Prognostic importance of red blood cell distribution width in patients with glioma: A meta-analysis

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Abstract. The present study aimed to investigate whether red blood cell distribution width (RDW) was an independent prognosis factor for patients with glioma after surgery. Potential studies were found in four databases including PubMed, Embase, China National Knowledge Infrastructure and the Cochrane Library on 21st July, 2022. To evaluate the prognosis after surgery, hazard ratios (HRs) and 95% confidence intervals (CIs) were pooled to calculate the overall survival (OS) of patients with glioma. Stata V16.0 software was used for data analysis. A total of 8 studies were included, involving 1,468 patients. After collecting and analyzing the data, RDW was demonstrated to be a prognostic factor for OS of patients with glioma (HR=1.51; I^2=0.00%; 95% CI, 1.29-1.74; P<0.01). Patients with high preoperative RDW levels had a high risk of poor survival after neurosurgery. High preoperative RDW levels may be associated with poor prognosis and warrant further clinical attention.

Introduction

Gliomas account for ~80% of malignant brain tumors, with an incidence of 6 per 100,000 annually (1). Despite advances in treatment, prognosis remains poor, particularly for glioblastoma, with a median survival of 14-16 months (2). At present, the comprehensive treatment of glioma is based mainly on surgical resection combined with radiotherapy and chemotherapy (3). Surgery can relieve patients' symptoms, prolong survival and obtain tumor tissue to confirm the pathological diagnosis. For adjuvant therapy, the Stupp regimen-which consists of maximal safe resection, followed by concurrent radiotherapy (60 Gy in 30 fractions) with daily temozolomide (75 mg/m^2), and then at least six cycles of adjuvant temozolomide (150-200 mg/m^2 for 5 days every 28 days)-has been the standard treatment regimen for gliomas since 2005 (4).

Red blood cell distribution width (RDW) is a part of the complete blood count test and reflects the heterogeneity of red blood cell sizes (5). This parameter is derived using the following formula: (Standard deviation of the mean corpuscular volume/mean corpuscular volume) x100. RDW is initially used to identify anemia, but it can also reflect the nutritional status of the body. Elevated RDW may reflect tumor-associated systemic inflammation and altered erythropoiesis, both of which are poor prognostic indicators in glioma patients (6-8). The prognostic value of RDW for some cancers including laryngeal cancer, endometrial cancer, esophageal cancer, and colorectal cancer has also been increasingly discussed (9-13). Moreover, previous studies have reported that a high RDW is associated with poor outcomes in patients with glioma. Schneider *et al* (14) reported that RDW was an independent prognostic factor for glioma, but other studies reported no association (15-21). Therefore, the present meta-analysis aimed to evaluate the prognostic effect of RDW for patients with glioma.

Materials and methods

Search strategy. Eligible studies were searched for in four databases including PubMed, Embase, the Cochrane Library and China National Knowledge Infrastructure (CNKI) on 21st July, 2024. The search strategy included RDW and glioma. For RDW, 'red blood cell distribution width' OR 'red cell distribution width' OR 'RDW' was searched. For glioma, 'glioma' OR 'gliomas' OR 'glial cell tumors' OR 'glial cell tumor' OR 'mixed glioma' OR 'mixed gliomas' OR 'malignant glioma' OR 'malignant gliomas' OR 'glioblastoma' OR 'anaplastic astrocytoma' OR 'diffuse astrocytoma' OR 'anaplastic

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oligodendroglioma' OR 'oligodendroglioma' OR 'brain tumor' was searched. The search scope was limited to titles and abstracts, and only studies in English or Chinese were permitted. The present study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (22).

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Patients with glioma who underwent primary surgery; ii) patients divided into a high RDW group and a low RDW group; and iii) overall survival (OS) was reported. The exclusion criteria were as follows: i) The type of the study article was letter, case report, comment, review or conference; ii) data was repeated or overlapped; and iii) insufficient data of prognosis.

Study selection. After performing the searching strategy, duplicate studies were removed. Subsequently, titles and abstracts were scanned to find potential studies. Finally, the full text was read to evaluate whether there were sufficient data and the quality was qualified. The selection process was performed by two authors individually. If there was a disagreement, a third author would make a judgment.

Data collection. The study information included the first author, published year, published country, study period, cut-off value of RDW and Newcastle-Ottawa Scale (NOS) score. For survival, OS data was collected. The data collection was performed by two authors and information would be checked to ensure accuracy.

Quality assessment. NOS was used to assess the quality of the included studies (23). High-quality studies would be scored as 9 points. A score of 7 or 8 points meant medium quality. Studies which were scored <7 points represented low quality.

Statistical analysis. In order to calculate the survival, hazard ratios (HRs) and 95% confidence intervals (CIs) were pooled. To evaluate the statistical heterogeneity, the I^2 value and the χ^2 test were used (24,25). According to the Cochrane handbook (26), I^2<30% was considered non-important, the I^2 range from 30 to 60% was considered moderate and I^2 >60% was considered substantial. A funnel plot was used to evaluate the publication bias. Subgroup analysis was performed to explore the effect of varying RDW cut-off values among the included studies. The studies were divided into two subgroups based on the median RDW threshold (13.6%): The low cut-off group (<13.6%) and the high cut-off group (≥13.6%). Meta-regression analysis was performed to assess whether different RDW cut-off values influenced the OS outcome. A random-effect model was used as the default model, and P<0.1 was considered to indicate a statistically significant difference. All data analysis was performed using Stata V18.0 software (StataCorp LLC).

Results

Study selection. There were 52 studies found after performing the searching strategy (17 studies in PubMed, 19 studies in Embase, 0 studies in the Cochrane Library and 16 studies in CNKI). After removing the duplicate studies, 30 were left for screening. After browsing titles, abstracts, and full-text step-by-step, 8 studies were finally included for analysis (Fig. 1).

Baseline characteristics. A total of 8 studies that included 1,468 patients were finally included in the present meta-analysis. The earliest study was published in 2016. The study period was from 2006 to 2020. Studies were published in China, Kazakhstan, Germany and the United States. The cut-off values ranged from 12.5 to 14.1%. The information of the studies including sample size, group population and NOS are shown in Table I.

OS of RDW. After pooling the HRs and 95% CIs using a random effects model, the RDW was found to be an independent prognostic factor of OS (HR=1.51; I^2=0.00%; 95% CI, 1.29-1.74; P<0.01) for patients with glioma (Fig. 2). Patients with high RDW levels had a higher risk of poor survival. The publication bias is shown in Fig. 3.

Subgroup analysis based on RDW cut-off values. To evaluate the impact of different RDW thresholds across the included studies, a subgroup analysis was performed by stratifying the studies according to the median cut-off value of 13.6%. Studies were divided into a low cut-off group (<13.6%) and a high cut-off group (≥13.6%). As shown in Fig. 4, the low cut-off group reported a predictive value (HR=1.60; I^2=48.27%; 95% CI, 1.15-2.21; P<0.01), whereas the high cut-off group demonstrated no predictive value (HR=1.29; I^2=86.46%; 95% CI, 0.78-2.15; P=0.32). The between-group heterogeneity was not significant (P=0.49), indicating no substantial impact of cut-off values on the prognostic significance of RDW in patients with glioma (Fig. 4).

Meta-regression analysis. Meta-regression demonstrated no significant association between RDW cut-off values and survival risk (HR=0.92 per 1% increase; 95% CI, 0.47-1.81; P=0.769). Substantial residual heterogeneity was observed (I^2=78.87%), suggesting unmeasured confounders (Fig. 5).

Sensitivity analysis. A meta-analysis was performed with each study excluded, and the sensitivity was analyzed. The results did not change significantly after analysis with each study excluded (Fig. 6).

Discussion

The present meta-analysis included 8 studies involving 1,468 patients. Patients were divided into high and low RDW groups according to different cut-off values. After analysis of the data, patients in the high RDW group were found to have worse survival. Moreover, after pooling the HRs and 95% CIs for OS, RDW was demonstrated to be an independent prognostic factor for gliomas.

Gliomas are an invasive brain malignancy, and prognosis is poor. Moreover, gliomas place a considerable mental and economic burden on patients and their families (27,28). Therefore, prognostic factors including age, initial neurological status, degree of resection, postoperative complications

Table I. Baseline characteristics of included studies.

First author, year	Country	Study dates	Sample size, n	High/low RDW (%)	Cut-off value, %	NOS	(Refs.)
Auezova *et al*, 2016	Kazakhstan	2009-2012	178	67/111	13.95	8	(15)
Liang *et al*, 2017	China	2012-2014	109	26/83	14.1	7	(16)
Xu *et al*, 2017	China	2010-2015	173	NA	13.2	7	(18)
Auezova *et al*, 2019	Kazakhstan	2015-2016	159	93/66	12.75	8	(19)
Kaisman-Elbaz *et al*, 2020	US	2006-2017	112	37/75	14	8	(20)
Schneider *et al*, 2021	Germany	2014-2019	257	NA	14	7	(14)
Yan *et al*, 2021	China	2016-2020	261	129/132	12.6	9	(21)
Bao *et al*, 2018	China	2012-2017	219	156/63	12.5	9	(17)

RDW, red blood cell distribution width; NA, not applicable; NOS, Newcastle-Ottawa Scales.

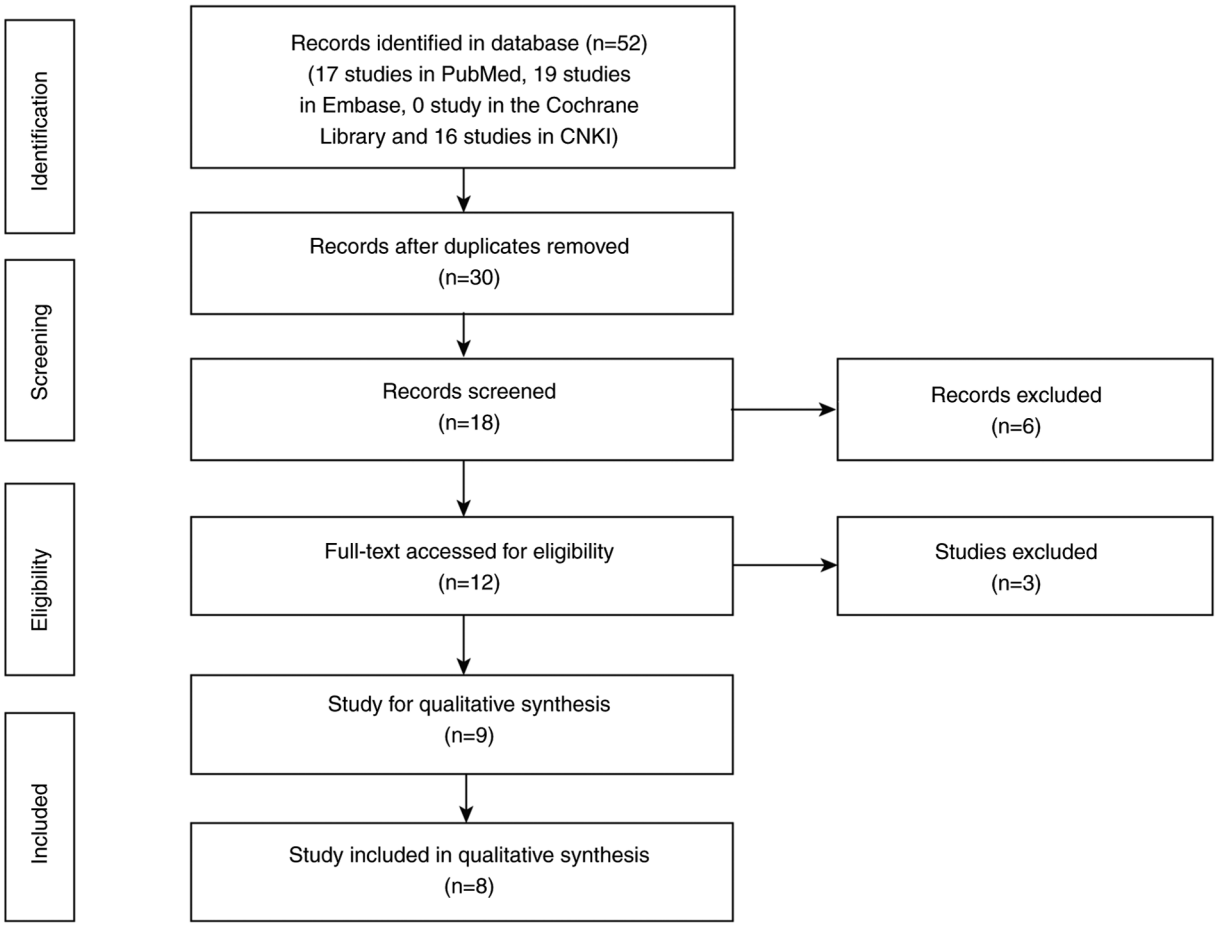

Figure 1. Flowchart of study selection.

and duration of intensive care are important (29-31). However, a large proportion of these prognostic indicators are postoperative indicators, and only a few indicators are known before surgery.

Previous studies have reported that patients with glioma with a high preoperative RDW have poor survival. Schneider *et al* (14) and Kaisman-Elbaz *et al* (20) demonstrated that RDW was an independent prognostic factor for OS in patients with glioblastoma. Liang *et al* (16) also examined patients with glioblastoma and revealed that the pretreatment RDW was superior to the mean cell volume and mean corpuscular hemoglobin concentration as a prognostic factor. Several previous studies on patients with glioma reported that a low RDW led to improved clinical outcomes and contributes to patients follow-up optimization (14,16,18,21). Xu *et al* (18) reported that RDW was a sex-specific predictor of tumor grade

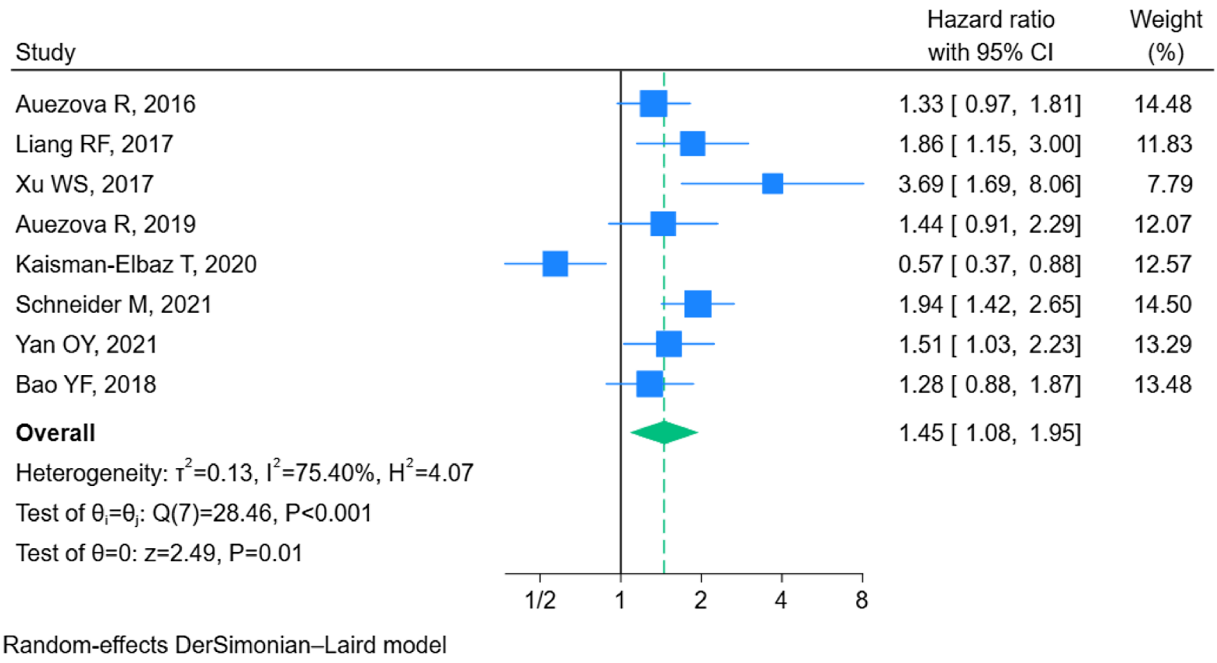

Figure 2. Overall survival of high-RDW group and low-RDW group. RDW, red blood cell distribution width; CI, confidence interval.

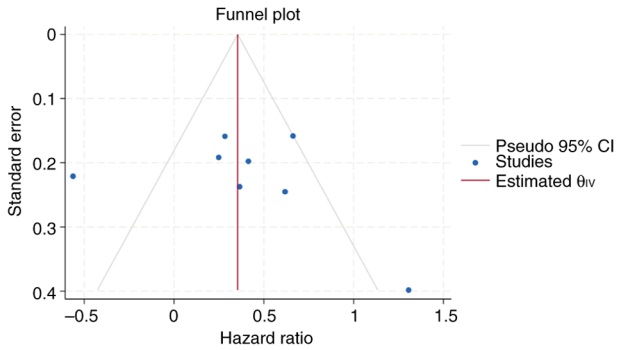

Figure 3. Funnel plot of overall survival. CI, confidence interval.

and progression in female patients with high-grade glioma, but not in male patients (17).

The present findings should be interpreted in the context of potential confounding factors. RDW is influenced by a variety of physiological and pathological conditions, including systemic inflammation, anemia, nutritional deficiencies and chronic diseases. Since most of the included studies were retrospective and did not include individual patient-level data, adjustments for these potential confounders through multivariate analysis were not feasible. Consequently, the observed association between RDW and survival in patients with glioma might be partially attributed to these unmeasured variables. Future studies with detailed clinical data are needed to validate the independent prognostic value of RDW after adjusting for such factors.

The exact mechanisms underlying the relationship between RDW and gliomas have yet to be fully elucidated. We hypothesize that inflammation may be a key factor. Previous studies have demonstrated that an increase in the RDW is notably associated with increases in other inflammatory markers, including C-reactive protein, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (32,33). Therefore, RDW is considered to be associated with an inflammatory response. Previous studies have reported an association between chronic inflammation and tumors (34-37). The development of cancer is accompanied by the complex action of inflammatory cells in the local microenvironment where the tumor site and the environment can stimulate tumor cell proliferation and infiltration (38-40). Although gliomas do not tend to metastasize outside of the central nervous system, exosomes serve an important role in the systemic inflammatory response (41). Glioma-derived exosomes can transmit local inflammation throughout the body, by converting M1 macrophages into tumor-associated macrophages (TAMs) through transcription regulation. In addition, reprogrammed TAMs can produce exosomes, which further leads to a systemic inflammatory response (42).

Elevated RDWs may reflect underlying chronic inflammation and immune dysregulation, both of which serve important roles in glioma progression (34-37). Proinflammatory cytokines such as IL-6 and TNF-α can impair erythropoiesis and increase anisocytosis, indirectly increasing the RDW (32,33). Additionally, glioma cells and TAMs can release exosomes that modulate systemic inflammatory responses and promote immune escape (42). These exosomes may reprogram macrophages and other immune cells to support tumor cell proliferation and invasion. Thus, the RDW may serve as a surrogate biomarker of tumor-promoting inflammation and immune evasion, contributing to poor clinical outcomes in patients with glioma.

The potential mechanisms are still unclear; however, to the best of our knowledge, the present meta-analysis is the first to summarize the current studies on the prognostic value of RDW for gliomas, and all the included studies were published since 2016. Although the cut-off values for RDW varied across studies (ranging from 12.5 to 14.1%), meta-regression

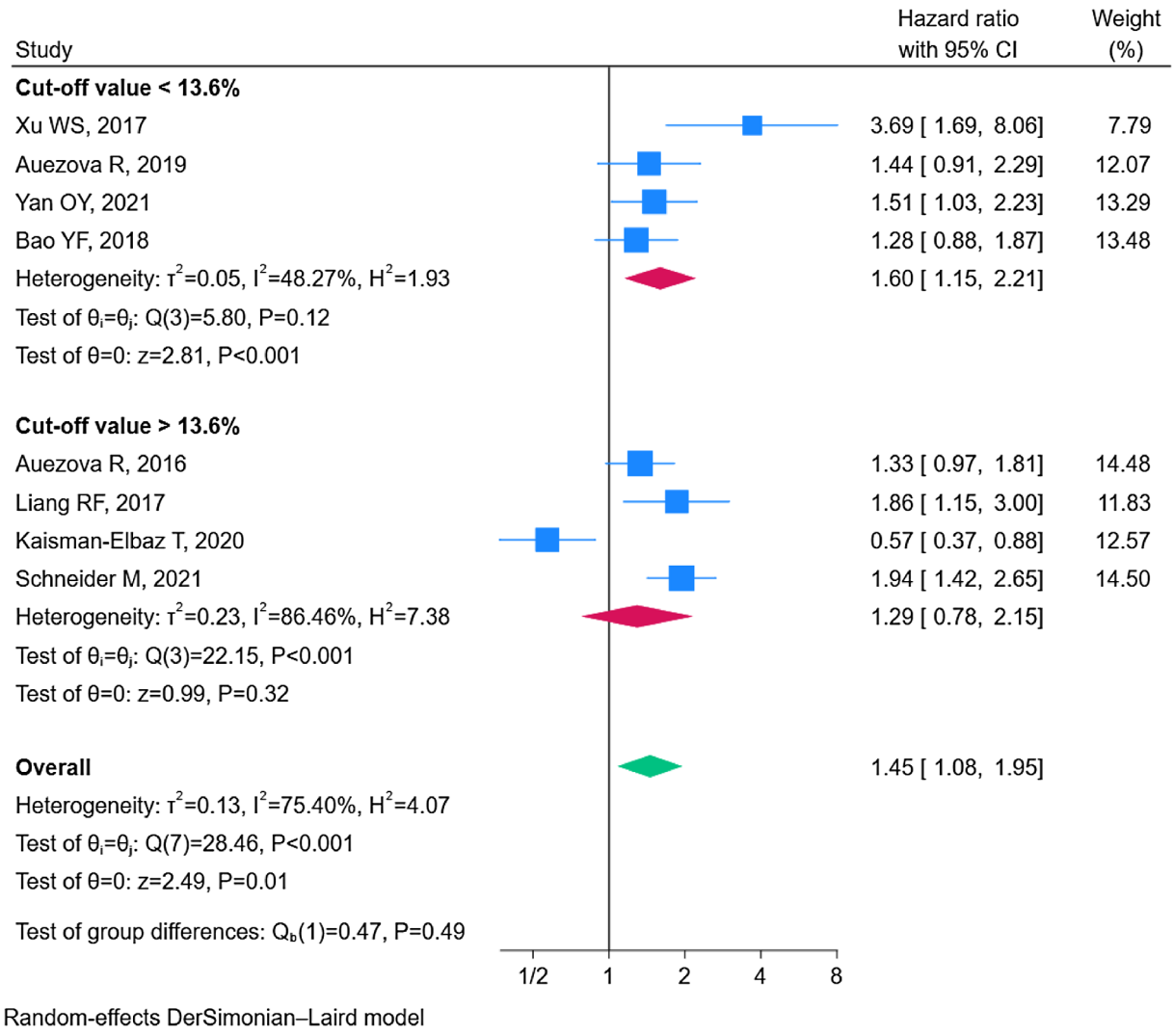

Figure 4. Subgroup analysis based on RDW value of 13.5.

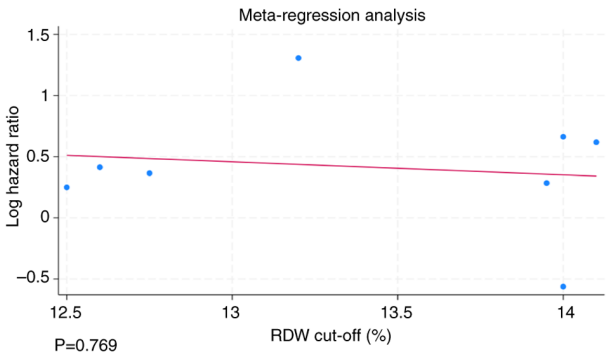

Figure 5. Meta-regression analysis. RDW, red blood cell distribution width.

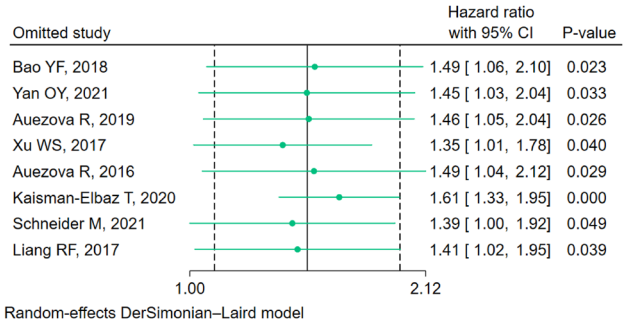

Figure 6. Sensitivity analysis. CI, confidence interval.

analysis did not reveal a statistically significant impact of these differences on the pooled survival outcomes. These findings suggest that the prognostic value of RDW in patients with glioma is relatively consistent regardless of the specific cut-off thresholds used. However, only OS was reported in the included studies, and additional survival indicators, including disease-free survival and cancer-specific survival, are needed. Furthermore, subgroup analysis of histological subtypes was limited because most of the included studies did not report subtype-specific outcomes. In the future, studies should stratify survival outcomes by tumor grade and molecular classification.

In conclusion, the prognosis of patients with glioma could be predicted and the appropriate treatment chosen according to low-cost blood tests. Meanwhile, high preoperative RDW levels may be associated with poor prognosis and warrant further clinical attention.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

YC and FC analyzed and interpreted data. YC wrote the manuscript. YXL and LX conceived the study. YXL and LX confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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