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Original Article

Neutrophil-to-lymphocyte Ratio as an Effective Biomarker for Meningioma: A Systematic Review and Meta-analysis

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Abstract

Background and objectives: Previous studies showed that tumors are associated with the increased inflammatory burden and neutrophil-to-lymphocyte ratio (NLR) is also associated with inflammatory conditions. However, there is no review on the role of NLR in meningioma. The goal of this study was to see if NLR has any prognostic and diagnostic value in meningioma.

Methods: The search was conducted on PubMed, Scopus, and Web of Science up to 3 August 2023. A total of 23 studies were included in the systematic review, of which 13 were included in the meta-analysis.

Results: It was found that patients with high-grade meningioma had higher levels of NLR compared to those with low-grade meningioma (standardized mean difference [SMD] = 0.72, 95% confidence interval [CI]: 0.21–1.23, $p = 0.006$)]. In addition, we found that there was no difference between NLR levels of patients with meningioma and those with gliomas (SMD, −0.19, 95% CI: −0.47–0.10, $p = 0.20$). Also, higher levels of NLR were found in patients with meningioma compared with healthy controls (SMD = 0.56, 95% CI: 0.24–0.88, $p = 0.01$). Studies showed that an NLR > 2.4 differentiated high-grade and low-grade meningioma, an NLR > 2.74 differentiated high and low progression-free survival groups, and an NLR > 2.59 was associated with recurrence, with high sensitivity and specificity. However, the NLR did not predict postoperative pneumonia following meningioma resection. Because of the contradiction, our study did not clearly demonstrate the difference in NLR levels in meningioma and other pathologies, so more studies are needed on this subject.

Conclusions: NLR had significant diagnostic and prognostic value in meningioma. In general, we inferred a strong link between systemic inflammation assessed by NLR and meningioma, based on elevated levels of NLR in patients with meningioma compared to healthy controls. In addition, NLR had significant predictive potential for the progression and recurrence of meningioma. The predictive potential increased when combined with other diagnostic tools such as fibrinogen level. NLR may guide clinical decision making as an inflammatory marker and its relationship to therapeutic efficacy.

Keywords: Neutrophil-to-lymphocyte ratio; Meningioma; Systematic review; Inflammation.

Abbreviations: AM, atypical meningioma; AUC, area under the curve; CI, confidence interval; F-NLR, fibrinogen-NLR; IL, interleukin; NLR, neutrophil-to-lymphocyte ratio; NOS, Newcastle–Ottawa scale; PFS, progression-free survival; POP, postoperative pneumonia; ROC, receiver operating characteristic; SMD, standardized mean difference; TLE-HS, temporal lobe epilepsy with hippocampal sclerosis; WHO, World Health Organization.

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Introduction

Meningioma, which arises from arachnoid cells, is the most prevalent cerebral tumor, accounting for nearly one-third of such malignancies.[1] According to the World Health Organization (WHO) classification, meningiomas are grade I, II (atypical), or III (anaplastic).[2] Meningiomas are mostly benign (grade 1) and well controlled. In contrast, a small percentage are categorized as high-grade (grades 2 and 3) with more aggressive characteristics and a greater risk of recurrence and mortality despite optimal management.[3] Surgical excision or radiation therapy can cure or stabilize most cancers. Recurrent instances, on the other hand, are challeng-

ing to treat, and surgery and radiation are the only options. As a result, a reliable prognostic indicator is essential for early patient detection.[4]

There is growing evidence that inflammation contributes to cancer development and progression.[5] In recent decades, there has been a surge of attention on the function of the immune system and inflammation in cancer genesis, progression, and treatment. Cancer biology is currently changing from focusing on cancer cells to a more holistic view that places cancer cells inside a complex of stromal cells, such as fibroblasts, vascular cells, and inflammatory immune cells that create the tumor microenvironment.[6] The inflammation-causing agent may promote chronic stimulation of cellular turnover and local mutagenic consequences, and increased formation of reactive oxygen species, which are either a side product of regionally enhanced metabolism or are created, may be able to account for this for the carcinogenic potential of inflammation.[7] Some sensitive biomarkers can be collected before therapy, which could be innovative and practical for patients to develop a therapy approach and estimate prognosis. Inflammatory markers include C-reactive protein, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, absolute neutrophil count, and total monocyte count.[8,9] Other biomarkers are also currently being used in meningiomas such as circulating tumor biomarkers, DNA methylation markers, and proteomic markers. These indicators can assist in identifying special protein and molecular-level pathways, classifying meningiomas into different subtypes, and developing real-time clinical biomarkers.[10–12]

Neutrophils are inflammatory cells that secrete a variety of chemical mediators, including elastase and matrix metalloproteinase enzymes, along with growth factors. These mediators are well known for encouraging tumor growth and progression by developing a tumor microenvironment. Moreover, since the immune response to cancer is dependent on lymphocytes, a low number of tumor-infiltrating lymphocytes is a poor prognostic indicator. NLR status could indicate the imbalance between protumor and antitumor immunological status, which could explain why patients with greater NLRs have a worse prognosis in various cancers.[13]

As a novel inflammatory marker, NLR has been introduced as a reliable diagnostic and prognostic predictor in various conditions such as thyroid conditions, type 2 diabetes mellitus,[14] irritable bowel disease,[15] COVID-19 infection,[16] inflammatory bowel disease,[17] and Hashimoto's disease.[18] Tumors are associated with an increased inflammatory burden, and NLR is associated with inflammatory conditions such as thyroid disorders,[19,20] gastrointestinal conditions,[21] irritable bowel disease,[15] COVID-19 infection,[16] diabetes mellitus,[22] cardiac conditions,[23] and thyroiditis.[18] All these conditions are associated with increased inflammatory burden as meningioma is. So, we decided to study NLR in meningioma.

NLR may guide the clinical decision making process as an inflammatory marker because of its relationship to therapeutic efficacy. As a result, the goal of this study was to see whether NLR had value in predicting meningioma. It is the first systematic review and meta-analysis that we are aware of that looked into the relationship between higher pretreatment NLR and the pathogenesis, differential diagnosis, staging, and predicting survival and outcome of this cancer.

Material and methods

This study followed the preferred reporting items for systematic reviews and meta-analysis guidelines for reporting systematic reviews and meta-analysis.

Search strategy and study selection

We searched three databases until 3 August, 202, PubMed, Web of Science, and Scopus. The search strategy included "(meningioma) AND ((neutrophil-lymphocyte ratio) OR NLR OR (neutrophil-lymphocyte ratio))". To avoid missing related articles, we checked the references of the relevant papers. After eliminating the duplicates, the titles and abstracts of the available articles were evaluated by two authors. Following that, they independently evaluated the entire content of potentially relevant papers.

Inclusion and exclusion criteria

The strategy of collecting articles is shown in Figure 1. The requirements for inclusion were: (1) observational study; (2) Study of the relationship between NLR level in the blood and the prognosis or diagnosis of meningioma; and (3) Available full text. The exclusion criteria were: (1) Animal or cell study; (2) Literature or systematic review; (3) Case or series report; (4) Duplicate paper; (5) Lack of data even after contacting the authors.

Data extraction and quality assessment

The first author's name, publication year, the country in which the study was performed, number of participants, NLR value, endpoint measure, clinical features, and details required to evaluate the quality of each study, were independently reviewed by two authors using a data extraction form prepared beforehand. Consultation with a second reviewer was done to resolve disagreements that arose during the research selection and data extraction process. The Newcastle–Ottawa scale was also used to evaluate the quality of the included studies.

Meta-analysis

If there were enough studies available in the specific context (at least three studies), we conducted a meta-analysis. We used the combined SMD along with the 95% confidence interval (CI) to analyze the relationship between the NLR and meningioma. To gauge the heterogeneity between studies, we used the I^2 statistic and the chi-square test. A p-value < 0.10 in the chi-square test or an $I^2 \geq 50\%$ indicated significant statistical heterogeneity. Owing to the observed heterogeneity among the included studies, we used a random-effects model (DerSimonian-Laird) to calculate the combined effect sizes and their corresponding 95% CIs. All analyses were two-sided, and a p-value of <0.05 was considered statistically significant. We performed all statistical procedures with Stata 17 software (Stata Corporation LP, College Station, TX, USA).

Results

Selection and characteristics of studies

A total of 343 studies were found while searching the literature. Owing to duplications, 14 studies were deleted after assessment and 228 were eliminated after analyzing the titles and abstracts. After a full text examination, 29 papers were eliminated: 15 studies had no data on the NLR, nine had irrelevant populations, and five were review articles. The remaining 23 studies with 6614 patients were considered for the systematic review and 13 were included in the meta-analysis.[24–46] General characteristics of the included studies are shown in Tables 1 and 2. Table 3 shows the quality scores of studies and Table 4 shows the cutoff values reported in the studies.[24–46]

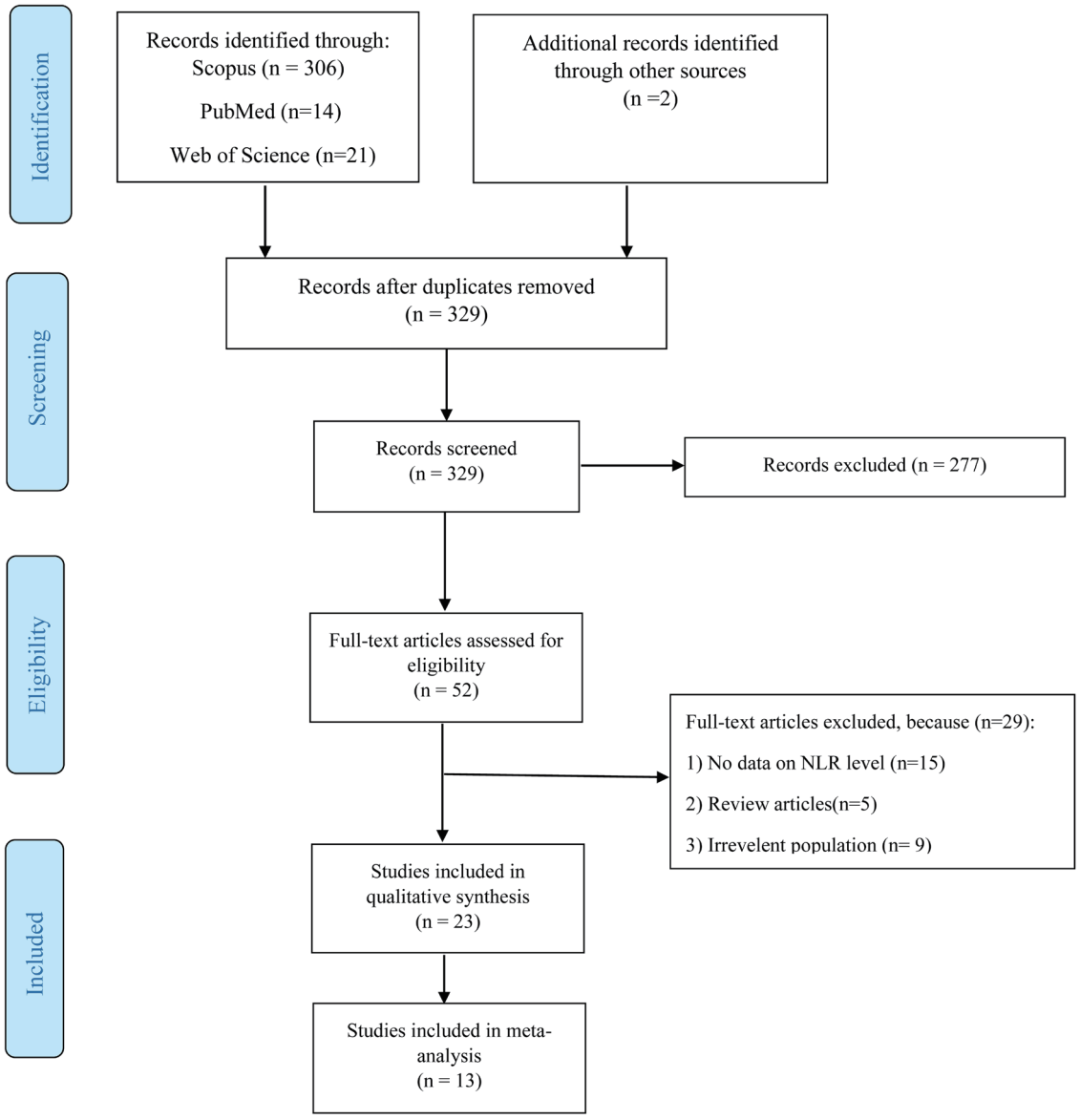

Fig. 1. Flow chart of the literature search and study selection. NLR, neutrophil-to-lymphocyte ratio.

NLR and outcomes in meningioma

The efficacy of NLR in estimating patient outcomes, including progression-free survival (PFS) and tumor recurrence, was explored in five studies.[24–28] In a retrospective analysis in 2020, Kuranari et al. investigated the predictive importance of preoperative NLR in 160 meningioma patients in Japan.[24] According to the receiver operating characteristic (ROC) curve, the NLR cutoff value was 2.6 as a predictor of tumor recurrence, with an area under the curve (AUC) of 0.55, a sensitivity of 34.1%, and a specificity of 81.9%. Multivariate analysis found that an NLR of 2.6 or higher was an independent predictor of shorter PFS in meningioma patients, with a hazard ratio of 2.29 (95% CI: 1.13–4.64, $p = 0.022$). In a subgroup analysis, patients were categorized by tumor condition (primary vs. recurrent), WHO grade (grade I vs. grades II and III), the extent of resection (total gross removal vs. subtotal removal), tumor location (skull base or not skull base), and having peritumoral brain edema. In a category of patients with primary meningioma, gross removal, skull base, and the one without peritumoral brain edema, a preoperative NLR of 2.6 and above was significantly related to a shorter PFS ($p = 0.029$, 0.004, 0.013, and 0.034, respectively). Only a preoperative NLR of 2.6 or higher was associated with shorter PFS in grade I meningioma patients (AUC = 0.57, sensitivity = 35.48%, specificity = 81.37%, and $p = 0.003$). In contrast, an NLR ≥ 2.6 was not significantly related to shorter PFS in a subset of recurrent meningioma (AUC = 0.55, sensitivity = 46.15%, specificity = 71.43%, and $p = 0.32$). Furthermore, in the immunohistochemical analysis, increased peripheral NLR was not linked to inflammatory markers inside the tumor, such as neutrophils, CD8+, CD4+, or CD163+ cells. However, more CD4+ and CD163+ cells were seen in recurrent than in primary meningiomas.

In 2020, Chen et al. described a unique grading model for estimating the prognosis of atypical Meningioma (AM) in China.[25] It was based on regular preoperative blood tests of 268 patients. The NLR

Table 1. Characteristics of studies included the systematic review

First author[Ref.]	Sample size, *n*	Study design	Year of publication	Country	Mean age	Male percentage	Cutoff value of NLR	Outcome
Kurunari[24]	160	Retrospective	2020	Japan	61	24	2.6	NLR was an independent predictor of shorter progression-free survival in Grade 1 meningioma patients.
Chen[25]	268	Retrospective	2020	China	54.45	37.3	2.74	NLR could predict 3-year progression-free survival in patients with atypical meningioma.
Chen[26]	183	Retrospective	2021	China	33.9	34	2.59	NLR was associated with the recurrence of atypical meningioma.
Gao[27]	274	Retrospective	2021	China	53.8	40.1	1.79	NLR was linked to the postoperative development of grade II meningioma.
Yuksel[28]	23	Retrospective	2021	Turkey	61.39	14	_	NLR could not predict the short-term prognosis of operated meningioma grade I patients.
Kemerdere[29]	61	Retrospective	2018	Turkey	51.91	42.4	_	NLR was higher in patients with grade II intracranial meningioma than in grade I.
Liang[34]	944	Retrospective	2019	China	50	29	_	NLR in grade II and III meningioma patients was higher than in grade I.
Ashwath[35]	160	Retrospective	2019	India	40.14	38	_	The NLR levels of patients with grade I meningioma were lower than those with grades II and III.
Lin[36]	672	Retrospective	2019	China	52.50	27%	1.69	NLR was higher in high-grade than low-grade intracranial meningioma patients.
Kashani[37]	95	Retrospective	2020	Iran	52	39	_	No significant difference was observed between NLR in high and low-grade meningioma.
Kayhan[30]	170	Retrospective	2018	Turkey	57.50	40.6	_	NLR levels in patients with meningioma were higher than in healthy controls.
Liu[31]	142	Prospective	2020	China	53.30	75	_	NLR was higher in meningioma patients than in glioma patients and healthy controls.
Zheng[32]	1849	Retrospective	2017	China	52	28	_	Meningioma patients had higher NLR than those with acoustic neuroma and those with epilepsy.
Sharma[33]	355	Retrospective	2021	India	54.5	39	2.15	NLR levels of meningioma patients were not different from those with glioma or acoustic neuroma.
	35	Prospective	2021	Indonesia	Most were 41–50	57	_	NLR levels were similar in patients with meningioma, glioma, or brain metastases.
Zuo[44]	1156	Retrospective	2019	China	58	33	_	NLR could predict postoperative pneumonia in cases of meningioma after surgery.
Chen[45]	282	Retrospective	2020	China	_	_	_	NLR could not predict postoperative pneumonia in cases of meningioma after surgery.
Deng[46]	321	Retrospective	2020	China	52	34.3	_	NLR could not predict postoperative pneumonia in cases of meningioma after surgery.
Silva[38]	89	Retrospective	2022	Brazil	53	30.3	_	High-grade meningioma patients had higher levels of NLR compared to those with low-grade meningioma
Manjunath[39]	780	Retrospective	2022	India	43.5	34	2.65	Patients with high-grade meningioma had higher levels of NLR compared to those with low-grade meningioma
Ozdemir[40]	94	Retrospective	2022	Turkey	53.15	26.59	3.29	Higher levels of NLR were observed in patients with high-grade meningioma compared to those with low-grade meningioma
Teng[41]	1975	Retrospective	2022	China	_	28.75	_	Patients with high-grade meningioma had higher levels of NLR compared to those with low-grade meningioma
Guidry[42]	209	Retrospective	2023	USA	59	_	_	Patients with high-grade meningioma had higher levels of NLR compared to those with low-grade meningioma

NLR, neutrophil-to-lymphocyte ratio.

Table 2. Characteristics of studies included in the meta-analysis

First author	Year	Meningioma		Healthy controls		Glioma		High-grade meningioma		Low-grade meningioma	
		n	NLR	*n*	NLR	*n*	NLR	*n*	NLR	*n*	NLR
Kamardere[29]	2018	61	3.42 ± 3.62	35	1.83 ± 0.49	–	–	13	5.90 ± 6.28	48	2.75 ± 2.17
Liang[34]	2019	–	–	–	–	–	–	150	3.93 ± 6.45	794	6.97 ± 13.34
Ashwath[35]	2019	–	–	–	–	–	–	30	3.12 ± 0.74	26	1.68 ± 0.53
Lin[36]	2019	–	–	–	–	–	–	97	2.16 ± 0.91	575	1.88 ± 0.74
Kashani[37]	2020	–	–	–	–	–	–	26	8.94 ± 12.72	69	8.57 ± 8.04
Liu[31]	2020	20	2.93 ± 1.71	49	1.78 ± 0.55	73	2.50 ± 1.22	–	–	–	–
Zheng[32]	2017	271	4.22 ± 7.02	682	1.74 ± 1.68	750	8.30 ± 16.54	–	–	–	–
Sharma[33]	2021	58	2.48 ± 2.90	107	2.10 ± 2.96	154	5.98 ± 10.92	–	–	–	–
Silva[38]	2022	–	–	–	–	–	–	16	8.10 ± 10.56	73	4.86 ± 5.06
Manjunath[39]	2022	–	–	–	–	–	–	114	3.19 ± 0.43	666	2.70 ± 0.16
Ozdemir[40]	2022	–	–	–	–	–	–	21	3.16 ± 2.20	73	2.26 ± 1.30
Teng[41]	2023	–	–	–	–	–	–	310	2.86 ± 1.75	1665	2.17 ± 0.97
Guidry[42]	2020	–	–	–	–	–	–	66	4.76 ± 4.62	143	4.10 ± 4.26

NLR, neutrophil-to-lymphocyte ratio.

level in patients with a PFS of <3 years was significantly higher than in those with a PFS ≥ 3 years (3.24 ± 1.39 vs. 2.29 ± 1.75, $p = 0.001$). Similarly, the plasma fibrinogen level in patients with a PFS of <3 years was significantly higher than that in those with a PFS ≥ 3 years (3.61 ± 1.16 vs. 2.73 ± 0.65, $p < 0.001$). According to the ROC curve analysis for predicting 3-year PFS, the fibrinogen cutoff level and the NLR were 2.95 g/L (AUC = 0.786, 95% CI: 0.715–0.846, sensitivity = 77.1%, specificity = 71.1%) and 2.74 (AUC = 0.743, 95% CI = 0.669–0.808, sensitivity = 87.3%, specificity = 73.3%), respectively. The AUC of the NLR outperformed the neutrophil count (z = 3.153, $p = 0.002$) and lymphocyte count (z = 2.138, $p = 0.033$) in terms of predictive capability. After controlling for confounders in the multivariate analysis, NLR (OR = 0.77, 95% CI: 0.62–0.99, $p = 0.025$) and plasma fibrinogen level (OR = 0.27, 95% CI = 0.15–0.48, $p < 0.001$) were found to be independent predictors of 3-year PSF. According to this study, the fibrinogen-NLR (F-NLR) score method may also help estimate the prognosis of patients with AM. Based on the cutoff value, the F-NLR grades were categorized as 0 (neither hyperfibrinogenemia nor high NLR), 1 (hyperfibrinogenemia (fibrinogen-lymphocyte ratio >2.95), or high NLR (>2.74), or 2 (both hyperfibrinogenemia and high NLR). This grading model had an AUC of 0.824 (95% CI: 0.738–0.891, sensitivity = 62.5%, specificity = 87.9%), which was higher than those of NLR and fibrinogen level, only (0.630 [95% CI: 0.530–0.722) and 0.722 (95% CI: 0.627–0.805), respectively]. This result was confirmed by DeLong's test, where the AUC of the F-NLR grading model was significantly higher than those of the fibrinogen level and NLR (z = 2.462, $p = 0.014$; z = 4.075, $p < 0.001$, respectively).

Again, in 2021 Chen et al. conducted a retrospective study in China in 183 patients in training ($n = 128$) and external validation ($n = 55$) cohorts to find a comprehensive model to estimate postoperative recurrence in AM patients.[26] The NLR was 2.00 (1.53–3.04), 1.95 (1.52–2.74) in the training cohort and 2.61 (1.55–3.31) in the validation cohort ($p = 0.073$). ROC curve analysis found the optimal cutoff value of NLR for predicting tumor recurrence in the training cohort group was 2.59, with an AUC of 0.638 (95% CI: 0.549–0.72, sensitivity = 59.26%, specificity = 75.25%, and $p = 0.026$). The univariable analysis found that an NLR of >2.59 was associated with AM recurrence, with an HR of 3.62 (95% CI: 1.67–7.82), and $p = 0.001$.[26]

In another study in 2021 in China, Gao et al. used the clinical data of 274 patients with primary grade II meningioma to make a clinical predictive model relying on preoperative hematological and clinical parameters.[27] According to the ROC analysis, 1.79 was the best cutoff value for NLR to predict patient PFS. When the hematological parameters were integrated into the LASSO Cox regression model, an increased level of NLR was an independent predictor for progression (weighting coefficient: 0.833, $p = 0.701$). This study concluded that the postoperative development of grade II meningioma is linked to preoperative hematological markers like NLR.[27] Also in 2021, Yuksel et al. performed a retrospective study in Turkey in 23 patients with grade 1 meningioma to see if regular blood indicators could be used to predict prognosis in these patients.[28] This study did not recognize NLR as a predictor of short-term prognosis ($p > 0.05$).[28] However in general, the data suggests that the NLR has significant predictive potential for the progression and recurrence of meningioma. The predictive potential increases when combined with other diagnostic tools such as the fibrinogen level.

Differences in NLR levels in meningioma patients and healthy controls

Four studies compared the NLR levels of patients with meningi-

Table 3. Quality assessment of included studies using the NOS questionnaire

First author	Is the case definition adequate?	Repre-sentative-ness of the cases	Selec-tion of controls	Defini-tion of controls	Comparability of cases and controls based on the design or analysis	Ascertain-ment of exposure	Same method of ascertain-ment for cases and controls	Nonre-sponse rate	Final score
Kuranari[24]	•	•	_	•	••	•	•	•	8
Chen[25]	•	•	_	•	••	•	•	•	8
Chen[26]	•	•	_	•	••	•	•	•	8
Gao[27]	•	•	•	•	•	•	•	•	8
Yuksel[28]	•	•	_	•	•	•	•	•	7
Kemerdere[29]	•	•	_	•	•	•	•	•	7
Liang[34]	•	•	•	•	••	•	•	•	9
Ashwath[35]	•	•	_	•	••	•	•	•	8
Lin[36]	•	•	_	•	••	•	•	•	8
Kashani[37]	•	•	_	•	••	•	•	•	8
Kayhan[30]	•	•	_	•	•	•	•	•	8
Liu[31]	•	•	_	•	••	•	•	•	8
Zheng[32]	•	•	•	•	••	•	•	•	9
Sharma[33]	•	•	_	•	••	•	•	•	8
Dharmajaya[43]	•	•	_	•	•	•	•	•	7
Zuo[44]	•	•	•	•	••	•	•	•	9
Chen[45]	•	•	•	•	•	•	•	•	8
Deng[46]	•	•	_	•	••	•	•	•	8
Silva[38]	•	•	•	_	••	•	•	•	8
Manjunath[39]	•	•	•	•	•	•	•	•	8
Ozdemir[40]	•	•	_	•	•	•	•	•	7
Teng[41]	•	•	•	•	••	•	•	•	9
Guidry[42]	•	•	_	•	••	•	•	•	8

NOS, Newcastle–Ottawa scale. "•" indicates one score; "••" indicates two score; "_" indicates zero score.

oma with healthy controls.[29–33]

The number of studies was sufficient to conduct a meta-analysis. In the meta-analysis, it was found that patients with meningioma had higher levels of NLR than healthy controls (SMD = 0.56, 95% CI: 0.24–0.88, p = 0.01). A random-effects model was used owing to the high heterogeneity between studies (I^2 = 74.2%, p = 0.009) (Fig. 2).

NLR and meningioma grade

There are three stages of meningeal tumors. We found 10 studies

Table 4. Cutoff values reported in included studies

First author	Cutoff value	Sensitivity	Specificity	Differentiated groups
Ashwath[35]	2.4	80%	92%	High-grade vs. low-grade meningioma
Chen X[25]	2.74	87.3%	73.3%	High PFS vs. low PFS
Chen X-Y[26]	2.59	59.26%	75.25%	Recurrence vs. nonrecurrence group
Gao[27]	4.15	_	_	High PFS vs. low PFS
Kuranari[24]	2.6	34.1%	81.9%	Recurrence vs. nonrecurrence group
Lin[36]	1.69	73.20%	43.83%	High-grade vs. low-grade meningioma
Gao[27]	3.29	_	_	High-grade vs. low-grade meningioma
Silva[38]	4.1	_	_	High RFS vs. low RFS
Sharma[33]	2.15	89.7%	66.7%	High-grade vs. low-grade meningioma

PFS, progression-free survival.

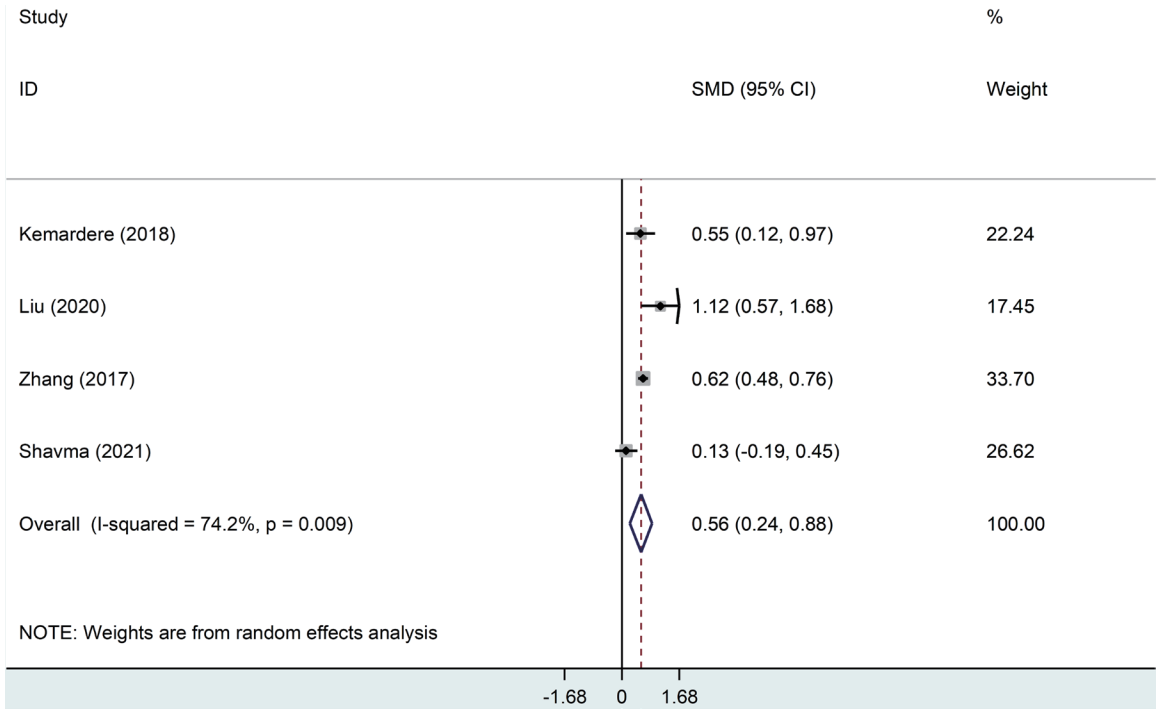

Fig. 2. Meta-analysis of differences in the NLR levels of meningioma patients and healthy controls. CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; SMD, standardized mean difference.

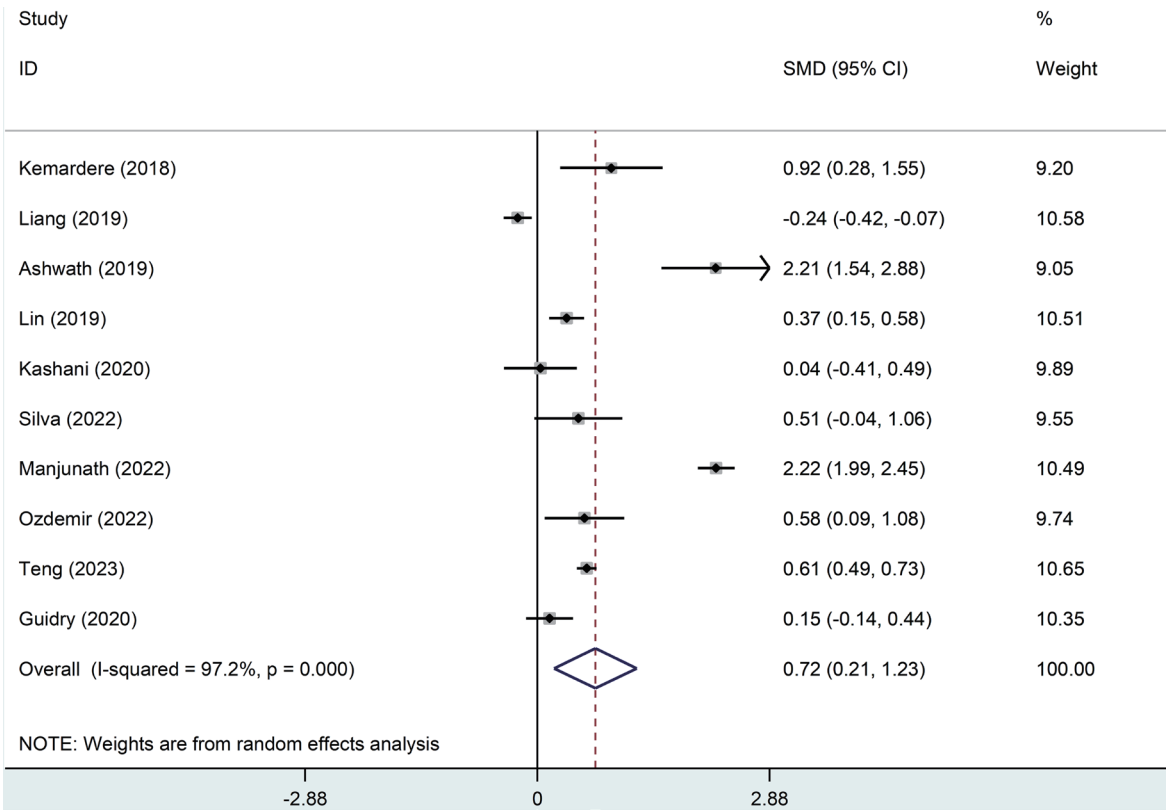

Fig. 3. Meta-analysis of differences in the NLRs of patients with high-grade meningioma and those with low-grade meningioma. CI, confidence interval; SMD, standardized mean difference.

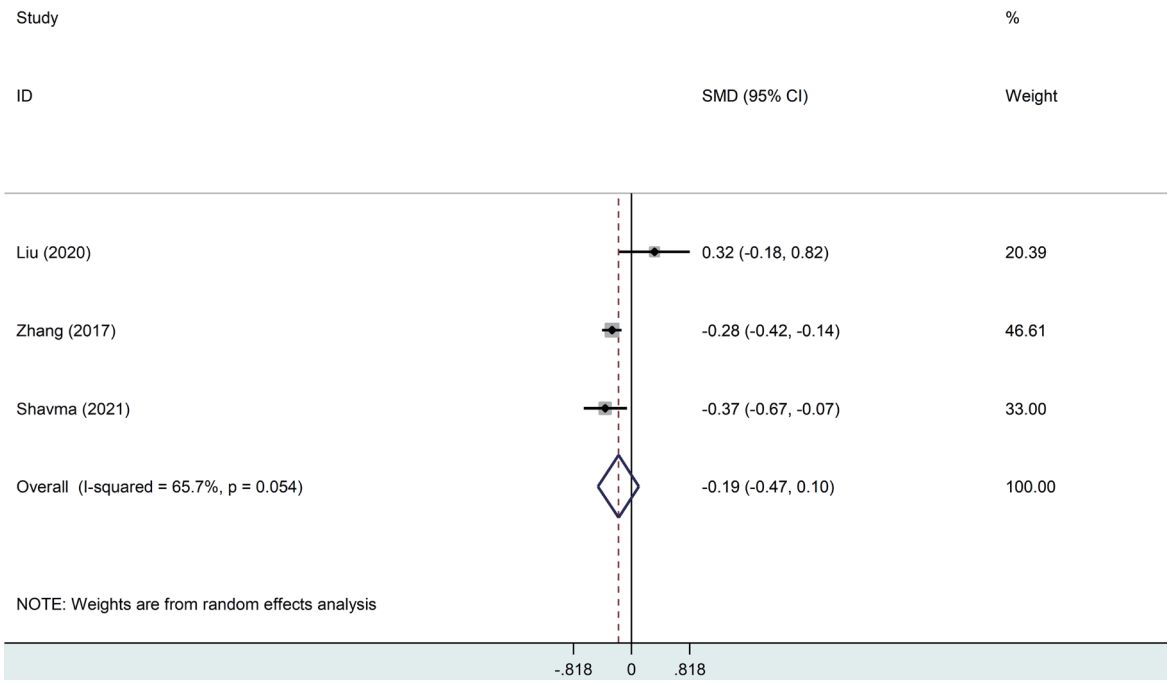

Fig. 4. Meta-analysis of differences in the NLRs of patients with meningioma and those with gliomas. CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; SMD, standardized mean difference.

in this context and conducted a meta-analysis to evaluate the role of NLR in meningioma staging.[29,34–42] In the meta-analysis, it was found that patients with high-grade meningioma had higher levels of NLR than those with low-grade meningioma (SMD = 0.72, 95% CI: 0.21–1.23, $p = 0.006$). A random-effects model was used owing to the high heterogeneity between studies ($I^2 = 97.2\%$, $p < 0.001$) (Fig. 3).

Role of NLR in differentiating between meningioma and other brain pathologies

Five studies reported the use of NLR to differentiate meningioma from other brain pathologies.[30–33,43] In 2018, Kayhan et al. conducted a study in Turkey with 30 healthy controls and 140 patients with brain pathologies, including 39 with temporal lobe epilepsy with hippocampal sclerosis (TLE-HS), 37 with glioblastoma multiforme, 32 with meningioma (grade I), and 32 with intracranial metastasis.[30] NLR levels within patients with meningiomas were higher than those in healthy controls (4.12 ± 2.5 vs. 1.81 ± 0.5, $p < 0.05$) and in the TLE-HS group (4.81 ± 4.4 vs. 1.92 ± 1.1, $p = 0.001$). However, there were no differences in the NLR levels in the meningioma group, metastasis group ($p > 0.05$), and glioblastoma multiforme group ($p > 0.05$).[30]

Similarly, in another study in 2020 in China, Liu et al. assessed the NLR in 73 patients with glioma, 20 with meningioma, and 49 healthy controls.[31] The results showed higher NLRs in meningioma compared with glioma and healthy controls (2.93 ± 1.71 vs. 2.50 ± 1.22 and 1.78 ± 0.55, respectively, both $p < 0.05$).[31] In contrast, in a multicenter cohort study, Zheng et al. analyzed the data of 750 patients with glioma, 271 with meningioma, 44 with acoustic neuroma, 102 with epilepsy, and 682 healthy controls in 2017 in China.[32] They found that glioma patients had higher preoperative NLRs (2.25 [95% CI: 0.19–22.47]) than patients with meningioma (1.82 [95% CI: 0.71–10.14], $p < 0.05$), who themselves had higher NLRs than those with acoustic neuromas (1.60 [95% CI: 0.80–2.81], $p < 0.05$) and nonlesional epilepsy (1.55 [95% CI: 0.69–3.67], $p < 0.05$). Likewise, in 2021, Sharma et al. investigated the predictive value of peripheral inflammatory blood indicators such as NLR in patients of meningioma ($n = 58$), glioma ($n = 154$), and acoustic neuroma ($n = 36$) in India.[33] The NLRs of patients with meningioma were not different from those with glioma (2.47 [95% CI: 0.44–15.04], $p > 0.05$) and acoustic neuroma (1.94 [95% CI: 1.75–1.9], $p > 0.05$). Additionally, in 2021 in Indonesia, a case-control study was conducted by Dharmajaya et al. in patients with brain tumors.[43] A total of 35 patients were categorized into three groups, meningioma ($n = 15$), glioma ($n = 10$), and brain metastasis ($n = 10$). NLR levels in these three groups were similar ($p > 0.05$).[43] There are enough studies for a meta-analysis of the differences between patients with meningioma and those with gliomas.[31–33] In the meta-analysis, it was found that there was no difference between the NLRs of patients with meningioma and those with gliomas (SMD = −0.19, 95% CI: −0.47 to 0.10, $p = 0.20$). A random-effects model was used owing to high heterogeneity between studies ($I^2 = 65.7\%$, $p = 0.05$) (Fig. 4). Because of the inconsistency, this study could not demonstrate the exact difference in NLR levels in meningioma and other pathologies, so more studies are recommended.

NLR and pneumonia following resection of meningioma

The relationship between NLR and postoperative pneumonia (POP) after meningioma excision was assessed in three studies in China.[44–46] In 2019, Zuo et al. conducted a study in 1156 patients undergoing meningioma resection in which 51 developed POP.[44] In this study, NLR was higher in patients with pneumonia than in those without pneumonia (2.73 [95% CI: 2.1–4.72] vs. 2.27 [95% CI: 1.75–3.24]). High NLRs were associated with POP in univariate Cox regression ($p = 0.018$). In multivariate Cox regression,

NLRs between 2.5 and 5 predicted POP in cases of meningioma after surgery (OR = 2.8, 95% CI: 1.06–4.06; $p = 0.033$).[44] Conversely, in 2020, Chen et al. after analyzing 282 patients, reported that NLR did not predict POP within 30 days (OR = 1.021, 95% CI: 0.840–1.242).[45] Similarly, in 2020, a retrospective study by Deng et al. in 321 patients with posterior fossa meningioma who had microsurgical removal, found that 44 developed POP.[46] NLR levels in patients developing POP and those without POP were not different (2 [95% CI: 1.7–2.8] vs. 1.9 [95% CI: 1.4–2.5]; $p = 0.179$).[46] Based on the findings of these investigations, we conclude that NLR did not predict POP following meningioma resection.

Discussion

To understand and infer the possible mechanisms underlying NLR as an independent predictive factor of meningioma progression, recurrence, and higher grade, it is imperative to look into the literature on the roles of neutrophils and lymphocytes separately in the progression of cancer. Although both protumorigenic and antitumorigenic effects of neutrophils on different types of tumors have been displayed in the literature, evidence supports the positive mechanical effect of neutrophils on both the initiation and propagation of tumor growth.[47] Research has demonstrated several possible mechanisms that may be involved at the molecular level. One of these is the induction of angiogenesis by neutrophils. Deryugina et al. found that neutrophils release a large amount of promatrix metalloproteinase-9, an important angiogenesis-inducing molecule, into the tumor microenvironment that helps mediate tumor development.[48] The protein Bv8 has also been implicated as a driver in tumor angiogenesis and is largely derived from neutrophils.[49,50] Immunosuppression in the tumor microenvironment is another mechanism by which neutrophils may mediate tumor development. This may occur by neutrophil-mediated induction of enzymes such as arginase 1 and nitric oxide synthase to decrease T-cell activation, and inhibit tumor growth, thereby contributing to unchecked tumor growth.[47] Upregulation of the transforming growth factor-beta pathway has also been shown to lead to tumor growth suppression by immunosuppression in the tumor microenvironment.[51,52] Neutrophils have also been shown to contribute to the initiation of tumor development.[53] This was most likely because of the production of proteases, reactive oxygen species, and reactive nitrogen species by neutrophils recruited to the tumor microenvironment by signaling chemokines such as CXCL8.[54,55] However, neutrophils have now also been widely implicated in contributing to tumor metastasis, potentially by signaling mechanisms involving cytokines such as interleukin-17 (IL17).[56,57] It is currently known that neutrophils may change into N1 anti-tumor or N2 protumor subtypes, and that it is possible to polarize each of these subtypes via treatments such as intratumoral injection of different substances like pro-oxidants or bacterial products. Metabolic reactions and the generation of reactive oxygen species, like hydrogen peroxide, are activators and chemoattractants of N1 neutrophils, facilitating their recruitment and the subsequent activation of a lethal respiratory burst in malignancies. A better knowledge of the specific mechanisms of N1 neutrophil activation, regulation, and recruitment is now required to fully leverage their antitumor potential against malignancies both locally and distantly.[58]

Neutrophils thus appear to play a significant and varied role in tumor development, from initiation and progression of the primary tumor to the development and progression of distant metastases.[56] Although some research has been done on lymphocytes in isolation on tumor development, most studies in this area are in the context of variation of lymphocyte subsets in various tumors or the context of NLR.[59–61] Several studies have shown that tumors typically have a higher degree of lymphocyte infiltration than normal tissue.[62,63] However, peripheral lymphocyte counts in cancer patients have shown a wider degree of variation. This appears to result from variation in lymphocyte count by subset in cancer patients. For example, a study by Palazón-Carrión et al. demonstrated more plasma CD4+ and CD8+ T lymphocytes that expressed the OX40 receptor in patients with advanced breast cancer than in healthy controls.[64] However, the healthy controls had higher plasma levels of T-lymphocytes that expressed PD-1 protein.[64] Interestingly, other studies have shown similar variations of the T lymphocyte population by subtype in the tumor itself. Iurchenko et al. reported that high-grade endometrial adenocarcinomas had high levels of CD4+ and CD8+ T-lymphocytes and low levels of FOXP3+ lymphocytes located within primary tumors.[65] This suggests a variation of lymphocyte count by subtype may be present in both primary tumors and in the peripheral circulation in patients with cancer. Thus, it appears that the overall increase in circulating neutrophils in the peripheral blood may be more significant than the corresponding increase in overall lymphocyte count. This may be the result of several of the aforementioned factors, including a blunted overall increase in lymphocytes because of regional variation in subtype count with a corresponding decrease in some lymphocyte populations, compared with a significant increase in total neutrophil count not limited by such drastic subtype variations. Thus, it would logically follow that the NLR, which measures neutrophil count relative to lymphocyte count as a peripheral blood marker, would therefore be significantly elevated in patient settings of tumor presence. This would include patients with meningioma, as shown by the results of this study, which found the NLR to be an independent predictive factor for meningioma development and progression. While chronic inflammation has been linked to various ailments, specific markers of inflammation have been associated with cancer. For example, tumor-associated macrophages, tumor-associated dendritic cells, and tumor-infiltrating lymphocytes all participate in the tumor inflammatory microenvironment.[66] In addition, other molecular markers have also been cited in cancer-associated inflammation, ranging from cytokines and chemokines such as TNF, IL1, IL6, and IL8.[66] Based on the literature, the same inflammatory markers for predicting progression, recurrence, and prognosis may vary for a specific tumor and among tumors of different origins. For example, a study of IL6, C-reactive protein, and TNF found weak associations with increased risk of cancer for all three markers, but further analysis revealed that the relationship between cancer incidence and the investigated inflammatory markers may have been site specific.[67] The relevance of inflammatory markers when determining prognosis for tumors has become more established in recent years. Studies have found that elevation of inflammatory markers, including white blood cell count, NLR, and specifically, high-sensitivity C-reactive protein and high-sensitivity inflammation-based prognostic indices were significantly associated with worse overall survival in those with metastatic neuroendocrine tumors.[68] A comparative study of large B-cell lymphoma treatment found that patients with high tumor burdens had greater immune dysregulation and high serum inflammatory markers.[69] Among patients with gliomas, pretreatment systemic immune-inflammation indices were identified by multivariate analysis as independent prognostic factors for overall survival.[70] Measurements of platelet-to-lymphocyte ratio in patients with advanced gastric and colorectal cancer treated with anti-PD-1 regimens had significant value for predicting immune-

related adverse events.[71] Other studies have shown the use of procalcitonin levels as a marker for the prediction of glioma severity, but not among other brain tumors, including meningioma.[43] The results further reiterate the potential of different inflammatory marker relevance based on the type of tumor identified. The NLR is a peripheral inflammatory marker that has shown potential for clinical use in various tumors, including meningioma, the focus of this review. An increased NLR has proven to be a useful prognostic factor of many diseases, including as an indicator for early detection or poststroke cognitive impairment.[72] Retrospective analysis of NLR in thymic epithelial patients showed elevation in serum NLR levels with associations that aided in predicting poor patient outcomes, aggressive tumor behavior, and guided therapy choice based upon individual patient NLR levels.[73] In analyzing patients with gliomas, multivariate analysis found pretreatment NLR to be an independent prognostic factor for overall survival.[70] Studies showed that an NLR > 2.4 differentiated high-grade and low-grade meningioma, an NLR > 2.74 differentiated high PFS and low PFS groups, and an NLR > 2.59 was associated with recurrence with high sensitivity and specificity. For other types of cancer, there are studies of the significance of NLR in predicting the response to treatment and the occurrence of distant metastases in malignant tumors. For instance, Wang et al. categorized NLR values, affirming that the NLR indeed possessed predictive capabilities for anticipating the response to chemotherapy.[74] Medina et al. reported that NLR could be used to track the postoperative progress of patients with ovarian peritoneal carcinomatosis but not to identify infectious complications.[75] Numerous subsequent studies confirmed that an elevated NLR prior to surgery or treatment correlated with unfavorable surgical results, drug resistance, and decreased efficacies of immunotherapy and chemotherapy.[76–79]

Elevated NLRs have been seen in both meningioma and gliomas, with a lack of significance attributed to extracranial influences of alternative inflammation sources.[43] The specific difference in NLR values for meningioma versus those of other brain pathologies has not been fully identified, so further research in meningioma is warranted moving forward. The value of the NLR as an inflammatory marker allows clinical applicability to a wide range of diseases, including meningioma. A recent prospective study found an increase in NLR values with age and variation among sex in an attempt to provide reference NLR values.[80] The precise value regarding quantification of what an elevated NLR may mean merits further study. Given the general increase in NLR associated with both prediction of meningioma progression and meningioma grade,[24–29,34–37] studies specifically regarding NLR values for meningioma are necessary for future clinical use of NLR values. Our findings support the NLR as a promising biomarker that can be readily integrated into clinical settings to aid in the prediction and prevention of meningioma and its complications. In addition, as evidenced by our results, restoring balance to the immune system may serve as an attractive therapeutic target. Theoretically, a reduction in NLR values could be used to measure therapeutic efficacy, reflecting the restoration of balance within this system.

Limitations and future directions

There is one major limitation in our systematic review. Most of the studies were retrospective. To verify these findings, further prospective research should be carried out in the future. We conducted a systematic search of databases, and the only complication related to meningioma was that its relationship with NLR was reported in pneumonia. However, more research on this topic needs to be undertaken.

Conclusions

In general, we may infer a strong link between systemic inflammation assessed by NLR and meningioma based on elevated levels of NLR in patients with meningioma compared with healthy controls. In addition, NLR has significant predictive potential for the progression and recurrence of meningioma. This predictive potential increases further when combined with other diagnostic tools such as the fibrinogen level. In addition, NLR increases with increased tumor grade, which should aid physicians in making better decisions. The predictive potential increases even further when combined with other diagnostic tools such as the erythrocyte count. However, NLR did not predict POP following meningioma resection. Because of the current contradiction, our study did not demonstrate the exact difference in NLR levels in meningioma and other pathologies, so more studies are recommended on this subject.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this article.

Author contributions

Contributed to the design of the study (all authors), undertook the initial searches and screened articles for inclusion (SK, MY, AA), wrote the initial draft of the manuscript (FZM, CB), and edited the initial draft (AC, RR, ME). All authors approved the final manuscript.

Data sharing statement

All data generated or analyzed during this study are included in this published article

References

[1] Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013-2017. Neuro Oncol 2020;22(12 Suppl 2):iv1–iv96. doi:10.1093/neuonc/noaa200, PMID:33123732.

[2] Sahm F, Reuss DE, Giannini C. WHO 2016 classification: changes and advancements in the diagnosis of miscellaneous primary CNS tumours. Neuropathol Appl Neurobiol 2018;44(2):163–171. doi:10.1111/nan.12397, PMID:28295484.

[3] Magill ST, Vasudevan HN, Seo K, Villanueva-Meyer JE, Choudhury A, John Liu S, *et al*. Multiplatform genomic profiling and magnetic resonance imaging identify mechanisms underlying intratumor heterogeneity in meningioma. Nat Commun 2020;11(1):4803. doi:10.1038/s41467-020-18582-7, PMID:32968068.

[4] Behling F, Hempel JM, Schittenhelm J. Brain Invasion in Meningioma-A Prognostic Potential Worth Exploring. Cancers (Basel) 2021;13(13):3259. doi:10.3390/cancers13133259, PMID:34209798.

[5] Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014;15(11):e493–e503. doi:10.1016/S1470-2045(14)70263-3, PMID:25281468.
[6] Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity 2019;51(1):27–41. doi:10.1016/j.immuni.2019.06.025, PMID:31315034.
[7] Zitvogel L, Pietrocola F, Kroemer G. Nutrition, inflammation and cancer. Nat Immunol 2017;18(8):843–850. doi:10.1038/ni.3754, PMID:28722707.
[8] Tan D, Fu Y, Su Q, Wang H. Prognostic role of platelet-lymphocyte ratio in colorectal cancer: A systematic review and meta-analysis. Medicine (Baltimore) 2016;95(24):e3837. doi:10.1097/MD.0000000000003837, PMID:27310960.
[9] Abu-Shawer O, Abu-Shawer M, Hirmas N, Alhouri A, Massad A, Alsibai B, *et al*. Hematologic markers of distant metastases and poor prognosis in gynecological cancers. BMC Cancer 2019;19(1):141. doi:10.1186/s12885-019-5326-9, PMID:30755184.
[10] Nazem AA, Ruzevick J, Ferreira MJ Jr. Advances in meningioma genomics, proteomics, and epigenetics: insights into biomarker identification and targeted therapies. Oncotarget 2020;11(49):4544–4553. doi:10.18632/oncotarget.27841, PMID:33346248.
[11] Scheie D, Kufaishi HHA, Broholm H, Lund EL, de Stricker K, Melchior LC, *et al*. Biomarkers in tumors of the central nervous system - a review. APMIS 2019;127(5):265–287. doi:10.1111/apm.12916, PMID:30740783.
[12] Li Z, Gao Y, Zhang J, Han L, Zhao H. DNA methylation meningioma biomarkers: attributes and limitations. Front Mol Neurosci 2023;16:1182759. doi:10.3389/fnmol.2023.1182759, PMID:37492524.
[13] Nagasaki T, Akiyoshi T, Fujimoto Y, Konishi T, Nagayama S, Fukunaga Y, *et al*. Prognostic Impact of Neutrophil-to-Lymphocyte Ratio in Patients with Advanced Low Rectal Cancer Treated with Preoperative Chemoradiotherapy. Dig Surg 2015;32(6):496–503. doi:10.1159/000441396, PMID:26544755.
[14] Bilgin S, Aktas G, Zahid Kocak M, Atak BM, Kurtkulagi O, Duman TT, *et al*. Association between novel inflammatory markers derived from hemogram indices and metabolic parameters in type 2 diabetic men. Aging Male 2020;23(5):923–927. doi:10.1080/13685538.2019.1632283, PMID:31250688.
[15] Aktaş G, Duman TT, Atak B, Kurtkulağı Ö, Bilgin S, Başaran E, *et al*. Irritable bowel syndrome is associated with novel inflammatory markers derived from hemogram parameters. Fam Med Pr Ca Re 2020;22(2):107–110. doi:10.5114/fmpcr.2020.95311.
[16] Aktas G. Hematological predictors of novel Coronavirus infection. Rev Assoc Med Bras (1992) 2021;67(Suppl 1):1–2. doi:10.1590/1806-9282.67.Suppl1.20200678, PMID:34259763.
[17] Posul E, Yilmaz B, Aktas G, Kurt M. Does neutrophil-to-lymphocyte ratio predict active ulcerative colitis? Wien Klin Wochenschr 2015;127(7-8):262–265. doi:10.1007/s00508-014-0683-5, PMID:25576331.
[18] Aktas G, Sit M, Dikbas O, Erkol H, Altinordu R, Erkus E, *et al*. Elevated neutrophil-to-lymphocyte ratio in the diagnosis of Hashimoto's thyroiditis. Rev Assoc Med Bras (1992) 2017;63(12):1065–1068. doi:10.1590/1806-9282.63.12.1065, PMID:29489971.
[19] Liao CP, Booker RC, Brosseau JP, Chen Z, Mo J, Tchegnon E, *et al*. Contributions of inflammation and tumor microenvironment to neurofibroma tumorigenesis. J Clin Invest 2018;128(7):2848–2861. doi:10.1172/JCI99424, PMID:29596064.
[20] Afsin H, Aktas G. Platelet to Lymphocyte and Neutrophil to Lymphocyte Ratios are useful in differentiation of thyroid conditions with normal and increased uptake. Ethiopian Journal of Health Development 2021;35(3):1–5.
[21] Buse Balci S, Aktas G. A comprehensive review of the role of hemogram derived inflammatory markers in gastrointestinal conditions. Iran J Colorectal Res 2022;10(3):75–86. doi:10.30476/ACRR.2022.97244.1160.
[22] Duman TT, Aktas G, Atak BM, Kocak MZ, Erkus E, Savli H. Neutrophil to lymphocyte ratio as an indicative of diabetic control level in type 2 diabetes mellitus. Afr Health Sci 2019;19(1):1602–1606. doi:10.4314/ahs.v19i1.35, PMID:31148989.
[23] Şahin Ş, Sarıkaya S, Alcelik A, Erdem A, Taşlıyurt T, Akyol L, *et al*. Neutrophil to lymphocyte ratio is a useful predictor of atrial fibrillation in patients with diabetes mellitus. Acta medica mediterranea 2013;29(4):847–851.
[24] Kuranari Y, Tamura R, Tsuda N, Kosugi K, Morimoto Y, Yoshida K, *et al*. Prognostic significance of preoperative neutrophil-to-lymphocyte ratio in patients with meningiomas. Front Oncol 2020;10:592470. doi:10.3389/fonc.2020.592470, PMID:33330078.
[25] Chen X, Wang G, Zhang J, Zhang G, Lin Y, Lin Z, *et al*. A novel scoring system based on preoperative routine blood test in predicting prognosis of atypical meningioma. Front Oncol 2020;10:1705. doi:10.3389/fonc.2020.01705, PMID:33014845.
[26] Chen XY, Chen JY, Huang YX, Xu JH, Sun WW, Chen Y, *et al*. Establishment and validation of an integrated model to predict postoperative recurrence in patients with atypical meningioma. Front Oncol 2021;11:754937. doi:10.3389/fonc.2021.754937, PMID:34692542.
[27] Gao P, Kong T, Zhu X, Zhen Y, Li H, Chen D, *et al*. A clinical prognostic model based on preoperative hematological and clinical parameters predicts the progression of primary WHO grade ii meningioma. Front Oncol 2021;11:748586. doi:10.3389/fonc.2021.748586, PMID:34707993.
[28] Yuksel U, Ozdemir A, Kisa U, Ogden M, Bakar B. Can routine blood biochemistry parameters be predictive prognostic marker (s) in operated patients with meningioma WHO grade 1? Arquivos Brasileiros de Neurocirurgia: Brazilian Neurosurgery 2021;40(2):e137–e45. doi :10.1055/s-0040-1722246.
[29] Kemerdere R, Akgun MY, Toklu S, Alizada O, Baran O, Tanriverdi T. Diagnostic value of preoperative systemic inflammatory markers in patients with intracranial meningiomas. Romanian Neurosurgery 2018;32(4):613–621. doi:10.2478/romneu-2018-0079.
[30] Kayhan A, Korkmaz TS, Baran O, Kemerdere R, Yeni SN, Tanriverdi T. Preoperative systemic inflammatory markers in different brain pathologies: an analysis of 140 patients. Turk Neurosurg 2019;29(6):799–803. doi:10.5137/1019-5149.JTN.24244-18.2, PMID:30649826.
[31] Liu S, Zhu Y, Zhang C, Meng X, Sun B, Zhang G, *et al*. The clinical significance of soluble programmed cell death-ligand 1 (spd-l1) in patients with gliomas. Front Oncol 2020;10:9. doi:10.3389/fonc.2020.00009, PMID:32038986.
[32] Zheng SH, Huang JL, Chen M, Wang BL, Ou QS, Huang SY. Diagnostic value of preoperative inflammatory markers in patients with glioma: a multicenter cohort study. J Neurosurg 2018;129(3):583–592. doi:10.3171/2017.3.JNS161648, PMID:29099300.
[33] Sharma G, Jain SK, Sinha VD. Peripheral inflammatory blood markers in diagnosis of glioma and IDH status. J Neurosci Rural Pract 2021;12(1):88–94. doi:10.1055/s-0040-1721166, PMID:33551616.
[34] Liang RF, Li M, Li JH, Zuo MR, Yang Y, Liu YH. The significance of preoperative hematological inflammatory markers in patients with meningiomas. Clin Neurol Neurosurg 2019;182:1–4. doi:10.1016/j.clineuro.2019.04.020, PMID:31048144.
[35] Ashwath KG, Aggarwal A, Praneeth K, Singla N, Gupta K. Neutrophil-to-lymphocyte ratio: can it be used as an adjunct tool to predict histopathological grade of brain tumor? J Neurosci Rural Pract 2019;10(4):648–652. doi:10.1055/s-0039-3399489, PMID:31831985.
[36] Lin M, Hu T, Yan L, Xiao D, Zhao H, Yan P. Can systemic inflammatory markers be used to predict the pathological grade of meningioma before surgery? World Neurosurg 2019;127:e677–e684. doi:10.1016/j.wneu.2019.03.241, PMID:30947006.
[37] Khayat Kashani HR, Azhari S, Nayebaghayee H, Salimi S, Mohammadi HR. Prediction value of preoperative findings on meningioma grading using artificial neural network. Clin Neurol Neurosurg 2020;196:105947. doi:10.1016/j.clineuro.2020.105947, PMID:32521393.
[38] de Oliveira Silva CB, Araújo B, Ongaratti BR, dos Santos TM, Rech CGSL, Coutinho LB, *et al*. Preoperative hematological inflammatory markers associated with grade and survival in Meningiomas. Surg Exp Pathol 2022;5(1):1–8. doi:10.1186/s42047-022-00106-w.
[39] Manjunath N, Mishra S, Garg K, Suri V, Sharma MC, Tandon V, *et al*. Is there any relationship between systemic inflammatory markers and meningioma grade? Neurol India 2022;70(1):223–230. doi:10.4103/0028-3886.338647, PMID:35263887.
[40] Özdemir AF, Kaçıra T, Kemerdere R, Tanrıverdi T. The significance of preoperative neutrophil to lymphocyte ratio in patients with meningiomas. Cerrahpaşa Med J 2022;46(3):245–224. doi:10.5152/cjm.2022.22049.

[41] Teng H, Yang X, Liu Z, Liu H, Yan O, Jie D, *et al*. The performance of different machine learning algorithm and regression models in predicting high-grade intracranial meningioma. Brain Sci 2023;13(4):594. doi:10.3390/brainsci13040594, PMID:37190559.
[42] Guidry BS, Chotai S, Tang AR, Le CH, Grisham CJ, McDermott JR, *et al*. Association between preoperative hematologic markers and aggressive behavior in meningiomas. Clin Neurol Neurosurg 2023;226:107629. doi:10.1016/j.clineuro.2023.107629, PMID:36822137.
[43] Dharmajaya R, Sari DK. Role and value of inflammatory markers in brain tumors: A case controlled study. Ann Med Surg (Lond) 2021;63:102107. doi:10.1016/j.amsu.2021.01.055, PMID:33659053.
[44] Zuo MR, Liang RF, Li M, Xiang YF, Zhang SX, Yang Y, *et al*. A comprehensive study of risk factors for post-operative pneumonia following resection of meningioma. BMC Cancer 2019;19(1):100. doi:10.1186/s12885-019-5271-7, PMID:30674295.
[45] Chen Y, Lin YX, Pang Y, Zhang JH, Gu JJ, Zhang GQ, *et al*. Systemic inflammatory response index improves the prediction of postoperative pneumonia following meningioma resection. Chin Med J (Engl) 2020;134(6):728–730. doi:10.1097/CM9.0000000000001298, PMID:33725709.
[46] Deng Y, Wang C, Zhang Y. Risk factors for postoperative pneumonia in patients with posterior fossa meningioma after microsurgery. Heliyon 2020;6(5):e03880. doi:10.1016/j.heliyon.2020.e03880, PMID:32420476.
[47] Coffelt SB, Wellenstein MD, de Visser KE. Neutrophils in cancer: neutral no more. Nat Rev Cancer 2016;16(7):431–446. doi:10.1038/nrc.2016.52, PMID:27282249.
[48] Deryugina EI, Zajac E, Juncker-Jensen A, Kupriyanova TA, Welter L, Quigley JP. Tissue-infiltrating neutrophils constitute the major in vivo source of angiogenesis-inducing MMP-9 in the tumor microenvironment. Neoplasia 2014;16(10):771–788. doi:10.1016/j.neo.2014.08.013, PMID:25379015.
[49] Shojaei F, Singh M, Thompson JD, Ferrara N. Role of Bv8 in neutrophil-dependent angiogenesis in a transgenic model of cancer progression. Proc Natl Acad Sci U S A 2008;105(7):2640–2645. doi:10.1073/pnas.0712185105, PMID:18268320.
[50] Shojaei F, Wu X, Zhong C, Yu L, Liang XH, Yao J, *et al*. Bv8 regulates myeloid-cell-dependent tumour angiogenesis. Nature 2007;450(7171):825–831. doi:10.1038/nature06348, PMID:18064003.
[51] Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, *et al*. Polarization of tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. Cancer Cell 2009;16(3):183–194. doi:10.1016/j.ccr.2009.06.017, PMID:19732719.
[52] Batlle E, Massagué J. Transforming growth factor-β signaling in immunity and cancer. Immunity 2019;50(4):924–940. doi:10.1016/j.immuni.2019.03.024, PMID:30995507.
[53] Ng MSF, Tan L, Wang Q, Mackay CR, Ng LG. Neutrophils in cancer-unresolved questions. Sci China Life Sci 2021;64(11):1829–1841. doi:10.1007/s11427-020-1853-4, PMID:33661490.
[54] Long W, Chen J, Gao C, Lin Z, Xie X, Dai H. Brief review on the roles of neutrophils in cancer development. J Leukoc Biol 2021;109(2):407–413. doi:10.1002/JLB.4MR0820-011R, PMID:32970873.
[55] Antonio N, Bønnelykke-Behrndtz ML, Ward LC, Collin J, Christensen IJ, Steiniche T, *et al*. The wound inflammatory response exacerbates growth of pre-neoplastic cells and progression to cancer. EMBO J 2015;34(17):2219–2236. doi:10.15252/embj.201490147, PMID:26136213.
[56] Gonzalez H, Hagerling C, Werb Z. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes Dev 2018;32(19-20):1267–1284. doi:10.1101/gad.314617.118, PMID:30275043.
[57] Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, Hau CS, *et al*. IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. Nature 2015;522(7556):345–348. doi:10.1038/nature14282, PMID:25822788.
[58] Ralph SJ, Reynolds MJ. Intratumoral pro-oxidants promote cancer immunotherapy by recruiting and reprogramming neutrophils to eliminate tumors. Cancer Immunol Immunother 2023;72(3):527–542. doi:10.1007/s00262-022-03248-8, PMID:36066649.
[59] Kim EY, Song KY. The preoperative and the postoperative neutrophil-to-lymphocyte ratios both predict prognosis in gastric cancer patients. World J Surg Oncol 2020;18(1):293. doi:10.1186/s12957-020-02059-4, PMID:33172490.
[60] Wang Q, Li S, Qiao S, Zheng Z, Duan X, Zhu X. Changes in T Lymphocyte Subsets in Different Tumors Before and After Radiotherapy: A Meta-analysis. Front Immunol 2021;12:648652. doi:10.3389/fimmu.2021.648652, PMID:34220806.
[61] Zhou Q, Dong J, Sun Q, Lu N, Pan Y, Han X. Role of neutrophil-to-lymphocyte ratio as a prognostic biomarker in patients with breast cancer receiving neoadjuvant chemotherapy: a meta-analysis. BMJ Open 2021;11(9):e047957. doi:10.1136/bmjopen-2020-047957, PMID:34561257.
[62] Stenström J, Hedenfalk I, Hagerling C. Regulatory T lymphocyte infiltration in metastatic breast cancer-an independent prognostic factor that changes with tumor progression. Breast Cancer Res 2021;23(1):27. doi:10.1186/s13058-021-01403-0, PMID:33602289.
[63] Blessin NC, Spriestersbach P, Li W, Mandelkow T, Dum D, Simon R, *et al*. Prevalence of CD8(+) cytotoxic lymphocytes in human neoplasms. Cell Oncol (Dordr) 2020;43(3):421–430. doi:10.1007/s13402-020-00496-7, PMID:32141029.
[64] Palazón-Carrión N, Jiménez-Cortegana C, Sánchez-León ML, Henao-Carrasco F, Nogales-Fernández E, Chiesa M, *et al*. Circulating immune biomarkers in peripheral blood correlate with clinical outcomes in advanced breast cancer. Sci Rep 2021;11(1):14426. doi:10.1038/s41598-021-93838-w, PMID:34257359.
[65] Iurchenko NP, Glushchenko NM, Buchynska LG. Comprehensive analysis of intratumoral lymphocytes and FOXP3 expression in tumor cells of endometrial cancer. Exp Oncol 2014;36(4):262–266. PMID:25537221.
[66] Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. Ann Afr Med 2019;18(3):121–126. doi:10.4103/aam.aam_56_18, PMID:31417011.
[67] Il'yasova D, Colbert LH, Harris TB, Newman AB, Bauer DC, Satterfield S, *et al*. Circulating levels of inflammatory markers and cancer risk in the health aging and body composition cohort. Cancer Epidemiol Biomarkers Prev 2005;14(10):2413–2418. doi:10.1158/1055-9965.EPI-05-0316, PMID:16214925.
[68] Zou J, Li Q, Kou F, Zhu Y, Lu M, Li J, *et al*. Prognostic value of inflammation-based markers in advanced or metastatic neuroendocrine tumours. Curr Oncol 2019;26(1):e30–e38. doi:10.3747/co.26.4135, PMID:30853807.
[69] Jain MD, Zhao H, Wang X, Atkins R, Menges M, Reid K, *et al*. Tumor interferon signaling and suppressive myeloid cells are associated with CAR T-cell failure in large B-cell lymphoma. Blood 2021;137(19):2621–2633. doi:10.1182/blood.2020007445, PMID:33512407.
[70] Luo Y, Deng R, Zhong Q, Luo D, Li X, Chen X, *et al*. The prognostic value of inflammation markers in postoperative gliomas with or without adjuvant treatments. Medicine (Baltimore) 2021;100(25):e26437. doi:10.1097/MD.0000000000026437, PMID:34160435.
[71] Fan X, Wang D, Zhang W, Liu J, Liu C, Li Q, *et al*. Inflammatory markers predict survival in patients with advanced gastric and colorectal cancers receiving anti-pd-1 therapy. Front Cell Dev Biol 2021;9:638312. doi:10.3389/fcell.2021.638312, PMID:33791296.
[72] Lee M, Lim JS, Kim CH, Lee SH, Kim Y, Hun Lee J, *et al*. High neutrophil-lymphocyte ratio predicts post-stroke cognitive impairment in acute ischemic stroke patients. Front Neurol 2021;12:693318. doi:10.3389/fneur.2021.693318, PMID:34276542.
[73] Wang L, Ruan M, Yan H, Lei B, Sun X, Chang C, *et al*. Pretreatment serum neutrophil-to-lymphocyte and monocyte-to-lymphocyte ratios: Two tumor-related systemic inflammatory markers in patients with thymic epithelial tumors. Cytokine 2020;133:155149. doi:10.1016/j.cyto.2020.155149, PMID:32512341.
[74] Wang YQ, Jin C, Zheng HM, Zhou K, Shi BB, Zhang Q, *et al*. A novel prognostic inflammation score predicts outcomes in patients with ovarian cancer. Clin Chim Acta 2016;456:163–169. doi:10.1016/j.cca.2016.03.013, PMID:27006072.
[75] Medina Fernández FJ, Muñoz-Casares FC, Arjona-Sánchez A, Casado-Adam A, Gómez-Luque I, Garcilazo Arismendi DJ, *et al*. Postoperative time course and utility of inflammatory markers in patients with ovarian peritoneal carcinomatosis treated with neoadjuvant chemotherapy, cytoreductive surgery, and HIPEC. Ann Surg Oncol 2015;22(4):1332–1340. doi:10.1245/s10434-014-4096-5, PMID:25234021.

[76] Chen W, Zhong S, Shan B, Zhou S, Wu X, Yang H, *et al*. Serum D-dimer, albumin and systemic inflammatory response markers in ovarian clear cell carcinoma and their prognostic implications. J Ovarian Res 2020;13(1):89. doi:10.1186/s13048-020-00693-w, PMID:32771026.
[77] Winarno GNA, Pasaribu M, Susanto H, Nisa AS, Harsono AB, Yuseran H, *et al*. The platelet to lymphocyte and neutrophil to lymphocyte ratios in predicting response to platinum-based chemotherapy for epithelial ovarian cancer. Asian Pac J Cancer Prev 2021;22(5):1561–1566. doi:10.31557/APJCP.2021.22.5.1561, PMID:34048186.
[78] Boland JL, Zhou Q, Martin M, Callahan MK, Konner J, O'Cearbhaill RE, *et al*. Early disease progression and treatment discontinuation in patients with advanced ovarian cancer receiving immune checkpoint blockade. Gynecol Oncol 2019;152(2):251–258. doi:10.1016/j.ygyno.2018.11.025, PMID:30470581.
[79] Sastra WIG, Aditya PPK, Gradiyanto OE, Ketut S. Predictive value of preoperative inflammatory markers and serum CA 125 level for surgical outcome in Indonesian women with epithelial ovarian cancer. Cancer Biomark 2022;34(1):123–129. doi:10.3233/CBM-201415, PMID:34806598.
[80] Fest J, Ruiter R, Ikram MA, Voortman T, van Eijck CHJ, Stricker BH. Reference values for white blood-cell-based inflammatory markers in the Rotterdam Study: a population-based prospective cohort study. Sci Rep 2018;8(1):10566. doi:10.1038/s41598-018-28646-w, PMID:30002404.