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Review Article

Prognostic Significance of Platelet-to-Lymphocyte Ratio in Gliomas: A Meta-analysis

Huayue Cong[1, 2], Aixia Sui[1, *], Liuyi Yang[1, 2], Huiling Song[1, 2], Jing Zhao[1], Yong Liu[3], Mingming Zhang[1], Weiliang He[1]

[1]Hebei General Hospital, Shijiazhuang, China

[2]College of Postgraduate, North China University of Science and Technology, Tangshan, China

[3]Department of Oncology, Baoding First Central Hospital, Baoding, China

Email address:

15732189181@163.com (Aixia Sui), 2681355568@qq.com (Huayue Cong), 442456941@qq.com (Liuyi Yang), 1031086205@qq.com (Huiling Song), zzzjmail@163.com (Jing Zhao), lahupi@163.com (Yong Liu), zhangmm197612@126.com (Mingming Zhang), hwl19851007@126.com (Weiliang He)

[*]Corresponding author

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Abstract: *Background and objective:* Inflammatory factors are associated with tumour initiation, progression, invasion, and metastasis. It is a potential prognostic factor for multiple solid tumours. Such as cholangiocarcinoma, bladder cancer, nasopharyngeal carcinoma and so on. However, there is no clear evidence that elevation of the systemic inflammatory marker, platelet-to-lymphocyte ratio (PLR), has this type of predictive value in patients with glioma. This meta-analysis aimed to explored the prognostic significance of the preoperative inflammatory marker PLR in patients with glioma. *Methods:* Systematic retrieval of articles published between the time of their conception and September 2020 in PubMed, EMBASE, and Cochrane library databases, A meta-analysis was performed via Review Manager 5.3, using the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for overall survival (OS) to assess the predictive significance of PLR in patients with glioma. *Result:* We selected nine studies and showed that in patients with glioma, increased PLR was correlated with poor OS (HR = 1.37, 95% CI: 1.09–1.71, P = 0.007, I^2 = 55%). By analysing the I^2, we estimated moderate heterogeneity in several of the published articles that were incorporated. *Conclusion:* Our meta-analysis provides evidence that increased PLR is correlated with poor OS in patients with glioma cancer.

Keywords: Glioma, Platelet to Lymphocyte Ratio, Meta-analysis, Overall Survival

1. Background

Glioma, a malignant tumour originating from brain glial cells, comprises 32% of primary central nervous system tumours, accounting for more than 80% of brain tumours [1]. Currently, the treatment of glioma is primarily surgical resection combined with chemotherapy and radiotherapy. At present, there are emerging targeted therapy and immunotherapy. Although good progress has been made regarding treatment options, the prognosis of patients is still extremely poor [2]. The prognosis of Glioblastoma (GBM, World Health Organization grade IV) is extremely poor [3]. It is essential to evaluate the prognosis of glioma, identify patients with glioma early, and provide them with the most appropriate individualized treatment. This will be helpful in improving overall survival in patients with glioma.

Current projections include traditional prognostic factors and emerging prognostic factors, such as the following: tumour location, patient's age, patient's physical condition, pathological classification, closed lip stage, isocitrate dehydrogenase value, and extent of surgery [3]. Projections

also include emerging prognostic factors such as expression of microRNA-210 [4], LncRNA SNHG16 [5], lncSNHG15 [6], and accuracy of apparent diffusion coefficient derived from diffusion-weighted imaging [7]. However, these traditional predictors are imprecise, and their early detection is not possible. In addition, emerging technologies are expensive and their applicability in routine practice is difficult. Presently, it is recognized that inflammatory factors are associated with tumour initiation, progression, invasion, and metastasis. Platelet-lymphocyte-ratio (PLR) is a simple, convenient, and readily available systemic inflammatory marker. An increase in platelet levels is beneficial to the growth and metastasis of intracranial tumours. A decrease in lymphocytes leads to worsening of the immune system and poor prognosis. It is a potential prognostic factor for multiple solid tumours including cholangiocarcinoma [8], bladder cancer [9], nasopharyngeal carcinoma [10], gastric carcinoma [11], urinary cancer [12], and oral cancers [13]. Platelets promote angiogenesis, exacerbate tumour growth and spread. The higher the lymphocyte content is in patients with cancer, the better the prognosis is during treatment. However, there is some controversy regarding whether it can be useful in determining the prognosis of brain glioma. This meta-analysis aimed to explored the prognostic significance of the preoperative inflammatory marker PLR in patients with glioma.

2. Materials and Methods

2.1. Overview

This meta-analysis was designed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta Analyses statement (PRISMA) [14] and was registered at the International Prospective Register of Systematic Reviews (number CRD42020222092). Systematic retrieval of articles published between the time of their conception and September 2020 in PubMed, EMBASE, and Cochrane library databases, which explored the prognostic significance of the preoperative inflammatory marker PLR in glioma patients, was performed. A combination of the following search terms wear employed in our literature searches as follows: (glioblastoma OR glioma) AND (PLR OR platelet lymphocyte ratio OR platelet to lymphocyte ratio OR platelet-to-lymphocyte ratio). To expand the range of our search, we also screened the references.

2.2. Study Selection

Eligible studies were included: (1) patients were diagnosed with gliomas; (2) there was clinical significance of PLR for glioma prognosis; (3) the cut-off value of PLR was reported; and (4) individual HRs and 95% CIs were extracted or calculated. Articles that included all of these criteria were selected.

Studies were deleted: (1) they were animal experiments, reviews, case reports, letters, or conference abstracts; (2) there was insufficient information on extracted or calculated HRs and 95% CIs; and (3) they were duplicate studies or studies with overlapping data.

2.3. Data Extraction

Two autonomous reviewers obtained the articles that met inclusion criteria. The following items was extracted: author, year of publication, country, number of simples, mean age, tumour-node-metastasis stage, treatment (chemotherapy or radiotherapy), cut-off PLR value, HR, and 95% CI. If multiple estimates were presented in the same article, multivariate analysis was considered better than univariate analysis.

2.4. Quality Assessment

Two reviewers individually evaluated the study quality using the Newcastle-Ottawa quality assessment scale (NOS) [15]. In this scoring system, the higher the score (from 0 to 9) the better the quality of the article. Generally, studies with a score > 5 are rated as high-quality. Evaluation criteria of the scale includes: (1) a selection of the study population, i.e. how the exposure group was representative, how the non-exposure group was selected, how exposure factors were determined, and what are the outcome indicators that were not observed at the beginning of the study (0–4); (2) comparability between groups, i.e. comparability was considered when the study was designed and the data analysed (0–2); and (3) outcome evaluation, i.e. whether the study results were evaluated sufficiently, whether there was sufficient follow-up time, and whether the follow-up times of both the exposed and non-exposed groups were adequate (0–3).

2.5. Statistical Analyses

All the data were merged via a classical meta-analysis method applying Review Manager, version 5.3. HRs and 95% CIs of PLR and OS associations that were reported in each study were collected. Heterogeneity was evaluated utilizing the inconsistency index (I^2). According to the value of I^2, we chose different models, and when I^2 was < 25%, we chose the fixed model. Otherwise, we selected the random effects model. When I^2 > 50%, we applied subgroup analysis and sensitivity analysis to find the root causes of heterogeneity. We used funnel plots to evaluate publication bias. A 95% CI and $p < 0.05$ were used to evaluate the statistical significance of each survey and each result variable. All p values were two-tailed.

3. Results

3.1. Literature Information

The flow diagram (Figure 1) shows the literature selection process. In the search of the three databases, 87 records were originally identified, of which 74 remained after the removal of duplicates. Subsequently, an additional 43 were removed because they were found irrelevant after screening the titles or abstracts. After carefully reading the full text of the remaining 31 articles, 22 were deleted for non-compliance with inclusion criteria. Ultimately, 9 articles were determined eligible.

3.2. Study Characteristics and Quality Assessment

As seen in Figure 2, 9 articles [16-24] were selected for our meta-analysis. All reported retrospective studies. Data from a total of 1,938 cases (males [n = 1,125] and females [n = 813]) from the studies were included. Among the 9 articles, one report was from Turkey, one from Italy, and seven were from China. The PLR interception values in the survey ranged from 87 to 228.6. The average intercept was 146. NOS scores were also recorded, as seen in Figure 2.

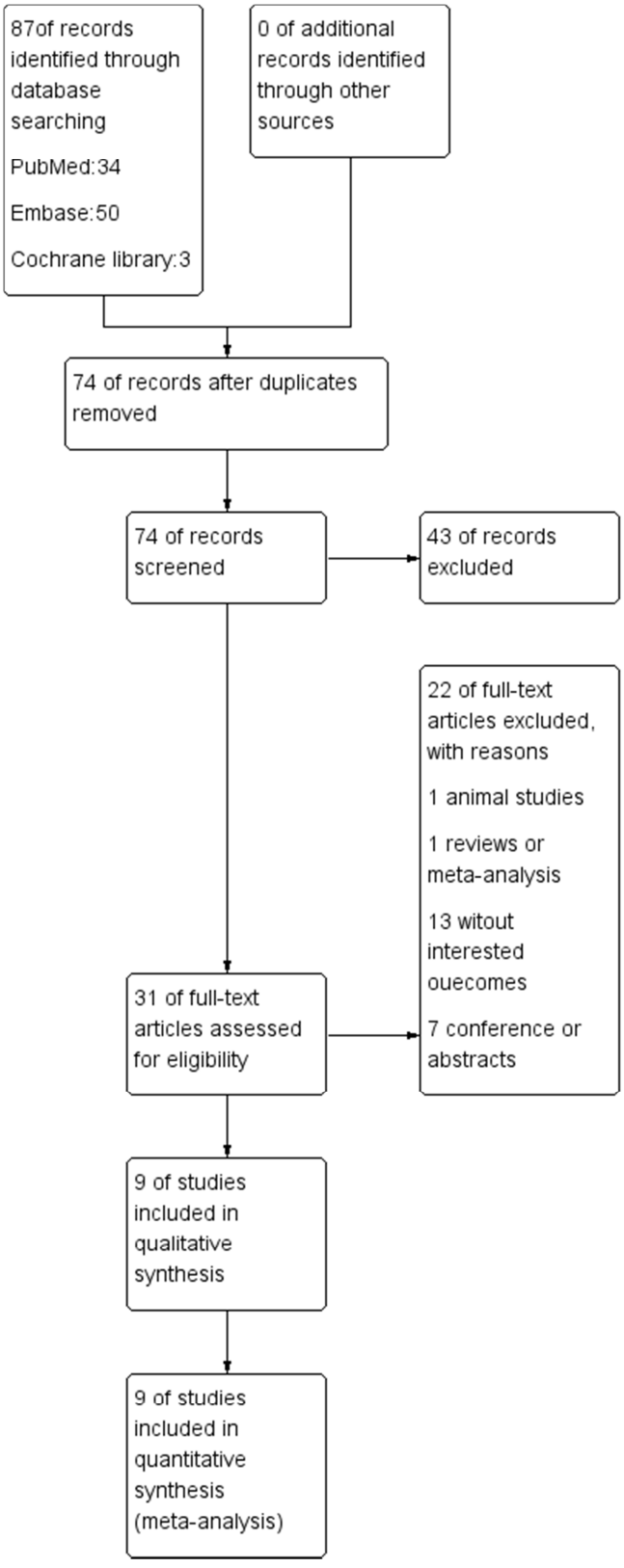

Figure 1. *The flow chart of study selection procedure in the meta-analysis.*

Author	year	country	number of simples (male/female)	Mean age	TNM	treatment	Cut-off PLR	HR	95% CI	NOS score
Yunfei Hao	2019	China	187(116/71)	55	NA	S+C/R	228.6	1.364	0.856-2.171	7
Yajuan Lv	2019	China	192(113/79)	53.24	NA	S+C/R	87	1.531	0.969-2.419	6
Yifeng Bao	2019	China	219(124/95)	>50	I-IV	NA	127	1.294	0.907-1.845	7
ÖZLEM YERSAL	2018	Turkey	80(39/41)	56.8	I-IV	S+C/R	135	0.649	0.365-1.125	6
Peng-Fei Wang	2018	China	706(407/299)	45	II-IV	NA	133.26	1.96	1.43-2.78	6
Junli Wang	2018	China	112(70/42)	50	I-IV	NA	200	1.03	0.559-1.896	7
Peng-Fei Wang	2017	China	166(96/70)	52.1	NA	NA	175	2.068	1.296-3.300	6
Sheng Han	2015	China	152(95/57)	50.4	I-IV	NA	135	1.023	0.668-1.565	7
Alessandra Marini	2020	Italy	124(65/59)	>60	NA	S+C/R	175	1.7	0.97-2.32	7

Figure 2. *Baseline Characteristics of Included Studies.*

3.3. PLR and OS

The association between PLR and OS from the 9 selected studies was subjected to data analysis utilizing Review Manager 5.3. As shown in Figure 3, increased PLR was associated with poor prognosis in patients with glioma (HR = 1.37, 95% CI: 1.09–1.71, P = 0.007, I^2 = 55%). The I^2 value was equal to 55%, which indicated moderate heterogeneity in several of the articles that were incorporated. Next, we applied subgroup analysis and sensitivity analysis to find the root causes of the observed heterogeneity.

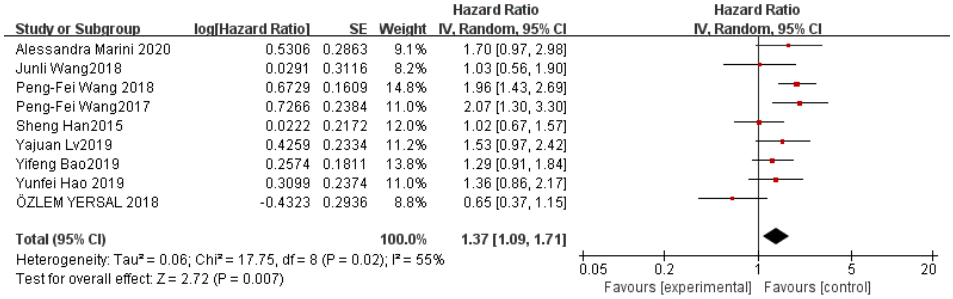

Figure 3. *Forest plots for the association between PLR and OS.*

3.4. Subgroup Analysis

The selected literature studies were combined with moderate heterogeneity. We conducted subgroup analyses based on race, PLR cut-off value, and sample size to find the root causes of heterogeneity. When we conducted a subgroup analysis according to race, it was observed that as the PLR rose, Asians exhibited a poor prognosis (HR = 1.46, 95% CI: 1.18–1.79), although non-Asians did not (HR = 1.05, 95% CI: 0.41–2.70, P = 0.92) (Figure 4). When subgroup analysis was conducted, a high PLR (PLR cut-off value > 146) had unfavourable OS in patients with glioma (HR: 1.53, 95% CI: 1.16–2.04). This was not observed in those with a PLR cut-off value of ≤ 146 (HR: 1.26, 95% CI: 0.90–1.77) (Figure 5). When the sample size was > 215 (HR = 1.61, 95% CI: 1.07–2.41), poor OS was observed when there was an increase in PLR (Figure 6). When the sample size was < 215, the result was not apparent. Based on the results of subgroup analysis, PLR interception value had a specific effect on heterogeneity. As such, we determined that increased PLR is correlated with poor OS in patients with glioma cancer.

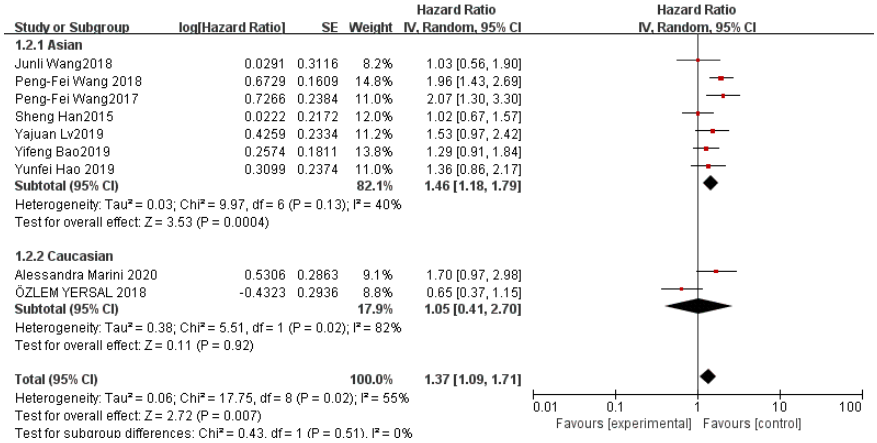

Figure 4. *Hazard ratios (HRs) for OS according to subgroup analyses: race.*

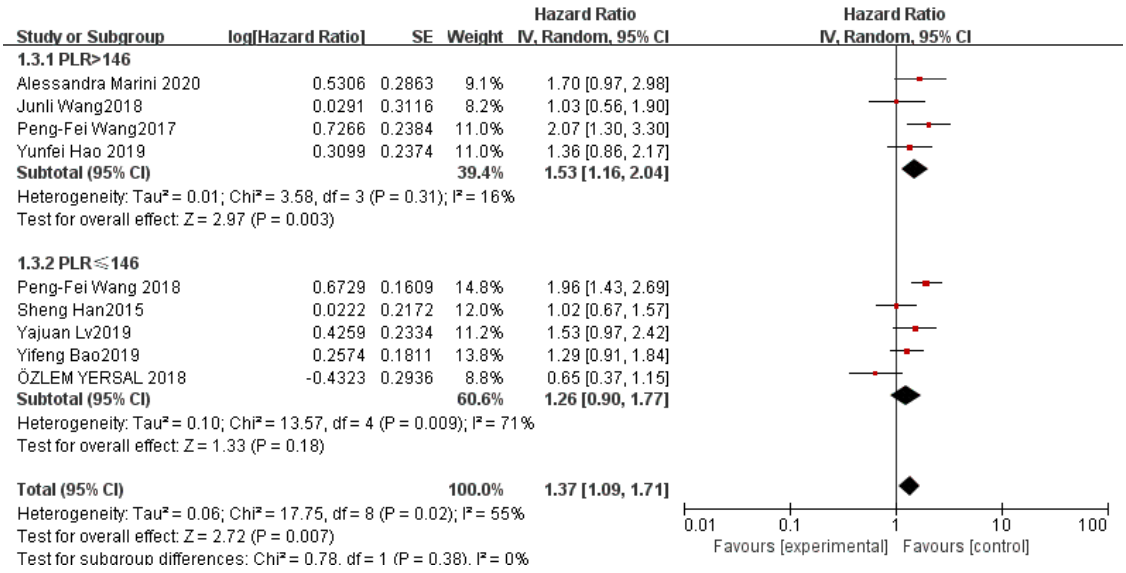

Figure 5. *Hazard ratios (HRs) for OS according to subgroup analyses: PLR cut-off.*

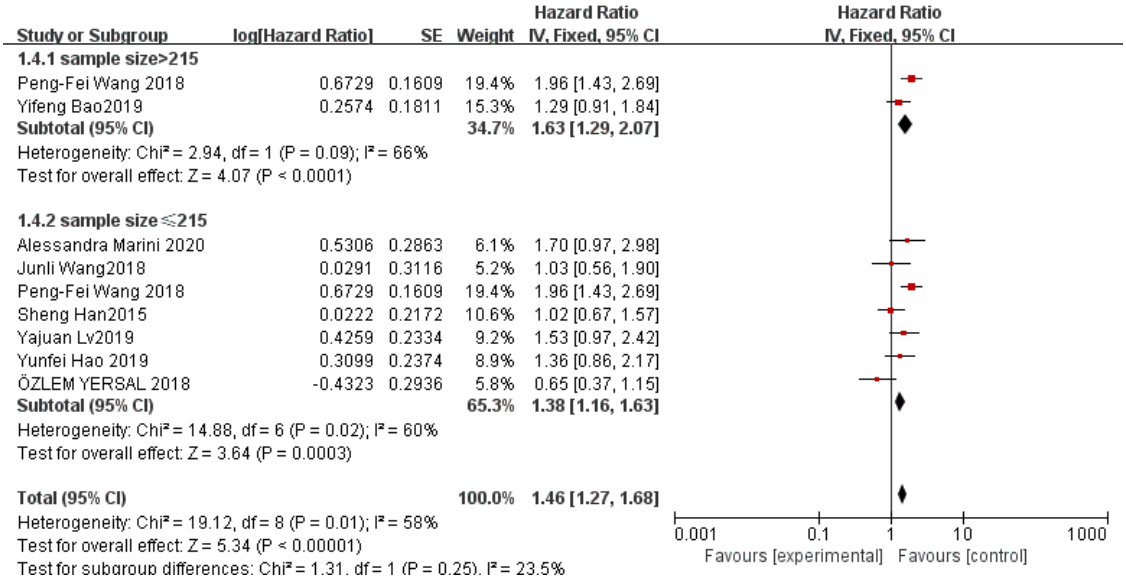

Figure 6. *Hazard ratios (HRs) for OS according to subgroup analyses: sample size.*

3.5. Sensitivity Analysis

A total of 9 groups of data were included in the meta-analysis. Because of moderate heterogeneity, the inclusion and exclusion criteria, the data collection and processing methods, the outcome indicators, and the statistical methods presented in each article, samples were carefully examined. No low-quality study was identified. The heterogeneity did not change significantly after excluding articles one by one. This indicates that the combined HR of this meta-analysis had good stability.

3.6. Publication Bias

We used funnel plots to evaluate whether there was a significant shift in the included articles. The funnel plot was largely symmetrical (Figure 7), which suggests that there is no apparent publication bias.

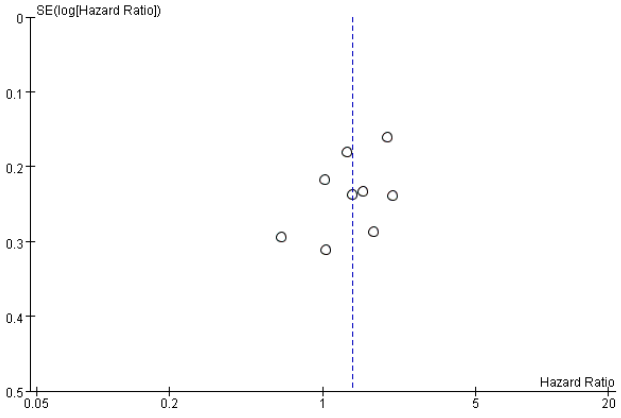

Figure 7. *Funnel plot.*

4. Discussion

In this study, we collected data for analysis, and the association between PLR and glioma prognosis was evaluated. Our results indicate that the higher the preoperative PLR, the lower the OS in patients with glioma (HR = 1.37, 95% CI: 1.09–1.71, P = 0.007, I^2 = 55%; P [heterogeneity] = 0.02). An I^2 equal to 55% indicated that there was moderate heterogeneity in the articles that were included. Subgroup analysis and sensitivity analysis were conducted to find the root causes of heterogeneity. We surmised that the PLR cut-off value might have been the source of the heterogeneity. However, this is not conclusive because the number of articles was limited, the specific data for each patient could not be obtained, and the best PLR cut-off value could not be accurately calculated. This meant that a precise analysis could not be performed. Future studies should aim to obtain the most appropriate PLR cut-off value. In contrast, sensitivity analysis showed that the combined HRs of the meta-analysis had good stability. In addition, the analysis of publication bias by funnel plot indicated that there was no apparent publication bias in the included articles.

As stated in the introduction, Inflammatory factors are very important in the development of tumours [25], and progression of glioma is closely associated with inflammatory factors [26]. As already mentioned, PLR has been found to be a useful biomarker in determining prognosis for many other cancers. Our meta-analysis suggests it may have similar prognostic values in cases of glioma. We found that increased PLR is correlated with poor prognosis in patients with glioma cancer.

The specific mechanisms involved in how elevated PLR affects patients with glioma is not particularly clear. We considered this from two aspects. (1) Hypercoagulability is a common abnormal condition in patients with malignant tumours [27]. Tumour cells can damage vascular endothelium and cause platelet adhesion and aggregation. This releases more activated platelet substances, including adenosine diphosphate, thromboxane a2, and tumour-related proteins. These can lead to hypercoagulability [28]. Platelets promote angiogenesis through the cytokine vascular endothelial growth factor [29], exacerbate tumour growth and spread [30], and activate platelets to protect tumour cells from immune attacks. (2) Studies have found that the higher the lymphocyte content is in patients with cancer, the better the prognosis is during treatment [31]. In contrast, the lower the lymphocyte content, the worse the immune system performs, leading to lower survival rates [32-33]. It is important to point out that our study, which included seven articles from Asian countries and two from non-Asian countries, had possible selection bias. Subgroup analysis showed that higher PLR in Asian patients with glioma was associated with lower OS, although this was not found to be the case in non-Asian patients with glioma. Future investigations need to be conducted to explore the influence of genetic, environmental, and cultural factors in patients with glioma. Additionally, sample sizes should be increased as much as possible to provide high-quality reference data.

This meta-analysis had a significant strength in that most of the data on HR was from multivariate analyses. In addition, we found that PLR is an economical, fast, and readily available marker. The limitations of our study include the following: (1) all of the articles included were retrospective studies; (2) the sample size was small; and, (3) because the articles included were limited and the specific data for each patient could not be obtained, the optimal PLR cut-off value could not be accurately provided.

5. Conclusion

While prospective, large-scale, multi-platform, and multicentre studies are also needed to assess optimal PLR intercept values and their utility in patients with glioma, our meta-analysis has confirmed that high PLR is correlated with poor OS in individuals being treated for glioma cancer. We conducted subgroup analyses based on race, PLR cut-off value, and sample size. Based on the results of subgroup analysis, PLR interception value had a specific effect on heterogeneity. The combined HR of this meta-analysis had good stability, and there is no apparent publication bias. PLR is easy and inexpensive to obtain; therefore, we suggest that it be applied as a prognostic biomarker to identify high-risk patients with glioma and lead to optimal treatment.

List of Abbreviations

NA: Not available
S: Surgery
R: Radioation
C: Chemotherapy

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Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Ai-xia Sui and Huayue cong conceived of the study, and

participated in its design and coordination and helped to draft the manuscript. Yong liu, Mingming Zhang, and Liuyi yang searched the paper. Huiling song, Weiliang He, and Jing zhao collected data. Ai-xia Sui and Huayue cong participated in the design of the study and performed the statistical analysis. Ai-xia Sui revised the manuscript. All authors read and approved the final manuscript.

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