PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of bevacizumab in the treatment of adult gliomas:a systematic review and meta-analysis
AUTHORS	Wang, huan; Guo, Jianxin; Wang, Tianze; wang, kai; Wu, Zhuojun; Sun, Tianze

VERSION 1 – REVIEW

REVIEWER	Grill, Jacques Institut Gustave-Roussy
REVIEW RETURNED	08-Mar-2021

GENERAL COMMENTS	The authors have made a literature review of existing data on bevacizumab use in glioblastoma in adults only. They did not consider the only randomized trial performed in children (HERBY) which indeed did not show any benefit of the use of bevacizumab on top of standard of care in newly diagnosed high-grade gliomas before the age of eighteen. This may justify a comment. The abstract is confusing and some parts such as "At 30 months (0.62...Non-Bev group" is incorrect and the following sentence non-informative. It should be rewritten as well as the rest of the paper where some sentence can not be understood due to grammatical errors. Other publications have been published on the same topic, not always with the same conclusions. They have to be confronted to understand why they achieve different conclusions. The fact that the survival benefit is not sustained after 18 months can not be attributed to side effects (that would occur while on treatment). Other explanation may be discussed such as changes in the pattern of relapse (more invasive e.g.). Legend of figure 5 is incorrect. As such the manuscript needs rewriting by a native English speaking person.

REVIEWER	Simpkin, Andrew National University of Ireland Galway, School of Medicine
REVIEW RETURNED	09-Apr-2021

GENERAL COMMENTS	This study uses random effect meta-analysis to combine odds ratios and hazard ratios for the association between Bevacizumab. The authors use separate meta-analysis for overall and progression free survival outcomes, and separate again where hazard ratios and odds ratios are combined, giving four sets of results. They provide a sensitivity analysis to check for undue influence of single studies, each study is removed one at a time to check how this affects their conclusion. Overll they

	correctly apply the methods, and there are just a number of minor corrections on my behalf: 1. Abstract Results, L9: standalone p-values should be avoided, please give estimates and 95%CI instead or along with p-values 2. Abstract Results, L10: this sentence needs a rewrite, e.g. The PFS odds ratios of the BEV group compared to the non-BEV group were 3.31 (95% CI 2.74 to 4.00, p<0.001) at 6 months,... 3. Abstract Results L14: Again needs to be rewritten: There was no significant difference in PFS rate at 24 months 4. Abstract Results L16: Typo, should say BEV group lower than non-BEV 5. Abstract Results L18: The last sentence is not a result? Is there something to say about adverse events? 6. Page 6 L11: Was fixed or radnom effect meta-analysis used? 7. Page 6 L 13: Were HR and OR combined, treated separately? 8. Page 6 L22: What does "the level is alpha=0.1a" mean? 9. Page 6 L27: Consider rewriting this sentence: "results were stable otherwise they were unstable" is not useful - what is done in either case? 10. No I-squared is reported for your first result? 11. Page 10 L14, L25, L34. You find the I squared p-value to be small and large, yet make the same decision, i.e. to use a random effect model? This seems odd. I would recommend using the RE model anyway, but commenting on heterogeneity as it might affect your conclusions. Can you address this inconsistency? 12. Page 10 L17: Consider rearranging these results as it is hard to read, e.g. put the OR values at 6 month (3.31, 95% CI), 12 months (2.05, 95% CI) ... as shown in panel C of Figure 3 13. Figures 3 to 6 are unreadable. Please fix all Figures, splitting where required and improve image quality 14. The authors have left out a very similar systematic review and meta-analysis of BEV from Cancers 2019 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6895972/ which should be discussed and may even highlight others studies to be included.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Jacques Grill, Institut Gustave-Roussy

Thank you for asking your question and carefully reading the article "Phase II, Open-Label, Randomized, Multicenter Trial (HERBY) of Bevacizumab in Pediatric Patients With Newly Diagnosed High-Grade Glioma". The article is at the forefront of the research direction, highlighting the biological differences between children and adults, and the importance of pediatric specific research in the future. considering that there are some differences between children and adults, stratification is needed if meta analysis is needed. However, at present, there is only one randomized controlled trial for children, which can not be stratified. In the future, our group will continue to pay attention to the randomized controlled trial of children, and then include it in the meta analysis of children. For your question, we think it is very meaningful, we consult and refer to the relevant literature Reference 1:Wireless Phone Use and Risk of Adult Glioma: Evidence from a Meta-Analysis,Reference 2:Seizures at presentation are correlated with better survival outcomes in adult diffuse glioma: A systematic review and meta-analysis found that the age can be limited, so we decided to limit the inclusion criteria, abstract and topics to adult gliomas, thank you for your comments, so as to make the article more complete and rigorous. The corrections are as follows:topics:Efficacy and safety of bevacizumab in the treatment of adult gliomas:a systematic review and meta-analysis. abstract:Participants Adults aged 18 years and above, whose histology was confirmed to be HGG.

With regard to the second question, it is indeed our error. Thank you sincerely for your question, We modify it and provide additional information in this paper.The modifications are as follows:abstract: When compared with the PFS rate of each stage,it was found that the PFS in the BEV group was higher than that in the Non-BEV group at 6 months (3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (1.31,95%CI 1.02 to 1.69, p=0.03).But at 24 months (0.83, 95%CI 0.50 to 1.37, p=0.47), there was no significant difference between the two groups.At 30 months (0.62, 95%CI 0.39 to 0.97, p=0.04), the PFS of the BEV group was lower than that of the Non-BEV group.Text:Through the results found it was found that the PFS in the BEV group was higher than that in the Non-BEV group at 6 months (3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (1.31,95%CI 1.02 to 1.69, p=0.03).But at 24 months (0.83, 95%CI 0.50 to 1.37, p=0.47), P > 0.05, so there was no significant statistical difference between the two groups.At 30 months (0.62, 95%CI 0.39 to 0.97, p=0.04), 0.61 < 1, the diamond falls on the group that supports Non-BEV group,so the PFS of the BEV group was lower than that of the Non-BEV group.At the same time, the results of OS and Adverse reaction are also explained and supplemented, mark it in red in the article.

The sentence may be difficult to understand due to grammatical problems. For this reason, we made all corrections and searched for professional polishing agencies to make further revisions. The second paragraph of the discussion proposed that other publications also published the same topic, but all conclusions were consistent. It shows that BEV can improve the PFS of glioma patients to a certain extent, but it has no obvious significance in improving OS. However, the above article does not propose that PFS is limited for improvement. Our group has concluded through this research that this limited time may be 30 months. This is the innovation of our paper.In response to your suggestion,We decided to add at the end of the second paragraph, "Through the above studies, it can be seen that BEV can improve the PFS of patients with glioma to a limited extent, but it has no obvious significance in improving OS." This may make the article more clear.

We have made other explanations for the fact that the survival period did not last after 18 months, referring to the following articles to classify it as a change in the pattern of recurrence, more aggressive, drug resistance, increased hypoxia, dose, etc., modified as follows.

From the above research results, it can be concluded that long-term use of BEV does not increase the patient’s PFS, BEV can improve the PFS of glioma patients within 18 months,but the PFS of patients may be reduced after 30 months. Nagham Kaka found that BEV could have a role in the treatment of particular subgroups of patients with newly diagnosed GBM.Several studies have found that the median PFS of

patients with methylation is longer than that of MGMT unmethylated tumors treated with RT and TMZ combined with BEV.Sandmann and colleagues found that BEV combined with standard TMZ and RT can improve the survival rate of neurotumors, while poorly differentiated mesenchymal tumors may make tumors resistant to BEV over time. Adilijiang andColleagues found that treatment with BEV and TMZ results in the upregulation of certain microenvironment related genes in IDH1 mutant tumors in vitro, specifically those involving immune response and extracellular matrix organization.Therefore, The question of whether the limitation of BEV in the treatment of gliomas is due to fixed subsets deserves constant attention.

Studies have shown that antiangiogenic therapy can lead to a transition of glioma to a more aggressive phenotype.In retrospective analysis a trend toward enhanced infiltra-tive disease was seen in bevacizumab-treated glioma patients suggesting that enhanced tumor inhibition may be a conse-quence of VEGF signaling blockade.Shiao-Pei Weathers shows that determining the best biological dose and the subgroup of patients most likely to obtain long-lasting benefits can improve the durability of bevacizumab.Victor A Levin found treatment for recurrent GBM with BEV appears to improve survival at a dose lower than that in the FDA drug insert. Study suggest that the higher dosage of BEV utilized may have impacted survival benefits.Animal models also suggest that higher dose of anti-VEGF treatment, resulting in more hypoxia, may increase tumor aggressiveness.Ryota Tamura found that high doses and long-term use of anti-VEGF/VEGFR may lead to hypoxia.Shiao-Pei Weathers proposed in tumors where excessive vascular pruning takes place, hypoxia exacerbated by antiangiogenic therapy is likely responsible for initiating a cascade of events. As mentioned above, there are many possible reasons for the limited efficacy of antiangiogenic therapy.But The lack of a long-lasting response to current antiangiogenic treatment underscores the need for a better understanding of how to use antiangiogenic therapy to optimize radiation and chemotherapy treatments.

CONCLUSIONS

The evidence suggests that BEV can significantly prolong the PFS of patients with glioma within 18 months and shorten the PFS of patients after 30 months. This limitation may be related to the subgroup of patients, the change of recurrence mode, the optimal dose of drug, the increase of hypoxia, the enhancement of invasiveness and so on.BEV treatment has no obvious meaning in improving OS, and it has some side effects, which are acceptable, but we still need to pay close attention to it and take active measures to reduce the side effects.Therefore, it is necessary to carry out more samples and higher quality large-scale research in the future.

The references are as follows：

1.Progression-Free but No Overall Survival Benefit for Adult Patients with Bevacizumab Therapy for the Treatment of Newly Diagnosed Glioblastoma:A Systematic Review and Meta-Analysis.
2.Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma.
3.A randomized trial of bevacizumab for newly diagnosed glioblastoma.
4.Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis.
5. Next generation sequencing-based transcriptome predicts bevacizumab efficacy in combination with temozolomide in glioblastoma.
6.Acquired resistance to anti-VEGF therapy in glioblastoma is associated with a mesenchymal transi-tion.
7.VEGF inhibits tumor cell invasion and mesenchymal transition through a MET/VEGFR2 complex.
8.Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence.
9.Mechanisms of neovas- cularization and resistance to anti-angiogenic therapies in glioblas-toma multiforme.
10.Resistance to Antiangiogenic Therapy.
11.Impact of bevacizumab administered dose on overall survival of patients with progressive glioblastoma.

12.Rela-tion between bevacizumab dose intensity and high-grade glioma survival: a retrospective study in two large cohorts.
13.Anti-VEGF treatment reduces blood supply and increases tumor cell invasion in glioblastoma.
14.The role of vascular endothelial growth factor in the hypoxic and immunosuppressive tumor microenvironment: perspectives for therapeutic implications.
Figure 5 the legend is modified as follows
We split all the pictures in order to improve the quality of the pictures,All the legends are shown below:
Figure 1: document screening process and results
PubMed (n=259), The Cochrane Library (n=153), EMbase (n=155), CNKI (n=118), CBM (n=358), WanFang (n=65).
Figure 2: bias risk assessment form
Figur 3:HR of median PFS in BEV group and Non-BEV group in the treatment of glioma
Figur 4:OR of PFS at each follow-up time in BEV group and Non-BEV group in the treatment of glioma
Figure 5:HR of median OS in BEV group and Non-BEV group in the treatment of glioma
Figure 6: OR of OS at each follow-up time in the treatment of glioma in the BEV group and Non-BEV group
Figure 7: OR of adverse reactions in the treatment of glioma in the BEV group and Non-BEV group
Figure 8:A: the sensitivity analysis of PFS6 ;B: the sensitivity analysis of PFS12; C:the sensitivity analysis of PFS18;D:the sensitivity analysis of PFS24;E:the sensitivity analysis of PFS30
Figure 9:A: the sensitivity analysis of OS6 ;B: the sensitivity analysis of OS12; C:the sensitivity analysis of OS18;D:the sensitivity analysis of OS24;E:the sensitivity analysis of OS30
Figure 10:A: funnel chart of PFS at each follow-up time;B: funnel chart of OS at each follow-up time
At the same time, the article has been revised by a special retouching organization.You are welcome to communicate with us again if you have any questions. Thank you very much for your questions, which have greatly improved the quality of our articles. I hope my reply will make you satisfied.Finally, I wish you a happy life.

Reviewer: 2
Dr. Andrew Simpkin, National University of Ireland Galway

1. Abstract Results, L9: standalone p-values should be avoided, please give estimates and 95%CI instead or along with p-values
Thank you for your question, we changed it to(0.71, 95%CI, 0.65 to 0.79,P<0.00001).
2. Abstract Results, L10: this sentence needs a rewrite, e.g. The PFS odds ratios of the BEV group compared to the non-BEV group were 3.31 (95% CI 2.74 to 4.00, p<0.001) at 6 months,...
3. Abstract Results L14: Again needs to be rewritten: There was no significant difference in PFS rate at 24 months
4. Abstract Results L16: Typo, should say BEV group lower than non-BEV
Thank you for your careful review of our paper. For the question of 2,3, 4, we revise it as follows:
Question 2
When compared with the PFS rate of each stage,it was found that the PFS in the BEV group was higher than that in the Non-BEV group at 6 months (3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (1.31,95%CI 1.02 to 1.69, p=0.03).
Question 3
But at 24 months (0.83, 95%CI 0.50 to 1.37, p=0.47), there was no significant difference between the two groups.
Question 4

At 30 months (0.62, 95%CI 0.39 to 0.97, p=0.04), the PFS of the BEV group was lower than that of the Non-BEV group.

5. Abstract Results L18: The last sentence is not a result? Is there something to say about adverse events?

The lack of summary of the results is indeed our lack of consideration. In response to your suggestion, we decided to add “The results showed that BEV had no significant effect on improving OS, but the adverse reaction in BEV group was significantly higher than that in non-BEV group” at the end of the results.

6. Page 6 L11: Was fixed or radnom effect meta-analysis used?

Thank you for your question. To this end, our team consulted the relevant literature and consulted relevant professional teachers,finally revised as follows:The test for heterogeneity used I2 statistics.If there is no significant heterogeneity among studies (I2≤50%), we used the fixed effects model for data consolidation.While there is significant heheterogeneity(I2>50%) between the results of the study, the random effects model for data analysis would be used.

References are as follows：

[1]Association between soft drinks consumption and asthma: a systematic review and meta-analysis Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis.

[2]Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis.

[3]Safety of corticosteroids in young children with acute respiratory conditions: a systematic review and meta-analysis.

[4]Efficacy and Safety of Valproic Acid for Spinal Muscular Atrophy: A Systematic Review and Meta- Analysis.

[5]Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis.

[6]Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomised clinical trials

7. Page 6 L 13: Were HR and OR combined, treated separately?

This should be the relationship of or, because in the original data, the median PFS and median OS are HR, and the result of each stage is OR. After referring to the “Efficacy and Safety of Valproic Acid for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis literature”, modify it to “The dichotomy data is expressed as the combined risk ratio (RR) or risk ratio (hazard ratio; HR),The measurement data is expressed as the mean difference (WMD).”

8. Page 6 L22: What does "the level is alpha=0.1a" mean?

Thank you very much for your suggestion. This is indeed the problem I wrote wrong. I originally intended to express the sensitivity result expressed by Q test. $\alpha = 0.1$ is the test level.After consulting the relevant professional teachers, I adopted I2 to classify the heterogeneity,Modify the same as the sixth question.

9. Page 6 L27: Consider rewriting this sentence: "results were stable otherwise they were unstable" is not useful - what is done in either case?

Thank you for your careful review, we will correct it to adopt the method of examining the impact of individual studies and eliminate them one by one, if the value obtained is within the confidence interval on both sides, the result is stable.otherwise, they were regarded as unstable.

10. No I-squared is reported for your first result?

Thank you very much for your suggestion. We modified it to I2=43%<50%.

11.Page 10 L14, L25, L34. You find the I squared p-value to be small and large, yet make the same decision, i.e. to use a random effect model? This seems odd. I would recommend using the RE model anyway, but commenting on heterogeneity as it might affect your conclusions. Can you address this inconsistency?

Thank you for your careful review of the article. Your suggestion has made a great breakthrough in the quality of our articles.After consulting, our team learned that fixed effects and random effects can be classified by I2. We have done the picture by using the RE model and found that there is no significant difference between it and the figure made after I2 classification.After deliberation, our team thinks that the model after I2 classification is more specific.I2 is just the solution to our contradiction, so we choose I2 .Because the median PFS has no obvious heterogeneity and the median OS has no statistical significance,There is no obvious heterogeneity of individual adverse reactions and it is not the data that we mainly want to show in this article. Considering that there are too many pictures, we only do sensitivity analysis of OS and PFS in each stage of the main data that we want to show.modify as follows:
1.There was no significant difference in the heterogeneity test (I2=43%<50%), so the fixed effect model was used for data analysis.
2.There was a significant difference in the total heterogeneity test (I2=71%>50%), so the random effect model was used.

3.there was a significant difference in the total heterogeneity test (I2=72%>50%), so the random effect model was used.
4.there was no significant difference in the heterogeneity test (I2=38%<50%), so the fixed effect model was used for data analysis.
5.There was a significant difference in the total heterogeneity test (I2=58%>50%), and the random effect model was used.

References are as follows：

[1]Association between soft drinks consumption and asthma: a systematic
review and meta-analysis Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis.
[2]Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis.
[3]Safety of corticosteroids in young children with acute respiratory conditions: a systematic review and meta-analysis.
[4]Efficacy and Safety of Valproic Acid for Spinal Muscular Atrophy: A Systematic Review and
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[5]Use of isotretinoin and risk of depression in patients with acne: a systematic review and meta-analysis.
[6]Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomised clinical trials.

12. Page 10 L17: Consider rearranging these results as it is hard to read, e.g. put the OR values at 6 month (3.31, 95% CI), 12 months (2.05, 95% CI) ... as shown in panel C of Figure 3
Thank you for your suggestion. We will change it to “Through the results found it was found that the PFS in the BEV group was higher than that in the Non-BEV group at 6 months (3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (1.31,95%CI 1.02 to 1.69, p=0.03).But at 24 months (0.83, 95%CI 0.50 to 1.37, p=0.47), P > 0.05, so there was no significant statistical difference between the two groups.At 30 months (0.62, 95%CI 0.39 to 0.97, p=0.04), 0.61 < 1, the diamond pattern falls on the group that supports Non-BEV group,so the PFS of the BEV group was lower than that of the Non-BEV group.as shown C infigure 3 .”At the same time, we have revised all the problems in the article.
13.Figures 3 to 6 are unreadable. Please fix all Figures, splitting where required and improve image quality
We repaired and split all the pictures.See the article or attachment for the picture.
Figure 3:HR of median PFS in BEV group and Non-BEV group in the treatment of glioma
Figur 4:OR of PFS at each follow-up time in BEV group and Non-BEV group in the treatment of glioma
Figure 5:HR of median OS in BEV group and Non-BEV group in the treatment of glioma

Figure 6: OR of OS at each follow-up time in the treatment of glioma in the BEV group and Non-BEV group
Figure 7: OR of adverse reactions in the treatment of glioma in the BEV group and Non-BEV group
Figure 8:A: the sensitivity analysis of PFS6 ;B: the sensitivity analysis of PFS12; C:the sensitivity analysis of PFS18;D:the sensitivity analysis of PFS24;E:the sensitivity analysis of PFS3
Figure 9:A: the sensitivity analysis of OS6 ;B: the sensitivity analysis of OS12; C:the sensitivity analysis of OS18;D:the sensitivity analysis of OS24;E:the sensitivity analysis of OS30
Figure 10:A: funnel chart of OS at each follow-up time;B: funnel chart of PFS at each follow-up time
14.The authors have left out a very similar systematic review and meta-analysis of BEV from Cancers 2019 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6895972/ which should be discussed and may even highlight others studies to be included.
Thank you for your suggestion, we have downloaded “Progression-Free but No Overall Survival Benefit for Adult Patients with Bevacizumab Therapy for the Treatment of Newly Diagnosed Glioblastoma: A Systematic Review and Meta-Analysis”this article and studied it carefully, and both of articles have emphasized the limitation of BEV in the treatment of gliomas. Our article found that this limitation may be 30 months. This article is really worth studying, taking into account the problems of the subgroup, we also refer to other relevant literature, and make the following modifications and supplements to the discussion
：
From the above research results, it can be concluded that long-term use of BEV does not increase the patient’s PFS, BEV can improve the PFS of glioma patients within 18 months,but the PFS of patients may be reduced after 30 months. Nagham Kaka found that BEV could have a role in the treatment of particular subgroups of patients with newly diagnosed GBM.Several studies have found that the median PFS of patients with methylation is longer than that of MGMT unmethylated tumors treated with RT and TMZ combined with BEV.Sandmann and colleagues found that BEV combined with standard TMZ and RT can improve the survival rate of neurotumors, while poorly differentiated mesenchymal tumors may make tumors resistant to BEV over time. Adilijiang andColleagues found that treatment with BEV and TMZ results in the upregulation of certain microenvironment related genes in IDH1 mutant tumors in vitro, specifically those involving immune response and extracellular matrix organization.Therefore, The question of whether the limitation of BEV in the treatment of gliomas is due to fixed subsets deserves constant attention.
Studies have shown that antiangiogenic therapy can lead to a transition of glioma to a more aggressive phenotype.In retrospective analysis a trend toward enhanced infiltra-tive disease was seen in bevacizumab-treated glioma patients suggesting that enhanced tumor inhibition may be a conse-quence of VEGF signaling blockade.Shiao-Pei Weathers shows that determining the best biological dose and the subgroup of patients most likely to obtain long-lasting benefits can improve the durability of bevacizumab.Victor A Levin found treatment for recurrent GBM with BEV appears to improve survival at a dose lower than that in the FDA drug insert. Study suggest that the higher dosage of BEV utilized may have impacted survival benefits.Animal models also suggest that higher dose of anti-VEGF treatment, resulting in more hypoxia, may increase tumor aggressiveness.Ryota Tamura found that high doses and long-term use of anti-VEGF/VEGFR may lead to hypoxia.Shiao-Pei Weathers proposed in tumors where excessive vascular pruning takes place, hypoxia exacerbated by antiangiogenic therapy is likely responsible for initiating a cascade of events. As mentioned above, there are many possible reasons for the limited efficacy of antiangiogenic therapy.But The lack of a long-lasting response to current antiangiogenic treatment underscores the need for a better understanding of how to use antiangiogenic therapy to optimize radiation and chemotherapy treatments.
CONCLUSIONS
The evidence suggests that BEV can significantly prolong the PFS of patients with glioma within 18 months and shorten the PFS of patients after 30 months. This limitation may be related to the subgroup of

patients, the change of recurrence mode, the optimal dose of drug, the increase of hypoxia, the enhancement of invasiveness and so on.BEV treatment has no obvious meaning in improving OS, and it has some side effects, which are acceptable, but we still need to pay close attention to it and take active measures to reduce the side effects.Therefore, it is necessary to carry out more samples and higher quality large-scale research in the future.

The references are as follows：

3.Progression-Free but No Overall Survival Benefit for Adult Patients with Bevacizumab Therapy for the Treatment of Newly Diagnosed Glioblastoma:A Systematic Review and Meta-Analysis.
4.Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma.
3.A randomized trial of bevacizumab for newly diagnosed glioblastoma.
4.Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis.
5. Next generation sequencing-based transcriptome predicts bevacizumab efficacy in combination with temozolomide in glioblastoma.
6.Acquired resistance to anti-VEGF therapy in glioblastoma is associated with a mesenchymal transi-tion.
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8.Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence.
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10.Resistance to Antiangiogenic Therapy.
11.Impact of bevacizumab administered dose on overall survival of patients with progressive glioblastoma.
12.Rela-tion between bevacizumab dose intensity and high-grade glioma survival: a retrospective study in two large cohorts.
13.Anti-VEGF treatment reduces blood supply and increases tumor cell invasion in glioblastoma.
14.The role of vascular endothelial growth factor in the hypoxic and immunosuppressive tumor microenvironment: perspectives for therapeutic implications.

The above are all my responses to your questions. Thank you very much for your questions, which have greatly improved the quality of our articles. I hope my reply will make you satisfied. Finally, I wish you a happy life.

VERSION 2 – REVIEW

REVIEWER	Simpkin, Andrew National University of Ireland Galway, School of Medicine
REVIEW RETURNED	03-Jun-2021

GENERAL COMMENTS	I'd like to thank the authors for their response. The manuscript has improved substantially, however there are still some outstanding issues: 1. You have added a comparison with the systematic review and meta-analysis of Kaka 2019. However two studies contained in this review are missing here and these meet your criteria (adults, clinical trial, BEV vs non-BEV groups, outcomes available). These studies should be included: Wirsching et al 2018 https://pubmed.ncbi.nlm.nih.gov/29648580/ Balana et al 2016 https://pubmed.ncbi.nlm.nih.gov/26847813/ Please include these studies and update results. It is vital in a systematic review to include all relevant studies. 2. Abstract results, please include that these are odds ratios starting on e.g. "...higher than that in the Non-BEV group at 6 months (odds ratio 3.31, 95% CI ...)", while the following may be written using the acronym OR. This issue also occurs in the Results section. Please make sure to explain what numbers mean throughout the manuscript. 3. For the sensitivity analysis, you do not explain what will be done if a study is found to be stable or unstable. Will it be removed?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Andrew Simpkin, National University of Ireland Galway

1. You have added a comparison with the systematic review and meta-analysis of Kaka 2019. However two studies contained in this review are missing here and these meet your criteria (adults, clinical trial, BEV vs non-BEV groups, outcomes available). These studies should be included:

Wirsching et al 2018 https://pubmed.ncbi.nlm.nih.gov/29648580/

Balana et al 2016 https://pubmed.ncbi.nlm.nih.gov/26847813/

Please include these studies and update results. It is vital in a systematic review to include all relevant studies.

Thank you very much for your review, which is very important to our article. We read these two articles carefully and found that the article of Balana does meet our inclusion criteria, and we included it. Because this article of Wirsching was designed as a non-comparative trial. We need comparative trial, so we did not include it. We have included the research of Balana and made all the updates to the articles and pictures. As follows：

Progression-free survival

SevenSix studies10,12-14,18-2019 reported median progression-free survival (BEV group, n=1160) and Non-BEV group (n=1027).There was no significant difference in the heterogeneity test (I2=3443%<50%),

so the fixed effect model was used for data analysis.Results suggested that the median progression-free survival of gliomas treated with BEV was significantly longer than that of malignant gliomas treated with Non-BEV (HR 0.71, 95%CI, 0.65 to 0.789,P<0.00001), As shown in figure 3.

Ten studies10-19 compared PFS ratios at different follow-up between the Bev group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I2=71%>50%), so the random effect model was used. Through the results found it was found that the PFS in the BEV group was higher than that in the Non-BEV group at 6 months (OR 3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (OR 2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (OR 1.31,95%CI 1.02 to 1.69, p=0.03).But at 24 months (OR 0.83, 95%CI 0.50 to 1.37, p=0.47), P > 0.05, so there was no significant statistical difference between the two groups.At 30 months (OR 0.62, 95%CI 0.39 to 0.97, p=0.04), 0.61 < 1, the diamond pattern falls on the group that supports Non-BEV group,so the PFS of the BEV group was lower than that of the Non-BEV group.as shown in figure 4.

Overall survival time

SevenSix studies10,12-14,18-2019 reported the median overall survival time, and there was a significant difference in the total heterogeneity test (I2=712%>50%), so the random effect model was used. Results suggesting that there was no significant difference in median overall survival time between the BEV group and Non-BEV group (HR 0.903, 95%CI, 0.735 to 1.106,P=0.3054), as shown in figure 5.

Six studies10,12-14,18-19 compared OS ratios at different follow-up between the Bev group and the Non-BEV group. there was no significant difference in the heterogeneity test (I2=38%<50%), so the fixed effect model was used for data analysis. Through the results found it was found that the OS in the BEV group was higher than that in the Non-BEV group at 6 months(OR 1.41；95%CI, 1.07-1.84；P=0.01),12 months(OR 1.31；95%CI, 1.09-1.58；P=0.005).But at18 months （OR 0.95；95%CI, 0.79-1.14；P=0.58）, 24 months（OR 1.10；95%CI, 0.89-1.35；P=0.39）, and 30 months（OR 0.90；95%CI, 0.69-1.18；P=0.44), P > 0.05, so there was no significant statistical difference between the two groups,as shown in figure 6.

Adverse reaction

As shown in figure7, there were six studies10-11,13-15 that compared adverse reactions between the BEV group and the Non-BEV group. There was a significant difference in the total heterogeneity test (I2=548%>50%), and the random effect model was used. The results showed the combined OR values of hypertension, hemorrhage, hematencephalon, albuminuria, and thromboembolism as follows: hypertension (OR 5.144.94, 95%CI 3.7960 to 6.9678, P<0.00001), hemorrhage (OR 2.62, 95%CI 1.96 to 3.49, P<0.00001), hematencephalon (OR 2.206, 95%CI 1.080.96 to 4.7240, P=0.035), albuminuria (OR 4.042, 95%CI 2.5619 to 6.377.36, P<0.00001) and thromboembolism (OR 1.5773, 95%CI 0.8893 to 2.773.23, P=0.1309).Through the results found it was found that the adverse reactions in the BEV group was higher than that in the Non-BEV group .

2. Abstract results, please include that these are odds ratios starting on e.g. "...higher than that in the Non-BEV group at 6 months (odds ratio 3.31, 95% CI ...)", while the following may be written using the acronym OR. This issue also occurs in the Results section. Please make sure to explain what numbers mean throughout the manuscript.

Thank you very much for your problem, and we have corrected it. As follows：

Results: A total of 110 clinical center trials were included in this study for meta-analysis, including 2392 patients. The results of the meta-analysis showed that the median progression-free survival (PFS) rate of the BEV group was significantly higher than that of the Non-BEV group (P<0.00001). When comparing PFS rate between two groups, we found that the PFS rate in the BEV group was higher than that in the Non-BEV group at 6 months (OR 3.31, 95%CI 2.74 to 4.00, p<0.00001), 12 months (OR 2.05, 95%CI 1.70 to 2.49, p<0.00001) and 18 months (OR 1.31,95%CI 1.02 to 1.69, p=0.03). But at 24 months (OR 0.83, 95%CI 0.50 to 1.37, p=0.47), there was no significant difference between the two groups. At 30 months (OR 0.62, 95%CI 0.39 to 0.97, p=0.04), the PFS rate of the BEV group was lower than that of the Non-BEV group. Moreover, The results showed that BEV had no significant effect on improving OS, but the adverse reaction in BEV group was significantly higher than that in non-BEV group.

3. For the sensitivity analysis, you do not explain what will be done if a study is found to be stable or unstable. Will it be removed?

Thank you very much for your problem, and we have corrected it.As follows：

If the results are unstable, it is proved that the elimination research has a great impact on the overall research results. We will conduct a professional analysis of the elimination research to find out the reasons for its impact on the results and study it.

You are welcome to communicate with us again if you have any questions. Thank you very much for your questions, I hope my reply will make you satisfied. Finally, I wish you a happy life.

Reviewer: 2

Competing interests of Reviewer: None

Thank you very much for your problem, and we have added it to the the article. Finally, I wish you a happy life.