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High expression of microRNA 221 is a poor predictor for glioma

Yanlin Song, MD[a,b], Min He, MD[c], Jing Zhang, MD[a], Jianguo Xu, MD, PhD[a,*]

Abstract

Background: MicroRNA 221 has been found to be a good marker for several cancers. Some studies also focused on the relationship between microRNA 221 and glioma. However, the results are controversial. We aimed to systematically evaluate the prognostic role of microRNA 221 in glioma through performing a meta-analysis.

Methods: The articles which were included in our study were searched on the Web of Science, EMBASE, PubMed, Cochrane Library and China National Knowledge Infrastructure. The basic characteristics and relevant data were extracted. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled to evaluate the prognostic role of microRNA 221 in glioma.

Results: Eight studies with 1069 patients were included. We systematically evaluated the role of microRNA 221 for overall survival (OS) and disease free survival (DFS) in glioma patients (HR for OS = 1.66, 95% CI, 1.34–2.04; HR for DFS = 1.14, 95% CI, 1.02–1.26). Subgroup analyses were performed according to the nation of the studies, the origin of the samples, the stage of the tumors, the cut-off value, and the method for detecting the microRNA 221. No significant publication bias was found ($P = .133$).

Conclusion: In conclusion, high expression of microRNA 221 was related to poor prognosis of glioma. These findings may assist future exploration on microRNA 221 and help predict the prognosis of glioma. However, due to the significant heterogeneity of these studies, more studies are warranted.

Abbreviations: CI = confidence interval, DFS = disease free survival, HR = hazard ratio, OS = overall survival, PRISMA = preferred reporting items for systematic review and meta-analysis, Q-PCR = quantitative polymerase chain reaction, SE = stand error.

Keywords: glioma, microRNA 221, prognosis, survival

1. Introduction

Glioma is still the most common and malignant tumor in central nervous system (CNS) for now.[1,2] The high morbidity and mortality of glioma has promoted the progression of the treatment of glioma in last decade.[3] Although the median survival time of glioma was longer than before, 5-year survival rate was <10%.[4] Finding a novel biomarker is important for improving the outcome of glioma patients.

MicroRNAs which were identified in 1990s were related to the regulation of gene expression.[5] And the regulation processes always occur on post-transcriptional level. Sometimes, the regulation might lead to the translation inhibition or mRNA degeneration by combining with targeted mRNA.[6,7] It has been proved that MicroRNAs play an important role on cell proliferation, apoptosis, differentiation, and metabolism.[8–10] And the aberrant expression of microRNAs always occurs in the tumor.[11] Given that microRNAs are much conserved small non-coding RNA, it can be a good predictor for the prognosis of the tumor patients. It has been reported that microRNA 133, 210, 310, 155, and 650 are good markers for the prediction of the prognosis of glioma.

MicroRNA 221 was proved to be related to the survival, growth, invasion, and malignant of glioma cells by previous studies.[12–17] It has been found that high expression of microRNA 221 is associated to the poor prognosis of liver cancer, colorectal cancer, and ovarian cancer.[18–20] Some clinical

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YS, MH, and JZ have contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]

[a] Department of Neurosurgery and National Clinical Research Center for Geriatrics, [b] Department of Biotherapy and Cancer Center, [c] Department of Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, P.R. China.

[*] Correspondence: Jianguo Xu, West China Hospital, No. 37, Guoxue Alley, Chengdu 610041, P.R. China (e-mail: jianguo_1229@126.com).

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research has demonstrated the prognostic role of microRNA 221 in glioma. However, the results of these studies are controversial. In order to reach a consensus, we systematically evaluated the prognostic role of microRNA in glioma.

2. Method

2.1. Search strategy

We designed, conducted, and reported the study based on the preferred reporting items for systematic review and meta-analysis (PRISMA) statement. And the data were analyzed according to the Cochrane Handbook. We developed the article by the order of guidelines of system reviews. Since this is a meta-analysis, ethical approval was not necessary.

The articles which were used in our study were searched (to November 24, 2019) on the Web of Science, EMBASE, PubMed, Cochrane Library, and China National Knowledge Infrastructure. The keywords for searching were showed below: microRNA 221 (microRNA 221-3p or hsa-miR-221), glioma (astrocytoma or glioblastoma or ependymoma or subependymal or ganglioglioma or gliosarcoma or medulloblastoma or oligodendroglioma), prognosis. Boolean operators (AND/OR) were used to combine these keywords and their synonyms or Medical Subject Headings.

2.2. Study selection

The articles were screened by JZ and YS independently. And the articles which were found before were managed by EndNote 8. Firstly, we screened the articles by the title and abstract. Then the potential articles were carefully read in full text. The inclusion criteria included: the patients were diagnosed with glioma and the diagnosis was verified by histopathological examination; the expression of microRNA221 was measured; the patients were followed up for overall survival or disease free survival. Enough data were reported in the article to estimate the prognostic role of microRNA221 for glioma. The articles which did not have enough data, case reports, reviews, letters, and conference abstract were excluded.

2.3. Data extraction

The relevant data in eligible articles were extracted by JZ and YS independently. The hazard ratio (HR) with 95% confidence interval (CI) were extracted firstly. Besides, the related data which can calculate the HR and 95% CI were extracted too. The following information was also extracted from each article: the name of first author, year of publication, name of the investigated microRNA, the nation of the study, type of samples, number of samples, the methods for testing microRNA, cut off of microRNA221 and the characteristics of patients (sex, age, and stage).

2.4. Study quality assessment

The Newcastle Ottawa Scale (NOS) was used for assessing the quality of the included studies.[21] The scale assessed 3 aspects of these studies, including selection, comparability and outcome, and each item was assigned 1 to 2 points. So the maximum score for a given study was 9 points. In this article, studies with score of 7 points or >7 points were considered to be a high quality study.[22]

2.5. Statistical analysis

The Log[HR] and stand error (SE) were calculated from the HR and 95% CI. If HR was not showed in the article, we could get the data by the method of Troiano et al.[23] Then all calculated data were used for the construction of forest plots which is used to estimate the pooled prognostic role of microRNA221 in glioma patients. The P value $<.05$ was considered to be significant. Besides, the 95% CI cannot overlap 1. The Higgins Index (I^2) was calculated to assess the heterogeneity of these studies. $I^2>50\%$ and/or P value $<.1$ was considered to be significant. The data were investigated with random-effect models no matter the heterogeneity was significant or not. If the heterogeneity was significant, we performed sensitivity analysis of these studies which can figure out the contribution of each article in the heterogeneity. Sub-group analysis was used to learn about the contribution of the nation of the studies, the origin of the samples, the stage of the tumors, the cut-off value, and the method for detecting the microRNA 221. At last, publication bias was assessed by Begg funnel plots. All analysis was conducted by STATA 11.0 (College Station, TX, StataCorp.)

3. Results

3.1. Study research

At the beginning, 81 articles were found in the first round research. And no duplicates were found in these articles. Then 70 articles were excluded after screened by the titles and abstracts. The rest 11 articles were further filtered by full-text reading. After step by step screening, only 8 articles which met the inclusion criteria were retained. The process of study screening was showed in the Fig. 1.

3.2. Study characteristics

Among the 8 articles, 7 articles analyzed HR for the overall survival while only one article analyzed HR for progression-free survival. The basic characteristics were extracted from these articles. As shown in Tables 1 and 2, these studies were conducted from 2011 to 2018 in 2 different countries.[14,24–30] A total of 1069 patients were involved in the study. The samples were isolated from tumor or blood. Quantitative polymerase chain reaction (Q-PCR) was used to test most samples. Only one study evaluated the expression of microRNA 221 by immunohistochemistry scoring. Three articles only studied the relationship between microRNA 221 and prognosis in stage IV glioma patients, and other articles investigated patients in all stages. And the cut-off value included mean, median, and 60%.

3.3. Overall analysis

In 8 included articles, 10 data sets were used to analyze the prognostic role of microRNA 221 for glioma patients (Fig. 2). Among these data, 7 data sets were used to analyze the role of microRNA 221 on OS and 3 data sets were used to analyze the role on disease free survival (DFS). The pooled HR of higher microRNA 221 for overall survival (OS) was 1.66 (95% CI, 1.34–2.04) and the HR for DFS was 1.14 (95% CI, 1.02–1.26). The heterogeneity was evaluated for OS ($I^2=50.2\%$, $P=.062$) and DFS ($I^2=0\%$, $P=.663$). Next we learned about the contribution of each article

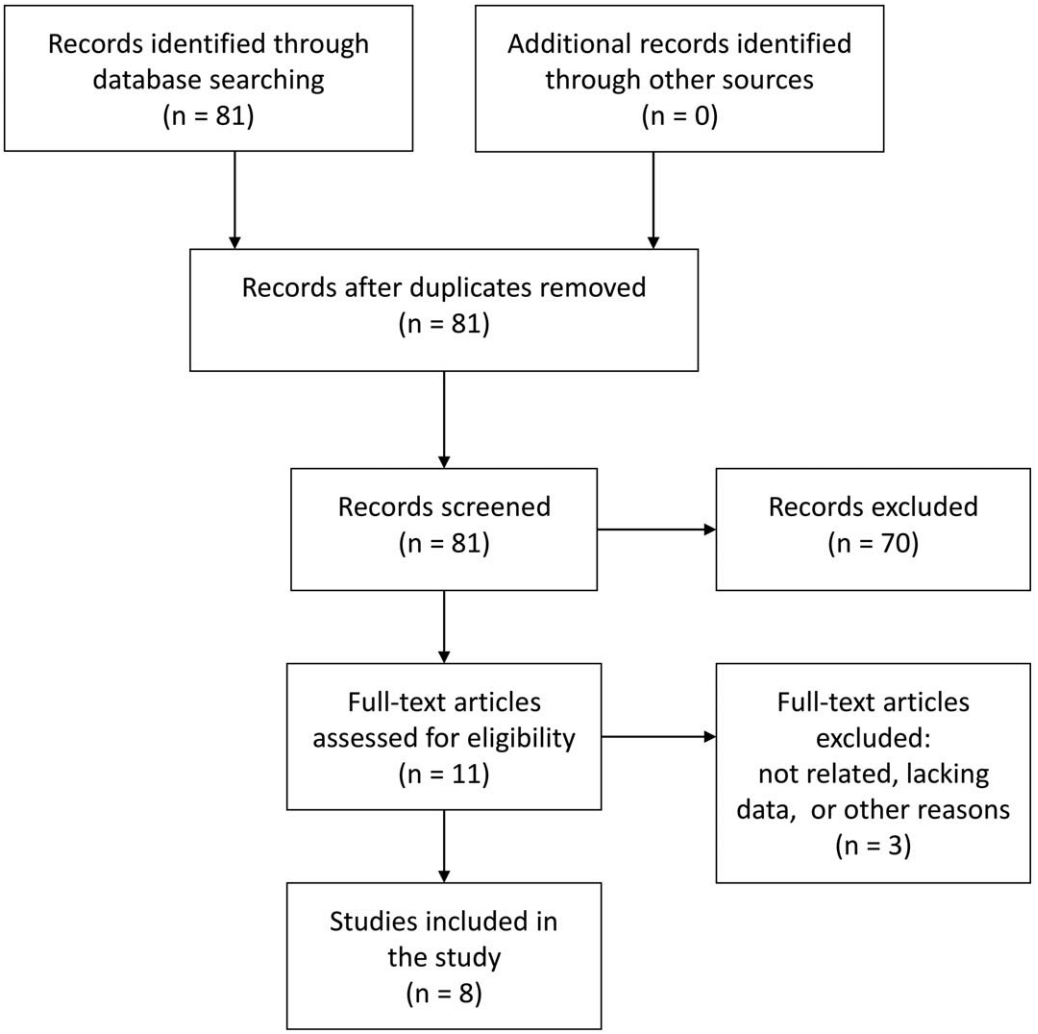

Figure 1. Selection process of studies.

on heterogeneity of OS. After excluding the article by RZ, CZ, SS separately, I^2 shrank to 39.10%, 47.20%, 5.50%. So we believed that the study by SS was the major resource of the OS heterogeneity. So we analyzed the HR after excluding this study. The pooled HR changed to 1.75 (95% CI, 1.45–2.1), which was still significant.

3.4. Subgroup analysis

We also analyzed the effects of other factors, like nation of study, type of study, the origin of the samples, the stage of the tumors, the cut-off value, and the method for detecting the microRNA 221 on the HR of OS (Table 3). Among 7 data sets, 2 were from the United States and 5 were from China. The pooled HR in

Table 1

Characteristics of the included articles.

Author	Year	Country	Sample	Number	Stage	Histological classification	Quality score (NOS)
Chen Y	2018	China	Tissue	114	IV	Glioblastoma	9
Sun C	2017	USA	Tissue	548	IV	Glioblastoma	8
Xue L	2017	China	Tissue	165	I-IV	Glioma	8
Li X	2016	China	Tissue	45	I-IV	Glioma	8
Zhang R	2016	China	Blood	50	I-IV	Glioma	8
Zhang C	2012	China	Tissue	36	I-IV	Glioma	8
Srinivasan S	2011	USA	Tissue	111	IV	Glioblastoma	7
Chen W	2016	USA	Tissue	89	IV	Glioblastoma	7
				102	IV	Glioblastoma	7
				109	IV	Glioblastoma	7

NOS = Newcastle Ottawa Scale.

Table 2

Information of the included studies.

Author	Year	Cut-off	Methods	Results	HR	95% CI	*P* value
Chen Y	2018	None	Q-PCR	OS	2.112	1.125–3.9651	.02
Sun C	2017	Median	Q-PCR	OS	1.4586	1.1358–1.8731	.0031
Xue L	2017	Median	Q-PCR	OS	1.656	1.135–2.486	.0089
Li X	2016	Mean	Q-PCR	OS	2.18	1.02–4.65	.044
Zhang R	2016	None	Q-PCR	OS	2.4	1.42–4.05	.0011
Zhang C	2012	Median	IHC	OS	2.63	1.25–5.56	.011
Srinivasan S	2011	60%	Q-PCR	OS	1.27	1.0968–1.4706	.0014
Chen W	2016	Median	Q-PCR	DFS	1.25	0.98–1.6	.77
		Median	Q-PCR	DFS	1.13	0.96–1.32	.14
		Median	Q-PCR	DFS	1.09	0.93–1.3	.26

CI = confidence interval; HR = hazard ratio; Q-PCR = quantitative polymerase chain reaction.

China studies was 2.03 (95% CI, 1.58–2.60). And the pooled HR in USA was also significant (HR = 1.32 95% CI, 1.16–1.49). Then we calculated the HR of different samples. Only one study detected the microRNA in blood. So we analyzed the HR by excluding this study. After excluding this study, the HR changed to 1.54 (95% CI, 1.27–1.87). Next, we analyzed the HR in different stages of glioma. The pooled HRs in stage IV and stage I–IV studies were 1.38 (95% CI, 1.15–1.66) and 2.01 (95% CI, 1.54–2.64), respectively. After that, the HRs of different cut-off values were calculated. The expression of microRNA 221 was divided into high and low degree by different cut-off values. Among these studies, 3 studies defined the median value as the cut-off point, one study defined the mean value as the cut-off point, and one study defined 60% as the cut-off value. The rest 2 studies did not show the definite cut-off value in the article. We divided them into non-median cut-off value group along with the studies of mean cut-off value and 60% cut-off value. The pooled HR of this group was still significant (HR = 1.80 95% CI, 1.20–2.69) which reached a same conclusion with the median cut-off group (HR = 1.60 95% CI, 1.27–2.00). At last, the HR of different methods for detecting the microRNA 221 was analyzed. We calculated the HR by excluding the study which used immunohistochemistry to score the level of microRNA 221 (HR = 1.60, 95% CI, 1.30–1.94).

Overall, the factors mentioned above did not change the conclusion that microRNA 221 was a potential marker for the prognosis of glioma patients.

3.5. Publication bias

We showed the publication bias by funnel plot. And we analyzed the publication bias by Begg test. As shown in Fig. 3, no significant bias was found in this study ($P = .133$).

4. Discussion

In this article, we analyzed the pooled HR from the selected studies (HR for OS = 1.66, 95% CI, 1.34–2.04; HR for DFS = 1.14, 95% CI, 1.02–1.26). Besides, we also analyzed the influence of the nation of the study, the origin of the samples, the stage of the tumors, the cut-off value, and the method for detecting the microRNA 221 for HR of OS (Table 2). Not surprisingly, these factors did not influence our conclusion that microRNA 221 was related to the prognosis of glioma. In order to find out the major resource of heterogeneity, the sensitivity analysis was performed. We calculated the I^2 by excluding each study which were included in our research. After excluding the article by SS, I^2 shrank to 5.50%. So we believed that the study by SS was the major resource of heterogeneity. The different cut-off value (60%) might be the reason for the heterogeneity in the context of our included information. In addition, other information not included in the article might also be a reason for the significant heterogeneity, including different treating strategies and follow-up time. The pooled HR was still significant for OS after excluding this article (HR = 1.75, 95% CI, 1.45–2.1). Before this study, many kinds of microRNAs (like microRNA 650, microRNA 320, microRNA 155, microRNA 210, and microRNA 133) had been proved to be related to the prognosis of glioma.[2,4,31–33] And microRNA 221 had been identified to be a good marker of liver cancer, colorectal cancer, and ovarian cancer.[18–20] Since a lot of studies had investigated the role of microRNA 221 on proliferation, invasion and angiogenesis of glioma cells, numerous articles were published to verify the relationship between microRNA 221 and glioma.[12–17] However, different conclusions were drawn from these studies. So our study systematically analyzed the effects of microRNA 221 and further supported the role microRNA 221 on the prognosis of glioma.

Previous research has shown that high expression of microRNA 221 increased the ability of proliferation, invasiveness, and migration of glioma cells, which might partially explain the relationship between microRNA 221 and the short survival of glioma patients.[12,16,34,35] The study performed by Zhang et al[35] showed that the suppression of microRNA 221 resulted in the down-regulation of G1 to S shift through the up-regulation of p27 in vivo and in vitro. Another study by Cai et al[34] also proved the effects of microRNA 221 on the proliferation of glioma cells. The study also confirmed that high expression of microRNA 221 promoted the migration and invasion of glioma cells via targeting SEMA3B. The same conclusion was also drawn from the research of Zhang et al[12] and Quintavalle et al.[16] But different mechanisms were suggested. It was confirmed that microRNA 221 was associated with the resistance of chemotherapy and radiotherapy.[36–39] And the resistances were both related to the activation of AKT. The resistance of chemotherapy (carmustine) was related to the down-regulation of phosphatase and tensin homolog deleted on chromosome ten, but radiotherapy was independent to phosphatase and tensin homolog deleted on chromosome ten status.[37,38] High expression of microRNA 221 also induced the resistance of temozolomide by targeting DNM3 genes.[36]

Glioma is a heterogeneous disease which arises from brain parenchyma.[24] High grade glioma always means high mortality and poor prognosis. Many kinds of biomarker has been proved

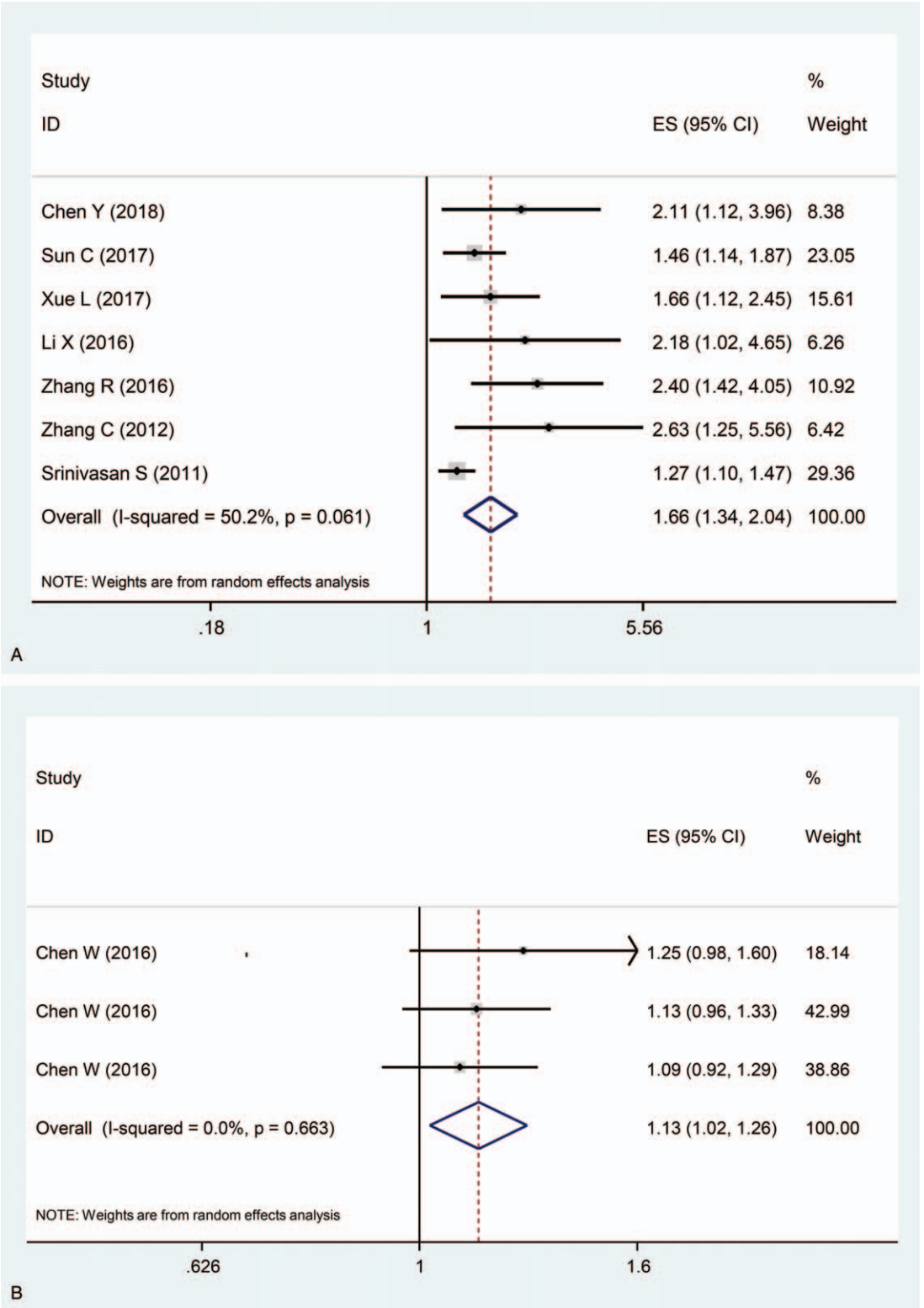

Figure 2. Pooled hazard ratio of higher microRNA 221 for overall survival and disease free survival in patients with glioma.

before. Apart from the expression of chondroitin sulfate, inflammation factors, matrix metallopeptidase 2, and matrix metallopeptidase 9, microRNAs have been verified to be good markers for the prognosis of glioma recently.[40–42] Unlike the other factors mentioned before, microRNAs is a group of factors which can provide more evidence for the prognosis of glioma. More predictors of microRNAs means more evidence for the prognosis of glioma.

Table 3

Summary of meta-analysis results.

	Data sets	Pooled HR (95% CI)	*P* value	Heterogeneity (I^2, *P*)	Conclusion
OS	7	1.66 (1.34–2.04)	<.001	50.2%, .06	Positive
DFS	3	1.14 (1.02–1.26)	.018	0.0%, .66	Positive
China	5	2.03 (1.58–2.60)	<.001	0.0%, .75	Positive
USA	2	1.32 (1.16–1.49)	<.001	0.0%, .35	Positive
Tissue	6	1.54 (1.27–1.87)	<.001	39.1%, .15	Positive
Blood	1	2.4 (1.42–4.05)	.0011	—	—
IV	3	1.38 (1.15–1.66)	<.001	32.4%, .23	Positive
I–IV	4	2.01 (1.54–2.64)	<.001	0.0%, .59	Positive
Cut-off (median)	3	1.60 (1.27–2.00)	<.001	11.0%, .33	Positive
Other cut-off values	4	1.80 (1.20–2.69)	<.001	65.4%, .034	Positive
Method (Q-PCR)	6	1.60 (1.30–1.94)	<.001	47.2%, .09	Positive
Method (IHC)	1	2.63 (1.25–5.56)	.011	—	—

CI = confidence interval, HR = hazard ratio, Q-PCR = quantitative polymerase chain reaction.

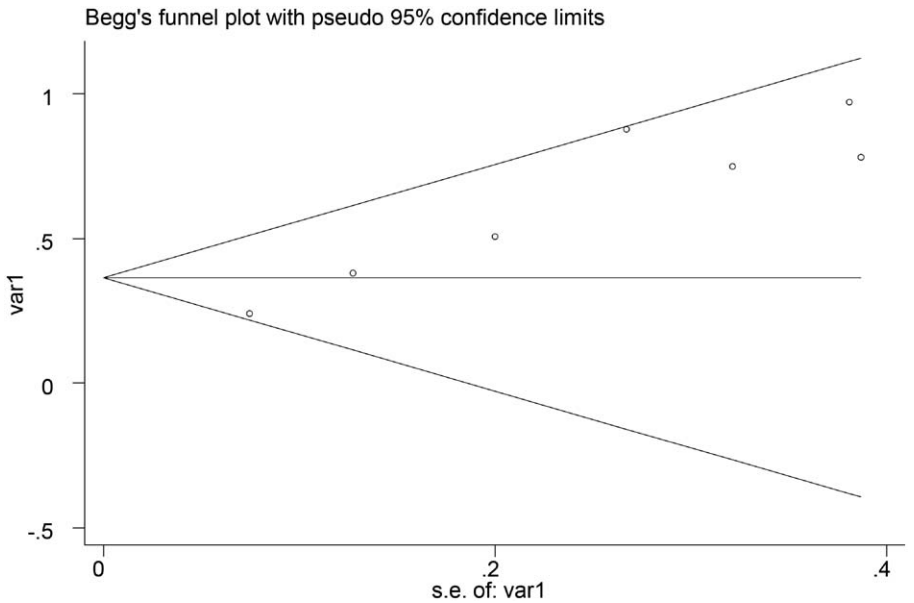

Figure 3. The Begg publication bias plot of the included studies.

However, there are still some limitations in our study. Firstly, the origin of the sample was mostly from tumor tissue. But the microRNA 221 in blood has even greater potential for glioma patients as for the non-invasive detection. So more studies were needed to further evaluate the prognostic role of microRNA 221 in blood for glioma. Besides, a significant change occurred in the classification of glioma patients since 2016.[22] Both molecular parameters and histology were considered in the diagnosis on the 2016 World Health Organization (WHO) classification of CNS tumors while the previous classification only considered the histology. But the included studies did not distinguish the different molecular parameters of glioma patients. So more studies based on 2016 WHO classification of CNS tumors are warranted in the future.

In conclusion, our study proved that high expression of microRNA 221 is associated to the poor prognosis of glioma. These findings may assist future exploration on microRNA 221 and help predict prognosis of glioma. However, due to the significant heterogeneity between the studies, more studies are warranted.

Author contributions

Conceptualization: Yanlin Song, Min He, Jing Zhang, Jianguo Xu.
Data curation: Yanlin song, Min He, Jing Zhang.
Formal analysis: Yanlin Song, Min He, Jing Zhang.
Methodology: Yanlin song, Min He.
Project administration: Yanlin Song, Jianguo Xu.
Supervision: Jianguo Xu.
Writing – original draft: Yanlin Song, Min He, Jing Zhang.
Writing – review & editing: Jianguo Xu.

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