Systematic Review and Meta-Analysis

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The value of MGMT promote methylation and IDH-1 mutation on diagnosis of pseudoprogression in patients with high-grade glioma

A meta-analysis

Min Zhou, MD[a,b,c], Chaoshi Niu, MD[a,b,c,*], Li Jia, MD[a,b], Hu He, MD[a,b,c]

Abstract

Objective: To date, there are several published studies on the value of IDH-1 (isocitrate dehydrogenase-1) mutation and MGMT (O6-Methylguanine-DNA methyltransferas) promoter methylated status on the diagnosis of pseudoprogression (PSP) and true tumor progression after or within chemo-radiotherapy of high grade glioma (HGG). We performed a meta-analysis about the significant value of these 2 molecular markers on the diagnosis of PsP in high- grade glioma.

Methods: We searched the eligible studies from PubMed, Medline, Embase, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI) and Wan Fang Database. The relevant studies published before October 2018 were identified. ORs (odds ratios) with 95%CIs (confidence intervals) were used to evaluate the value using fixed- or random-effect model.

Results: Thirteen studies about MGMT promoter methylated status and 4 studies about IDH-1 mutations were found eligible for this present meta-analysis. Significant value of MGMT promoter methylation status (OR = 4.02, 95%CI = 2.76–5.87, $P < .001$) and IDH-1 mutations (OR = 12.78, 95%CI = 3.86–42.35, $P < .001$) were observed.

Conclusions: This meta-analysis provided evidences that MGMT promoter methylation status and IDH-1 mutations could distinguish PSP from true tumor progression.

Abbreviations: HGG = high grade glioma, IDH = isocitrate dehydrogenase, MGMT = O6-Methylguaniue-DNA methyltransferas, MRI = magnetic resonance imaging, ORs = Odds ratios, PSP = pseudoprogression, RT = radiotherapy, TMZ = temozolomide.

Keywords: high grade glioma, IDH, meta-analysis, MGMT, pseudoprogrssion, tumor progression

1. Introduction

Glioblastoma multiform is the most common and aggressive primary malignant brain tumor in adults. The incidence rate of glioma is 6.02 per 100,000, according for 45.2% of primary malignant brain tumors.[1,2] These diseases are more common in elderly people with a median age of 65 years. Despite the evaluation of multiple treatment approaches, the disease is still a major challenging public health problem with very poor prognosis. The median overall survival of these patients is only 15 months.[3] The milestone studies by Stupp et al[4] presented chemoradiotherapy with concurrent and consolidative temozolomide (TMZ) to high grade gliomas had greater superiority than RT alone, has established postoperative chemoradiotherapy as the standard care for patients with high grade gliomas. However current treatment protocols have demonstrated an increased incidence of pseudoprogression or radiation necrosis.[5,6] On follow up MRI, a percentage of patients demonstrate increased contrast enhancing lesions, which subsequently recover or stabilize without further treatment spontaneously, known as a treatment relate effect. It occurs in 10% to 32% of patients with gliomas treated with current standard therapy.[7,8] Patients with PSP exhibit contrast enhancement, which mimics true tumor progression on conventional MRI, leading to misdiagnosis of tumor progression.[9–11] Inaccurate diagnosis of PSP may lead to unwanted discontinuation of effective treatment. Therefore, it is important to discriminate PSP from real tumor progression to avoid unnecessary and harmful surgical interventions.[11] Nowadays several approaches have been employed to distinguish PSP from tumor progression. However, no single approach can diagnose PSP precisely, only according to surgery, biopsy or follow-up visit.[12–14]

Through genome research, a lot of studies have reported that methylation of O-6-methylguanine-DNA methyltransferase

Editor: Undurti N. Das.

This study was supported by a grant (no. 1408085MKL69) from Natural Science Foundation of Anhui Province.

The authors report no conflicts of interest.

[a] Department of Neurosurgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, [b] Anhui Provincial Stereotactic Neurosurgical Institute, [c] Anhui Province Key Laboratory of Brain Function and Brain Disease, Hefei, Anhui, PR China.

[*] Correspondence: Chaoshi Niu, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, PR China (e-mail: niuchaoshi@126.com).

How to cite this article: Zhou M, Niu C, Jia L, He H. The value of MGMT promote methylation and IDH-1 mutation on diagnosis of pseudoprogression in patients with high-grade glioma: a meta-analysis. Medicine 2019;98:50(e18194).

Received: 13 June 2019 / Received in final form: 12 October 2019 / Accepted: 28 October 2019

http://dx.doi.org/10.1097/MD.0000000000018194

(MGMT) gene promoter and mutations of isocitrate dehydrogenase-1 (IDH-1) have high incidences in gliomas.[15,16] PSP has been frequently found in tumors with hyper-methylation of MGMT promoter gene more than in tumors with MGMT promoter gene un-methylation.[17] The correlation between IDH-1 mutations and MGMT promoter methylation has been observed. A study of Li et al[7] showed that IDH-1 mutations were observed in 57% of the MGMT promoter methylated glioblastoma, but only 21% of the MGMT un-methylated glioblastoma. The mechanisms of this correlation have not been worked out. Several clinical studies have documented the predictive value of MGMT promoter methylation status and IDH-1 mutations in PSP, but are contracted by others.[18–23] However, to date, there have been no meta- analysis performed to precisely evaluate the association of MGMT promoter methylation or IDH-1 mutations with PSP; therefore, we collected all relevant studies and carried out a meta-analysis to evaluate the value of IDH-1 mutation and MGMT promoter methylation status on distinguishing PSP from true tumor progression in HGG after chemo-radiotherapy.

2. Materials and methods

2.1. Literature search

All relevant studies about MGMT and IDH-1 mutation status on diagnosing pseudoprogression in glioma were reviewed by two investigators independently. The PubMed, Elsevier Science Direct, Embase, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI) and Wan Fang were searched to obtain related studies estimating the relationship between MGMT, IDH and gliomas, published from January 1960 to October 2018. The key words for our search were used: pseudoprogression, glioma or high grade glioma or glioblastoma, and MGMT OR O-6-Methylguanine-DNA methyltransferase, and IDH-1 or IDH or isocitrate dehydrogenase-1. The relevant Chinese characters of the key words were used for searching In CBM, CNKI and Wan Fang database. The references of all the included articles were also searched manually. As this is a meta-analysis, and we will collect data from previously published studies, therefore, Ethical approval for this study is not required

2.2. Inclusion and exclusion criteria

Studies included in this meta-analysis if they matched the following criteria:

(1) only full text published in English or Chinese,
(2) all studies in published literature,
(3) both retrospective and population-based studies,
(4) all studies about primary glioma not recurrent glioma,
(5) all studies of high grade glioma not low grade glioma,
(6) Only articles that present sufficient data were included.
(7) When data was presented in more than one article, the article with the most details was chosen.

Studies were excluded by the following criteria:

(1) evaluating the therapy effect of glioma not by Macdonald criteria,
(2) the method to analyze MGMT status was not methylation-specific polymerase chain reaction (MSP),
(3) animal studies, duplicate publications.

2.3. Data extraction

Study characteristics and original data were extracted from eligible studies independently, according to the inclusion and exclusion criteria above. The following information was extracted from each study: first author's name, publication year, MGMT methylated status or IDH-1 mutations, total population of the studies, numbers of each gene, characters of patients (age, sex, tumor grade), the method of analyzing MGMT gene promoter methylation status, country of origin. All the information was verified by three investigators. Disagreements were discussed and resolved by consensus.

2.4. Statistical analysis and publication bias

We firstly used χ^2 test-based Cochran Q statistic test and I^2 statistics to test the heterogeneity of the included studies. For Q statistic test, P value more than .05 indicated no distinct significant heterogeneity; for the I^2 statistics, an I^2 value less than 50% was considered no statistical heterogeneity. Then the ORs (odds ratios) and 95% CIs (confidence intervals) were evaluated by Mantel-Haenszel method in a fixed-effect model, otherwise, the ORs and 95%CIs were achieved by DerSunibuan-Laird method in a random-effect model. ORs and their 95%CIs were used to assess the value of MGMT promoter methylation and IDH-1 mutations status on distinguishing PSP from true tumor progression. The value of MGMT promoter methylation status and IDH-1 mutation were evaluated respectively. We used the Z test to determine the significance of the pooled OR, and $P < .05$ was considered statistically significant. The ORs were also performed for the comparison of the value of MGMT and IDH-1. All analyses were performed using Stata 12.0 software.

Publication bias was investigated with the funnel plots and Egger test. Funnel plot asymmetry was further assessed by using Egger linear regression test using Stata 12.0 software. The P value of Egger linear regression test less than .05 was considered representative of statistically significant publication bias.

3. Results

3.1. Search results

The 308 relevant studies from databases identified by the search strategy when we reviewed the discussion and introduction of the included were selected, 294 studies were excluded because they are Reviews, letters or commentaries, and duplicate publications et al. Finally, a total of 14 studies as shown in Figure 1, met our inclusion and exclusion criteria. Of these, 13 studies were about MGMT promoter methylation status, 4 eligibility studies were about IDH-1 mutation, 3 studies were about both MGMT promoter methylation status and IDH-1 mutation. The details of these eligible studies' characteristics were shown in Tables 1 and 2.

3.2. Results of the meta-analysis

In the analysis of 13 studies on MGMT promoter methylation, the heterogeneity was not significant (Q = 9.00, $P = .703$, $I^2 = 0.0\%$). Fixed-effect model was used to estimate the value of MGMT promoter methylation on the diagnosis of PSP. We observed a significant value for MGMT promoter methylation (pseudoprogression vs true tumor progression, OR = 4.02, 95% CI = 2.76–5.87, $P < .001$) (Fig. 2).

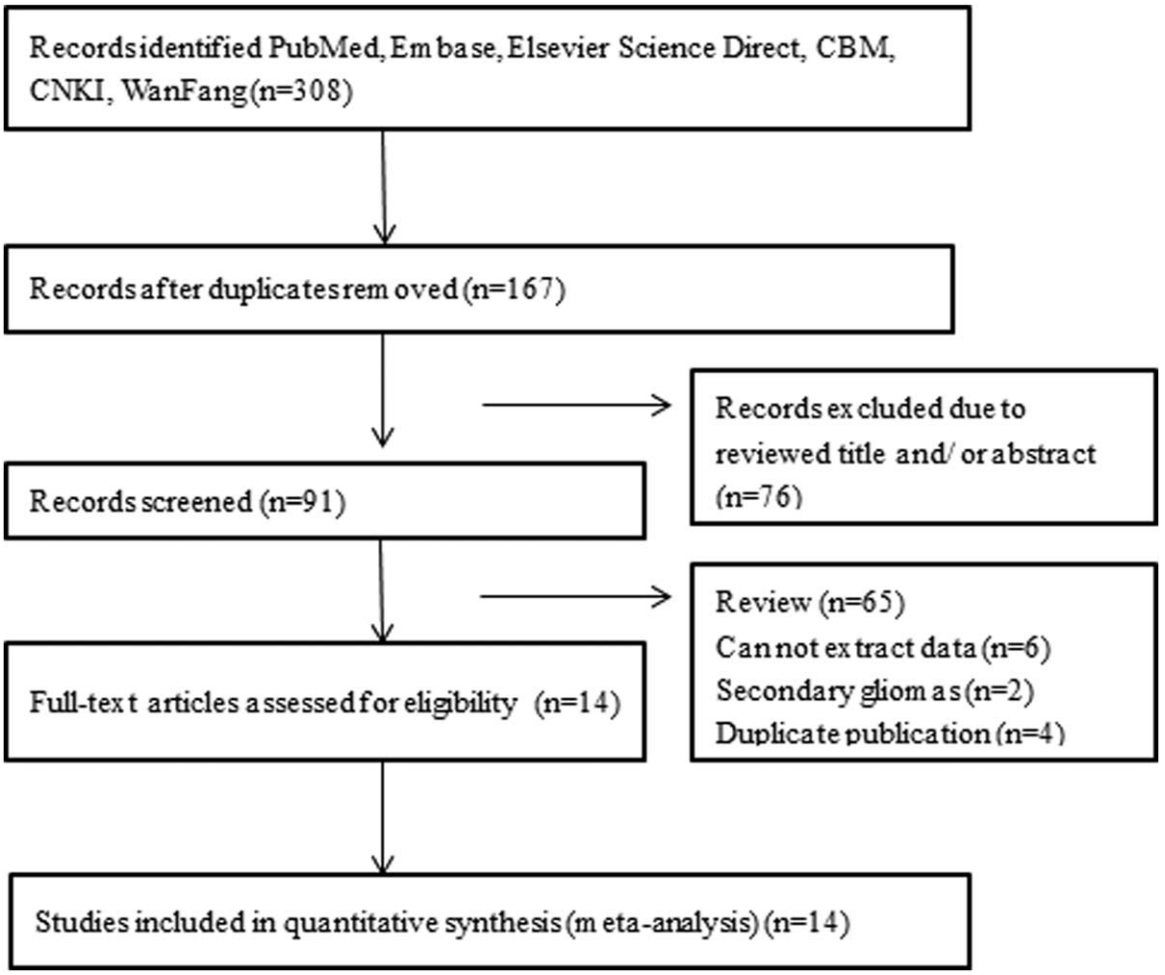

Figure 1. Flow chart of meta-analysis for exclusion/ inclusion of studies.

Four studies provided the data regarding the association between IDH-1 mutation and PSP in glioma. We observed a significant value of IDH-1 mutation on diagnosis of PSP (pseudoprogression vs true tumor progression, OR = 12.78, 95%CI = 3.86–42.35, $P < .001$) (Fig. 3) in fixed-effect model (Q = 0.75, $P = .862$, $I^2 = 0.0\%$).

3.3. Publication bias

We used Egger test to assess the publication bias of studies about MGMT promoter methylation status and IDH-1 mutation on the diagnosis of PSP. We draw the Egger funnel plots as Figures 4 and 5. The results did not suggest any obvious evidences of publication bias.

Table 1

Study and patient characteristics of included studies about MGMT methylated status.

Author	Year	Pseudoprogression		Progression	
		MGMT methylated	MGMT unmethylated	MGMT methylated	MGMT unmethylated
Lin et al	2018	1	0	4	1
Li et al	2013	7	2	5	10
Mieghem et al	2013	9	4	15	27
Galldiks et al	2015	6	4	2	8
Kong et al	2011	15	8	9	18
Fabi et al	2009	2	0	0	2
Rodan et al	2009	6	3	3	3
Park et al	2011	4	7	1	13
Yoon et al	2017	25	14	9	27
Li et al	2016	20	18	7	21
Brands et al	2008	21	11	2	16
Chu et al	2013	9	6	9	6
Balana et al	2017	34	16	25	41

Table 2

Study and patient characteristics of included studies about IDH-1 mutations status.

Author	Year	Pseudoprogression		Progression	
		IDH-1 mutation	IDH-1 wild	IDH-1mutation	IDH-1 wild
Li et al	2013	6	3	3	12
Li et al	2016	13	25	1	37
Balana et al	2017	2	1	0	8
Motegi et al	2013	2	36	0	49

4. Discussion

Although pseudoprogression (PSP) is a treatment-related effect on imaging in patients with HGG, a phenomenon of the continuation of the subacute of radiation damage, diagnosed only according to reoperation or follow up visit, some researchers have found some molecular markers can be helpful for the prediction of PSP. One of them is MGMT promoter methylation status. This meta-analysis of 13 studies,[17–21,23–30] involving 536 patients, showed that MGMT promoter methylated had a significant value in distinguishing PSP from enhancing-lesions on MR scans in patients undergoing treatment for HGG. Among these studies, some study has demonstrated this different. In all eligible studies, MGMT status was evaluated by MSP (diagnostic accuracy of 68%), which is a standard method used to analyze the methylation status of MGMT promoter but without providing quantitative results.[28] This leads to some inaccuracy in determining the prognosis of PSP. Park et al compared MSP and methylation-specific multiplex ligation probe amplification (MS-MLPA, a semi-quantitative method to test the MGMT status). They demonstrated MS-MLPA was a greater predictive value of MGMT status in PSP ($P=.003$) than MSP ($P=.070$). Moreover, the combination of MS-MLPA and MSP provided a strong diagnostic accuracy of 93% for the identification of PSP.

In 2008, Parsons et al identified the genetic alterations in HGG.[31] They found recurrent mutation in the active site of isocitrate dehydrogenase-1 (IDH-1) in 12% of GBM patients. IDH-1 mutation as a new biomarker to diagnose pseudoprogression from true tumor progression has been reported by some investigators. Because of the small size of patients in each study, the conclusions still remain controversial. In the present meta-

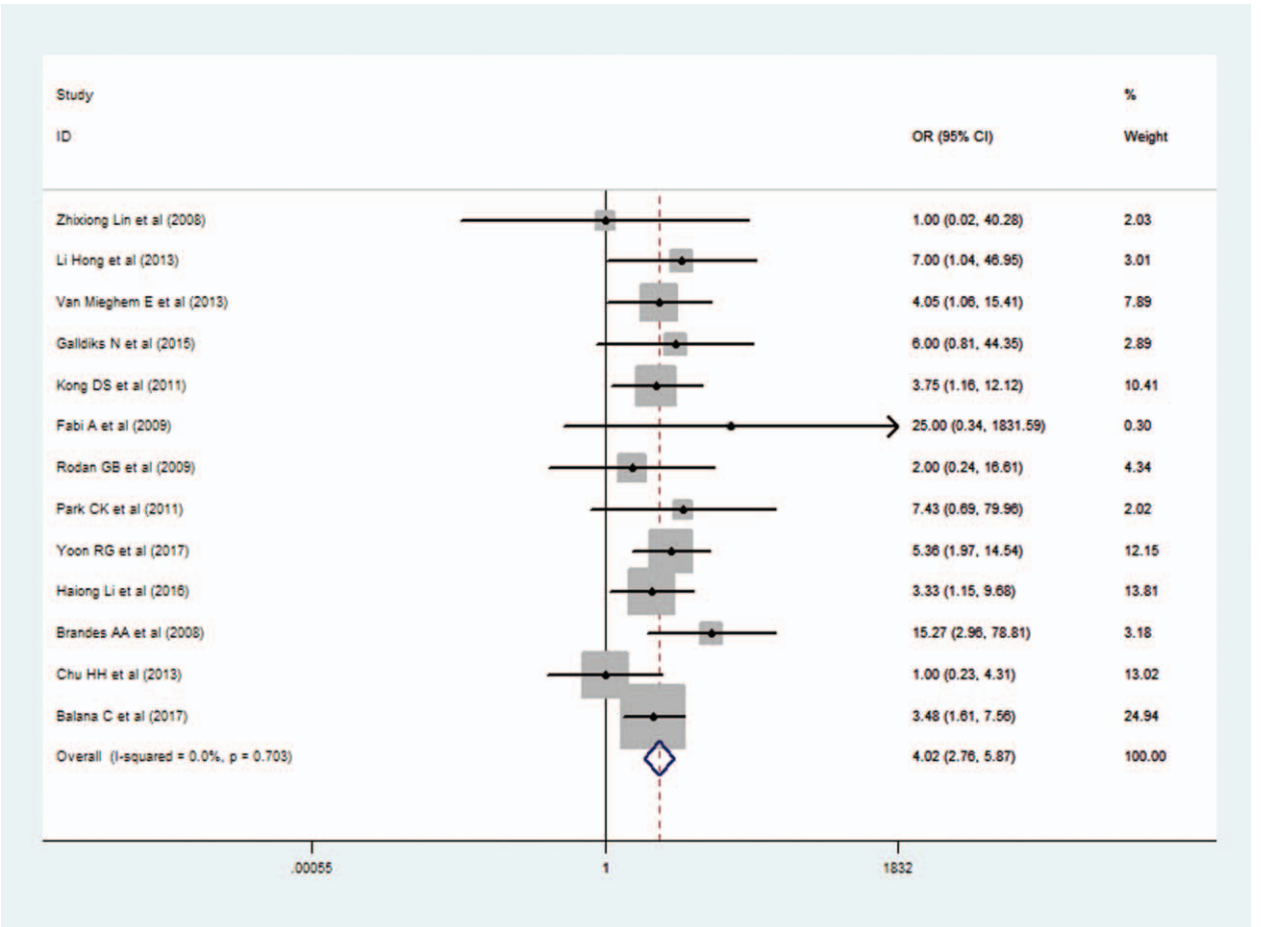

Figure 2. Forest plot for the value of MGMT promoter methylated: pseudoprogression vs true tumor progression.

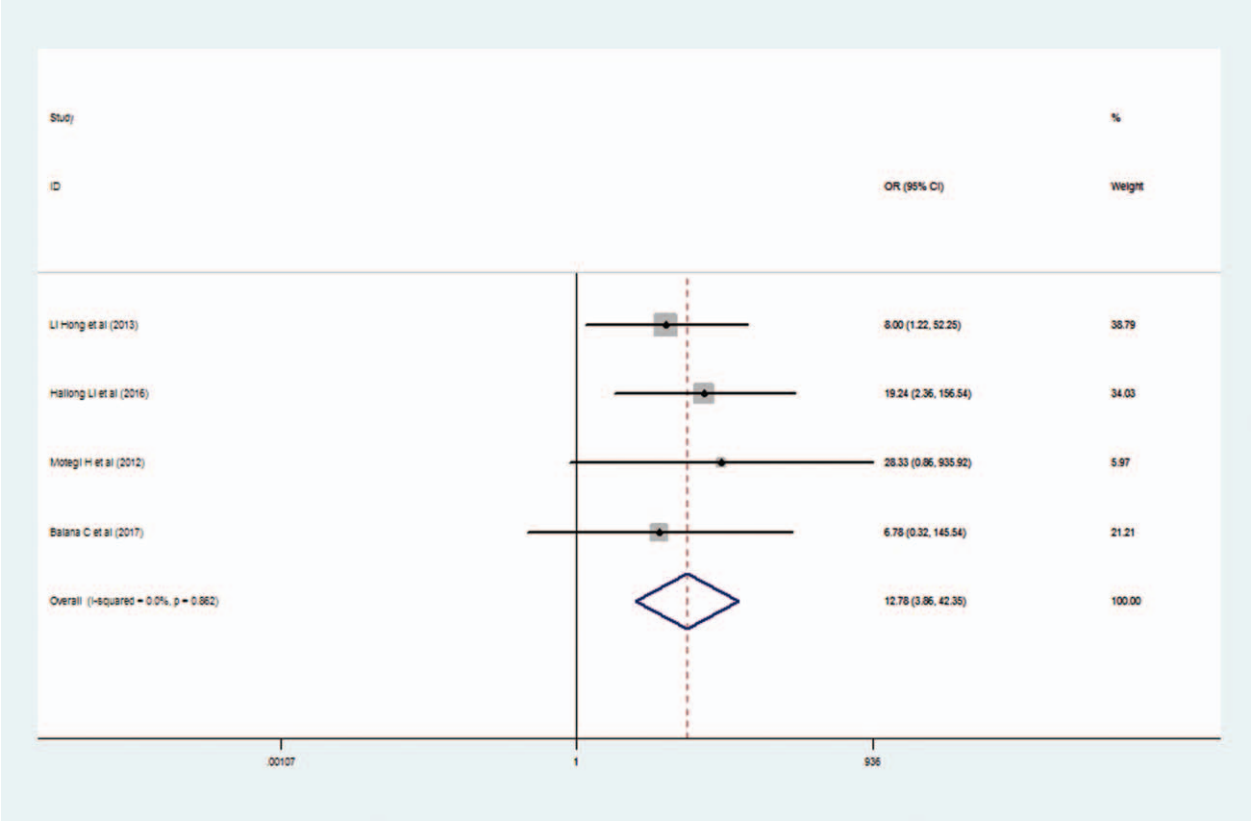

Figure 3. Forest plot for the value of IDH-1 mutation: pseudoprogression vs true tumor progression.

analysis, there were four studies included.[21,24,25,32] Through the analysis, the combined evidence suggested that IDH-1 mutation had a predictive value of PSP.

As far as we know, this is the first meta-analysis of investigating the value of MGMT promoter methylation status and IDH-1 mutation to diagnose PSP. However some limitations of this study should be discussed here. First, heterogeneity and confounding factors between-study may have distorted the meta-analysis. However, this was not a major problem because PSP, MGMT and IDH-1 are heterogeneous. Second, different response evaluation criterions of brain tumors also influence the diagnosis of PSP. Some studies have demonstrated that the Response Assessment in Neuro-Oncology (RANO) criteria is more useful than Macdonald criteria.[33] However, no meta-analysis of RANO criteria was possible due to inadequate data. Also MSP, the analysis method of MGMT promoter methylation status is not sufficient to provide a solid clinical decision making due to nonnegligible false negative or false positives in clinical outcome prediction. Third, the occurrence of pseudoprogression can be changed by different radiation or temozolomide dose. Moreover, different patient populations may also contribute to heterogeneity. In this meta-analysis, all eligible studies were published papers. It is possible that some related unpublished

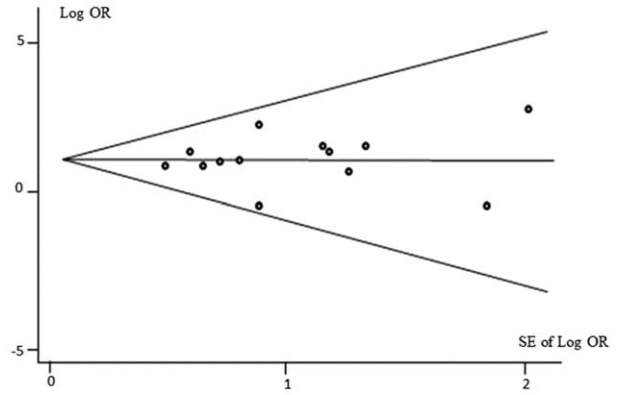

Figure 4. Funnel plot of publication bias for MGMT promoter methylated.

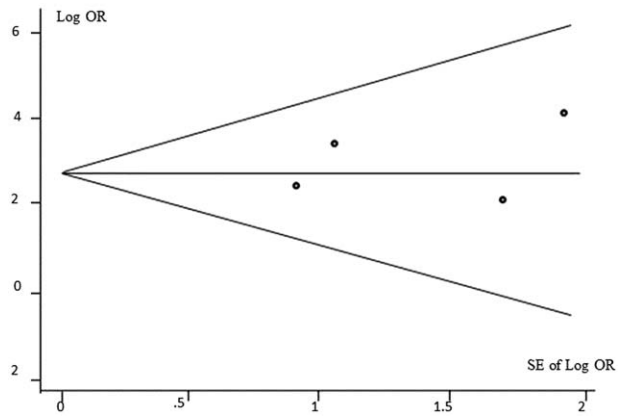

Figure 5. Funnel plot of publication bias for IDH-1 mutation.

studies were missed, but those studies have met the including criterion. Thus, some inevitable publication bias may exist in the results, although neither the funnel plots nor Egger's tests indicated remarkable publication bias in the meta-analysis (Figs. 4 and 5). In the analysis of IDH-1 mutation, only four studies were conducted. Therefore, to conduct a more precise analysis of this value to predict pseudoprogression from tumor progression or radiation necrosis, and so do the small size of patients group in the analysis of MGMT promoter methylation status, additional studies with large sample size and involving different gene types were warranted.

5. Conclusion

In conclusion, despite the possible limitations, results of the present meta-analysis suggest that there was a significant value of IDH-1 mutation and MGMT promoter methylation status on a diagnosis of pseudoprogression in high-grade glioma with current therapies. In the future, further studies with large sample sizes and studies design stratified by ethnicity are warranted to confirm our findings.

Author contributions

Conceptualization: Li Jia.
Data curation: Chao Shi Niu.
Investigation: Li Jia, Hu He.
Project administration: Chao Shi Niu.
Resources: Min Zhou.
Software: Min Zhou, Li Jia, Hu He.
Supervision: Min Zhou, Hu He.
Writing – original draft: Min Zhou.
Writing – review & editing: Min Zhou.

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