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A Systematic Review and Meta-Analysis on the Effectiveness of Radiotherapy and Temozolomide Treatment With or Without Bevacizumab in Patients With Glioblastoma Multiforme

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Abstract:

Glioblastoma multiforme (GBM) is the most frequent primary brain malignancy in adults. Despite improvements in imaging and therapy, the prognosis remains poor. To evaluate and compare the impact of combining bevacizumab with temozolomide and radiotherapy on progression-free survival (PFS) and overall survival (OS) in patients diagnosed with GBM. A comprehensive search was conducted across multiple databases, including PubMed, Embase, Scopus, and The Cochrane Library, covering the period from their inception to December 2022. The collected data underwent analysis employing appropriate statistical methods. Six articles were included in this systematic review and meta-analysis. The addition of bevacizumab to the combination of temozolomide/radiotherapy did not increase the OS in GBM patients. The pooled odds ratio (OR) was 0.843 (95% CI: 0.615–1.156, $P = 0.290$). The addition of bevacizumab to radiotherapy/temozolomide did not increase the PFS in patients with GBM. The pooled OR was 0.829 (95% CI: 0.561–1.224, $P = 0.346$). The funnel plot demonstrated the absence of the alleged pleiotropic effects by showing no evidence of observable variability across the estimations. This study does not support the benefit of the addition of bevacizumab to temozolomide and radiotherapy in improving OS and PFS in GBM patients.

Key Words:

Bevacizumab, glioblastoma multiforme, overall survival, progression-free survival, radiotherapy, temozolomide

Key Message:

This study does not support the benefit of the addition of bevacizumab to temozolomide and radiotherapy in terms of OS and PFS in patients with GBM.

Glioblastoma multiforme (GBM) stands as the most common primary brain cancer in adults. Although advancements in imaging and treatment have been made, the outlook for patients continues to be bleak.[1] Based on the results of the EORTC-NCIC trial, the recommended initial treatment for glioblastoma is maximal surgical tumor resection followed by a combination of radiation and temozolomide, with adjuvant temozolomide also included in the treatment plan.[2,3] Based on this information, patients diagnosed with unresected GBM experience a challenging prognosis. There were no notable disparities in overall survival (OS) between standard chemoradiotherapy and radiation alone, with median survival times of 9.4 months and 7.8 months, respectively.[2] Consequently, since the implementation of radiotherapy-temozolomide therapy in 2005, no further advancements in outcomes have been documented.[4]

Glioblastomas, which are characterized by a high degree of vascularization, demonstrate

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an elevated expression of vascular endothelial growth factor A (VEGF-A). VEGF-A plays a critical role in controlling tumor-related angiogenesis in glioblastomas.[5] Different strategies have been utilized to address this important side of tumor biology. Yet, the available evidence in favor of the efficacy of small-molecule tyrosine kinase inhibitors, including cediranib and sorafenib, in aiming at this pathway is limited.[6,7] Bevacizumab (BV) is a humanized monoclonal antibody designed to specifically target the VEGF-A ligand. It acts by binding to the circulating VEGF-A ligand, thereby modifying the ligand-endothelial cell interaction. This mechanism effectively inhibits angiogenesis in the tumor microenvironment.[7] Initial studies examining the effectiveness of BV in patients with recurrent glioblastoma showed promising clinical results. These included noticeable decreases in tumor size, prolonged periods without disease progression, and decreased dependence on glucocorticoids for the management of tumor-related edema.[8,9] Antiangiogenic therapies have been discovered to cause transient vascular normalization within tumors. This phenomenon leads to enhanced blood flow, increased oxygen availability, and improved delivery of chemotherapeutic medications to the tumor location. As a result, this vascular stabilization increases the efficacy of both radiotherapy and chemotherapy treatments.[10]

Since BV has been identified as a therapeutic option for recurrent GBM, it has been suggested that utilizing BV as the first line of treatment for newly diagnosed GBM may be preferable to waiting for recurrence before beginning BV therapy[11] In two significant trials, we observed that the inclusion of BV in radiotherapy-temozolomide therapy did not result in a significant increase in OS. However, it did lead to a notable improvement in median progression-free survival (PFS), while patients' functional status and quality of life remained unaffected. It is critical to take into account that using BV treatment was linked to an increase in unfavorable occurrences.[4,12] In contrast, another study recommended that combining neoadjuvant temozolomide with BV therapy may have the potential for greater effectiveness in treatment response and tumor size reduction as opposed to temozolomide alone. Importantly, this combination therapy did not adversely affect survival in patients with unresected glioblastoma.[13] In line with this, it has been discovered that in elderly patients aged 75 and above with glioblastoma, hypo-fractionated radiation treatment combined with either temozolomide or temozolomide/BV demonstrated benefits in terms of OS and PFS. Furthermore, the toxicity associated with this treatment approach was manageable.[14]

This systematic review and meta-analysis aimed to assess and compare the effects of adding BV to temozolomide and radiotherapy on the OS and PFS of patients diagnosed with resected or unresected GBM.

Methods

Literature search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were applied in this meta-analysis. Our objective was to compare the outcomes of GBM patients treated with BV, temozolomide, and radiation therapy versus a combination of temozolomide and radiotherapy. To ensure a comprehensive review, we conducted an extensive literature search in various databases, including Scopus, Embase, PubMed, and The Cochrane Library, covering the period from inception to December 2022.

To identify relevant studies, we employed specific keywords and Medical Subject Heading (MeSH) terms, such as "temozolomide," "bevacizumab," "radiotherapy," and "glioblastoma," within the titles, abstracts, and key sections. Language restrictions were not imposed, and duplicate articles were only taken into consideration once. We excluded review papers, unrelated studies, and commentaries/editorials. The remaining articles underwent a meticulous evaluation to determine their relevance to the subject matter. Furthermore, we manually searched the reference sections of identified studies and review papers for additional pertinent research. To ensure accuracy and reliability, the article search was independently conducted by two reviewers.

Selection of studies

This study's goal was to examine the effects of radiation and temozolomide with and without the addition of BV in individuals who had just received a diagnosis of GBM. To ensure a focused analysis, we established specific selection criteria. The included publications were (1) clinical trials, (2) conducted on patients with previously untreated GBM who had histologically-verified diagnosis, along with acceptable organ/bone marrow function, and (3) the OS and PFS data were available. Experimental studies, articles concerning the pediatric population, phase I studies, reviews, case reports, editorials, meeting abstracts, and technical reports were also disregarded. We also did not include studies that did not contain a control group. In addition, studies lacking OS and PFS data were not considered. In case of any discrepancies or disagreements, a debate was initiated, and a consensus was reached through discussion and resolution.

Data extraction

To minimize bias in the process, two authors independently collected data from the studies and judged against the resulting outcomes. Discussion clarified any contradictions between the authors. The first author's name, the publication year, the corresponding author, the number of patients registered, the length of follow-up, the treatment area, the odds ratios (ORs) for OS and PFS, and information on adverse events were all taken from each trial.

Quality assessment

To evaluate the risks of detection bias, attrition bias, selection bias, performance bias, and reporting bias in the chosen randomized clinical trial, we utilized the Cochrane Collaboration Tool. This tool enables us to perform a systematic evaluation of the trial's methodological quality and risk of bias. Each trial was carefully assessed for potential biases in these five domains. A low risk of bias was assigned to trials that had two or fewer components classified as high-risk, indicating a relatively low likelihood of bias in the study design or conduct. In contrast, trials were considered to have a high risk of bias if they had four or more components classified as high-risk, indicating a greater potential for bias. The Cochrane Collaboration Tool provides a structured framework for evaluating the risk of bias in clinical trials, enabling a

comprehensive assessment of the trial's internal validity and the reliability of its results.

Statistics

We used Comprehensive Meta-Analysis version 2 (Biostat Inc, Englewood, NJ) to perform the statistics. We presented the research findings by using a fixed-effects model. We used rates to present categorical outcomes, whereas we employed the median and associated 95% confidence interval (CI) to report time-to-event data. We evaluated the collected papers' heterogeneity by using the Chi-square, I^2, and prediction interval tests. We utilized Begg and Mazumdar's test and funnel plots to assess publication bias. All comparisons were deemed statistically significant if the two-tailed P value was 0.05 or below.

Results

General characteristics

An initial electronic search of the databases yielded a total of 949 articles, of which 170 articles were excluded due to being duplicated or marked as ineligible by automation tools. Accordingly, 779 articles were retrieved, of which 701 records were excluded. In total, 78 records were assessed for eligibility, and six articles were included in this systematic review and meta-analysis [Figure 1][1,4,12-15] There were no further articles found through a screening of studies citation list that qualified for inclusion. Table 1 lists the key characteristics of the studies that were included. With 958 patients assigned to the study group receiving BV with radiotherapy/temozolomide and 963 patients recruited for comparison, these six studies included a total of 1921 patients. Three studies were randomized clinical trials (RCTs),[4,13,14] two studies were prospective cohorts,[1,12] and one study was a retrospective cohort.[15]

The effects of BV on the PFS in patients with GBM

The results of this meta-analysis showed that the addition of BV to the combination of temozolomide/radiotherapy does not increase the PFS in patients with GBM. The pooled OR was 0.829 (95% CI: 0.561–1.224, $P = 0.346$; Figure 2a). I^2 displays the proportion of the observed variance that is attributable to sampling error or fluctuations in real effects.[16] In this study, we found that I^2 for the OS was 38.09, implying that rather than sampling error, roughly 38% of the variation in observed effects reflects variation in real effects. The prediction interval analysis showed that the OR was 0.83 with a 95% confidence interval of 0.56–1.22, meaning that the OR falls on both sides of the null value [Figure 3b].

The effects of BV addition on the OS in patients with GBM

We also found that the addition of BV to radiotherapy/temozolomide does not increase the OS in patients with GBM. The pooled OR was 0.843 (95% CI: 0.615–1.156, $P = 0.290$; Figure 2b). Here, we found that I^2 for the OS was 20.82, meaning that almost 21% of the variance in observed effects reflects variance in true effects rather than sampling error. The prediction interval analysis showed that the OR was 0.84 with a 95% confidence interval of 0.61–1.16, meaning that the OR falls on both sides of the null value [Figure 3a].

Publication bias

The funnel plot demonstrated the absence of the alleged pleiotropic effects by showing no evidence of observable

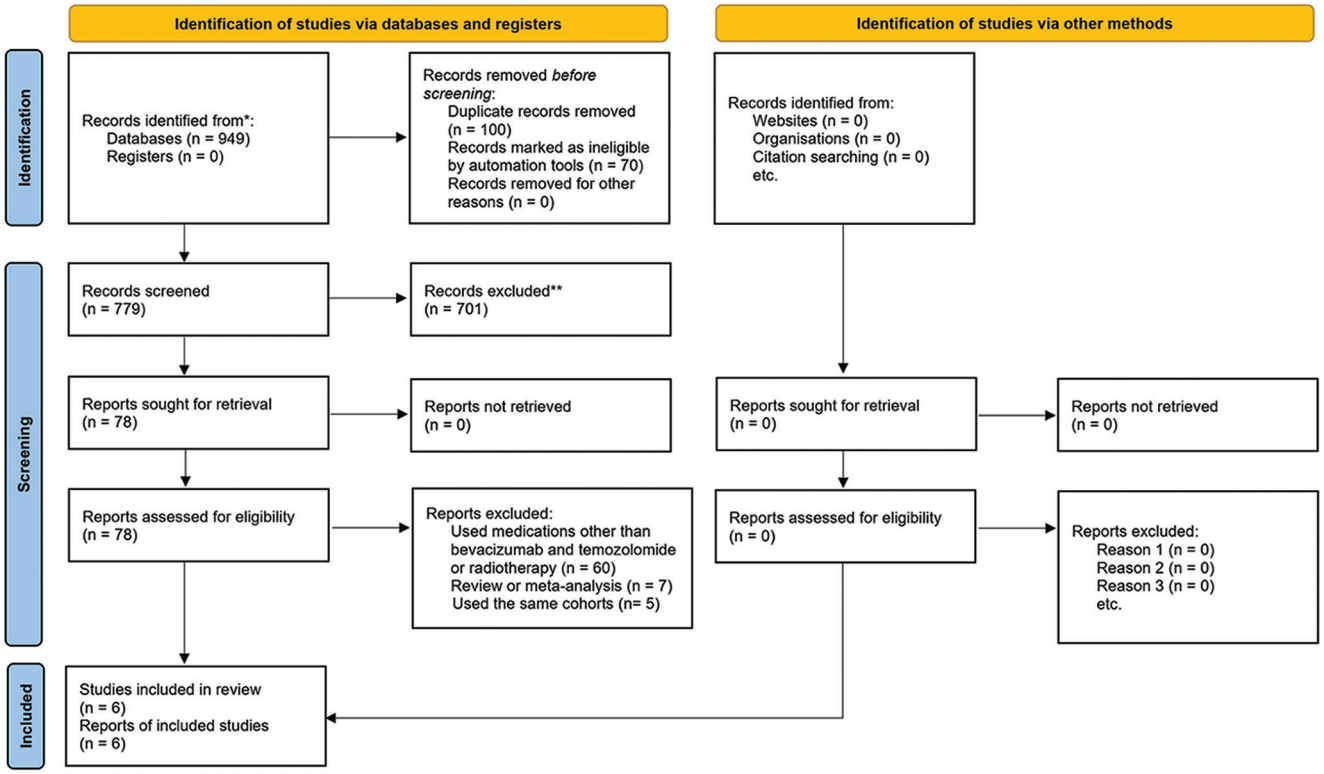

Figure 1: Flowchart of the literature research for the systematic review and meta-analysis

Table 1: The general characteristics of the studies included in the meta-analysis

Study	Design	Number of patients		Therapy regimen	Median OS (BEV vs. placebo; months)	Median PFS (BEV vs. placebo; months)	Median follow up
		RT/TMZ	RT/TMZ/BV				
Chinot *et al*., 2014	RCT	463	458	Intravenous BEV (10 mg per kilogram of body weight q2w) or placebo, plus RT (2 Gy 5 days a week; maximum, 60 Gy) and oral TMZ (75 mg per square meter of body-surface area per day) for 6 weeks. After a 28-day treatment break, maintenance BEV (10 mg per kilogram intravenously q2w) or placebo, plus TMZ (150–200 mg per square meter per day for 5 days), was continued for six 4-week cycles, followed by BEV monotherapy (15 mg per kilogram intravenously q3w) or placebo until the disease progressed or unacceptable toxic effects developed.	16.8 vs. 16.7	10.6 vs. 6.2	12.3 vs 8.5
Gilbert *et al*., 2014	RCT	309	312	RT was delivered 5 days a week for 6 weeks, for a total dose of 60 Gy. Treatment with TMZ, at a dose of 75 mg per square meter of body surface area, was started at the initiation of RT and was continued daily until the completion of RT, with a maximum of 49 doses. BEV (or placebo) was administered intravenously at a dose of 10 mg per kilogram of body weight every 2 weeks, starting at week 4 of RT, until disease progression, severe treatment-related toxicity, or completion of adjuvant therapy (maximum number of doses, 24 over 12 cycles). Maintenance treatment with TMZ began 4 weeks after the completion of RT at a starting dose of 150 mg per square meter for 5 consecutive days of a 28-day cycle, with an increase to 200 mg per square meter for subsequent cycles if no treatment-related adverse events of grade 2 or higher were noted.	15.7 vs. 16.1	10.7 vs. 7.3	20.5
Balana *et al*., 2016	RCT	45	48	In both arms, neoadjuvant treatment was TMZ (85 mg/m^2, days 1–21, two 28-day cycles), concurrent radiation plus TMZ, and six cycles of adjuvant TMZ. In the TMZ/BEV arm, BEV (10 mg/kg) was added on days 1 and 15 of each neoadjuvant cycle and on days 1, 15, and 30 of concurrent treatment.	10.6 vs. 7.7	4.8 vs. 2.2	18
Carlson *et al*., 2015	Prospective cohort	26	30	All patients received postoperative hypo-IMRT to the surgical cavity and residual tumor plus a margin to a total dose of 60 Gy and to the T2 abnormality with a margin of 30 Gy, both in ten fractions. Concurrent TMZ (75 mg/m^2/day) was given to all patients for 28 consecutive days followed by adjuvant TMZ (150–200 mg/m^2/day). Patients enrolled in the hypo IMRT/TMZ/BEV trial received concurrent and adjuvant BEV (10 mg/kg) on days 1 and 15 of each 28-day cycle.	16.3 in both arms	12.8 vs. 9.4	14.7 vs 13.9
Lai *et al*., 2011	Prospective cohort	100	100	Patients were treated with biweekly BEV (10 mg/kg) administered intravenously and TMZ (75 mg/m^2) administered orally daily during RT. RT was started within 3–6 weeks after surgery. Each patient received thirty 2.0 Gy fractions, totaling 60.0 Gy. After completion of RT, BEV was continued every 2 weeks. After a 2-week minimum interval after the last daily TMZ dose, patients were treated with biweekly BEV and TMZ every 4 weeks at 150–200 mg/m^2/d for the first 5 days of every 28-day cycle until progression or for a maximum of 24TMZ cycles (post-RT phase). For patients completing 24 cycles of TMZ, single-agent BV was continued every 2 weeks until progression	19.6 vs. 21.1	13.6 vs. 7.6	24.2 vs 41.8

Contd...

Table 1: Contd...

Study	Design	Number of patients		Therapy regimen	Median OS (BEV vs. placebo; months)	Median PFS (BEV vs. placebo; months)	Median follow up
		RT/TMZ	RT/TMZ/BV				
Ohno *et al*., 2019	Retrospective cohort	20	10	The TMZ dose was 75 mg/m²/day during radiotherapy and 150–200 mg/m²/day for 5 days every 28 days when administered as adjuvant treatment for a maximum of 24 cycles or 12 cycles, or until disease progression. The dose of BEV was 10 mg/kg every 2 weeks or 15 mg/kg every 3–4 weeks.	12.9 vs. NM	9.9 vs. NM	NM

BEV, bevacizumab; TMZ, temozolomide; RT, radiotherapy; OS, overall survival; PFS, progression-free survival; IMRT, intensity-modulated radiation therapy, NM, not mentioned

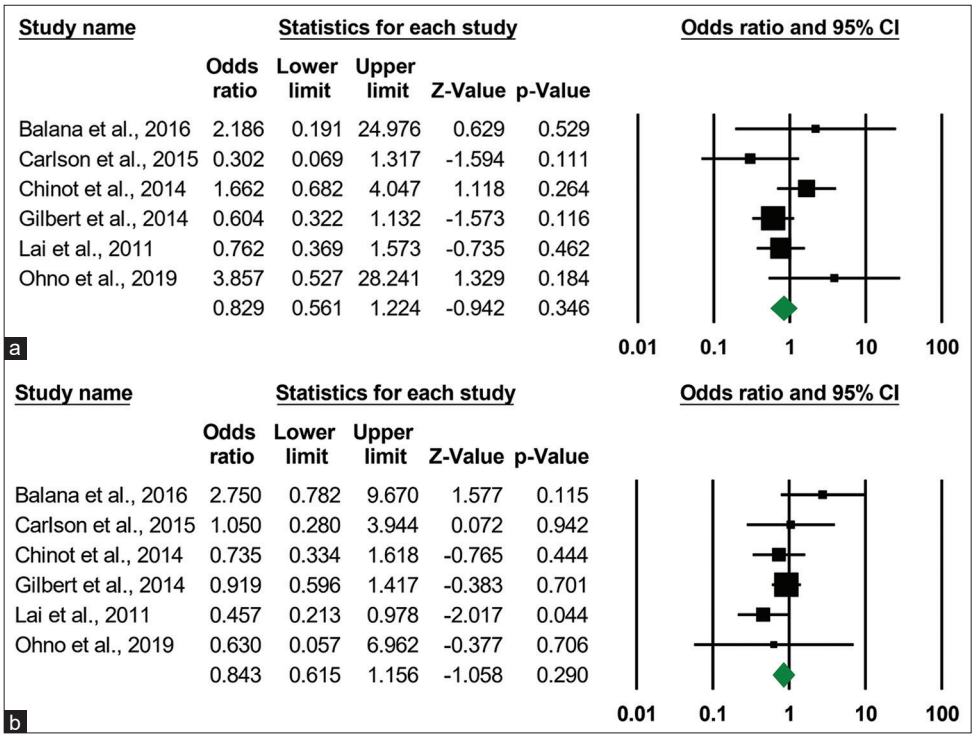

Figure 2: Forest plot of odds ratio (ORs) for the progression-free survival (a) and overall survival (b) for bevacizumab vs. placebo in patients with glioma multiforme. The green square shows the overall pooled effect. Black squares indicate the OR in each study. Horizontal lines represent a 95% confidence interval (CI)

variability across the estimations. No study was excluded from the trim and fill analysis based on deviation from the mean for OS, while only a single study was excluded from the left side of the mean in the case of PFS [Figure 4a and b]. Both Egger's (P = 0.850 for the OS, and P = 0.573 for the PFS) and Begg's tests (P = 0.795 for the OS, and P = 0.399 for the PFS) revealed no evidence of a substantial risk of publication bias.

Sensitivity analysis

The study demonstrated that the exclusion of any of the included studies in the meta-analysis had no significant impact on the results of the OS (P = 0.346) and PFS (P = 290) analyses presented [Figure 5a and b].

Safety and toxicities

The adverse effects related to the treatment could be divided into two hematologic and non-hematologic parts. According to Lai *et al*.'s study,[12] the study group experienced higher rates of thrombocytopenia and neutropenia than the control group did throughout the post-radiotherapy phase. Fatigue was the most frequent non-hematologic side effect, followed by venous thrombosis, hypertension, and proteinuria. Ohno *et al*.[15] reported grade 3/4 leukopenia in 15 patients (50%) accompanied by neutropenia in four, anorexia in four, hyponatremia in three, and skin rashes in four. In the 24 patients who underwent adjuvant chemotherapy, grade 3/4 leukopenia occurred in 11 (45.8%), neutropenia in one, anemia in one, and skin rashes in two (8.3%) patients. The study by Chinot *et al*.[4] discovered that the BV group had higher rates of serious adverse effects, grade 3 or higher adverse effects, and BV-related grade 3 or higher adverse effects than the placebo group. In addition, the BV group had significantly higher frequencies of both total and grade 3 or higher arterial thromboembolic events compared to the placebo group. In addition to these major side effects, the BV group also experienced increased bleeding, wound-healing issues, gastrointestinal perforations, and congestive heart failure. The Gilbert *et al*.[13] investigation yielded similar outcomes, where the greatest incidence of adverse effects was for severe lymphopenia, manifesting in 10% of patients across both trial cohorts. Yet, there was a greater occurrence of severe

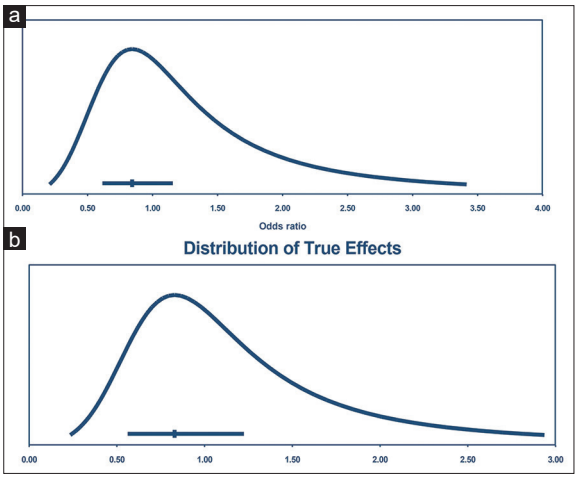

Figure 3: The prediction interval diagram for PFS (a) and OS (b) showing the dispersion of the data for the general and study populations

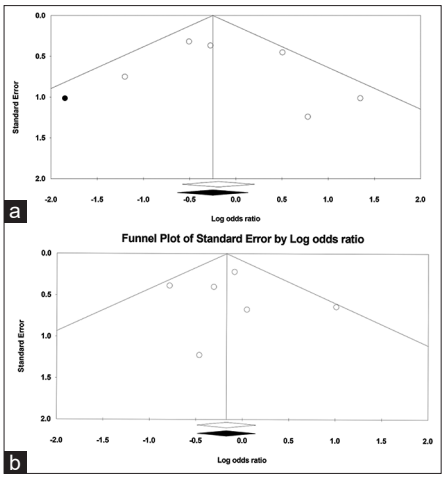

Figure 4: Funnel Plot of standard error against odd ratios for progression-free survival (a) and overall survival (b) after Duval and Tweedie's trim and fill

thrombocytopenia and neutropenia in the BV cohort compared to the placebo cohort.

Quality assessment

Three studies were not randomized or blinded.[1,12,15] Other measures of the tool were observed in all of the included studies [Figure 6].

Discussion

In the discipline of neuro-oncology, GBM treatment is of the highest importance.[17] The discovery of temozolomide has resulted in considerable improvements in OS and PFS in patients with GBM,[18] and now along with radiotherapy, it is the mainstay of GBM treatment.[19,20] GBM, however, continues to be the worst primary CNS tumor[21] Consequently, the advent of novel strategies is crucial to enhancing the GBM outcomes. According to evidence, the stepwise inhibitory effects of GBM can transform the formation of new blood vessels in the brain by neovascularization. This process can help control the growth and spread of tumors.[22] Due to its elevated expression in malignant gliomas, VEGF has been employed as a therapeutic target for malignant gliomas.[23] In 2009, the FDA approved BV, a humanized monoclonal antibody against the VEGF ligand, for recurrent GBM.[10] According to the findings, BV may be also advantageous for people with newly discovered GBM.[12] To evaluate the safety and probable benefits of incorporating BV into the existing therapeutic protocol for newly diagnosed GBM, we conducted a thorough meta-analysis. Our objective was to investigate the feasibility and efficacy of BV as an adjunctive therapy in the treatment of GBM. Our study is different from that of Marenco-Hillembrand *et al*.,[24] who investigated the therapeutic effects of all possible treatment options existing for newly diagnosed GBM between 1978 and 2018 and showed that the concurrent use of radiotherapy and temozolomide resulted in a statistically significant improvement in the survival of individuals diagnosed with glioblastoma. The main focus of this systematic review was the Stupp *et al*. paper[3] published in 2005 that found that survival significantly improved with concurrent temozolomide and radiotherapy compared to temozolomide alone[3] In addition, in the BV subgroup analysis, they did not include the studies from Lai *et al*.,[12] Ohno *et al*.,[15] and Carlson *et al*.[1] All of these studies have been included in our meta-analysis. Our meta-analysis distinguishes itself from the study conducted by Aravantinou-Fatorou *et al*.[25] as their analysis comprised only four studies, all of which were also incorporated in our study with one exception.[26] Notably, the study by Wirsching *et al*.,[26] included in the aforementioned meta-analysis, compared BV plus hypofractionated radiotherapy to radiotherapy alone, excluding temozolomide. It is crucial to acknowledge that the outcomes of this particular study are not directly comparable to those of the other studies, making their inclusion in the same group for analysis inappropriate.

The OS and PFS were the main endpoints chosen by all included studies. Based on the findings of the Carlson *et al*.[1] trial and the study conducted by Ohno *et al*.,[15] the inclusion of BV did not result in improved OS when compared to the combination of placebo, temozolomide, and radiation. However, it did lead to a marginal increase in PFS, although this change was not statistically meaningful (P = 0.39). The incorporation of BV resulted in a substantial enhancement of PFS in the AVAglio trial, RTOG 0825 trial, and the study conducted by Lai *et al*. However, the trend was not mirrored in OS outcomes[4,12,13] In the Balana *et al*. trial,[14] patients who received BV demonstrated a higher response rate, along with prolonged PFS and OS. Nonetheless, the differences in survival outcomes did not reach statistical significance. As a result of this meta-analysis, we conclude that BV for patients with GBM does not prolong median PFS or median OS. According to Fu *et al*.'s meta-analysis,[27] which supports our findings, adding BV to temozolomide plus radiation did not increase patients' OS in GBM. Still, they found that this previously unknown combination therapy was associated with an improved PFS. In direct relevance to this line of evidence, Yang *et al*.[28] found that BV addition did not improve OS in patients with GBM. However, it was able to prolong PFS in these patients.

The observed phenomenon could be explained by the fact that patients with GBM exhibited decreased neurocognitive function and lower survival rates when BV usage was continued. This could be indicative of the development of resistance to BV.[22] Another possible interpretation of the

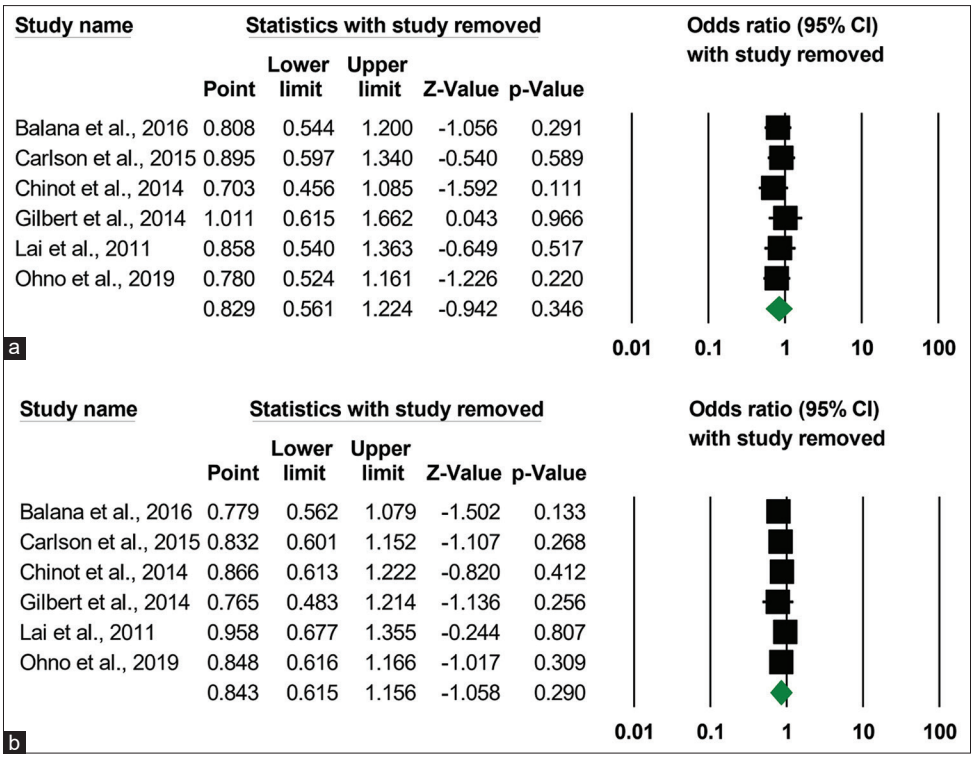

Figure 5: The Comprehensive Meta-Analysis (CMA) software's "leave-one-out" sensitivity analysis "one study deleted" feature

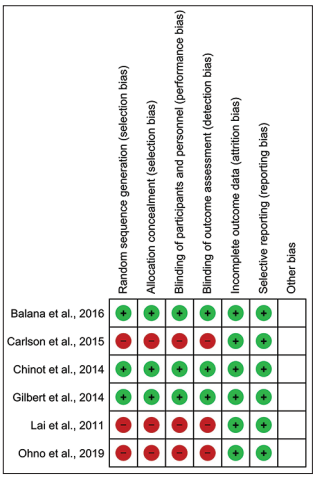

Figure 6: Different levels of bias risk for each factor in the studies that were considered. The Cochrane risk of bias tool was used to determine publication bias

observed results is that the vasculature might be the brisk regeneration following the discontinuation of BV therapy. It has been observed that BV treatment can induce radiographic changes, leading to an extension in PFS. This effect is attributed to the stabilization of the blood-brain barrier by BV, which diminishes the capacity of the MRI contrast agent gadolinium to effectively reach the tumor site. As a result, the identification of tumor progression, primarily based on radiographic diagnostic criteria, may be delayed, leading to a longer PFS. It is important to consider this explanation alongside other factors that may influence PFS outcomes in patients receiving BV treatment for a comprehensive understanding of the observed effects.[22]

Molecular markers hold promise in identifying specific subgroups of GBM patients who may exhibit increased vulnerability or resistance to BV treatment. Further investigations into patient subgroups based on various genetic variations could potentially reveal those who derive a survival benefit from BV therapy.

It is important to acknowledge several limitations of this study. First, the therapy benefits may not have been fully characterized due to the reliance on aggregated data from published studies rather than individual patient data. Second, the affordability of BV therapy was not taken into account as BV is a biologic therapy with relatively high costs, making it challenging to objectively evaluate its cost-effectiveness. Third, the small number of included studies, heterogeneity in study designs, and variations in treatment regimens across the three clinical investigations make it difficult to draw conclusive findings. Fourthly, it is important to note that the outcomes of this study are relevant specifically to patients diagnosed with newly developed GBM and may not be generalizable to individuals experiencing disease recurrence. Consequently, further studies are warranted to evaluate the impact of adding BV to the combination of temozolomide and radiotherapy in the context of recurrent cases.

Given the findings of this study, we are not sure of the evidence supporting the efficacy of adding BV to temozolomide and radiotherapy in terms of OS and PFS in patients with GBM. It is essential to mention that these conclusions are limited by the small number of included studies and the heterogeneity of data. Further research with a larger sample size and more homogeneous data is warranted to better address this issue in the future.

Declaration of figures' authenticity

All of the figures included were produced by the authors, who also attest that they are unique, free of copying, and have never been published in full or in part before.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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