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Review Article

The role of preoperative hematological inflammatory markers as a predictor of meningioma grade: A systematic review and meta-analysis

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ABSTRACT

Background: Inflammatory processes play an important role in the aggressiveness of a tumor. However, the relationship between inflammatory markers in meningioma grade is not well known. Knowledge of preoperative meningioma grade plays an important role in the prognosis and treatment of this tumor. This study aims to assess preoperative hematological inflammatory markers as a predictor of the pathological grade of meningioma.

Methods: To ensure comprehensive retrieval of relevant studies, we searched the following key databases, PubMed, Science Direct, and Biomed Central, with evidence related to preoperative hematological inflammatory markers among meningioma up to September 2023. The studies involved were selected based on established eligibility criteria. The analysis in this study uses Review Manager 5.4

Results: Six studies were obtained from the search results. The total number of patients 2789 (469 high-grade meningioma and 2320 low-grade meningioma) analysis shows elevated neutrophil-to-lymphocyte ratio (NLR) (mean difference [MD]: 0.29; 95% confidence interval [CI] 0.13–0.45; $P = 0.0004$), monocyte-to-lymphocyte ratio (MLR) (MD: 0.02; 95% CI 0.00–0.04; $P = 0.003$), and low lymphocyte-to-monocyte ratio (LMR) (MD: −0.82; 95% CI −1.46–−0.18; $P = 0.005$) significantly associated with high-grade meningioma compared to low-grade meningioma. No significant correlation between high-grade and low-grade meningioma based on platelet-lymphocyte ratio value is observed.

Conclusion: The parameters of NLR, MLR, and LMR have been found to be cost-effective preoperative methods that demonstrate potential value in the prediction of meningioma grade. To enhance the reliability of the findings, it is imperative to do further prospective study.

Keywords: Grade, Inflammatory markers, Meningioma

INTRODUCTION

Meningioma ranks as the most common brain tumor in adults. In cases of central nervous system (CNS) tumors, 39.3% are meningiomas and account for 55.4% of benign CNS tumors.[34] The

incidence rate of meningioma is 7.86 cases/100,000 people each year.[34] The incidence of meningioma increases in old age, and women have a higher incidence of non-malignant meningioma.[34] Although it is a slow-growing and asymptomatic tumor, meningiomas can be symptomatic and even aggressive in some cases.

Meningiomas originate from meningothelial (arachnoid) cells on the inner surface of the dura.[14,29] Based on the World Health Organization (WHO) diagnostic classification, meningiomas are categorized into grades I, II, and III.[27] The majority of meningiomas were grade I (80.1%), which are benign, while the percentage for high-grade meningioma was grade II (18.3%) and grade III (1.5%).[34] High-grade meningiomas are aggressive and have a higher risk of recurrence.[17]

Surgical management with total removal is still the main choice in cases of high-grade meningioma. In high-grade meningioma, adjuvant therapy is usually required due to the high risk of recurrence and poor prognosis.[3] The recurrence rate of grade I meningioma is (7-23%), grade II (50-55%), and grade III (72-78%).[17,34,37] Therefore, tumor grade determination is very important preoperatively in meningioma cases. Pathological grading affects prognosis, determination of adjuvant therapy, and subsequent follow-up plans.[26,27,51]

Various hematological inflammatory markers are currently attracting the attention of researchers, including their association with tumors. Progression of a tumor is closely linked to the inflammatory process. Immune cells in the inflammatory process will infiltrate the tumor; this process can be seen from the peripheral blood hematology test.[6] In the previous meta-analyses, inflammatory components, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), are regarded as potential predictors in determining prognosis of cancers.[40,48,50] Other studies conducted on glioma showed that hematological inflammatory markers play a role as a grade determinant.[1,19,46]

Regular blood tests performed before surgery are widely available and inexpensive. Therefore, predicting the grade of a tumor preoperatively using hematological indicators is promising. The previous meta-analyses have assessed hematological inflammatory parameters in meningioma progression and recurrence.[20] However, these studies were limited to NLR only. Based on our knowledge, this is the first meta-analysis to explore various hematological inflammatory parameters to predict meningioma grade. Therefore, this study aims to assess the role of hematological inflammatory markers on grade in meningioma patients.

MATERIALS AND METHODS

This study was carried out in compliance with the guidelines and criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol.

Search strategy

We systematically searched PubMed, Science Direct, and Biomed Central databases from their inception till September 2023. We use two stages in article search. The first search uses keywords with Boolean operators (inflammatory markers AND meningioma). Then, for the second search, we used Boolean operators for several hematological inflammatory markers: neutrophil-lymphocyte ratio AND meningioma, platelet lymphocyte ratio AND meningioma, and monocyte lymphocyte ratio AND meningioma.

Eligibility criteria

To be eligible for incorporation, investigations should clearly specify and depict the research population, the treatments, and the outcome or prognosis. The study included: (1) patients were diagnosed with low-grade and high-grade and histologically verified and graded according to the WHO diagnostic criteria, (2) preoperative levels of systemic inflammatory markers were evaluated, and (3) information on outcome results was documented. Studies were excluded: (1) review articles, case reports, conference abstracts, and letters, (2) animal or cell studies, and (3) not in English language.

Data synthesis and extraction

Data extracted from the identified publication included the first author, year published, study design, number of patients, preoperative hematology data, and results from each study, including tumor grade and mean and standard deviation (SD) values. The extracted data were displayed in tables and analyzed further [Table 1].

Study quality assessment

The quality of the included papers was evaluated by two reviewers using the Joanna Briggs Institute (JBI) critical assessment techniques for cohort studies. To determine the overall quality of reporting in the study, a scoring system was devised, where each "yes" response received one point, while "no" and "unclear" responses received zero points. Subsequently, the total score was divided by the total number of questions on the checklist. The resulting score was then used to classify the study's quality as high (<50%), moderate (50–69%), or indicating a low risk of bias (≥70%). This approach allowed for a conclusive assessment of the study's reporting quality based on a systematic evaluation of various criteria outlined in the checklist.

Statistical analysis

We extracted continuous data as a mean from each selected study. The data obtained were then analyzed and presented in a forest plot. We used the random effect model in the analysis

due to the possibility of different treatments between different and multiple studies. There were normally distributed and abnormally distributed data. Each demographic data was converted to mean and SD.

The I^2 statistic was employed to assess the level of statistical heterogeneity among the studies. Heterogeneity was categorized based on the I^2 value, with values below 50% indicating minimal to moderate heterogeneity and above 50% indicating substantial heterogeneity. Statistical analyses were conducted using Review Manager 5.4, which generated forest plots to summarize the meta-analysis results. Continuous variables were analyzed using the mean difference (MD). A significance level of $P < 0.05$ was set to determine statistical significance.

RESULTS

The flowchart for searching articles that fulfill the inclusion criteria for this study is shown in Figure 1.

A total of 1310 studies were obtained from the initial search of the database. After the duplicated papers were excluded, 1.070 articles were obtained. Then, screening was carried out based on the title and abstract. After screening, 26 articles were selected and then matched with eligibility criteria. After several stages of eligibility screening, a total of six studies were included in this study.[5,12,21,24,25,30] All collected studies describe hematological inflammatory markers and the association of the pathological grade of meningioma.

We included six studies with retrospective design involving a minimum of 89 patients and a maximum of 944 patients for the meta-analysis. The total number of patients was 2789, with 469 high-grade meningioma patients and 2320 low-grade meningioma patients. The outcomes included in the meta-analysis are NLR, PLR, MLR, and LMR. Table 1 provides a summary of the characteristics and outcomes of each study included in the study.

Quality of included studies

The quality assessment of the included observational studies using the JBI critical appraisal tool yielded varied results, which are summarized in Table 2. Four studies had a high risk of bias, and two studies had a low risk of bias.

NLR

Meta-analysis showed that the NLR is significantly higher in the high grade compared to the low-grade tumor group (MD: 0.29; 95% confidence interval [CI] 0.13–0.45; $P = 0.0004$), as shown in the forest plot in Figure 2. There is no significant heterogeneity in this study ($I^2 = 0\%$).

PLR

Meta-analysis showed no significant relationship between PLR values in high-grade and low-grade meningioma (MD:

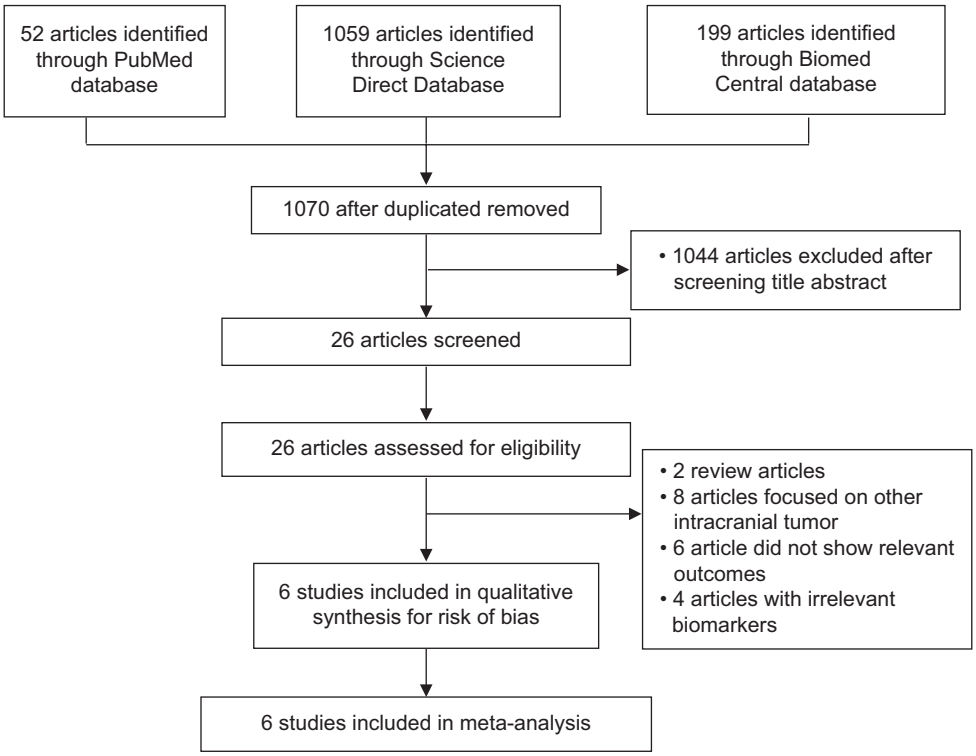

Figure 1: Study flow diagram in this review.

Table 1: Outcomes between included studies.

Author	Year	Study design	Tumor grade	*n*	NLR	PLR	MLR	LMR
Lin *et al*.[25]	2019	Retrospective	High Grade	97	2.17±0.91	120.27±34.03	0.23±0.1	NA
			Low Grade	575	1.89±0.74	117.16±38.31	0.21±0.07	NA
Liang *et al*.[24]	2019	Retrospective	High Grade	150	2.6±1.63	105.73±50.59	NA	5.6±3.98
			Low Grade	794	2.34±2.84	110.25±77.34	NA	6.39±8.81
Kashani *et al*.[21]	2020	Retrospective	High Grade	26	3.86±4.05	159±123.62	NA	5.93±2.67
			Low Grade	69	3.56±2.65	148±118.87	NA	5.91±5.6
Silva *et al*.[5]	2022	Retrospective	High Grade	16	8.23±10.56	194.57±89.49	NA	2.13±2.03
			Low Grade	73	4.92±5.06	164.04±81.52	NA	3.37±2.26
Manjunath *et al*.[30]	2022	Retrospective	High Grade	114	3.19±4.58	104.38±128.36	0.19±0.32	NA
			Low Grade	666	2.7±4.12	102.06±119.97	0.17±0.25	NA
Guidry *et al*.[12]	2023	Retrospective	High Grade	66	4.81±4.62	158±87.15	0.38±0.25	NA
			Low Grade	143	4.15 ±4.26	150.05±73.39	0.35±0.23	NA

Continuous variables are reported in mean±standard deviation. NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, NA: Not available

Table 2: Quality assessment of included studies.

Author (Year)	Design	Score based on appropriate JBI appraisal*											Score (%)	Risk of Bias
		1	2	3	4	5	6	7	8	9	10	11		
Lin *et al*. (2019)[25]	Retrospective	Y	Y	Y	Y	Y	Y	Y	U	U	U	Y	8/11 (72.7)	Low
Liang *et al*. (2019)[24]	Retrospective	Y	Y	Y	Y	Y	Y	Y	U	U	U	Y	8/11 (72.7)	Low
Kashani *et al*. (2020)[21]	Retrospective	Y	Y	Y	U	U	U	U	U	U	U	Y	4/11 (36.36)	High
Silva *et al*. (2022)[5]	Retrospective	U	Y	Y	U	U	U	U	Y	U	U	Y	4/11 (36.36)	High
Manjunath *et al*. (2022)[30]	Retrospective	U	Y	Y	U	U	U	U	U	U	U	Y	3/11 (27.27)	High
Guidry *et al*. (2023)[12]	Retrospective	U	Y	Y	U	U	U	U	U	U	U	Y	2/11 (0.09)	High

*Score gained/maximum score, Y=yes; N=no; U=unclear; NA=not applicable.

1.30; 95% CI −4.24–6.84; P = 0.65), as shown in the forest plot in Figure 3. There is no significant heterogeneity in this study (I^2 = 0%).

MLR

Meta-analysis showed that the MLR is significantly higher in the high-grade compared to the low-grade meningioma group (MD: 0.02; 95% CI 0.00–0.04; P = 0.003), as shown in the forest plot in Figure 4. There is no significant heterogeneity in this study (I^2 = 0%).

LMR

Meta-analysis showed that the LMR is significantly lower in the high-grade compared to the low-grade tumor group (MD: −0.82; 95% CI −1.46–−0.18; P = 0.005), as shown in the forest plot in Figure 5. There is no significant heterogeneity in this study (I^2 = 0%).

DISCUSSION

Meta-analysis addressing the relationship between hematological inflammatory markers and meningioma grade has not been reported to our knowledge. This study found that higher NLR and MLR and lower LMR were associated with high-grade meningiomas. These hematological parameters may be able to predict tumor grade before surgery. This may help clinicians to plan treatment early, thereby improving patient prognosis. These markers are also derived from a routine complete blood count, which is readily available and provides a cost-effective method for preoperative assessment. Therefore, hematologic parameters that are predictive of high-grade meningiomas, which have a poorer prognosis, can be used to guide the decision for advanced treatment.

Six studies met the inclusion criteria and were included for meta-analysis to explore the role of inflammatory markers in predicting meningioma grade. Meningiomas, the most common primary brain tumors, display a spectrum of biological behaviors that range from benign to aggressive. Meningiomas are a type of brain tumor that can exhibit varying levels of aggressiveness. Understanding the factors that can predict tumor grade is crucial for accurate prognosis and treatment planning. Table 1 outlines the outcomes from the included studies, showcasing the variations in NLR, PLR, MLR, and LMR levels between high-grade and low-grade meningiomas. Based on our study, NLR, MLR, and LMR have a role in predicting meningioma grade.

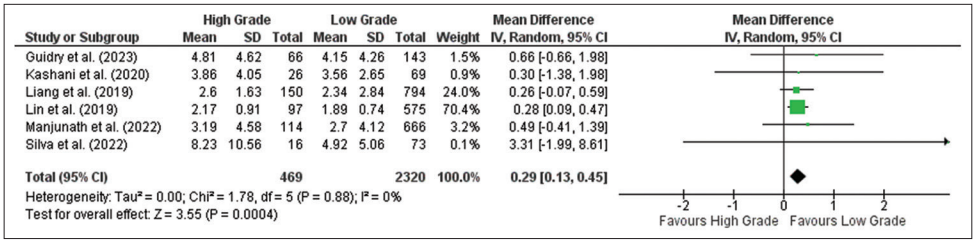

Figure 2: Forest plot of neutrophil-to-lymphocyte ratio between high-grade and low-grade tumor groups. CI: Confidence interval, SD: Standard deviation. The green box shows the effect value of each study and the size indicates the weight of the study. The black rectangle shows the combined effect value of each study. The analysis showed that NLR was higher in high grade meningioma than in low grade meningioma significantly.

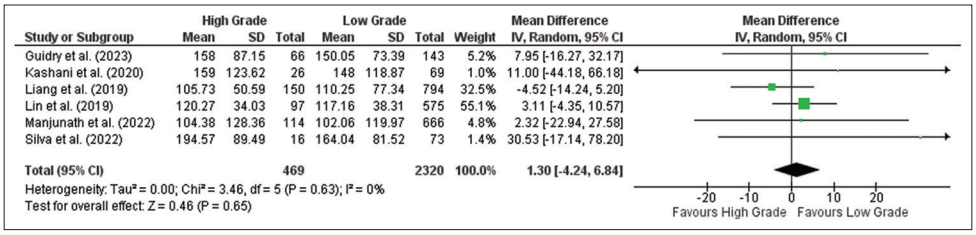

Figure 3: Forest plot of platelet-to-lymphocyte ratio between high-grade and low-grade tumor groups. CI: Confidence interval, SD: Standard deviation. The green box shows the effect value of each study and the size indicates the weight of the study. The black rectangle shows the combined effect value of each study. Analysis showed PLR has no significant relationship between high-grade and low-grade meningioma.

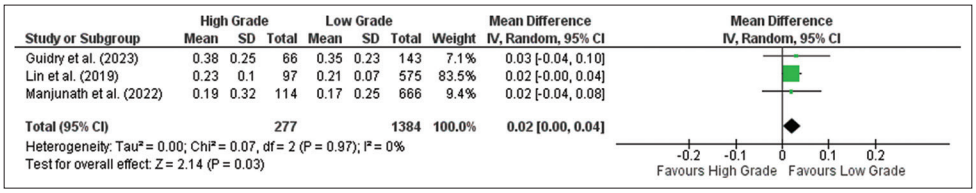

Figure 4: Forest plot of monocyte-to-lymphocyte ratio between high-grade and low-grade tumor groups. CI: Confidence interval, SD: Standard deviation. The green box shows the effect value of each study and the size indicates the weight of the study.The black rectangle shows the combined effect value of each study. The analysis showed that MLR was higher in high grade meningioma than in low grade meningioma significantly.

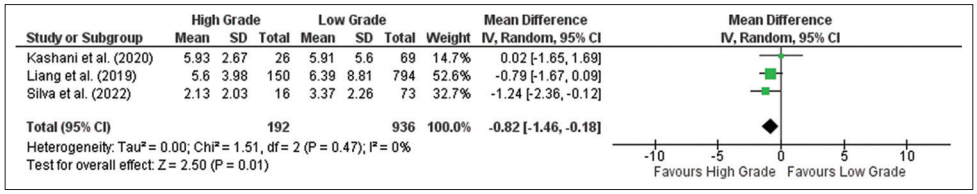

Figure 5: Forest plot of lymphocyte-to-monocyte ratio between high-grade and low-grade tumor groups. CI: Confidence interval, SD: Standard deviation. The green box shows the effect value of each study and the size indicates the weight of the study. The black rectangle shows the combined effect value of each study. The analysis showed that LMR was lower in high grade meningioma than in low grade meningioma significantly.

The quality assessment of the included studies varied, with most studies categorized as having a moderate or low risk of bias. In addition, heterogeneity between studies was observed in some analyses, which may be due to differences in patient characteristics and measurement methods. Nevertheless, this meta-analysis provides valuable insights

into the potential role of preoperative hematological inflammatory markers in meningioma management and prognosis.

Tumor tissue infiltration is a condition that involves an inflammatory process. Tumor-associated macrophages in the tumor stroma induce immune cell responses and various cytokines.[49] Furthermore, inflammatory processes are linked to the tumor microenvironment and play a role in every stage of tumorigenesis.[11] Inflammation plays a role in tumor invasion, angiogenesis, cell proliferation, and immune cell suppression.[13] Various cells such as neutrophils, lymphocytes, monocytes, and platelets play a role in the systemic inflammatory process,[33] and many studies have reported quantification of these cells as outcome indicators in patients with tumors.

Neutrophils are the most abundant component of white blood cells in the circulation.[31,38] In the case of solid tumors, neutrophils will dominate the tumor environment.[38,32,42] Neutrophils have a role in stimulating the secretion of proinflammatory cytokines and play a role in angiogenesis through the secretion of vascular endothelial growth factor (VEGF), Angiopoietin 1, and fibroblast growth factor.[8] NLR indicates the ratio between neutrophils and lymphocytes. A high NLR value indicates a relative ratio of neutrophilia and lymphopenia. Neutrophilia plays a role in the apoptosis of lymphocytes, NK cells, and T-cells.[4,7,35] Furthermore, neutrophilia will reduce the number of lymphocytes through the secretion of hydrogen peroxide and arginase.[4,10] On one side, lymphocytes play a role in defense by forming a barrier against cancer cells.[24] Some studies report that lymphocyte cell infiltration shows an association with a good response to the therapy given.[9] Therefore, NLR may represent a state of balance between immune cells and neutrophils[22], and high NLR values indicate immunosuppression.[28] Remarkably, across multiple studies in this meta-analysis, NLR consistently emerged as a strong predictor of tumor aggressiveness. Higher NLR values in high-grade meningiomas compared to low-grade cases (MD: 0.29; 95% CI 0.13–0.45; $P = 0.0004$) suggest a potential correlation between elevated neutrophil counts and increased malignancy. These results align with other studies that have confirmed that NLR is a powerful marker for assessing the prognosis of various cancers, such as glioma,[22] gastric cancer,[41] esophageal cancer,[36] breast cancer,[45] and colorectal cancer.[23]

Similar patterns were observed with MLR. This marker is significantly higher in the high grade compared to the low-grade meningioma group (MD: 0.02; 95% CI 0.00–0.04; $P = 0.003$), reinforcing the link between tumor grade and these inflammatory markers. Meanwhile, the LMR parameter showed significantly lower results in high-grade meningioma compared to low-grade meningioma (MD: −0.82; 95% CI −1.46–−0.18; $P = 0.005$). Monocytes can easily infiltrate the blood–brain barrier (BBB) in cases of brain tumors.[44] Monocytes play a role in the stimulation of tumor cell growth through the activation of various cytokines such as tumor necrosis factor, interleukin-1, interleukin-6, and macrophages.[24] The presence of tumor-associated macrophages that play a role in the progressivity of a tumor can be described by the number of circulating monocytes.[24] Recent studies on several cancers support the association between monocyte and lymphocyte ratio values and cancer prognosis. Xiang *et al*. reported that MLR is a predictor for stage, grade, and metastasis in ovarian cancer.[47] In another study on LMR, Song *et al.* reported that low LMR is associated with poor prognosis in esophageal cancer.[39]

Furthermore, lymphocytes in the circulating tumor microenvironment will become tumor-infiltrating lymphocytes (TIL) and act as anti-tumor through cytolytic activity, antiproliferation, and inhibit migration.[43,47] The host immune response to tumor progression and metastasis is reduced as a result of a decrease in lymphocytes.[15] An increased number of monocytes and fewer lymphocytes indicate an active inflammatory response, which this situation would support the growth of a tumor.[33] Therefore, based on this study, it is understandable that MLR and LMR significantly differentiate between high-grade and low-grade meningioma.

Platelets are associated with the formation of tumor cell-platelet aggregation that supports tumor cell growth and angiogenesis. The process of angiogenesis takes place through the secretion of VEGF.[18] As for PLR markers, based on the results of the meta-analysis, there was no significant association between high-grade and low-grade meningioma. Recent studies have reported different conclusions regarding the relationship between PLR and cancer prognosis. In a meta-analysis of glioma patients, Jarmuzek *et al*. reported PLR as a marker significantly associated with glioma prognosis.[16] Whereas in the analysis reported by Wang *et al*., PLR values did not have a significant association with glioma. Further studies still need to confirm the relationship between PLR values in intracranial tumors, including meningioma.[44]

Immunoexcitotoxicity, which is the interaction between inflammatory cytokines and glutamate receptors, is widely believed to have a significant impact on numerous neurological disorders and is currently being studied in relation to the growth and spread of tumors. Through its effects on metabolism, glutamate (a non-essential amino acid) plays a critical role in the progression of tumors. Activation of glutamate receptors can increase the effectiveness of effector T-cells or decrease cytokine production in immunosuppressive myeloid-derived suppressor cells, thereby enhancing antitumor immune responses. Inflammatory hematology ratios such as NLR, MLR, and LMR are believed to reflect the balance between

pro-tumor inflammatory responses and antitumor immune responses. However, the specific relationship between immunoexcitotoxicity, glutamate, and the hematological parameters in the context of tumor growth and invasion needs further research for a more comprehensive understanding.[2]

Although preoperative hematological markers may help in grade prediction and prognosis in the clinical setting, the results of this meta-analysis have several limitations and require further analysis. First, studies that discuss the role of inflammatory markers in meningioma are still limited and only involve retrospective studies. Studies with other designs and involving more samples are needed to strengthen the result. Second, the samples used in each study mostly included low-grade meningiomas rather than high-grade meningiomas. Third, hematological marker values can be affected by the presence of infection, comorbid diseases, and medication use, which can affect the inflammatory parameter values in each study. Finally, the studies included in this meta-analysis have varying quality assessments, including studies with a high risk of bias. The results obtained in this meta-analysis suggest that more studies should be conducted to validate its conclusions. Furthermore, studies with more robust study designs and larger sample sizes, such as multicenter randomized controlled trials (RCTs), are needed.

CONCLUSION

Preoperative hematological inflammatory markers, particularly NLR, MLR, and LMR, can serve as potential predictors of meningioma grade. These findings provide valuable insights into the role of inflammatory markers as predictors of meningioma grade. These markers can be obtained easily and cost-effectively from routine preoperative laboratory tests. They can provide valuable information for clinicians in determining the prognosis and treatment plan for meningioma patients. However, further research and validation studies are needed to confirm these findings and establish the clinical utility of these inflammatory markers in predicting meningioma grade. Nonetheless, the meta-analysis provides valuable insights into the potential role of preoperative hematological inflammatory markers in meningioma management and prognosis.

Ethics approval

The Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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