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Rise in post-resection neutrophil-to-lymphocyte ratio correlates with decreased survival in glioblastoma patients

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Abstract

Background. Neutrophil-to-lymphocyte ratio (NLR) is used in the prognostication of multiple malignancies. However, the NLR value in glioblastoma (GBM) is controversial. This controversy may be due to the unaccounted effect of dexamethasone on NLR. Using retrospective data from 230 isocitrate dehydrogenase-1 (*IDH*) wild-type GBM patients, we studied the prognostic value of NLR in relation to dexamethasone treatment in GBM.

Methods. We retrospectively analyzed 230 patients with GBM. NLR and dexamethasone use were used as dichotomous variables with cutoff values of 9.5 and 8 mg, respectively. Correlations between high NLR, as well as NLR change after surgery, and patient outcome measures, including post-surgical complications and survival, were assessed using Kaplan–Meier curves, logistic, and Cox regression analyses.

Results. We demonstrate in this study that high perioperative NLR (≥9.5 NLR) does not associate with survival of GBM patients (274 days, 95% confidence interval [CI] 211–337, vs. 229 days, 95% CI 52–406, $P = .9$). However, high positive change in NLR (≥6 units) (higher postoperative NLR relative to preoperative NLR) has a significant association with decreased survival in GBM patients (196 days, 95% CI 121–270, vs. 304 days, 95% CI 223–384, $P = .01$). High preoperative and perioperative average dexamethasone (≥8 mg) treatment did not change the perioperative NLR trend and were not associated with decreased survival.

Conclusions. We demonstrate that an increase in NLR after surgery associates with decreased GBM patient survival.

Key Points

- Neutrophil-to-lymphocyte ratio (NLR) change is predictive of survival in glioblastoma patients.
- NLR change is predictive of all-complication rate within 3 months postoperatively.
- Dexamethasone treatment does not impact NLR in glioblastoma patients.

Glioblastoma (GBM) has a median survival time that ranges from 14 to 16 months.[1,2] Despite advances in treatment, local recurrence remains a major contributor to mortality. Therefore, there is a need to identify biological parameters that can serve as prognostic and treatment response indicators. Traditional prognostic factors, such as the Karnofsky performance status (KPS), age, extent of resection, and $O^{(6)}$-*methylguanine-DNA methyltransferase* (*MGMT*) promoter methylation status are useful in identifying GBM patients at risk of shorter survival. However, individual patient trajectories are sometimes difficult to predict.

Importance of the Study

We assessed in this study correlations between neutrophil-to-lymphocyte ratio (NLR) and glioblastoma (GBM) patient outcome in relation to perioperative dexamethasone treatment. This is the first study to assess the prognostic value of perioperative NLR level on a relatively large Isocitrate dehydrogenase-1 (*IDH-1*) wild-type GBM patient cohort of 230 subjects. This study demonstrates how the use of NLR is different in GBM from other malignancies. We show that in GBM, change in NLR across the surgery day, rather than the average perioperative NLR measure, correlates with decreased GBM patient survival and complications. In addition, high dexamethasone treatment did not correlate with survival or complication events and did not predict change in perioperative NLR. Our study highlights the prognostic value of NLR in GBM and helps resolve the controversy around the utility of NLR in the prognostication of GBM.

High neutrophil-to-lymphocyte ratio (NLR) was shown to be a negative prognostic factor in more than 35 000 patients with different cancer types.[3] High NLR suggests an imbalance between the number of neutrophils and lymphocytes and a neutrophilic state that induces the apoptosis of lymphocytes.[4] Consequently, a high NLR may signify a downregulation of anti-tumorigenic activity, which is reliant on lymphocytes, natural killer cells, and T-cell function.[4–6]

Despite the robust neutrophilia and lymphopenia recorded in glioma,[7] the mechanism driving neutrophil recruitment in GBM is not clear. In GBM, it is postulated that increased tumor-associated neutrophils can contribute to immunosuppression, angiogenesis, and tumor growth.[8] The clinical significance of NLR has been previously studied but with inconsistent results. A meta-analysis summarized 16 reports on the relationship between preoperative and postoperative NLR and glioma patient prognosis.[9] The 16 reports used NLR cutoff values that ranged from 2.5 to 7.5 with an average of 4.0. The meta-analysis showed that high preoperative NLR is predictive of unfavorable overall survival in glioma patients of different grades and that low NLR is predictive of better survival in GBM patients.[9] Furthermore, other studies created prognostic nomograms that included NLR for GBM.[10,11] However, 12 of the 16 studies included in the meta-analysis originated in Asia, and subgroup analysis based on ethnicity showed that low NLR predicted a positive prognosis in Asians but not in Caucasians.[9] On the other hand, other studies have demonstrated that there is no link between NLR and patient survival on multivariate analysis.[10,12]

In this study, we aimed to verify the utility of NLR as a prognostic marker in isocitrate dehydrogenase-1 (*IDH-1*) wild-type GBM patients and the role of dexamethasone in contributing to perioperative NLR changes. We also assessed the association between the timing of dexamethasone treatment and NLR changes. Our findings highlight a potential role for neutrophils in tumor progression after glioblastoma surgical resection.

Materials and Methods

Patient Selection and Data Collection

McGill University Health Centre Research Ethics Board Neuroscience and Psychiatry Panel (study number 2021-7322) approval was acquired instead of individual patient consent, given the retrospective nature of the study. A group of 443 adult patients diagnosed with GBM and treated at the Montreal Neurological Hospital (MNH) from 2014 to 2018 were considered. Exclusion criteria included a previous grade II or III glioma or a pre-existing diagnosed malignancy, *IDH*-1 gene mutation, first resection or follow-up at a different facility, biopsy conducted at another facility more than 3 months before presentation at the MNH, and inadequate follow-up or insufficient perioperative information (including NLR values; Figure 1A). After satisfying the exclusion criteria, 230 patients were examined. Data were collected from the electronic medical record system, which included age at histological diagnosis, sex, body mass index (BMI), tumor *IDH 1* and *IDH 2* pathological variants, tumor *MGMT* promoter methylation status, KPS,[13] dexamethasone treatment and dose, extent of resection, type of adjuvant therapy, and blood laboratory values that include white blood cell count, neutrophils, lymphocytes, monocytes, and eosinophils. Extent of resection was dichotomized into biopsy only; subtotal resection in 1 group and gross total resection in another group. Adjuvant therapy was dichotomized as any adjuvant therapy in 1 group and no adjuvant therapy in another. Blood laboratory values were recorded at 11 time points, when available. These time points included laboratory values measured 3–30 days prior to surgery. Laboratory values were also recorded from the date of operation (Day 0) to 7 days postoperatively. Patient outcome parameters include any complication (thromboses and infection events) within 3 months, and survival at 2 years. Thrombotic events include deep vein thrombosis, pulmonary embolism with or without a deep vein thrombosis, and/or stroke. Infection events include localized wound infections at the surgical site, urinary tract infections, pneumonia, sepsis, and meningitis. A STROBE research reporting guideline was used in our manuscript.

Statistical Methods

Statistical analysis and graphical presentation were completed with *IBM SPSS Statistics* for Macintosh, version 28.0.0.0 (IBM Corp.) and *GraphPad Prism* (9.0). Quantitative variables were described through measures of central tendency (mean and median) and dispersion (standard deviation and interquartile range). NLR was

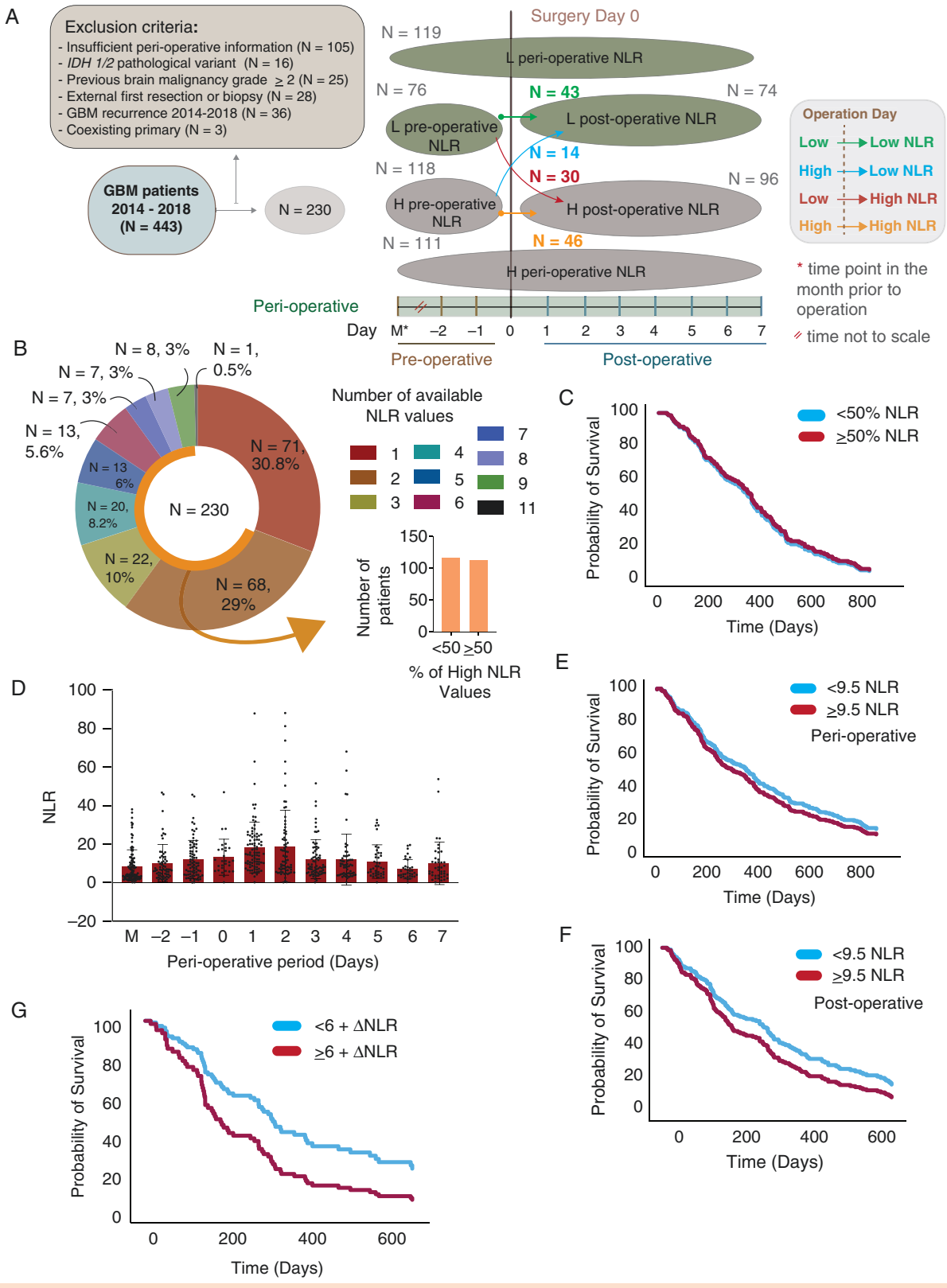

Figure 1. Assessing correlation between neutrophil-to-lymphocyte ratio (NLR) and survival. (A) Flow schematic for glioblastoma (GBM) patients ($N = 230$) after exclusion of patients as per the adopted exclusion criteria were stratified based on perioperative NLR level (high NLR ≥ 9.5) or based on preoperative and postoperative NLR levels. Within model 1, patients were also grouped based on changes in preoperative and postoperative NLR levels (high to high, high to low, low to high, and low to low). (B) Pie chart showing the breakdown of patients based on the

available number of NLR values on independent perioperative days and based on the percentage of NLR values that are high (≥50%). The arrow indicates the patients who have 2 or more available NLR values on separate perioperative days and who were analyzed. The bar graph demonstrates the number of patients who have 2 or more NLR values with 50% or more of these NLR values being ≥9.5. (C) Kaplan–Meier curves for ≥50% high NLR values (229, 95% CI 152–306, *N* = 113) and <50% high NLR values (290, 95% CI 205–375, *N* = 117) (*P* = .2). (D) Bar graph with scatter plot demonstrating the average NLR value for each of the perioperative days and individual patient NLR values. (E) Kaplan–Meier curves for high (NLR ≥ 9.5) (247, 95% CI 163–330, *N* = 98) and low (277, 95% CI 189–364, *N* = 100) average perioperative NLR (*P* = .3). (F) Kaplan–Meier curves for high (NLR ≥ 9.5) (229, 95% CI 140–317, *N* = 96) and low (320, 95% CI 193–446, *N* = 74) average postoperative NLR (*P* = .09). (G) Kaplan–Meier curves for high (196, 95% CI 121–270, *N* = 42) and low (304, 95% CI 223–384, *N* = 36) positive NLR change (≥6 units) (+ΔNLR, postoperative NLR > preoperative NLR) (*P* = .01).

presented both dichotomously and as a continuous variable to identify the most appropriate method for correlation with different patient outcomes. The NLR cutoff value of 9.5 is computed by assessing the area under the curve (AUC) for death within 2 years and any complication events, including infection and thrombosis. AUC values that are significantly different from 0.5 were considered, and the NLR for the respective outcome variable was approximated from the receiver operator curve. Three NLR values approximated from AUC of different test variables were used to compute the average of 9.5 used as a cutoff for NLR to define low and high NLR in our study (Supplementary Figure 1A–E, Supplementary Tables 1 and 2). Survival was defined as the time interval between histological diagnosis and death. We used Kaplan–Meier method with log-rank test and Cox regression for univariate and multivariate analyses, respectively. Covariates in the multivariate analysis consisted of variables that had a *P*-value of .2 or less for the respective analysis. Statistical significance was set at $P < .05$.

Study Design

NLR was calculated by dividing the neutrophil over the lymphocyte counts. We computed different measures of NLR. The perioperative period includes a measure within 1 month prior to surgery (*M*) and days –2 and –1 prior to surgery to the postoperative period day 7 (Figure 1A). The first measure is the average perioperative NLR (from *M* to postoperative day 7). Preoperative NLR is the average of 3 time points, M, day –2, and day –1 NLR values, relative to surgery day. Postoperative NLR is the average value for any available NLR values from postoperative days 1 to 7. These periods are depicted in Figure 1A. We then grouped patients based on the percentage of available NLR values that are ≥9.5 (Figure 1B). Patients who have at least 2 or more independent NLR values with ≥50% of NLR values being ≥9.5 are grouped as high NLR (≥50% NLR). This serves our analysis by accounting for the number of available NLR values rather than just the value of NLR.

We also measured the average change in NLR (ΔNLR) by subtracting the average postoperative NLR from the average preoperative NLR. Cutoff values for positive change (+ΔNLR) were set using the median of 6. Average dexamethasone was calculated by dividing the total dosage in the perioperative period divided over the number of available data points on separate days. We divided low and high average dexamethasone use based on the average dexamethasone dose of 8 mg.[14]

Standard Clinical Approach and Follow-Up

The clinical approach included a contrast-enhanced brain MRI before the surgical procedure. Surgical management was described as biopsy only, subtotal resection (any residual enhancing tumor), or gross total resection (no residual enhancing tumor). These data are acquired from postoperative T1-weighted post-gadolinium axial sequences on 1.5-T MRI performed within 48 h after the operation. For patients who underwent multiple surgical procedures, data were collected at the time of the first surgery.

The dose of dexamethasone received by patients before and after surgery was determined by the treating physician to optimize the control of cerebral edema. The histopathological diagnosis and *MGMT* promoter methylation were assessed as part of a routine clinical practice and reported by a qualified neuropathologist. DNA was modified by bisulfite treatment and amplified by methylation-specific PCR. Capillary electrophoresis was used to detect products as previously described.[15] Methylation status was classified as methylated, unmethylated, or undetermined with a detection limit of 10% methylation in the DNA sample.

Results

Study Population

A group of 230 patients was analyzed in the perioperative period after satisfaction of exclusion criteria (Figure 1A, Table 1). The mean age of the patients at diagnosis was 64.4 ± 11.8 years. The mean BMI was 26 ± 5.1 kg/m^2. Female patients constituted 36% of the patient group, and patients with tumors showing methylation of the *MGMT* promoter constituted 42% of the patient cohort. Only 2 patients did not receive preoperative dexamethasone, but the remaining patients (*n* = 228) received either a low daily average preoperative dexamethasone (<8 mg, *N* = 72) or a high daily average pre-operative dexamethasone (≥8 mg, *N* = 156). Patients underwent biopsy (25%), subtotal resection (43%), or complete resection (33%) of the contrast-enhancing tumor. All patients received varying amounts of postoperative dexamethasone. As part of the treatment plan, 7% of patients received adjuvant chemotherapy only, 7% received adjuvant radiotherapy only, 73% received both adjuvant chemotherapy and radiotherapy, and 14% received no adjuvant therapy. The median perioperative NLR of the patient cohort was 9 (IQR 6–16) (*n* = 230). We assessed a difference in NLR based on the methylation

Table 1. Patient Cohort Characteristics

Patient Characteristics	
Age at diagnosis mean ± SD, *N*	64.4 ± 11.8, 230
Female sex—*n* (%)	88 (36%)
BMI mean ± SD, *N*	26.0 ± 5.1, 179
Tumor *MGMT* promoter methylation—*n* (%), *N*	90 (42%), 217
KPS score at presentation—*n* (%), *N*	
≥70%	150 (65%), 230
<70%	80 (35%)
Surgery type—*n* (%), *N*	
Biopsy only	57 (25%), 230
Partial resection	98 (43%)
Complete resection	75 (33%)
Adjuvant therapy received—*N* (%), *N*	
Adjuvant chemotherapy only	15 (7%), 228
Adjuvant radiotherapy only	15 (7%)
Adjuvant chemo- and radiotherapy	167 (73%)
None	31 (14%)
No preoperative dexamethasone—*N* (%)	2 (0.8%)
Preoperative dexamethasone	228 (99.2%)
Postoperative dexamethasone	229 (99%)
Preoperative dexamethasone—median mg (IQR)	12 (4–16)
Postoperative dexamethasone	11.9 (9.3–14.5)
Length of hospital stay (median days IQR), *N*	8 (4–17), 222
Time to recurrence	263 (133–387), 57
Time to progression	124.5 (82–201), 80
Time to infection	69 (19.5–112), 58
Time to thrombosis	60 (30–137), 41
Time to death	254 (133–457), 199
NLR measurements (median IQR), *N*	
Perioperative NLR	9 (5–16), 230
Postoperative NLR	11 (6–19), 169
Positive Δ NLR	6 (2–12), 94

Abbreviations: BMI:, body mass index; IQR, interquartile range; KPS, Karnofsky Performance Scale; *MGMT*: O^6-methylguanine-DNA methyltransferase; NLR, neutrophil-to-lymphocyte ratio; SD, standard deviation.
ΔNLR signifies a change in NLR from preoperative to postoperative NLR values = postoperative NLR—preoperative NLR.

status of the *MGMT* promoter and found no significant difference (unmethylated 14.3 ± 12.6, $n = 127$ vs. methylated 12.0 ± 8.9, $n = 90$). This information is presented in Table 1.

NLR Correlation With Complication and Survival

Using logistic regression models, we aimed to examine correlations between NLR measures and complication events. We found a significant correlation between high+ΔNLR (ΔNLR ≥ 6) and all-complication rates at 3 months (odds ratio [OR] 3.8, 95% confidence interval [CI] 1.2–11.7, $P = .02$) on univariate analysis (Table 2). Multivariate analysis that included KPS, combined adjuvant therapy, and high mean perioperative dexamethasone as covariates showed a correlation that approached statistical significance, but that had a wide CI and did not reach the a priori threshold *P*-value (adjusted odds ratio [aOR] 3.5, 95% CI 0.8–15.5, $P = .09$) (Table 2).

We next examined the association between NLR and survival with death events at 2 years. By computing Pearson's correlation coefficients (Supplementary Table 3), we measured a significant negative correlation between time-to-death and postoperative NLR ($r = –0.2$, $P = .02$). For survival, we found no difference in survival between patients with ≥50% independent high NLR values and patients with <50% high NLR values (Figure 1B) (229 days, 95% CI 152–306 vs. 290 days, 95% CI 205–375, $P = .2$) (Figure 1C, Tables 3). However, we also found no association between high perioperative NLR (Figure 1D) and median survival on univariate analysis (247 days, 95% CI 163–330 vs. 277 days, 95% CI 189–364, $P = .3$) (Figure 1E, Table 3). Kaplan–Meier analysis shows an insignificant correlation between high postoperative NLR and survival (229 days, 95% CI 140–317 vs. 320 days, 95% CI 193–446, $P = .09$) (Figure 1F, Table 3). However, subtracting average postoperative from preoperative NLR values shows that high + ΔNLR (≥6 ΔNLR) is associated with poor survival (196 days, 95% CI 121–270 vs. 304 days, 95% CI 223–384, $P = .01$) (Figure 1G, Table 3) on univariate but not on multivariate analysis (aHR 1.4, 95% CI 0.8–2.6, $P = .2$) (Table 4).

Dexamethasone Treatment and Association Between NLR and Survival

We first examined the distribution of average dexamethasone treatment across the perioperative period (Figure 2A). As shown in Table 3, high perioperative dexamethasone treatment did not associate with survival (274 days, 95% CI 211–337 vs. 229 days, 95% CI 52–406, $P = .9$) (Table 3). We then delineated the perioperative NLR values in 2 dexamethasone populations: 1 treated with low (<8 mg) or high (≥8 mg) average preoperative (Figure 2B). There was no significant change in perioperative NLR value when grouping patients according to high or low average preoperative (Figure 2C). Our results show a significantly higher postoperative NLR in patients treated with high preoperative dexamethasone ($P = .04$) (Figure 2D). We also grouped patients based on perioperative dexamethasone treatment (Figure 2E) but again we found no difference in perioperative NLR based on low or high perioperative dexamethasone treatment (Figure 2F).

Discussion

This study is the first to assess the importance of NLR in GBM while considering dexamethasone dosage and timing in a relatively large cohort of GBM patients. In contrast to

Table 2. Univariate and Multivariate Analyses of Several Patient Parameters With Complications of Glioblastoma Patients

Patient Parameters	All complications at 3 months	
	Univariate analysis	Multivariate analysis
	OR (95% CI), ***P***-value	aOR (95% CI), ***P***-value
Age ≥ 65	1.0(0.5–2.0); 0.8	-
BMI	0.9 (0.4–2.0); 0.8	-
KPS	**0.4 (0.2–0.8); 0.02**	2.3 (0.5–10.3); 0.3
Complete resection	0.6 (0.3–1.3); 0.2	-
Combined adjuvant therapy	0.5 (0.2–1.1); 0.1	0.5 (0.1–2.7); 0.5
Mean perioperative Dexamethasone ≥ 8 mg	2.4 (0.7–8.6); 0.16	2.0 (0.2–17.8); 0.6
Mean positive Δ NLR ≥ 6	**3.8 (1.2–11.7); 0.02**	3.5 (0.8–15.5); 0.09

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; KPS, Karnofsky Performance Scale; OR, odds ratio; NLR, neutrophil-to-lymphocyte.
ΔNLR signifies a change in NLR from preoperative to postoperative NLR values = postoperative NLR—preoperative NLR.

Table 3. Global Median Overall Survival With Event of Death at 2 Years for Different Patient Parameters

Patient parameters		Case number	Event number	Number censored	Overall Survival Median (95% CI)	Log rank (***P-value***)
Sex	Male	122	110	12	254 (181–328)	.92
	Female	76	66	10	263 (181–345)	
Age	<65	86	71	15	308 (207–409)	**<.001**
	≥65	112	105	7	213 (152–274)	
BMI (kg/m^2)	<25	68	61	7	274 (182–366)	.3
	≥25	85	75	10	328 (240–416)	
KPS	<70%	71	64	7	210 (154–266)	**.04**
	≥70%	127	112	15	302 (235–369)	
Methylated *MGMT*	Yes	113	109	4	332 (220–443)	**<.001**
	No	73	58	15	247 (177–317)	
Complete resection	Yes	140	127	13	407 (321–492)	**<.001**
	No	58	49	9	192 (156–228)	
Combined adjuvant therapy	Yes	137	117	20	365 (304–426)	**<.001**
	No	59	57	2	115 (69–160)	
Perioperative dexamethasone ≥ 8 mg	Yes	168	149	19	274 (211–337)	.9
	No	30	27	3	229 (52–406)	
Mean perioperative NLR ≥ 9.5	Yes	98	88	12	247 (163–330)	.3
	No	100	88	12	277 (189–364)	
High NLR values ≥ 50%	Yes	98	88	10	229 (152–306)	.2
	No	100	88	12	290 (205–375)	
Mean postoperative NLR ≥ 9.5	Yes	85	75	10	229 (140–317)	.09
	No	64	54	10	320 (193–446)	
Mean positive ΔNLR ≥ 6.0	Yes	42	38	4	196 (121–270)	**.01**
	No	36	28	8	304 (223–384)	

Abbreviations: BMI, body mass index; H, high; KPS, Karnofsky Performance Scale; L, low; *MGMT*, *O*^{6}-methylguanine-DNA methyltransferase; NLR, neutrophil-to-lymphocyte ratio.
Complete resection denotes near gross total resection and gross total resection. High NLR denotes an average of ≥9.5, high dexamethasone treatment denotes an average of ≥8 mg. Δ NLR signifies a change in NLR from preoperative to postoperative NLR values = postoperative NLR—preoperative NLR.

Table 4. Possible Risk Factors Associated With Death Within 2 Years After Surgery

Risk Factor	Overall survival (death at 2 years)			
	Univariate analysis		Cox regression analysis	
	HR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Female sex	0.98 (0.73–1.3)	.92	-	-
Age ≥ 65	1.7 (1.2–2.2)	**<.001**	1.5 (1.0–2.2)	**.03**
KPS ≥ 70	0.72 (0.5–0.9)	.04	0.6 (0.4–0.9)	**.01**
BMI (kg/m^2) ≥ 25	0.84 (0.6–1.2)	.3	-	-
Methylated *MGMT*	0.6 (0.4–0.8)	**<.001**	0.5 (0.3–0.7)	**<.001**
Complete resection	0.6 (0.4–0.8)	**<.001**	0.7 (0.5–1.0)	**.03**
Combined adjuvant therapy	0.3 (0.2–0.4)	**<.001**	0.3 (0.2–0.5)	**<.001**
Mean positive Δ NLR ≥ 6.0	1.8 (1.1–3.0)	**.01**	1.4 (0.8–2.6)	.2

Abbreviations: CI, confidence interval; BMI, body mass index; H, high; HR, hazard ratio; IQR, interquartile range; KPS, Karnofsky Performance Scale; L, low; *MGMT*, *O*^{6}-methylguanine-DNA methyltransferase; NLR, neutrophil-to-lymphocyte ratio.
Complete resection denotes near gross total resection and gross total resection. High ΔNLR denotes an average of ≥6. ΔNLR signifies a change in NLR from preoperative to postoperative NLR values = postoperative NLR—preoperative NLR.

other studies, we excluded *IDH 1* and *2* pathological variants due to biochemical differences that manifest in clinical parameters,[16–18] and due to reported immune landscape differences in *IDH 1* and *2* pathological variants.[19,20] In this study, we demonstrate that positive change in NLR relative to the surgery timing, rather than the average perioperative NLR, may have a prognostic value in GBM patients irrespective of dexamethasone administration.

In cancer, corticosteroid use can shift the immune system response.[21] Therefore, it is imperative to understand changes in inflammatory markers and their relevance in tumorigenesis while considering the dosage and timing of corticosteroid treatment. Although we show that high average preoperative and perioperative dexamethasone dose does not change NLR trend in the perioperative period, dexamethasone may be in part responsible for the increase in NLR n a subset of patients (Figure 2D). Our data also show that this increase in NLR (+ΔNLR ≥ 6) is associated with an unfavorable patient survival outcome (Figure 1G and Table 3).

There is an important distinction to be made here between change in NLR and average NLR values over a certain period. We report that positive change in NLR relative to the timing of surgery is associated with decreased survival at 2 years (Figure 1G and Table 3). While the change in NLR across the day of the operation is part of the overall trajectory of NLR, we cannot conclude from our data that there is an overall increase in NLR from GBM initiation to patient death. In other cancers, an increase in NLR over the disease course has been observed.[22] Change in NLR across a certain stressor, such as surgery, can provide an assessment of the patient's organ health and immunity status. These NLR values and changes can be more informative when measured on patients before the start of adjuvant therapy.[23,24] In fact, we believe that much of the controversy on the prognostic value of NLR in GBM is due to the retrospective nature and narrow observation windows of studies on this topic. The narrow observation windows may capture a slope not positive enough to demonstrate the overall decline in organ and immunity functions.

Alternatively, a better understanding of interactions between the GBM tumor (with its heterogeneity) and its tumor microenvironment can help rationalize NLR patterns in GBM patients in conjunction with NLR's role as a marker of systemic inflammation. Multiple studies demonstrated that neutrophils can directly promote GBM growth.[25,26] Despite data on low intratumoral presence of neutrophils relative to monocytes in GBM.[27] One study on murine models found that anti-tumorigenic neutrophils are likely to infiltrate early during tumor progression in mesenchymal GBM,[28] explaining the presence of neutrophils near the GBM necrotic core.[27,29] Intriguingly, the study also showed that further progression of GBM can remotely mediate the oncogenic reprogramming of bone marrow neutrophils.[28] This indicates that certain subtypes of GBM may have prooncogenic neutrophil reservoirs ready to be mobilized in acute inflammatory conditions. Disruption of the blood–brain barrier (BBB) (which is normally immune to neutrophil infiltration[30]) after resection[31] may allow for direct "on-site" contribution of GBM-reprogrammed neutrophils to residual tumor cell growth,[25,26] negatively impacting patient prognosis.

We do not expect post-resection NLR to remain high (≥6 ΔNLR) for long durations postoperatively. In fact, with this model, circulating oncogenic neutrophils may no longer be contributing to tumor growth after BBB stabilization.[30] However, the early neutrophil-mediated post-resection boost to residual GBM cells (during the window of BBB disruption[30]) may give patients with certain GBM subtypes a lead into tumor growth and recurrence (Figure 2G), decreasing survival. This model also helps to explain why in our study perioperative NLR, which accounts for pre-operative NLR values up to 30 days preoperatively, did not correlate with survival (Figure 1E). The inclusion of these NLR values in the pre-resection period accounts for nonacute phases during which neutrophils may be relatively quiescent and marginalized in comparison to the postoperative phase. We do not discredit here a possible function for high preoperative dexamethasone treatment

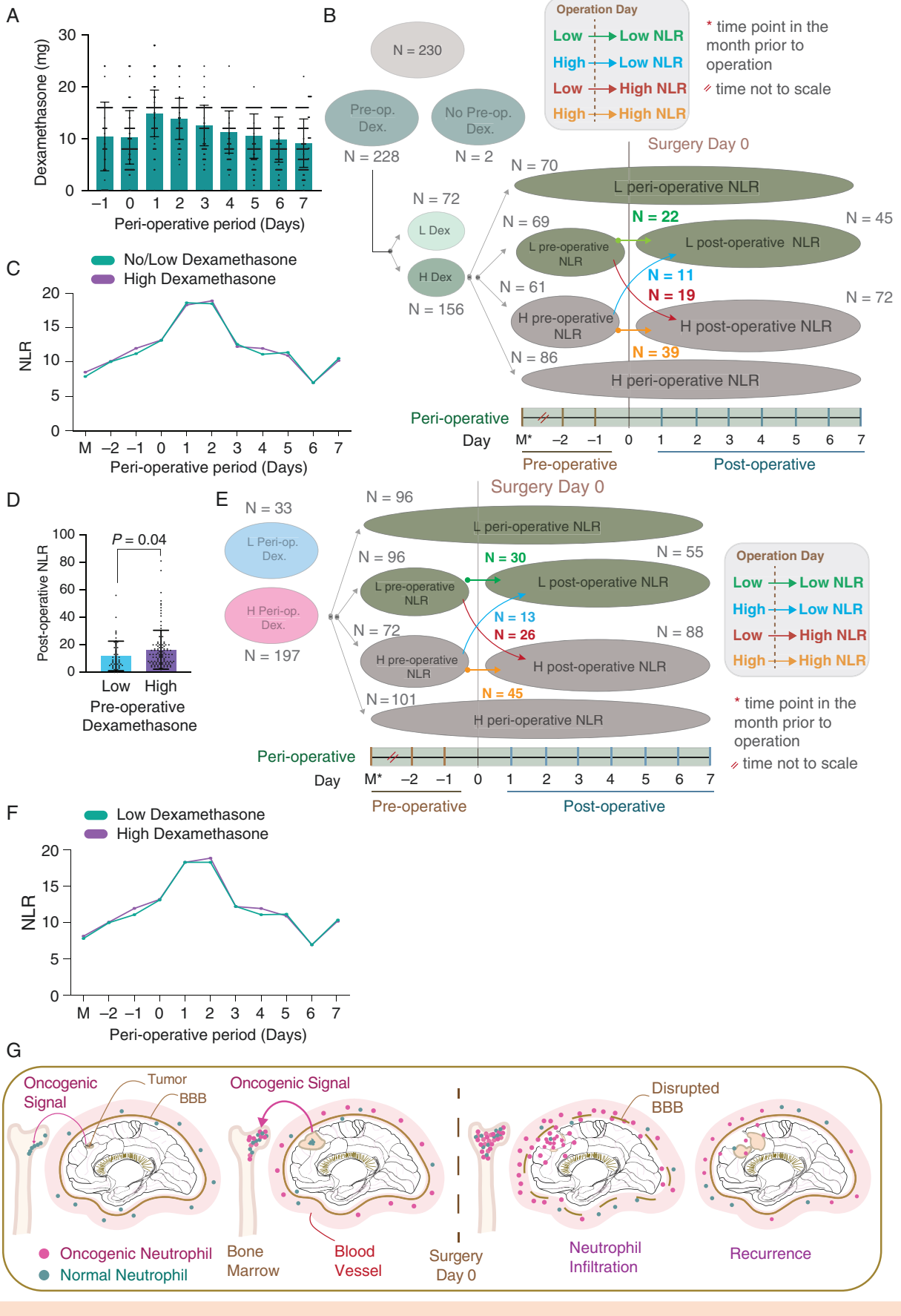
A
Dexamethasone (mg)
Peri-operative period (Days)
B
N = 230
Pre-op. Dex.
No Pre-op. Dex.
N = 228
N = 2
Operation Day
Low → Low NLR
High → Low NLR
Low → High NLR
High → High NLR
* time point in the month prior to operation
time not to scale
Surgery Day 0
N = 72
L Dex
H Dex
N = 156
N = 70
L peri-operative NLR
N = 69
L pre-operative NLR
N = 22
L post-operative NLR
N = 45
N = 61
H pre-operative NLR
N = 11
N = 19
H post-operative NLR
N = 72
N = 86
N = 39
H peri-operative NLR
Peri-operative Day
M* –2 –1 0 1 2 3 4 5 6 7
Pre-operative
Post-operative
C
No/Low Dexamethasone
High Dexamethasone
NLR
Peri-operative period (Days)
D
P = 0.04
Post-operative NLR
Low High
Pre-operative Dexamethasone
E
N = 33
L Peri-op. Dex.
H Peri-op. Dex.
N = 197
Surgery Day 0
N = 96
L peri-operative NLR
N = 96
L pre-operative NLR
N = 30
N = 55
L post-operative NLR
N = 13
N = 26
N = 72
H pre-operative NLR
N = 88
H post-operative NLR
N = 101
N = 45
H peri-operative NLR
Operation Day
Low → Low NLR
High → Low NLR
Low → High NLR
High → High NLR
* time point in the month prior to operation
time not to scale
Peri-operative Day
M* –2 –1 0 1 2 3 4 5 6 7
Pre-operative
Post-operative
F
Low Dexamethasone
High Dexamethasone
NLR
Peri-operative period (Days)
G
Oncogenic Signal
Tumor
BBB
Oncogenic Signal
Disrupted BBB
Oncogenic Neutrophil
Normal Neutrophil
Bone Marrow
Blood Vessel
Surgery Day 0
Neutrophil Infiltration
Recurrence

Figure 2. Delineation of perioperative dexamethasone treatment and neutrophil-to-lymphocyte ratio (NLR) change. (A) Bar graph with scatter plot demonstrating the average dexamethasone dose for each of the perioperative days and individual patient data points. (B) Flow schematic showing how high average preoperative dexamethasone (≥8 mg dexamethasone per day, $N = 156$) was controlled for and patients were grouped based on changes in preoperative and postoperative NLR (high to high, high to low, low to high, and low to low). (C) Line graphs for average NLR in the perioperative period grouped based on no or low average preoperative dexamethasone dose (<8 mg, $N = 74$) and high average preoperative dexamethasone dose (≥8 mg, $N = 156$). (D) Bar graph with scatter plot demonstrating the average postoperative NLR in patients treated with no or low preoperative and high preoperative dexamethasone ($P = .04$). (E) Flow schematic similar to A, but conditioning patients based on high average perioperative dexamethasone (≥8 mg dexamethasone per day, $N = 197$). (F) Line graphs for average NLR in the perioperative period grouped based on low average perioperative dexamethasone dose (<8 mg, $N = 33$) and high average perioperative dexamethasone dose (≥8 mg, $N = 197$). (G) Model describing how NLR change across surgery may contribute to decreased survival. Starting from the far left, tumor initiation may begin reprogramming bone marrow neutrophils on a small scale. This reprogramming creates neutrophils with oncogenic properties. As the tumor progresses, the neutrophil reprogramming signal becomes more pronounced with some mostly anti-oncogenic neutrophils infiltrating the tumor and localizing to the necrotizing core. Shortly after surgery and with disruption of the blood–brain barrier (BBB), GBM-reprogrammed neutrophils may invade the resection site and serve to promote the growth of residual tumor cells, escalating tumor growth and reducing patient survival.

in contributing to neutrophil demarginalization. However, we believe that the major contributing factor to neutrophil recruitment, BBB disruption, and any consequential potential direct tumor-enhancing neutrophil action is post-surgical stress.

The restricted access of neutrophils to the brain and the prevalence of tumor-associated monocytes in GBM tissue (rather than neutrophils)[27] has raised questions about the biological relevance of NLR in GBM. Together with the data reported in Magod et al.,[28] we think that our findings can help resolve the controversy around NLR utility in GBM.[9,12,32] We also provide clinical evidence that can help bridge between clinical data and the newly discovered oncogenic functions of neutrophils in GBM. Finally, we also demonstrate that although dexamethasone may contribute to the postoperative increase in NLR, dexamethasone dose did not independently associate with GBM patient outcome. Therefore, we do not believe that dexamethasone dose can affect the prognostic utility of NLR in GBM disease progression, further highlighting the emerging direct role of neutrophils on GBM growth.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

dexamethasone | glioblastoma | neutrophil-to-lymphocyte ratio | survival

Lay Summary

The neutrophil-to-lymphocyte ratio (NLR) is a measure of specific blood cells and has been linked to survival in patients with cancers outside of the brain. The authors of this study wanted to see if NLR was also linked to survival in patients with an aggressive brain cancer, called glioblastoma. To do this, they reviewed the medical records of 230 patients with glioblastoma and looked at their NLR levels before and after surgery. They found that patients whose NLR increased after surgery were more likely to have shorter lifespans.

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Conflict of Interest

None declared.

Authorship statement

A.H.M. collected raw data, conducted the analysis of the paper, and wrote the manuscript. R.S. helped with extraction and organization of raw data. W.D., S.J., R.K., H.L., R.A., and T.A. helped with the collection of the raw data. M.A.R.B. validated the statistical analyses. R.J.D. supervised the project.

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Data availability

Upon request, data may become available in adherence with internal privacy regulations and in accordance with the nature of the request made.

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