to determine the value of dNLR as a serum biomarker for predicting prognosis and detecting tumor recurrence.

Conclusion

This study revealed that for patients of glioblastoma, NLR ≥ 5 and dNLR ≥ 1.3 after the standard Stupp protocol correlated significantly with a worse prognosis. The potential of these 2 parameters for predicting PFS was also found in this study, though lacking significance. Whether the dNLR could be a reliable biomarker for detecting glioblastoma recurrence still warrants further well-designed and prospective studies.

Author contributions

Meng-Wu Chung initiated the conceptualization, did the formal analysis and wrote the original draft; Ching-Chieh Tzeng collected the clinical data and wrote the original draft; Yin-Cheng Huang, Kuo-Chen Wei, Peng-Wei Hsu and Chi-Cheng Chuang provided the resources and data curation; Ya-Jui Lin and Ko-Ting Chen did the formal analysis and prepared the tables; and Cheng-Chi Lee supervised and validated the manuscript and acquired the funding.

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Data availability

The data used to support the findings of this study are included within the article.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Chang Gung Memorial Hospital granted ethical approval for this study (IRB No. 104-2656B) and waived the requirement for obtaining written informed consent. This study was performed in line with the principles of the Declaration of Helsinki

Competing interests

The authors declare no competing interests.

Consent to participate

Not applicable.

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