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Bevacizumab for recurrent glioblastoma: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The phenomenon is that few randomized control trials (RCTs) directly compared the effects of bevacizumab with other types of standard treatments for recurrent glioblastoma (GBM). We conducted a systematic review and meta-analysis to assess the efficacy of bevacizumab in recurrent GBM patients.

MATERIALS AND METHODS: We searched electronic databases (Medline, Embase, and Web of Science) contrasting the bevacizumab with standard treatments up to May 2021. For the continuous outcomes of median progression-free survival (PFS) and median overall survival (OS), we summarized the mean difference (MD) as the effective index. We used relative risk (RR) to estimate the data with a random-effects model to get the outcomes of objective response rate (ORR), 12-month OS, 6-month PFS, and any mentioned adverse events.

RESULTS: A total of 807 patients in 5 RCTs included into our systematic review and meta-analysis. The results showed bevacizumab could provide benefits of the ORR (RR, 2.67; 95% CI: 1.14-6.26, p = 0.02), median PFS (MD, 1.12 months; 95% CI: 0.35-1.90 months, p = 0.005), but not the median OS (MD, -0.19 months; 95% CI: -1.37-0.99 months, p = 0.75). Whereas the rates of the secondary outcomes of interest were similar between the bevacizumab group and control group, including 6 month-PFS (RR, 1.23; 95% CI, 0.82-1.84, p = 0.32) and 12 month-OS (RR, 0.93; 95% CI, 0.79-1.09, p = 0.36). As for adverse events, patients with bevacizumab showed higher rates of grade 3/4 and any grade hypertension compared with those with standard treatments (RR, 3.71; 95% CI: 1.17-11.76, p = 0.03; RR, 2.68; 95% CI: 1.26-5.76, p = 0.01, respectively).

CONCLUSIONS: This study provides clear proof of the beneficial effects of bevacizumab treatment in recurrent GBM patients. The only observed adverse event was grade 3/4 or any grade hypertension.

Key Words:
Bevacizumab, Recurrent glioblastoma, Systematic review, Meta-analysis.

Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor with a poor overall prognosis[1,2]. The recurrent standard approach in multimodality therapy for GBM involves maximal safe surgical resection and radiotherapy followed by chemotherapy, which usually refers to 6 cycles of maintenance temozolomide[3]. For the patients with recurrent GBM, survival rates for 2-years range from 26%-33%, and for 5-years survival rates are less than 10% under current treatment[4-6]. Therefore, it is necessary to explore novel approaches to improve the outcomes of GBM patients.

Angiogenesis is one of the important mechanisms in the pathogenesis of GBM, accompanied by high expression of vascular endothelial growth factor (VEGF). Some novel approaches targeting anti-angiogenesis can be a promising aspect of treatment in recurrent GBM patients[7,8]. Bevacizumab, a VEGF antibody, has been included for analysis in multiple trials and is commonly used in patients with kidney, breast, ovarian, and colorectal cancers[9-11]. Bevacizumab was approved for patients with recurrent GBM by the Food and Drug Administration (FDA) due to encouraging radiological response rates and obvious augment in progression-free survival (PFS) in 2009[12,13]. Although the observed beneficial survival result in PFS, bevacizumab has no beneficial effect on overall survival (OS) outcome in some phase III randomized controlled trials (RCTs)[14,15]. Some previous trials[16-18] that compared bevacizumab with bevacizumab plus irinotecan or bevacizumab plus lomustine showed that bevacizumab might be the prime source of anti-glioblastoma effect on recurrent GBM. By contrast with many other anti-VEGF drugs that have been put into large RCTs, such as nivolumab (anti-VEGF

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neutralizing antibody), cediranib (VEGF inhibitor), aflibercept (soluble VEGFR), regorafenib (VEGF-TKI), bevacizumab showed controversial results regarding the aspects of PFS and OS.

Hence, there is an emergent need to conduct a systematic review and meta-analysis to explore the outcomes with bevacizumab *vs.* some specific cytotoxic treatment for patients with recurrent GBM, including lomustine, fotemustine, nivolumab or temozolomide, etc.

Materials and Methods

Search Strategy

We conducted the systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements[19]. PubMed, Embase, and Web of Science databases were broadly searched for available literature up to May 2021 with English languages. We used the following search terms: "high-grade glioma," "glioblastoma," "GBM," "standard cytotoxic treatment", "recurrent," and "bevacizumab." Two investigators independently completed the search and identification for relevant data.

Study Selection

In our meta-analysis, clinical trials should meet the mentioned eligibility criteria: (1) Adult patients with recurrent glioblastoma (≥18 years old) based on proved histology; (2) Comparison between intervention (bevacizumab) group and control group were two forms: bevacizumab versus some specific cytotoxic treatments, including lomustine, fotemustine, nivolumab, or temozolomide, and the other form is bevacizumab plus some specific cytotoxic treatments versus a certain cytotoxic treatment; (3) The trials could provide the outcomes of interest, including objective response rate (ORR), OS, PFS, and/or some certain adverse events; (4) RCTs were included. Trials targeting patients who are GBM patients with newly diagnosed or trials that were unable to provide relevant essential information, involving some outcomes of interest and patient baseline demographics were excluded. Non-RCTs including case reports, cohort studies, case-control studies and meta-analysis were also not included in our analysis.

Data Extraction and Quality Assessment

The titles and abstracts of associated studies were scanned briefly, and the full text of relevant studies was retrieved by two investigators. Any discrepancies between the two investigators were resolved by a third senior reviewer. The extracted information was as follows: patient baseline demographics and some final indexes of interest, such as isocitrate dehydrogenase (IDH) status; 06-methylguanine-DNA- methyltransferase (MGMT) status. Cochrane Collaboration's tool was used to assess the risk of bias of the included trials. In addition, representative study patients and adequate assessment of the outcomes were conducted in our systematic review and meta-analysis. We defined the primary outcomes as ORR, median PFS, and median OS, while the corresponding secondary outcomes were classified and designated as 12-month OS and 6-month PFS. Adverse events list involved grade 3/4 and any grade treatment-related adverse events (TRAE), any grade serious TRAE, grade 3/4 and any grade of hypertension, grade 3/4 and any grade of leukopenia, any grade of proteinuria, grade 3/4, and any grade of thrombocytopenia, grade 3/4 and any grade of fatigue, grade 3/4 and any grade of thromboembolic (pulmonary embolism), and grade 3/4 and any grade of nausea and vomiting.

Data Synthesis and Statistical Analyses

The Review Manager Version 5.3 software was used to analyze the statistical data with a random-effects model. For the continuous outcomes of median PFS and median OS, we summarize mean difference (MD) as the effective index. For the results of ORR, 12-month OS, 6-month PFS, and any mentioned adverse events, we use relative risk (RR) to estimate the data. I^2 statistic was calculated to measure the heterogeneity of the relevant studies, and with the value of 0%, less than 50%, 50%-75%, and more than 75% indicating no, low, moderate, and high heterogeneity, respectively. The significance level was defined at $p \leq 0.05$.

Results

From eligibility screening on the title and abstract of the electronic databases, we identified 1397 articles in total and 29 articles went through the full-text review stage. Finally, five eligible articles were included in our systematic review and meta-analysis (Figure 1). Among four phase II and one phase III RCTs of the final five trials, we analyzed the involved patients

with a total of 834 patients[20-24]. The baseline characteristic of the available trials was shown in Table I.

Risk of Bias Assessment

The risk of bias was moderate to high but was acceptable mainly due to the existing form of selection bias and limited included trials, which was depicted in Figure 2A and Figure 2B.

Outcomes

Analysis of Primary Outcomes

The ORR outcomes showed that there were strong positive effects for the recurrent patients treated with bevacizumab (361 participants) compared with control (329 participants) (RR, 2.67; 95% CI: 1.14-6.26, $p = 0.02$) (Figure 3A). Considering the high heterogeneity of the ORR outcomes ($I^2 = 82\%$), we conducted the sensitivity analysis to search for the source of high heterogeneity. The results showed that the trial of van den 2018 had a significant influence on heterogeneity[22]. After the trial was removed, the heterogeneity analysis showed that there was no heterogeneity in the remaining trials ($I^2 = 0$) and the odd remained statistically significant in Figure 3B ($p < 0.001$).

The results of median PFS suggested that the treatment with bevacizumab could prolong median PFS, with the number of treatments and control reached 433 and 401, respectively (MD, 1.12 months; 95% CI: 0.35-1.90 months, $p = 0.005$) (Figure 4A). Due to the moderate heterogeneity ($I^2 = 67\%$), a sensitivity analysis was performed and the result revealed that a remarkable cut down on heterogeneity when the trial of Reardon et al[24] was deleted (Figure 4B).

When we mentioned the outcome of the median OS with patients treated with bevacizumab (n = 433) compared with control (n = 401), the results showed that the bevacizumab group did not prolong median OS from the data of five trials (MD, -0.19 months; 95% CI: -1.37-0.99 months, $p = 0.75$) (Figure 5).

Analysis of Secondary Outcomes

For the outcomes of 6 month-PFS and 12 month-OS, the results indicated that there were no positive effects for 6 month-PFS (RR, 1.23; 95% CI, 0.82-1.84, $p = 0.32$) and 12 month-OS (RR, 0.93; 95% CI, 0.79-1.09, $p = 0.36$) in recurrent GBM patients treated with bevacizumab and control (Figures 6 and 7).

Adverse Events

Table II listed adverse events in our meta-analysis. The only observed significant results of adverse events of the mentioned adverse events were grade 3/4 and any grade hypertension between the bevacizumab group (n = 413) and the control group (n = 394) (RR, 3.71; 95% CI: 1.17-11.76, $p = 0.03$; RR, 2.68; 95% CI: 1.26-5.76, $p = 0.01$, respectively) (Figure 8A and 8B). There was no difference in the risks of remained adverse events, including grade 3/4 and any grade treatment-related adverse events (TRAE), any grade serious TRAE, grade 3/4 and any grade of leukopenia, any grade of proteinuria, grade 3/4 and any grade of thrombocytopenia, grade 3/4 and any grade of fatigue, grade 3/4, and any grade of thromboembolic (pulmonary embolism), and grade 3/4 and any grade of nausea and vomiting, between two groups (Table II).

Discussion

GBM is the most common primary malignant brain tumor with poor prognosis in adults despite the secure treatment of surgical options and chemoradiotherapy. In this study, we directly evaluate the effects of bevacizumab in recurrent GBM patients with the high quality of RCTs for the first time. Our meta-analysis indicated that the bevacizumab group improved the results of ORR and median PFS, but had no beneficial effect on the result of median OS in the recurrent GBM patients. The sensitivity analyses were done due to the moderate to high heterogeneities of ORR and PFS, and the odds still reached statistical significance. As for adverse events, we found the most commonly observed adverse event was hypertension. The results of this study suggested that bevacizumab is effective in patients with recurrent GBM but they need to be cautious with the occurrence of hypertension.

VEGF is highly expressed in GBM, and hence novel drugs of the anti-VEGF pathway have turned into a new therapeutic target[8]. Bevacizumab, a humanized monoclonal antibody against the VEGF-A ligand, can bind to its circulating target and then alter the kinetics of ligand binding to endothelial cells and down-regulate angiogenesis of cancer[25]. In the current study, compared with control, rate of increase in the objective response was 2.67-folds in bevacizumab group. Patients with bevacizumab treatment had a longer PFS with a MD of 1.12 months than

Table I. Characteristics of studies in meta-analysis.

Studies	Intervention	Patients, n	Age (years)	Female	WHO performance status	ECOG PS, n (%)	Surgery at the time of recurrence	Corticosteroid use	Days since last radiotheraphy/ MRI	IDH status, n (% of tested)	MGMT status, n (% of tested)
Taal et al[20] 2014	Bevacizumab 10 mg/kg	50	58 (37-77)	18 (64%)	0: 13 (26%) 1: 32 (64%) 2: 5 (10%)	/	5 (10%)	27 (54%)	254+ (101-2087)	Unmutated 38/39 (97%), Mutated 1/39 (3%), not done/ unknown 11	Unmethylated 24/42 (57%), methylated 8/42 (43%), not done/ unknown 8
	Lomustine 110 mg/m²	46	56 (28-73)	20 (43%)	0: 15 (33%) 1: 25 (54%) 2: 6 (13%)	/	6 (13%)	22 (48%)	298 (106-1092)	Unmutated 39/42 (93%), Mutated 3/42 (7%), not done/ unknown 4	Unmethylated 20/43 (47%), methylated 23/43 (53%), not done/ unknown 3
Brandes et al[23] 2019	Bevacizumab 10 mg/kg	59	59 (37-74)	20 (34%)	/	0: 29 (49%) 1: 19 (32%) 2: 11 (19%)	13 (22%)	42 (71%)	331 (163-2271)	/	/
	Fotemustine 75 mg/m²	32	56 (28-78)	9 (28%)	/	0: 13 (41%) 1: 16 (50%) 2: 3 (9%)	8 (25%)	20 (62%)	462 (162-1383)	/	/
Reardon et al[24] 2020	Bevacizumab 10 mg/kg	185	55 (22-76)	66 (36%)	/	/	/	79 (42.7%)		/	Unmethylated 67/185 (36.2%), methylated 42/185 (22.7%), not done unknown 76
	Nivolumab 3 mg/kg	184	55.5 (22-77)	68 (37%)	/	/	/	73 (39.7%)	/	/	Unmethylated 59/184 (32.1%), methylated 43/184 (23.4%), not done/unknown 82

Continued

Table I *(Continued)*. Characteristics of studies in meta-analysis.

Studies	Intervention	Patients, n	Age (years)	Female	WHO performance status	ECOG PS, n (%)	Surgery at the time of recurrence	Corticosteroid use	Days since last radiotheraphy/ MRI	IDH status, n (% of tested)	MGMT status, n (% of tested)
Brandes et al[23] 2019	Lomustine 90 mg/m² (CCNU) + Bevacizumab 10 mg/kg	61	56 (30-74)	17 (28%)	/	0: 26 (43%) 1: 23 (38%) 2: 12 (20%)	5 (8%)	20 (33%)	/	/	Unmethylated 26/61 (43%), methylated 11/61 (18%)
	Lomustine 90 mg/m² (CCNU) + placebo	62	58.5 (36-74)	17 (27%)	/	0: 24 (39%) 1: 27 (44%) 2: 11 (18%)	3 (5%)	19 (31%)	/	/	Unmethylated 25/62 (40%), methylated 12/62 (19%)
van den Bent et al[22] 2018	Bevacizumab 10 mg/kg + Temozolomide 200 mg/m²	78	44.6 (33.9-53.8)	21 (27%)	0: 31 (40%) 1: 38 (49%) 2: 9 (12%)	/	24 (31%)	22 (28%)	/	Unmutated 16/78 (21%), Mutated 48/78 (62%), not done/ unknown 14	Unmethylated 22/78 (28%), methylated 40/78 (51%), not done /unknown 16
	Temozolomide 200 mg/m²	77	43.1 (34.5-49.0)	32 (42%)	0: 34 (44%) 1: 35 (45%) 2: 8 (10%)	/	22 (29%)	27 (35%)	/	Unmutated 14/77 (18%), Mutated 53/77 (69%), not done/ unknown 10	Unmethylated 12/77 16%), methylated (51/77 (66%), not done/ unknown 14

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IDH, isocitrate dehydrogenase; MGMT, 06-methylguanine-DNA-methyltransferase.

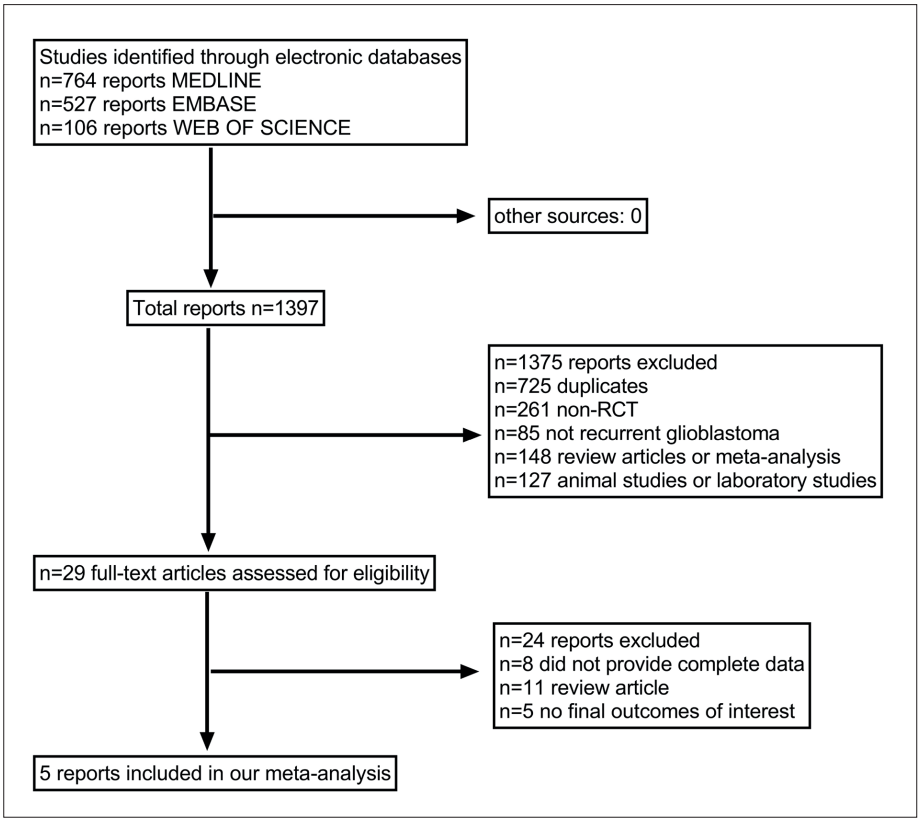

Figure 1. Flowchart of the study selection.

did those treated with control. When mentioned the positive results of ORR and median PFS, an underlying mechanism may be due to the potential impact of single nucleotide polymorphisms (SNPs). The previous results showed that the level of SNPs in the VEGF and VEGFR2 promoter regions were closely related to an up-regulated SPF[26,27]. Another possible enhancement

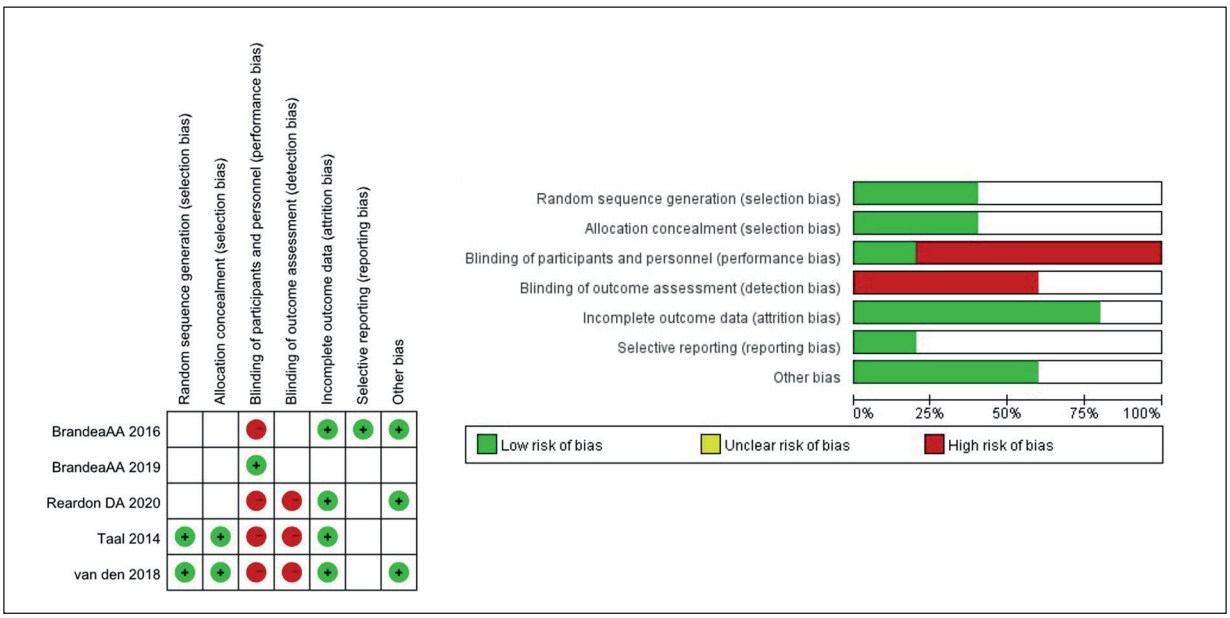

Figure 2. Risk of bias graph **(A)** and summary **(B)**.

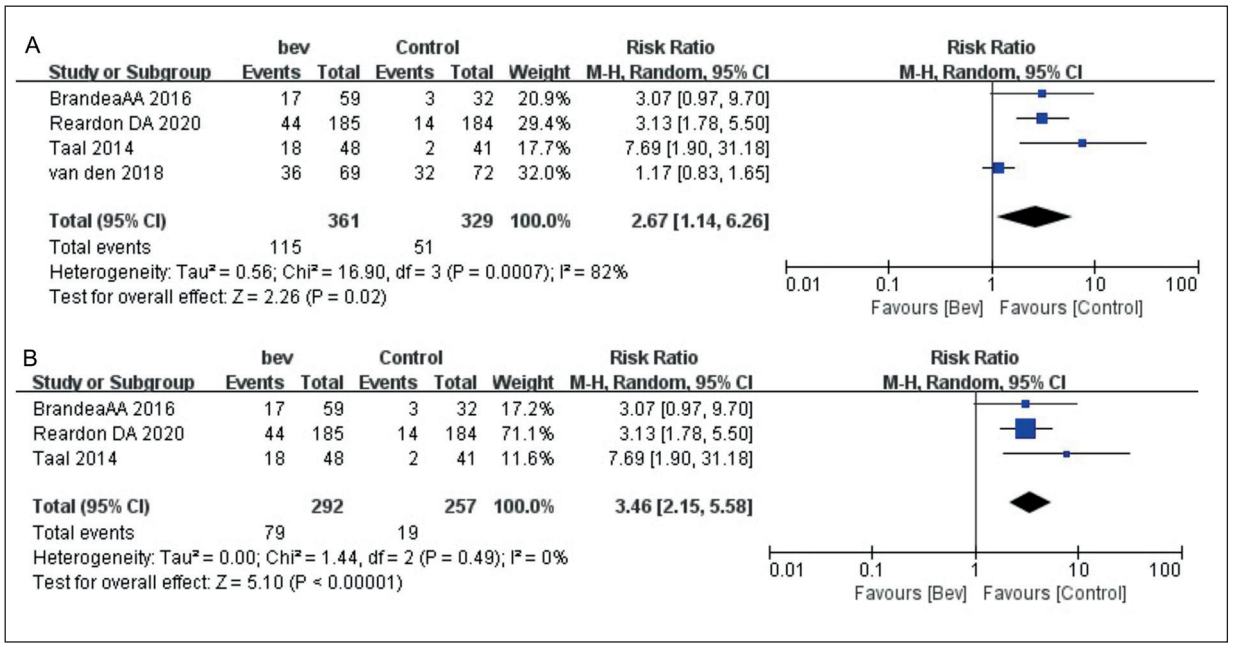

Figure 3. Forest plot of ORR in glioblastoma between bevacizumab and control groups. **A,** All of the studies were included. **B,** The study of van den 2018 was removed. ORR, objective response rate; Bev, bevacizumab.

effect in PFS may be due to the normalization of abnormal tumor vessels and thus increase tumor blood perfusion and improve outcomes by controlling vasogenic brain edema[28]. Of note, a previous study[29] showed that the early change of collagen II was inversely related to the outcome of PFS in newly diagnosed GBM patients. Altogether, the ameliorative cerebral blood flow, improved tumor control, and relieving of vasogenic brain edema are vital factors to influence the activity of anti-VEGF drugs and further affect the survival outcomes.

Furthermore, the OS outcome applied to first or second-line therapy in our systematic review

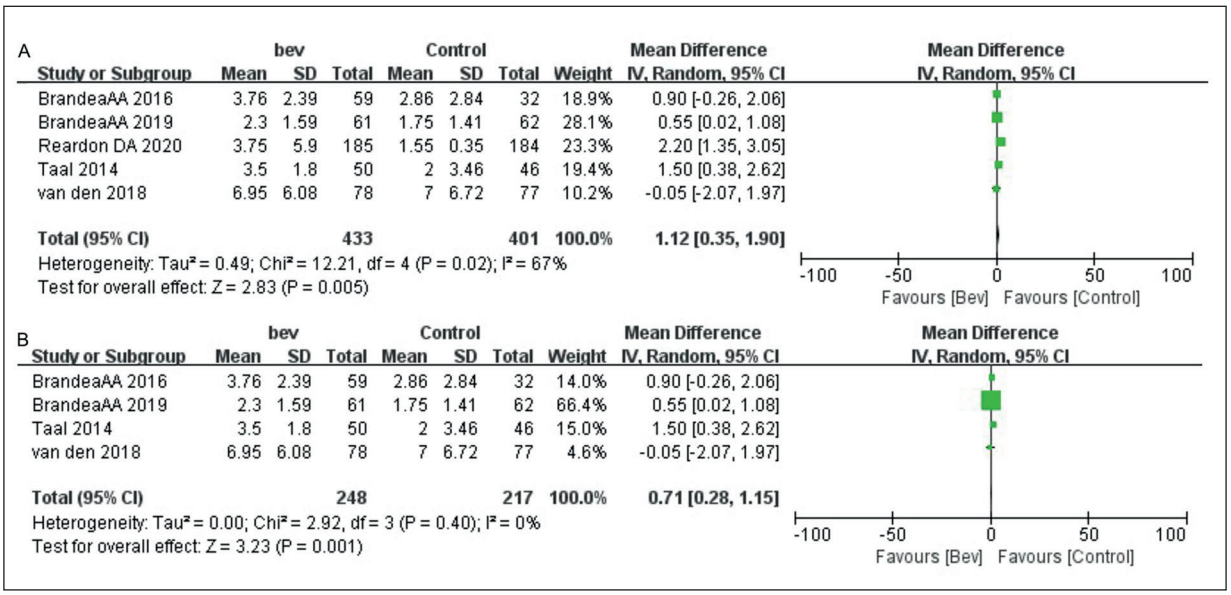

Figure 4. Forest plot of median PFS in glioblastoma between bevacizumab and control groups. **A,** All of the studies were included. **B,** The study of Reardon DA 2020 was removed. PFS, progression-free survival; Bev, bevacizumab

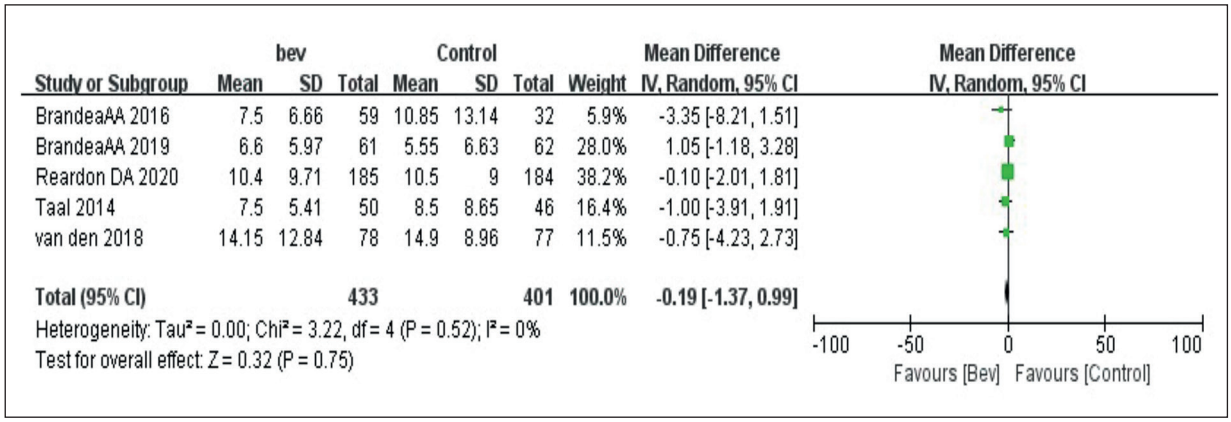

Figure 5. .Forest plot of median OS in glioblastoma between bevacizumab and control groups. OS, overall survival; Bev, bevacizumab.

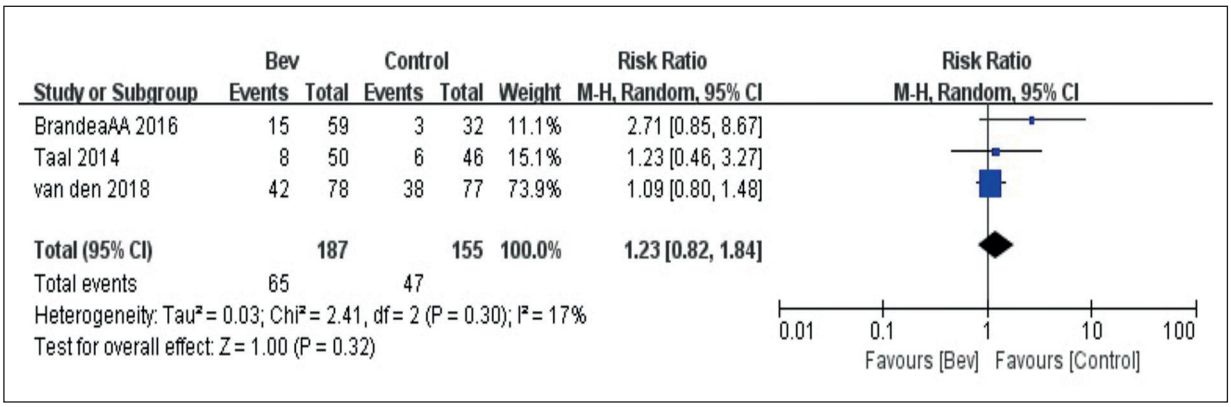

Figure 6. Forest plot of 6-month PFS in glioblastoma between bevacizumab and control groups. PFS, progression-free survival; Bev, bevacizumab.

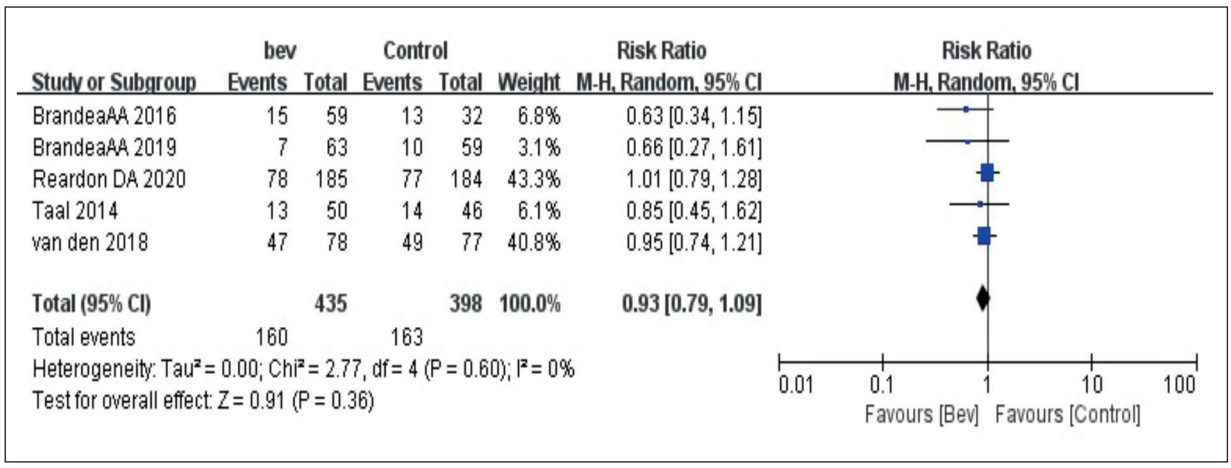

Figure 7. Forest plot of 12-month OS in glioblastoma between bevacizumab and control groups. OS, overall survival; Bev, bevacizumab.

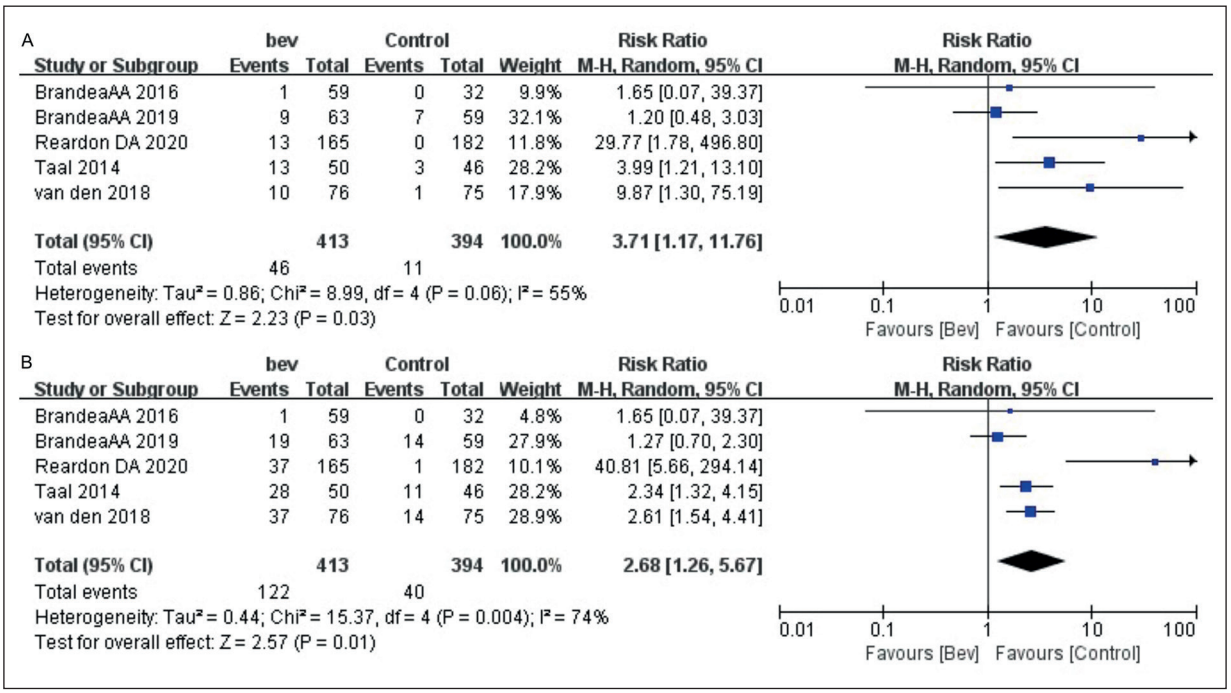

Figure 8. Forest plot of hypertension in glioblastoma between bevacizumab and control groups. **A,** Grade 3/4. **B,** Any grade. Bev, bevacizumab.

and meta-analysis consisted of the BELOB trial and the CheckMate 134 trial[20,24]. In the BELOB phase 2 trial, the bevacizumab arm presented a similar median OS value (median OS: 8 VS 8 months, respectively) compared with the lomustine arm[20]. Moreover, another published clinical trial of the CheckMate 143, an RCT describing the effect of nivolumab versus bevacizumab in patients with recurrent glioblastoma, indicated that median OS was comparable between two groups: nivolumab, 9.8 months; bevacizumab, 10.0 months[24]. A retrospective study by Sathornsumetee et al[30] demonstrated that increased expression with VEGF was not associated with overall survival benefits. The phenomenon of lacking a satisfying effect on the median OS may be attributed to few biomarkers for the occurrence of OS. Subsequently published analysis

Table II. Adverse events in the included RCTs.

Adverse events	Studies reporting	Bevacizumab group, n/n	Control group, n/n	RR (95% CI)*	*p*-value
Any grade TRAE#	3	178/287	160/273	1.01 (0.89, 1.14)	0.89
Grade 3/4 TRAE	4	103/354	83/362	1.30 (0.66, 2.59)	0.45
Any grade serious TRAE	3	42/287	28/273	1.68 (0.61, 4.63)	0.32
Any grade leukopenia	3	72/185	59/155	1.13 (0.12, 10.78)	0.92
Grade 3/4 leukopenia	3	6/185	12/153	0.46 (0.05, 3.99)	0.48
Any grade proteinuria	3	33/189	20/180	1.42 (0.62, 3.24)	0.41
Any grade thrombocytopenia	4	106/248	86/212	1.02 (0.41, 2.58)	0.96
Grade 3/4 thrombocytopenia	4	17/248	29/212	0.33 (0.07, 1.72)	0.19
Any grade fatigue	3	116/291	122/303	0.95 (0.64, 1.42)	0.82
Grade 3/4 fatigue	3	9/291	11/303	0.73 (0.07, 7.40)	0.79
Any grade thromboembolic	3	7/198	3/166	1.72 (0.53, 5.59)	0.37
Grade 3/4 thromboembolic	3	4/198	1/166	2.04 (0.40, 10.45)	0.39
Any grade nausea and vomiting	3	36/291	36/303	0.99 (0.66, 1.50)	0.98

Abbreviations: TRAE, treatment-related adverse events; RR, relative risk; CI, confidence interval.

indicated that potential tissue biomarkers, such as down-regulated carbonic anhydrase 9 (CA-9)[30], or down-regulated MMP-2[31], may be associated with a longer OS outcome in the patients with recurrent GBM. Lots of work needs to be proceeded to investigate the impact of specific predictive biomarkers of interest, especially applied to large RCTs.

Considering the safety of the bevacizumab treatment can directly influence the quality of life, we assessed the outcomes of TRAE of grade3/4 and any grade in the recurrent GBM patients treated with bevacizumab compared with some specific cytotoxic treatments, including lomustine, fotemustine, nivolumab, or temozolomide. The result in our systematic review and meta-analysis showed that the most common adverse event associated TRAE is increased risk of hypertension. The risks of remained mentioned adverse events, such as leukopenia, proteinuria and thrombocytopenia were similar between two groups. It has been demonstrated the SNPs on VEGF promoters may relate to safety indicators[26]. Therefore, clinical and laboratory monitoring is essential to avoid adverse events of bevacizumab.

There are some limitations shown in our meta-analysis. With included 5 RCTs, we drew the result that seems to lack efficient evidence owing to excluded single-arm trials, non-RCTs that may provide meaningful survival outcomes. So, the selection bias may lead to underestimated or overstated outcomes of our interest. In addition, some trials of IDH classification were not provided, which may restrict our accurate interpretation of the outcomes. Therefore, we expect more and larger RCTs to confirm the effects of bevacizumab in recurrent GBM patients.

Conclusions

The most valuable matter that we can acknowledge is that bevacizumab can effectively increase the rate of objective response and longer median progression-free survival in patients with recurrent GBM, but it didn't provide a beneficial effect on overall survival. Furthermore, hypertension is the most common adverse event after bevacizumab treatment. Altogether, many explorations needed to be conducted to verify the effects of bevacizumab of interest in recurrent GBM patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethical Statement

Ethics statement was not required since the research is a systemic review and meta-analysis of previously published studies.

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Data Availability Statement

All data generated or analyzed during this study are included in this article..

Authors' Contribution

Jianmin Kang designed the study. Tai Zhang and Qing Xin searched and collected the data. Tai Zhang and Qing Xin analyzed the results. Tai Zhang drafted the manuscript..

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