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NEURORADIOLOGY

REVIEW

Survival prediction using apparent diffusion coefficient values in recurrent glioblastoma under bevacizumab treatment: an updated systematic review and meta-analysis

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ABSTRACT

Bevacizumab is a common strategy for the treatment of recurrent glioblastoma. Survival status is a crucial issue for patients with recurrent glioblastoma, and the apparent diffusion coefficient (ADC) values of the lower Gaussian curve have been reported to have the potential to predict prognosis in recurrent glioblastoma. In the present study, we aimed to clarify the survival prediction of ADC values in patients with recurrent glioblastoma receiving bevacizumab treatment through a systematic review and meta-analysis of randomized clinical trials, comparing ADC values higher than the cut-off values with those lower than the cut-off values to determine which type of ADC values can be associated with significant survival benefits. Different survival indicators were analyzed, including overall survival (OS) and progression-free survival (PFS). Ten studies with a total of 782 patients with recurrent glioblastoma were included. The focused outcomes were OS and PFS. Our results showed that ADC values lower than the cut-off values were associated with significant benefits for OS status compared with ADC values higher than the cut-off values. Similar significant benefits were observed for PFS. The meta-analysis results suggest that ADC values lower than the cut-off values might be associated with significant benefits for OS and PFS when compared with ADC values higher than the cut-off values. However, bias in relation to the different stages of recurrent glioblastoma and different types, doses, and regimens of bevacizumab should not be ignored.

KEYWORDS

Glioblastoma, bevacizumab treatment, apparent diffusion coefficient, overall survival, progression-free survival

Glioblastoma is an aggressive and malignant brain tumor[1] with a median survival duration of 8–14 months.[2,3] Concurrent chemotherapy and radiotherapy with surgery is still unable to achieve a favorable prognosis, and most glioblastomas are recurrent.[1,4] Glioblastoma is a tumor characterized by cell anaplasia, necrosis, prominent angiogenesis, and hyperoxygenation,[5] which activate vascular endothelial growth factor A, a target molecule in the treatment of the disease.[6]

To inhibit this target molecule, bevacizumab, a humanized monoclonal antibody, is a reasonable option to treat glioblastoma. Its clinical efficacy has been established in many types of cancers, such as renal cell carcinoma,[7] colorectal cancer,[8] cervical cancer,[9] and lung cancer.[10] For glioma, the clinical effects of bevacizumab on overall survival (OS) and progression-free survival (PFS) might be controversial,[11-13] with one trial finding no evidence of improved OS with bevacizumab treatment.[11] In addition, bevacizumab has not been approved for chemotherapy in patients with recurrent glioblastoma in the European Union, probably due to the lack of evidence for its anti-tumor effects. However, bevacizumab was approved by the US Food and Drug Administration to treat recurrent glioblastoma in 2009. European guidelines also include bevacizumab as a treatment option for recurrent glioblastoma because of its demonstrated improvement in quality of life, safety,[13,14] and the prolongation of OS and PFS in patients.[15]

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Magnetic resonance imaging (MRI) is usually used to diagnose and evaluate therapeutic effects in patients with recurrent glioblastoma. A recent meta-analysis showed that perfusion MRI might be beneficial for predicting prognosis in patients with recurrent glioblastoma receiving bevacizumab treatment.[16] One type of MRI method, the diffusion-weighted MRI, uses the diffusion process of water molecules in the brain to generate contrast and obtain the diffusion values to detect the structural characteristics of brain white matter.[17-19] In addition, diffusion-weighted imaging might be useful for predicting prognosis in recurrent glioblastoma, especially by obtaining the mean apparent diffusion coefficient (ADC) value of the lower Gaussian curve, which is calculated from the histogram analysis.[20,21] In the current systematic review and meta-analysis, we aimed to clarify the role of high and low ADC values in prognosis prediction for patients with recurrent glioblastoma receiving bevacizumab treatment, especially regarding OS and PFS. We included up-to-date eligible studies to confirm the role of ADC values in a prediction biomarker.

Methods

Literature search criteria

A set of keywords was used to search for and collect relevant studies using the Web of Science, PubMed, Embase, Cochrane Central Register of Controlled Trials, and ScienceDirect databases. The keywords were as follows: "bevacizumab," "chemotherapy," "glioblastoma," "recurrent," "magnetic," "MRI," "apparent diffusion coefficient," "ADC," "cohort," "prognosis," "prediction," "treatment," "therapy," "survival," "outcome," "comparison," "prognostic," and "observational." We only considered articles published (including online) before September 2023.

The inclusion criteria for the articles were as follows: (1) cohort or observational studies, (2) comparisons between ADC values higher and lower than the cut-off values for the survival status of patients with recurrent glioblastoma receiving bevacizumab treatment, (3) outcome profiles at baseline and endpoint for survival (including OS and PFS), (4) inclusion of detailed survival data such as the *P* value, 95% confidence interval (CI), or hazard ratio (HR), and (5) publication in journals in the science citation index database and in the English language.

Main points

- The white matter diffusion value, the apparent diffusion coefficient (ADC), may help predict prognosis in recurrent glioblastoma, a type of brain cancer.
- For patients with recurrent glioblastoma receiving bevacizumab treatment, ADC may inform the survival prognosis.
- An ADC value lower than the cut-off values may predict improved status in overall survival and progression-free survival.

Reporting bias assessment

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was used to evaluate the risk of bias for the eligible studies, which included the following dimensions: patient selection, index test, reference standard, and flow and timing. We chose QUADAS because it is a useful and validated tool to evaluate the risk of bias of diagnostic accuracy studies in a systematic review.[22] The risk-of-bias assessment was reported and visualized according to the above four dimensions. In addition, a funnel plot was used to assess the publication bias of the included studies.

Data quality evaluation and collection

We performed the current systematic review and meta-analysis study according to the Cochrane Handbook for Systematic Reviews and Interventions and reported the results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] The following data were collected from the included articles: first, the HR and either the *P* value or 95% CI for OS as well as the patient number of patients with recurrent glioblastoma with ADC values higher than the cut-off values under bevacizumab treatment; second, the HR and either the *P* value or 95% CI for OS as well as the patient number for patients with recurrent glioblastoma with ADC values lower than the cut-off values receiving bevacizumab treatment; third, the HR and either the *P* value or 95% CI for PFS as well as the patient number for patients with recurrent glioblastoma with ADC values higher than the cut-off values receiving bevacizumab treatment; fourth, the HR and either the *P* value or 95% CI for PFS as well as the patient number for patients with recurrent glioblastoma with ADC values higher than the cut-off values receiving bevacizumab treatment.

Critical appraisal of data

Two researchers (D.L. and Z.L.) assessed the abstracts to screen out articles. Each reviewer independently evaluated the full text version of the included articles. An independent extraction of clinical outcome data from the text, tables, and figures of the selected citations was also performed. The included articles all had data on OS or PFS in the full text. A strong agreement was achieved through a collaborative review by all reviewers (kappa: 0.8). All researchers reviewed the final results.

Meta-analysis and statistical analysis

For OS or PFS, pooled HR estimates were generated with the associated 95% CI or *P* value or individual HR. The summary statistics for each eligible study were assessed, and we extracted the reported HRs and *P* value or 95% CIs if patient-level data were lacking. We used the Cochrane Collaboration Review Manager Software Package (Rev Man Version 5.4, Cochrane library, 11-13 Cavendish Square, London, UK). to perform the meta-analyses. The log HRs were calculated by transforming the HR and *P* value or beginning and end of the 95% CIs in the Rev Man calculation function. The risk estimates of eligible studies were also evaluated by the inverse variance weighted averages of log HRs in the random-effects model.

ADC values higher than the cut-off values were compared with those lower than the cut-off values to determine which type of ADC values could be associated with an improved OS and PFS profile. Chi-square tests were used to assess the heterogeneity between the eligible citations, and the derived I^2 statistic was applied to assess the statistical heterogeneity of the eligible citations in the meta-analysis. The cut-off value for the Higgins I^2 index was based on the suggestions of the Cochrane Handbook for Systematic Reviews of Interventions (2nd edition),[24] and two-sided *P* values were also calculated.

Results

Description of studies

The PRISMA flowchart for our article selection process is presented in Figure 1. Finally, 10 studies were included.[20,21,25-32] The QUADAS risk-of-bias assessment is presented in Figure 2. A symmetric distribution is shown in the funnel plot of eligible studies.

Log hazard ratio of apparent diffusion coefficient values higher than the cut-off values against those lower than the cut-off values for overall survival

The I^2 was 0%, which indicated low heterogeneity. The test for overall effect was $Z = 6.64$ ($P < 0.00001$), and the meta-analysis

results revealed a significant difference in the log HR of OS events between ADC values higher than the cut-off values and those lower than the cut-off values, suggesting a significant benefit for OS for ADC values lower than the cut-off values (Figure 3).

Log hazard ratio of apparent diffusion coefficient values higher than the cut-off values against those lower than the cut-off values for progression-free survival

The I^2 was 11%, which indicated low heterogeneity. The test for overall effect was $Z = 5.58$ ($P < 0.00001$), and the meta-analysis results revealed a significant difference in the log HR of PFS events between ADC values higher than the cut-off values and those lower than the cut-off values, suggesting a significant benefit for PFS for ADC values lower than the cut-off values (Figure 4).

Discussion

We found that ADC values lower than the cut-off values were superior to ADC values higher than the cut-off values for OS and PFS in patients with recurrent glioblastoma receiving bevacizumab treatment. In addition, the low heterogeneity within the eligible studies in the current meta-analysis was noted. Despite the characteristics of diffusion-weighted imaging for detecting the microstructure of the brain and tumor, the prognostic potential of ADC values in patients with recurrent glioblastoma receiving bevacizumab treatment still needs to be clarified. The low heterogeneity might decrease the potential impact from the statistical and clinical heterogeneity in the current meta-analysis. However, the possible biases in the eligible studies should not be ignored. Our meta-analysis was different from a previous meta-analysis[33] in terms of the following: (1) our met-analysis included the most up-to-date studies on ADC values for OS and PFS for recurrent glioblastoma with bevacizumab treatment; (2) our meta-analysis identified more significant differences with greater Z values; (3) the heterogeneity of our meta-analysis was lower than that of the previous meta-analysis; (4) our QUADAS assessment results showed a more stringent evaluation for the included studies. Therefore, our meta-analysis provides up-to-date and valuable information on the topic and can help confirm the prognostic role of ADC values in patients with recurrent glioblastoma receiving bevacizumab treatment.

ADC values measure the water diffusivity and viscosity of the brain, indicating that ADC values might represent the bio-physi-

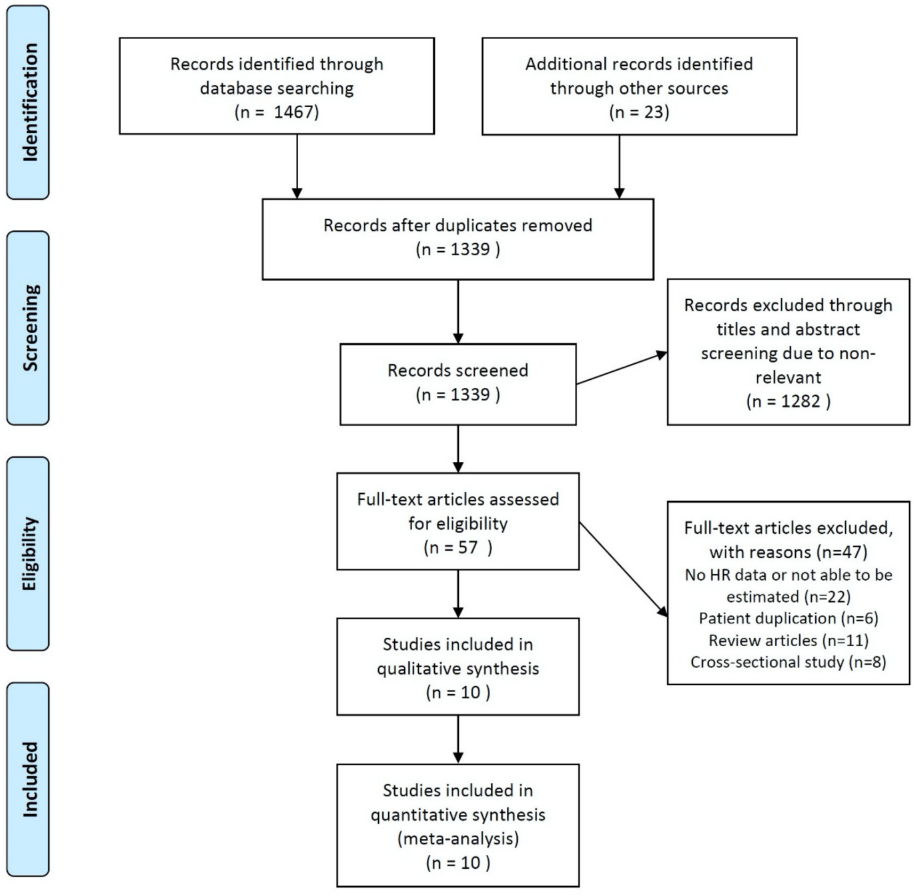

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for the selection of eligible studies. Identification of the potentially relevant literature and screening of the identified literature using abstract and title selection adhered to PRISMA guidelines. The assessment of the full text of the screened literature aimed to find eligible studies. Suitable studies were then included in the final meta-analysis. HR, hazard ratio.

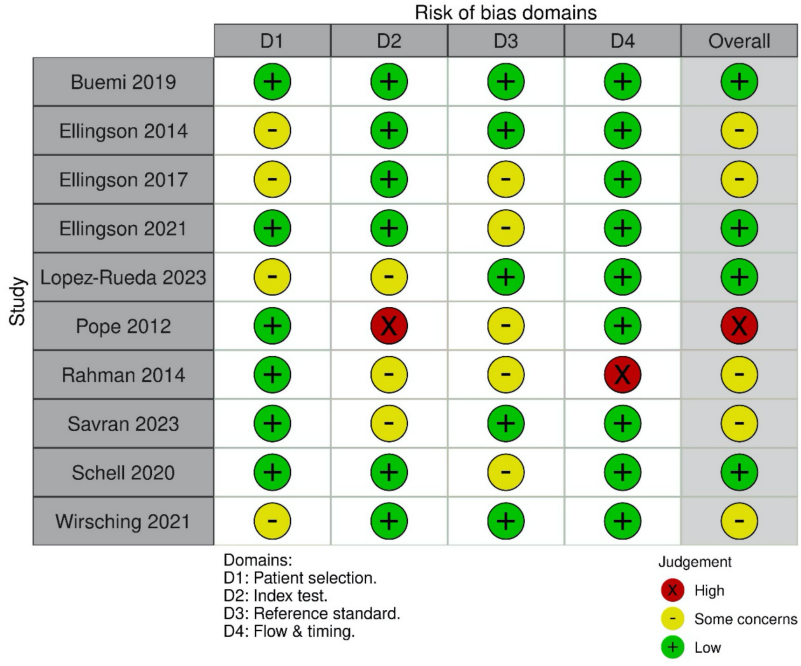

Figure 2. Risk-of-bias assessment. The Quality Assessment of Diagnostic Accuracy Studies tool was used to assess the risk of bias in the included articles.

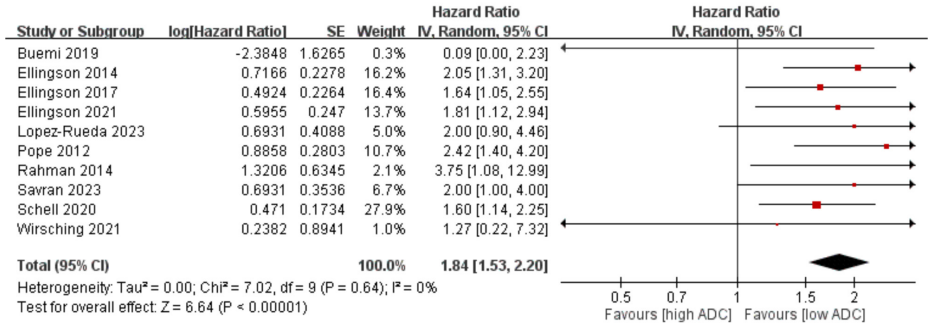

Figure 3. Forest plot of the log hazards ratio for the meta-analysis results for overall survival (OS): apparent diffusion coefficient (ADC) values higher than the cut-off values against those lower than the cut-off values. ADC values lower than the cut-off values showed a significant benefit in terms of improved OS compared with ADC values higher than the cut-off values (statistically significant). CI, confidence interval; SE, standard error.

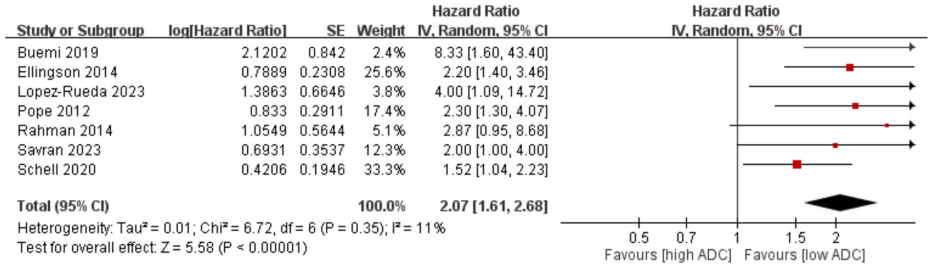

Figure 4. Forest plot of log hazards ratio for the meta-analysis results for progression-free survival (PFS): apparent diffusion coefficient (ADC) values higher than the cut-off values against those lower than the cut-off values. ADC values lower than the cut-off values showed a significant benefit in terms of improved PFS compared with ADC values higher than the cut-off values (statistically significant). CI, confidence interval; SE, standard error.

cal characteristics of tissue diffusivity within the glioblastoma area. Although ADC values might predict prognosis in recurrent glioblastoma, consistent pathological evidence and reliable biological models have not been established. One study suggested that ADC values might be associated with the oxygenated or cellular status of glioblastoma, which might influence and interfere with the effectiveness of bevacizumab in the case of an aggressive glioblastoma.[26] A recent biological study also suggested that ADC values might be associated with the increased expression of decorin, a small proteoglycan that modulates angiogenesis and viscosity;[20,34,35] it also binds to various macromolecules and activates metalloproteinases in the extracellular matrix.[20,36,37] This might explain the possible underlying mechanisms of the characteristics of independent imaging biomarkers related to ADC values in the prognosis of recurrent glioblastoma with bevacizumab treatment. These results suggest that patients with recurrent glioblastoma with ADC values lower than the cut-off values might be appropriate candidates for bevacizumab chemotherapy. By contrast, patients with ADC values higher than the cut-off values might not be suitable for bevacizumab chemotherapy. These findings might provide an initial model in terms of precision medicine for chemotherapy for patients with recurrent glioblastoma.

Our meta-analysis has several limitations. First, histopathological evidence to support the role of ADC values in the prediction of prognosis in recurrent glioblastoma is lacking. Determining consistent histopathological evidence in a future study is warranted to clarify the underlying biological mechanisms. Currently, most theoretical explanations relating to the role of ADC values in prediction are speculative and not based on solid evidence. In addition, the cut-off point or threshold of ADC values was diverse in the studies included in the meta-analysis. A further meta-analysis with a homogenous threshold in relation to this aspect is warranted in the future. Second, the age and gender variances in the included studies might influence the interpretation of our study results. More consistent age and gender distribution patterns might be needed in future randomized clinical trials to decrease the bias caused by different age and gender distributions. Third, variations in bevacizumab regimens might also bias our meta-analysis results. More consistent bevacizumab regimens might be helpful for improving the accuracy of the meta-analytic results. Fourth, the different techniques, doses, regimens, and durations of combined radiotherapy in the included studies might also influence the interpretations of our results. Fifth, the lack of a meta-analysis on treatment adverse events, toxicities, and compliance might prevent detailed conclusions. Sixth, most of the included studies were from Europe and the USA. The ethnicity bias might influence the interpretations of our current meta-analysis. Seventh, it is impossible to control the bias from the different brands, magnetic strengths, pulse sequences, and default settings of MRI machines at different sites in the different included studies. This type of bias should not be ignored. Eighth, one included study[20] involved patients with isocitrate dehydrogenase (IDH) mutation; the role of IDH mutation in ADC values might need to be clarified in our meta-analysis. Finally, the variable cut-off values of different included studies provide another limitation to our meta-analysis.

In conclusion, the meta-analysis results suggest that ADC values lower than the cut-off values might be associated with significant benefits for OS and PFS when compared with ADC values higher than the cut-off values. However, the bias caused by the different stages of recurrent glioblastoma and different types, doses, and regimens of bevacizumab should not be ignored.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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