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Impact of angiogenic inhibition in the treatment of newly diagnosed and recurrent glioblastoma: a meta-analysis based on randomized controlled trials

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Abstract. – OBJECTIVE: Glioblastoma (GBM) is the most common and aggressive primary malignant tumor of the central nervous system in adults with high recurrence and mortality rates. Although radiotherapy and temozolomide have become the standard therapeutic regimen for GBM as adjuvant chemoradiotherapy after surgical resection, clinical outcomes remain suboptimal. In recent years, targeted antiangiogenic therapy has attracted considerable attention, but its therapeutic efficacy and safety are still controversial.

MATERIALS AND METHODS: Randomized controlled trials (RCTs) of chemoradiotherapy with or without bevacizumab for the treatment of glioblastoma were collected by searching on the Pubmed, Embase, Cochrane, Ovid, Scopus, Web of Science, and Google Scholar databases from the date of database establishment to February 2022. Meta-analysis was performed using RevMan 5.3 software after two investigators independently screened the literature, extracted data, and assessed the risk bias of included studies.

RESULTS: A total of 7 RCTs were included. The meta-analysis showed that bevacizumab in combination with chemoradiotherapy was superior to chemoradiotherapy alone in terms of progression-free survival (PFS), with a statistically significant difference. Interestingly, bevacizumab in combination with chemoradiotherapy improved PFS more significantly in recurrent glioblastoma than in newly diagnosed glioblastoma. However, for overall survival (OS), the combination of bevacizumab with chemoradiotherapy was similar to chemoradiotherapy alone, which was not significantly different. With regard to safety, the incidence of most adverse events was higher in the combination of bevacizumab and chemoradiotherapy than in chemoradiotherapy alone, especially in terms of hematologic adverse events.

CONCLUSIONS: Current evidence suggests that angiogenesis inhibitor-containing chemoradiotherapy regimens are preferentially recommended for patients with recurrent glioblastoma to prolong their progression-free survival, provided that safety is acceptable, but this does not confer a significant benefit on overall patient survival.

Key Words:
Glioblastoma, Anti-angiogenesis, Bevacizumab, Chemoradiotherapy, Randomized controlled trial.

Introduction

As a high-grade glioma in WHO classification, glioblastoma (GBM) is the most common and primary central nervous system (CNS) malignant tumor in adults, which accounts for 47.1% of all primary CNS tumors and is more common in men than in women[1]. Even more, the incidence of GBM increases sharply after 54 years, and the median age of occurrence is 64 years[2]. The biological characteristics of GBM are diffuse distribution, infiltrative growth, strong aggressiveness, and high intensity of intra-tumoral vascularization[3], and GBM is not susceptible to complete removal and is prone to recurrence after surgery[4,5]. In addition, the overall survival of patients with glioblastoma is 15 to 18 months and the 5-year survival rate is lower than 5% after diagnosis[6]. The current standard treatment is the Stupp's regimen for newly diagnosed GBM patients under 70 years, which may improve the survival benefit for GBM patients after maximal tumor resection, postoperative radiotherapy, and adjuvant chemotherapy with temozolomide (TMZ) or nitrosoureas lomustine (CCNU)[7]. Even though complete surgical resection and radiotherapy effectively suppress

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glioblastoma, there are still imaging-negative subclinical tumor lesions[8,9]. A multicentre clinical trial[10] involving 573 patients from 85 institutions in 15 countries demonstrated that the median survival rate in the chemoradiotherapy group was longer than in the radiotherapy alone group, and that was tolerated better in the patients with glioblastoma. Meanwhile, newly diagnosed glioblastoma has a high recurrence rate and is also refractory to multiple combination regimens. Moreover, there are no effective first-line therapeutic regimens for recurrent glioblastoma as yet[11].

Although surgical resection and chemoradiotherapy are now widely practiced in the treatment of glioblastoma, patient survival rates remain low and recurrence rates are as high as expected. Vascular endothelial growth factor (VEGF) is less expressed in the normal human brain, but is abnormally high-expressed in WHO grade I-II human glioblastomas. Moreover, GBM has more intense angiogenesis and neovascular dependency compared to other intracranial malignancies[12,13]. Bevacizumab is a recombinant human anti-vascular endothelial growth factor monoclonal antibody (Avastin, Roche Pharma Ltd, Basel, Switzerland) that acts primarily by competing for VEGF and binding to VEGF receptors in glioblastoma[14]. Moreover, the combination of bevacizumab with chemoradiotherapy is more beneficial than bevacizumab alone[15], hence the combination regimens containing angiogenesis inhibitors are expected to be a novel approach for the treatment of GBM. However the addition of bevacizumab remains controversial: radiotherapy in combination with bevacizumab and TMZ for newly diagnosed GBM prolongs progression-free survival but does not improve overall survival, as well as bevacizumab has a high incidence of adverse events, which should be administered with considerable precaution in clinical practice[16]. In addition, bevacizumab in combination with lomustine prolongs progression-free survival compared to lomustine alone, but no significant improvement has been recorded in overall survival in the recurrent GBM[17].

To address the controversy of whether anti-angiogenic targeted therapy should be chosen in the conventional therapeutic regimen of glioblastoma, we sought to comprehensively investigate the clinical outcomes of bevacizumab in combination with chemoradiotherapy in terms of progression-free survival and overall survival compared to chemoradiotherapy alone, as well as the differences in safety and toxicity between the above two therapeutic regimens. Therefore, we performed a meta-analysis to provide more clinical evidence on the application of angiogenesis inhibitors in the treatment of newly diagnosed and recurrent glioblastoma.

Materials and Methods

Search Strategy

Two investigators independently searched on Pubmed, Embase, Cochrane, Ovid, Scopus, Web of Science, and Google Scholar according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria. The potential studies on the addition of angiogenesis inhibitors to glioblastoma therapeutic regimen were selected from the time of database establishment to February 2022. The search terms included: glioblastoma, bevacizumab, Avastin, VEGFR, glioblastoma, Grade IV astrocytoma, glioma, GBM, GB, randomized controlled trial (RCT).

Inclusion and Exclusion Criteria

Inclusion criteria: (i) the patient had been confirmed with glioblastoma by pathological histology and cranial magnetic resonance imaging (MRI), or he/she had been previously diagnosed with glioma and had pathologically confirmed glioblastoma after recurrence, according to the diagnostic criteria for glioblastomas in the World Health Organization Classification of Gliomas; (ii) age $\geq$ 18 years; (iii) the intervention was bevacizumab combined with chemoradiotherapy *vs.* chemoradiotherapy alone; (iv) the sample size, clinical outcomes, adverse events, and safety were reported in the included studies; (v) all the included studies should be randomized controlled trials (RCTs).

Exclusion criteria: (i) insufficient details about the treatment regimen, incomplete or incorrect data; (ii) unable to extract data on progression-free survival and overall survival; (iii) Repeated publication of the outcome or data from the same clinical trial; (iv) patients with heart, lung, liver, kidney and other serious organ failures; (v) bevacizumab alone compared with multiple chemotherapeutic agents; (vi) review, systematic review, Meta-analysis, case report, conference abstract, clinical guideline, animal studies.

Data Extraction

Based on the inclusion and exclusion criteria, two investigators independently screened the available studies to identify for inclusion criteria and

cross-checked the results of included studies. Any discrepancies were resolved through discussion with a third investigator. The database was established from the included data, and the following information was collated by the investigator: total number of patients, age, gender, detailed treatment for the intervention, clinical outcomes, and study type. Another investigator verified the correctness of the data against the original full text. The clinical outcomes were progression-free survival (PFS) and overall survival data (OS) with hazard ratios and confidence intervals (HR, 95% CI), and the adverse events were bleeding, thrombosis, hematologic toxic reactions, hypertension, wound dehiscence, gastrointestinal disturbances, proteinuria.

Study Quality Assessment

The investigators evaluated the quality of the included studies using the Cochrane Risk of Bias Assessment Tool, which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias, with "+" for fulfilling the criteria, "-" for not fulfilling the criteria, and "?" for unclear. The score ≤ 3 out of 7 in total were considered high risk of bias, 3 to 5 were considered moderate risk of bias, and ≥ 5 were considered low risk of bias.

Statistical Analysis

Data from the included studies were extracted, collated, and proofread according to the PRISMA criteria. When hazard ratio (HR) was not reported in the included studies, Engauge Digitizer 4.1 was used to extract survival data from survival curves and indirectly calculate HRs and 95% CIs. Heterogeneity of included studies was tested using the *Q*-test, and we considered high heterogeneity if the *p*-value was ≤ 0.01 or $I^2 \geq 70\%$ with random-effects models, otherwise fixed effects models were chosen. Subgroup analysis was performed to assess the difference in progression-free survival and overall survival for newly diagnosed glioblastoma and recurrent glioblastoma. To determine the stability of the Meta-analysis results, a sensitivity analysis was performed by excluding each included study, re-combining the remaining studies, and comparing the total effect size before and after exclusion. Forest plots and funnel plots were constructed on RevMan 5.3 (Cochrane Collaboration, 2014) to illustrate combined outcomes and assess publication bias, with $\alpha = 0.05$ as the test level.

Results

Search Results

The search identified 2,181 potentially relevant studies, of which 883 were included after removing duplicates, title, and abstract selection. In total, 156 studies were retained for full-text review. Review, systematic review, comment, letter, original studies on animals were excluded after reviewing the full-text articles. Finally, seven studies[16-22] involving 2,360 patients were selected and fulfilled the inclusion criteria (Figure 1).

Baseline Characteristics and Quality Assessment Of Included Studies

The general characteristics were obtained from the summarized baseline data and post-intervention clinical data in the included studies, as shown in Table I. The seven randomized controlled trials were included in the present study, which involved 2,360 patients treated with the chemoradiotherapy regimens (temozolomide 75 and 150-200 mg/m^2 or lomustine 90-110 mg/m^2) and chemoradiotherapy with or without bevacizumab (10 mg/kg). One study[19] was a four-arm trial and the others were two-arm trials. Four of the included studies were performed in patients with newly diagnosed glioblastoma and three in patients with recurrent glioblastoma. The final included studies were all in English and published between 2014 and 2019. The clinical outcomes involved progression-free survival, overall survival, objective response rate, O6-methylguanine-methyltransferase (MGMT) status, and adverse events. The study types included four multicenter RCTs and two open-label RCTs.

All seven included studies reported the process of randomization, while only one study[16] did not specify whether allocation concealment was performed. Two studies were not designated as blinded designs, three studies explicitly mentioned the blinding of investigator, and two studies were not detailed about attrition. All included studies presented anticipated outcomes based on the design of RCT. Three studies did not specify other potential sources of bias. The included studies were evaluated for quality using the Cochrane Risk Bias Assessment Tool (provided by Review Manager 5.3), with an overall score of 7. Three studies had a moderate risk of bias (all scored 4) and four studies had a low risk of bias (one scored 5, two scored 6, and one scored 7). The risk bias of the included studies is summarized in Figure 2A. Due

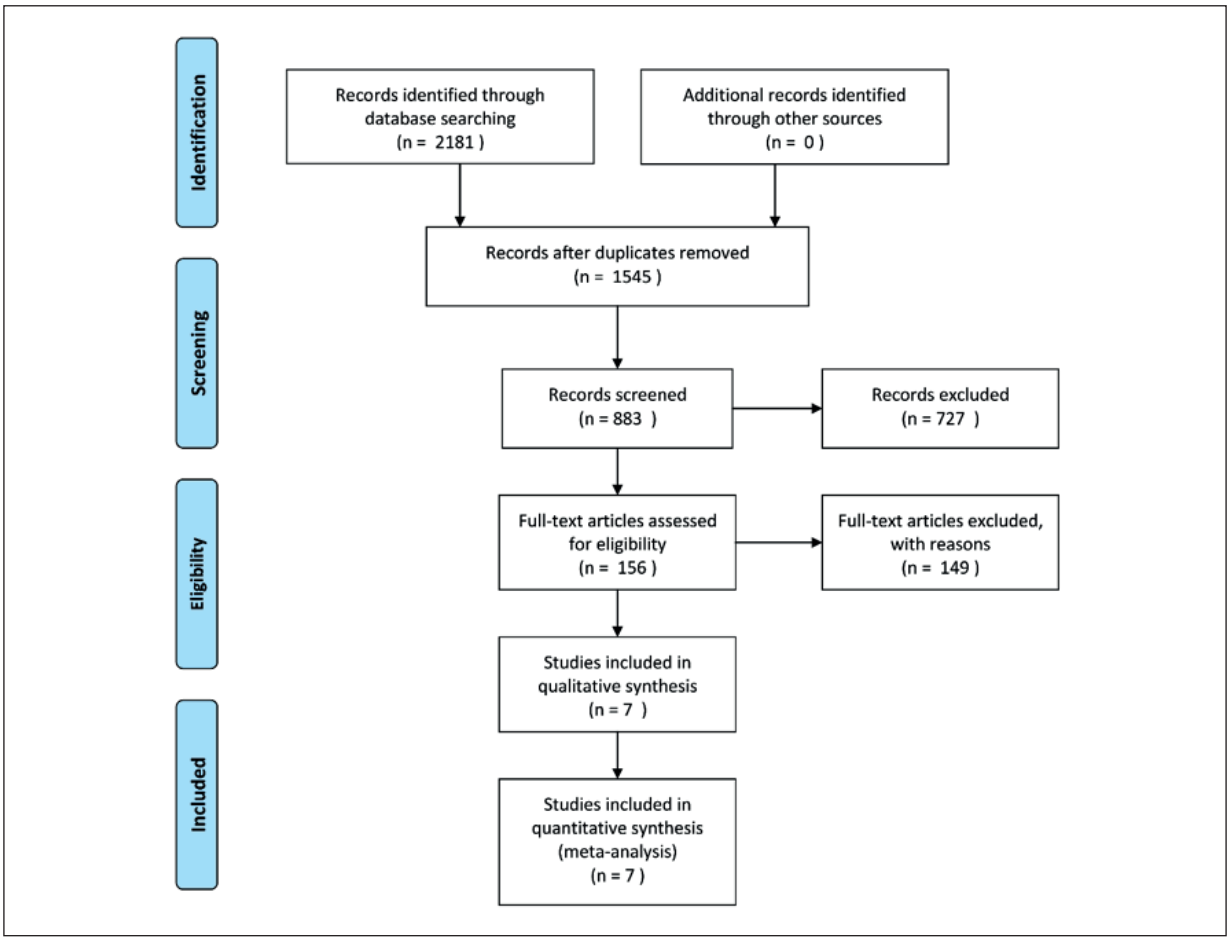

Figure 1. Flow diagram demonstrating inclusion/exclusion process for studies incorporated in final analyses.

to the fact that the two studies were open-label RCTs, there was a bias in investigator-administered blinding, as shown in the percentage risk of bias graph for the included studies (Figure 2B).

Primary Outcome: Progression-Free Survival

The treatment regimen of bevacizumab combined with chemoradiotherapy was superior to that of chemoradiotherapy alone in terms of improving progression-free survival, and the difference was statistically significant [HR = 0.64, 95% CI = (0.58, 0.70), I^2 = 62%]. For the newly diagnosed glioblastoma subgroup (weight 26.4%), the treatment regimen of bevacizumab combined with conventional chemoradiotherapy was superior to conventional chemoradiotherapy alone in terms of improvement in progression-free survival [HR = 0.68, 95% CI = (0.61, 0.76), I^2 = 62%]. The combined results in the recurrent glioblastoma subgroup [weight 26.4%, HR = 0.53, 95% CI = (0.44, 0.64), I^2 = 24%] were consistent with newly diagnosed glioblastoma subgroup. However, the treatment regimen of bevacizumab combined with conventional chemoradiotherapy in the recurrent glioblastoma subgroup was significantly superior to the newly diagnosed glioblastoma subgroup, and there was greater heterogeneity between the two subgroups (I^2 = 80.7%), indicating that the addition of bevacizumab to the treatment regimen is more effective in patients with recurrent glioblastoma (Figure 3).

Secondary Outcome: Overall Survival

In the comparison of prolonging overall survival, the therapeutical regimen of bevacizumab plus conventional chemoradiotherapy was slightly superior to that of conventional chemoradiotherapy alone, but it was not statistically different [HR = 0.95, 95%CI = (0.86, 1.04), I^2 = 16%]. In addition, the combined HR for the newly diagnosed subgroup was 0.95 [95% CI = (0.85, 1.06), I^2 =

Table I. Demographic and baseline characteristic of included studies.

Study ID	Patients	N	Arm1	n1	Arm2	n2	Outcomes	Styles
Balana et al[20] 2016	Newly Diagnosed	93	BEV (10 mg/kg/d) + TMZ (75 mg/m^2/d) + RT (2 Gy/6w)	48	TMZ (75 mg/m^2/d) + RT (2Gy/6w)	45	Response to neoadjuvant therapy, OS, PFS, toxicities, MGMT methylation	RCT
Chinot et al[16] 2014	Newly Diagnosed	921	BEV (10 mg/kg/2w, 15 mg/kg/3w) + RT (2Gy/5d/6w) + TMZ (150-200 mg/m^2/d)	458	TMZ (150-200 mg/m^2/d) + placebo+ RT (2 Gy/5d/6w)	463	OS, PFS, adverse events	Multi-center RCT
Gilbert et al[18] 2014	Newly Diagnosed	621	BEV (10 mg/kg/2w) + RT (2 Gy/5d/6w) + TMZ (75 mg/m^2/d/6w, 150-200 mg/m^2/d)	312	TMZ (75 mg/m^2/d/6w, 150-200 mg/m^2/d) +RT (2 Gy/5d/6w)	309	OS, PFS, MGMT Status, safety and toxicity	RCT
Wirsching et al[21] 2018	Newly diagnosed, Age: >65 years	75	BEV (10 mg/kg/2w) + RT (40 Gy in 15 fractions)	50	RT alone (40 Gy in 15 fractions)	25	OS, PFS, RTK II gene methylation subtype, safety, and tolerability	Multi-center open-label RCT
Brandes et al[22] 2019	Recurrent	123	BEV (10 mg/kg/2w) + Lomustine (90 mg/m^2/6w) + RT	61	Lomustine (90 mg/m^2/6w) + placebo+ RT	62	PFS, OS, safety	Multi-center RCT
Taal et al[19] 2014	Recurrent	90	BEV (10 mg/kg/2w) + Lomustine (oral, 110 mg/m^2/6w) + RT	44	Lomustine (oral, 110 mg/m^2/6w) + RT	46	ORR, PFS, OS, safety	Multi-center open-label RCT
Wick et al[17] 2017	Recurrent	437	BEV (10 mg/kg/2w) + Lomustine (110 mg/m^2/6w) + RT	288	Lomustine (110 mg/m^2/6w) + RT	149	PFS, OS, health-related quality of life, adverse events, neurocognitive outcome, MGMT status	RCT

Abbreviations: BEV = bevacizumab; TMZ = temozolomide; RT = radiotherapy; N = the total number of patients; n1/n2= the number of arm1/arm2 patients; w = weeks; d = days; PFS = progression free survival; OS = overall survival; EFS = event-free survival; ORR = objective response rate; MGMT = the methylation status of the promoter of O^6-methylguanine–DNA methyltransferase; RCT = randomized controlled trial.

55%, weight = 76.8%], and the combined HR for the recurrent subgroup was 0.95 [95% CI = (0.78, 1.16), I^2 = 0%, weight = 23.2%], both of which were generally consistent with the overall combined HR 0.95 [95% CI = (0.86, 1.04), I^2 = 0%, weight = 100%]. It indicates that the regimen of bevacizumab plus conventional chemoradiotherapy showed a slight difference in the improvement of overall survival between patients with newly diagnosed and recurrent glioblastoma (Figure 4).

Adverse Events

Common serious adverse events in patients with glioblastoma included bleeding, thrombosis, hematologic toxicity, hypertension, wound dehiscence, gastrointestinal disturbances, and proteinuria. The incidence of overall adverse events was higher in bevacizumab combined with chemoradiotherapy than in chemoradiotherapy alone. For thrombosis, hemorrhage, hematologic toxicity, hypertension, and proteinuria, the incidence of adverse events was higher in the bevacizumab combined with chemoradiotherapy arm than in the chemoradiotherapy alone arm for both newly diagnosed and recurrent glioblastoma patients. The incidence of wound dehiscence and gastrointestinal adverse events was lower in the bevacizumab combined with chemoradiotherapy than in chemoradiotherapy alone in patients with recurrent glioblastoma, but opposite results in patients with newly diagnosed glioblastoma were detected (Table II).

Sensitivity Analysis and Publication Bias Analysis

Sensitivity analysis was performed by removing each study to compare the pre-post variability of the combined HR values with their confidence intervals. We found that the combined HR values before and

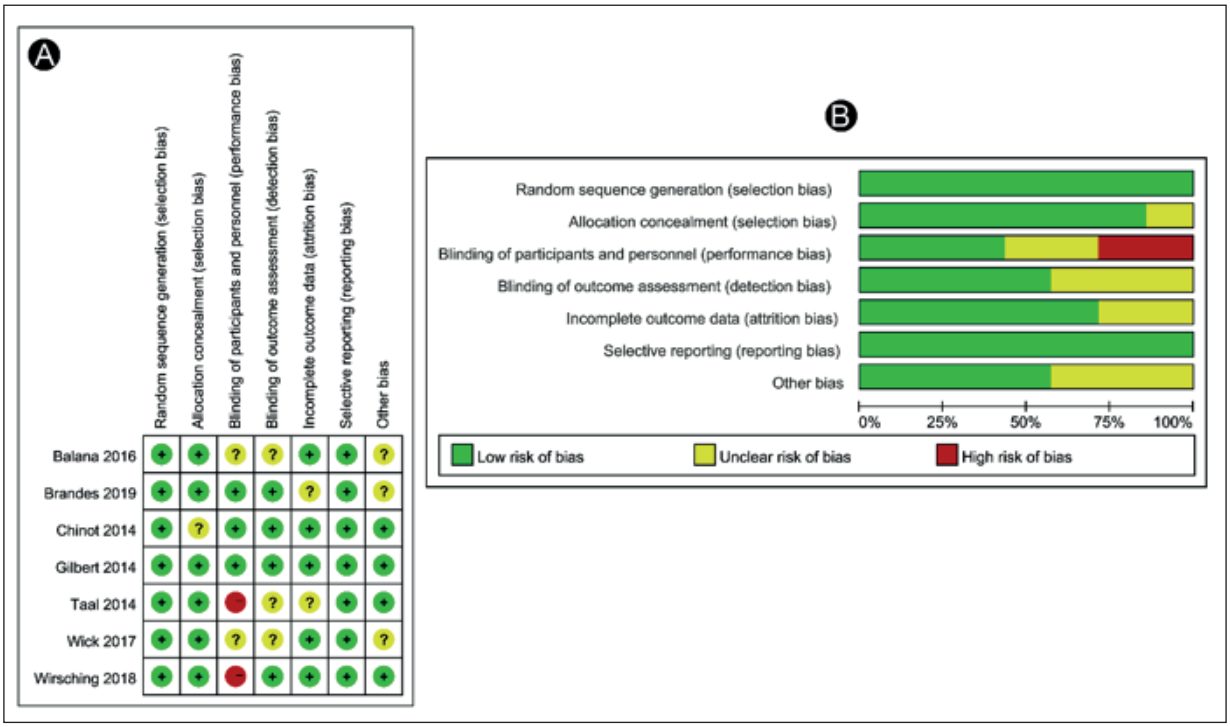

Figure 2. ***A***, Risk of bias summary: review authors' judgments about each risk of bias item for each included study. ***B***, Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

after removal did not fluctuate significantly, which suggests that the results of the meta-analysis were consistent and reliable. Funnel plots were used to assess the publication bias of the included studies. As shown in Figure 5, the majority of included studies were distributed centrosymmetrically within the funnel, indicating that there was no publication bias in the pooled results of PFS and OS.

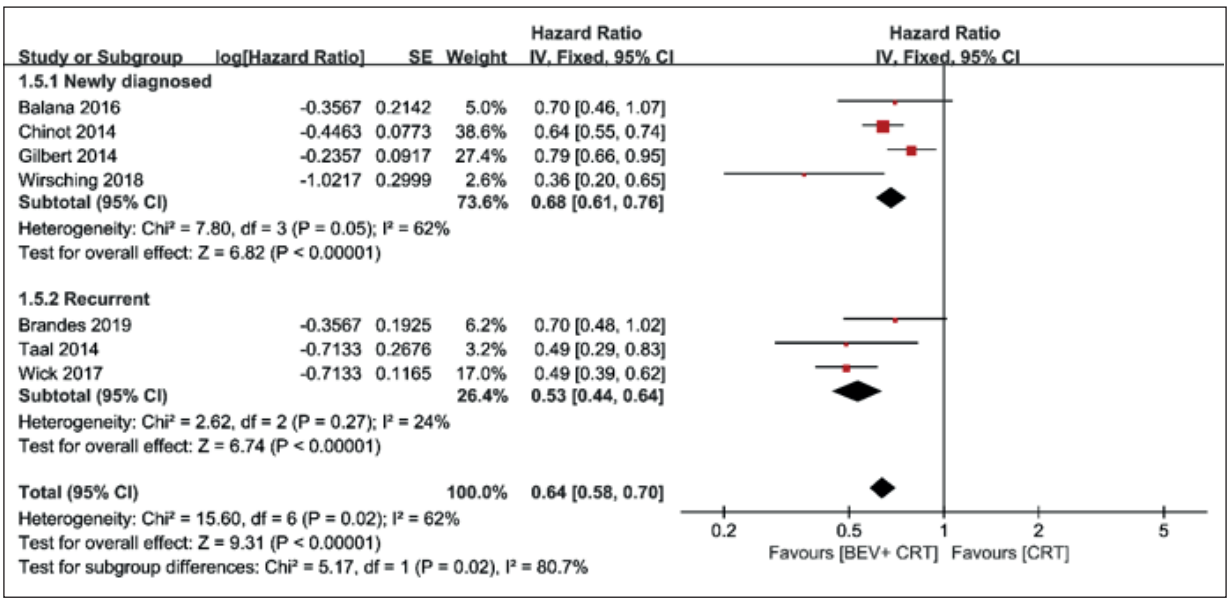

Figure 3. Forest plot of Hazard Ratio (HR) for composite endpoint: progression-free survival (PFS) in patients with glioblastoma (GBM). BEV+CRT = bevacizumab combined with chemoradiotherapy arm, CRT = chemoradiotherapy alone arm.

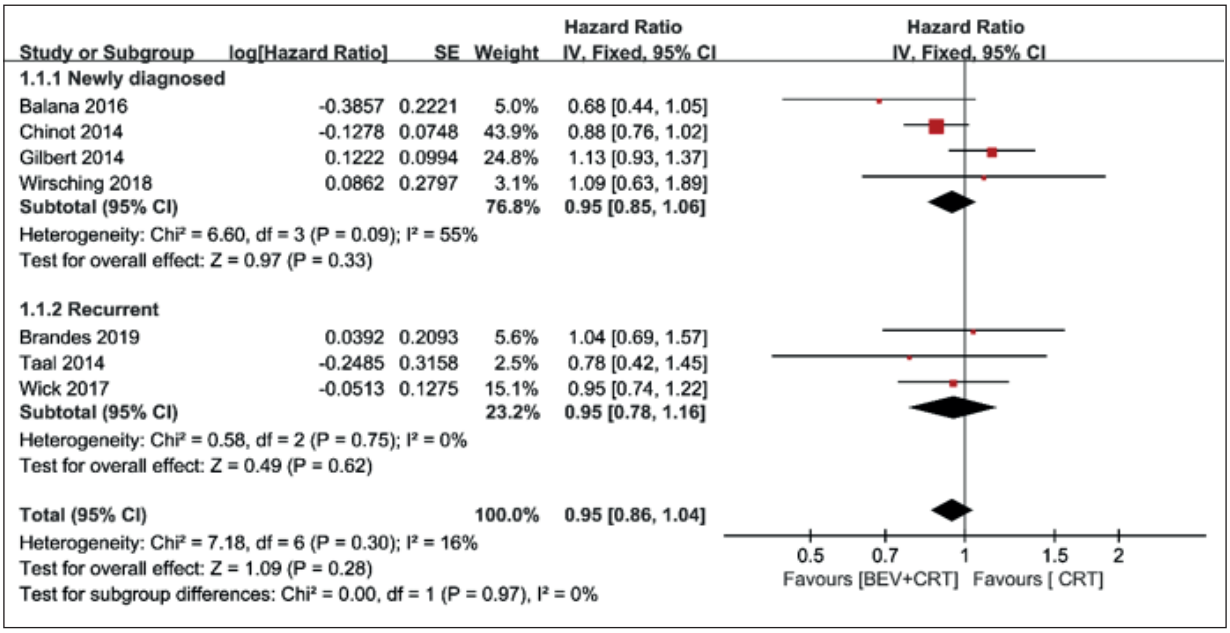

Figure 4. Forest plot of Hazard Ratio (HR) for composite endpoint: overall survival (OS) in patients with glioblastoma (GBM). BEV+CRT = bevacizumab combined with chemoradiotherapy arm, CRT = chemoradiotherapy alone arm.

Discussion

The present study provides further evidence that targeted angiogenesis inhibition is beneficial in the treatment of both newly diagnosed and recurrent glioblastoma, especially in improving progression-free survival in recurrent glioblastoma. Although bevacizumab contributed to prolonging progression-free survival for patients with recurrent glioblastoma, there was no significant overall survival benefit, which is consistent with previous clinical findings[17,23]. The lack of overall survival benefit from bevacizumab may be explained by the presence of bevacizumab resistance and more adverse events during the treatment, which partially reduce patients' willingness to treat and lead to no greater overall survival benefit. In a clinical trial on recurrent glioma, the 9-month survival rate in the bevacizumab-containing regimen was significantly superior than that of bevacizumab alone and lomustine alone, which suggested that bevacizumab may contribute to inhibiting the re-progression of high-grade glioma patients after recurrence[19]. Furthermore, previous studies[16,17] revealed that the median PFS of bevacizumab combined with chemoradiotherapy for newly diagnosed glioblastoma was 4.2 months and for recurrent glioblastoma was 10.6 months, while the median OS was 9.1 months in patients with newly diagnosed glioblastoma and 16.8 months in patients with recurrent glioblastoma, which is most comparable to the present pooled clinical outcomes.

The complicated mechanisms of glioblastoma angiogenesis and the lack of genomic stability make the treatment challenging. In addition, anti-angiogenic therapy has a dual effect, which acts not only on the intra-tumoral vascularity but also on the patient's general circulation[24]. The addition of bevacizumab would inevitably induce more serious adverse events compared to conventional chemoradiotherapy alone. Patients who received bevacizumab-related treatment had a high incidence of adverse events, such as thrombosis, hematological toxicity, hypertension, wound dehiscence, gastrointestinal disturbances, and proteinuria. The severity of most adverse events was defined as grade I and II, and only few patients suffered grade III-V adverse events. Although the overall incidence of adverse events was higher in the bevacizumab-containing regimen than in the chemoradiotherapy alone, it remains acceptable for patients with glioblastoma[16-22].

Although angiogenic inhibitors containing therapeutic regimens bring the promising for GBM treatment, there still remain many challenges: whether the combinated therapies are optimal for newly diagnosed and recurrent GBM, how to obtain the most survival benefit by individualizing treatment, and how to avoid chemoradiother-

Table II. Serious adverse events associated with bevacizumab in the included studies.

Study ID	Hematologic			Non-hematologic			
	Thrombosis	Hemorrhage	Hematologic toxicity	Hypertension	Wound dehiscence	Gastrointestinal events	Proteinuria
Newly diagnosed							
Balana et al[20] 2016	BEV+CRT: 2 (4.2%) CRT: 3 (6.6%)	BEV+CRT: 5 (10.5%) CRT: 0 (0%)	BEV+CRT: 7 (14.6%) CRT: 14 (31.1%)	BEV+CRT: 2 (4.2%) CRT: 0 (0%)	N/A	BEV+CRT: 3 (5.3%) CRT: 0 (0%)	N/A
Chinot et al[16] 2014	BEV+CRT: 58 (12.6%) CRT: 42 (9.3%)	BEV+CRT: 15 (3.3%) CRT: 9 (2%)	N/A	BEV+CRT: 52 (11.3%) CRT: 10 (2.2%)	BEV+CRT: 15 (3.3%) CRT: 7 (1.6%)	N/A	BEV+CRT: 25 (5.4%) CRT: 0 (0%)
Gilbert et al[18] 2014	BEV+CRT: 14 (4.6%) CRT: 12 (4%)	BEV+CRT: 0 (0%) CRT: 1 (0.3%)	BEV+CRT: 103(33.9%) CRT: 69(23%)	BEV+CRT: 4 (1.3%) CRT: 1 (0.3%)	BEV+CRT: 3 (1%) CRT: 1 (0.3%)	BEV+CRT: 2 (0.7%) CRT: 1 (0.3%)	N/A
Wirsching et al[21] 2018	BEV+CRT: 8 (16%) CRT: 2 (8%)	N/A	BEV+CRT: 2 (4%) CRT: 0 (0%)	BEV+CRT: 4 (8%) CRT: 2 (8%)	N/A	N/A	BEV+CRT: 3 (6%) CRT: 2 (8%)
Recurrent							
Brandes et al[22] 2019	BEV+CRT: 2 (3%) CRT: 1 (2%)	BEV+CRT: 4 (6%) CRT: 6 (10%)	BEV+CRT: 10 (16%) CRT: 10 (18%)	BEV+CRT: 9 (14%) CRT: 7 (12%)	BEV+CRT: 1 (2%) CRT: 1 (2%)	BEV+CRT: 0 (0%) CRT: 1 (2%)	BEV+CRT: 2 (3%) CRT: 0 (0%)
Taal et al[19] 2014	BEV+CRT: 3 (7%) CRT: 0 (0%)	N/A	BEV+CRT: 7 (14%) CRT: 17 (36%)	BEV+CRT: 11 (25%) CRT: 3 (7%)	N/A	BEV+CRT: 0 (0%) CRT: 2 (4%)	BEV+CRT: 1 (2%) CRT: 0 (0%)
Wick et al[17] 2017	BEV+CRT: 14 (4.9%) CRT: 0 (0%)	N/A	BEV+CRT: 152 (53.7%) CRT: 73 (49.7%)	BEV+CRT: 67 (23.7%) CRT: 1 (0.7%)	N/A	N/A	N/A

Abbreviations: BEV = bevacizumab; CRT: Chemoradiotherapy.

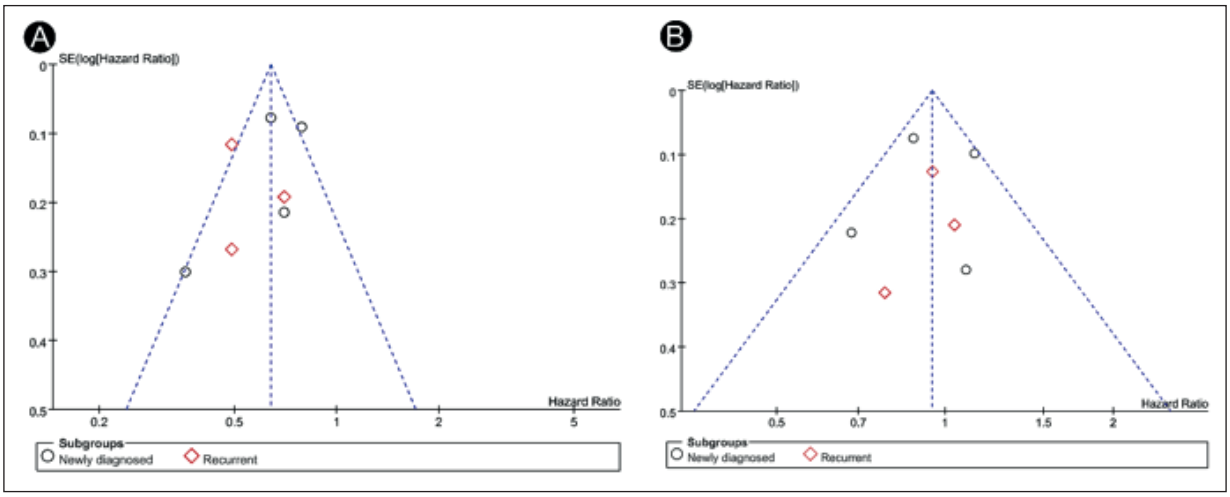

Figure 5. Funnel plots of the publication bias tests for direct comparisons. (**A**) Progression-free survival (PFS), (**B**) Overall survival (OS).

apy resistance[25,26]. Furthermore, the resistance to bevacizumab has somewhat constrained its more widespread clinical application, which is probably attributed to more severe hypoxia and the increase of hypoxia surrogates in tumor tissue, including carbonic anhydrase, hypoxia-inducible factor 1α (HIF-1α), hypoxia-inducible factor 2α (HIF-2α), or stromal-derived factor 1α (16-18). High doses of bevacizumab cause a rapid reduction in vascular permeability, which prevents the entry of bevacizumab into glioblastoma and promotes tumor hypoxia and resistance to chemotherapy[27,28]. By contrast, low-dose bevacizumab gradually decreases tumor vascular permeability, reducing tumor hypoxia and improving the drug delivery, ultimately resulting in a survival benefit for GBM patients[29]. Under hypoxic conditions, hypoxia-activated evofosfamide was reduced to brominated isophosphamide, which is expected to be beneficial in the treatment of bevacizumab-refractory glioblastoma[30].

The potential mechanism of treatment failure after antiangiogenic inhibitors in some glioblastoma patients is the upregulation of non-VEGF-mediated angiogenic pathways, vascular invasion, and increased pericyte coverage[31,32]. Resistance to angiogenesis inhibitors could be managed by combining them with multitarget inhibitors, such as receptor tyrosine kinase inhibitors (RTKIs) and epidermal growth factor receptor (EGFR) inhibitors[33,34]. Recent findings reveal that the EGFR gene amplification was associated with a significantly shortened duration of tumor progression in patients with recurrent GBM treated with bevacizumab[35]. The effects of the combination of EGFRvIII-targeting vaccine and bevacizumab were similar in progression-free survival to bevacizumab alone, but the presence of the combination significantly improved overall survival in patients with glioblastoma[36].

However, there are several limitations of the present meta-analysis. Firstly, some outcomes could not be combined due to a lack of data related to the molecular pathology of glioblastoma, such as objective response rate (ORR). Moreover, there are not sufficient clinical trials to compare the differences on efficacy and safety among multiple regimens of bevacizumab in combination with chemotherapy through a network meta-analysis. Except for vascular endothelial growth factor inhibitors (VEGF/VEGFR), clinical outcomes for other angiogenesis inhibitors, such as RTKIs (e.g., sorafenib and sunitinib) and integrin molecule inhibitors (e.g., cilengitide), were not included, due to insufficient clinical data[37,38]. In further studies, more randomized controlled trials should be included to investigate the significance of bevacizumab-related regimens in the treatment of newly diagnosed and recurrent glioblastoma.

Conclusions

We found that therapeutic regimens containing bevacizumab significantly prolonged progression-free survival in patients with glioblastoma compared to chemoradiotherapy alone, and the addition of bevacizumab improved progression-free survival more significantly in patients with recurrent glioblastoma than in patients with

newly diagnosed glioblastoma, which suggested that bevacizumab is preferentially recommended for the treatment of recurrent glioblastoma. In addition, it was further confirmed that bevacizumab did not significantly improve overall survival in patients with glioblastoma, which is consistent with previous studies. The combination of bevacizumab with conventional chemoradiotherapy regimens was also associated to an increased but acceptable incidence of adverse events, and therefore the safety remains something to consider before the addition of bevacizumab in chemoradiotherapy regimens.

Availability of Data and Materials

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

Conflict of Interests

The authors declare that they have no conflicts of interest.

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Authors' Contributions

Study Design: Z.S. and X.L., Data Analysis: S.L., H.Z. and Y.X., Main Manuscript Text: Z.S., X.L, D.L. and L.Z. All authors reviewed the manuscript.

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