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Prognostic role of microRNA-155 expression in gliomas: A meta-analysis

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ABSTRACT

Recent studies have reported that microRNA-155 (miR-155) is linked to the clinical outcomes of many tumors. However, its role in prognosis of gliomas remains unclear. This meta-analysis aims to evaluate the prognostic value of miR-155 in the survival of patients with gliomas. Hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival (OS) were pooled with random effects or fixed effects models on the basis of heterogeneity. Subgroup analysis and sensitivity analysis were performed to elucidate the possible confounding factors and investigate the source of heterogeneity. In addition, we assessed publication bias using the Begg's funnel plots, Egger's test, and Begg's test. Only non-laboratory studies were considered for our analysis. 9 studies from 6 articles containing 1259 glioma patients were included. The pooled HR of elevated miR-155 for OS in patients with gliomas was 1.40 (95%CI [1.19–1.63], P < 0.001) (I-squared = 52.4%, P = 0.032) suggesting that miR-155 might be a promising biomarker for the prognosis of gliomas in future clinical applications.

1. Introduction

Gliomas are the most common primary brain tumors, with a prevalence of between 5 and 10 cases per 100,000 people [1]. Histopathologically, gliomas are categorized into four malignancy grades based on the World Health Organization (WHO) classification [2]; glioblastoma multiforme (GBM, grade IV) is the most malignant and common primary brain tumors, with a median survival of 14.6 months, median progression-free survival of 6.9 months, and a 9.8% 5 year survival rate [3]. One significant challenge to treating GBM is the inevitable recurrence of these tumors. It is therefore of prime importance to obtain an accurate prognosis while the tumor is still in an early stage [4]. In the last decade, microRNAs have stirred up heated debates and have been considered as potential biomarkers for cancer prognosis.

MicroRNAs (miRNAs or miRs) are a family of abundant non protein coding, evolutionarily conserved and endogenously expressed 20–23 nucleotide single-stranded RNAs that regulate gene expression at the post-transcriptional level [5]. Additionally, they appear to act as pivotal regulators of many diseases, such as neurologic disorders, heart disease, vascular diseases, and particularly cancer [6]. MicroRNAs are aberrantly expressed in a variety of tumor types and regulate tumor biology by acting as oncogenes or tumor suppressors [7]. Recently, several studies have indicated that the expressions of microRNAs are linked to patients' survival, and they function as prognostic biomarkers [8,9].

Among the different microRNAs, miR-155 is regarded as important due to the significant differences in its expression in a variety of tumors including prostate cancer, esophageal cancer, leukemia, and non-small cell lung cancer [10–13]. Based on some laboratory studies, the overexpression of miR-155 is associated with high proliferation, low apoptosis, and high invasion of tumors [14,15]. Lately, some prognostic studies have shown elevated levels of miR-155 in gliomas, with a higher miR-155 expression associated with worse outcomes [16,17]. However, only a few studies to date have focused on the prognostic role of miR-155 expression in gliomas, revealing controversial findings. Most of these studies found high miR-155 expression in glioma tissues to correlate with poor survival, while others were unable to confirm these results [18]. Since published studies have had small sample sizes, it is necessary to carry out an integrated meta-analysis of the publications to identify the relationship between a miR-155 expression level and the survival of glioma patients.

This research, up to the moment of writing this manuscript, is the first meta-analysis to explore the potential prognostic value of miR-155 in glioma patients. Only non-laboratory studies were considered for the analysis. The investigation also provides more theoretical backings to a new treatment argument for a later research.

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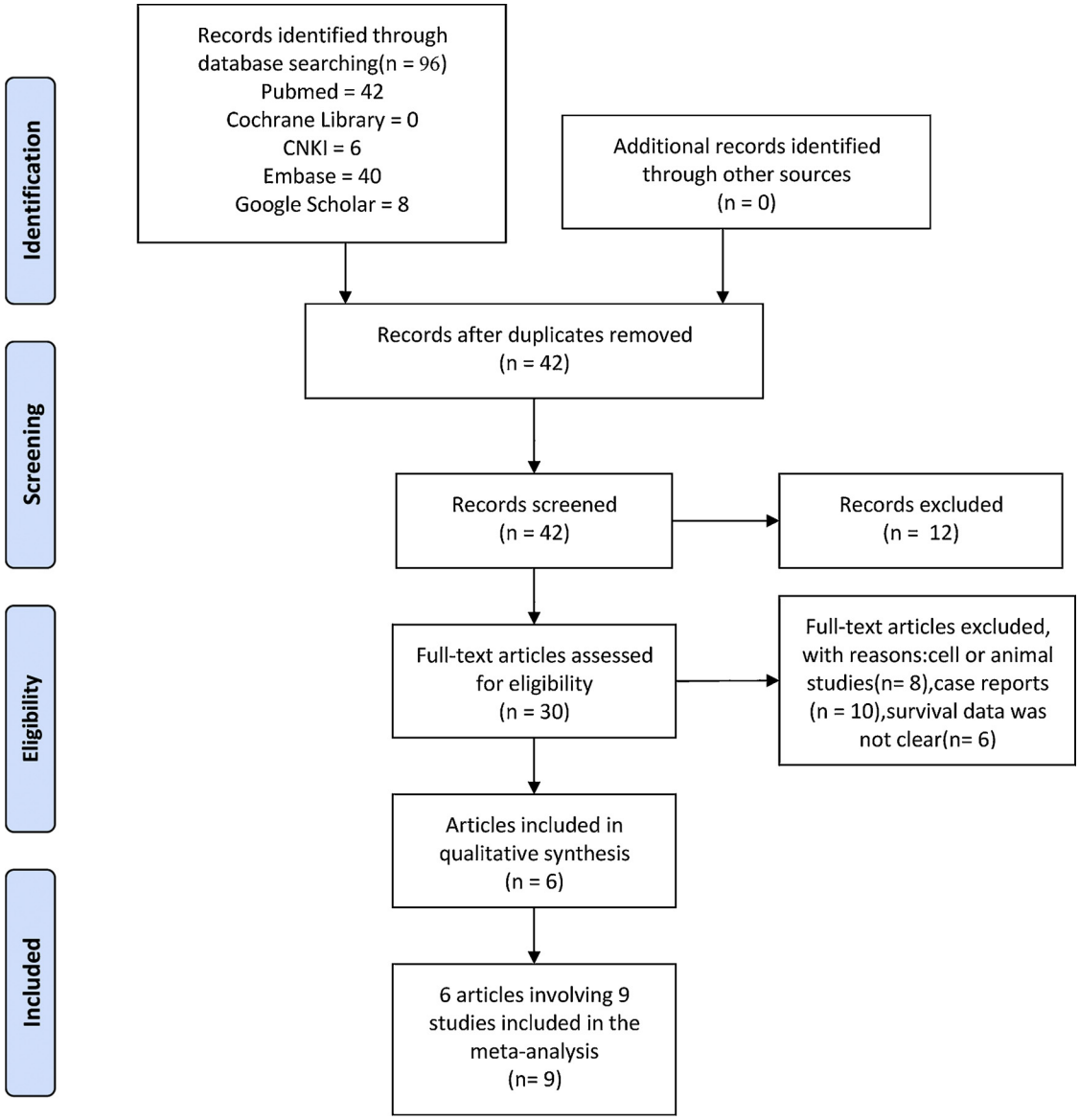

Fig. 1. Flow diagram shows search strategy.

2. Materials and methods

2.1. Search strategy

We performed a complete search for available literature in the electronic databases of Pubmed, Embase, Cochrane Library, China National Knowledge Infrastructure, and Google Scholar until April 2018, using the following words "(miR-155 OR miRNA-155 OR miR155 OR microRNA-155) AND (glioma OR glioblastoma OR CNS cancer OR glial cell tumor OR astrocytoma)." References in eligible studies were also screened to identify potentially related articles. We also contacted some authors when the crucial data were not reported in their original papers. Two authors completed this procedure independently and resolved any discrepancy through the consensus with a third reviewer.

2.2. Selection criteria

Inclusion criteria were as follows: 1) studies focusing on glioma and glioblastoma patients; 2) studies exploring the link between miR-155 expression and cancer prognosis; and 3) studies providing HR directly or key information to calculate HR indirectly, such as Kaplan-Meier curves and original prognostic data. Studies were excluded if they were either: a) reviews, letters, or laboratory studies; or b) studies that have overlapping or duplicate data.

2.3. Qualitative assessment

The quality of the studies selected was assessed independently by two authors using the modified Newcastle-Ottawa scale (NOS) [19]. The scale consisted of three aspects: selection (0–4 points), comparability (0–2 points), and outcomes (0–3 points); the full score was 9 points. Studies with more than 6 points were considered as high quality studies.

2.4. Data extraction

The following details were recorded for each enrolled study: first author's name, publication year, country, tumor grade, sample size, test method to assay miR-155 levels, the cutoff value to determine high or low expression of miR-155, sample sources, follow-up time, extraction method of HR, outcome and NOS. Directly extracted HR values were reported, while Kaplan-Meier curves were used to extract indirect HR

values via the described method [20]. We preferred extracting HRs and 95%CIs from the multivariate analysis if both multivariate analysis and univariate analysis of the results were performed.

2.5. Statistical analysis

HRs and 95%CIs were used to measure the effect size. The heterogeneity of the studies included in this meta-analysis was assessed by the I^2 statistic test. We used the random effects model to minimize the influence of heterogeneity while $I^2 > 50\%$ or $P < 0.10$ [21], otherwise, the fixed effects model was selected. Subgroup analyses were applied to identify the sources of any observed heterogeneity. Publication bias was examined using the Begg's funnel plot, Begg's test, and Egger's test. $P < 0.05$ was considered significant [22]. All analyses were performed by using software STATA version 12.0 and Engauge Digitizer version 4.1.

3. Result

3.1. Literature research

A total of 96 studies were retrieved from the initial search. After exclusion of duplicates and irrelevant articles, only 30 articles were identified as eligible for full-text review. Assessment of the full text of all 30 publications led to the exclusion of another 24 articles for the following reasons: cell or animal studies (n = 8), case reports (n = 10), and survival data was not clear (n = 6). Finally, six articles with 9 studies were included in this meta-analysis [16–18,23–25]. These six articles included a total of 1259 patients with gliomas (Fig. 1). None of the eligible studies scored less than six by NOS. Fig. 1 displays the selection workflow of all eligible studies in our meta-analysis.

3.2. Characteristics of included studies

The main characteristics of the 6 included articles are shown in Table 1. All of them were published in recent years and were from 3 different countries. One of the selected articles separately assessed the prognostic value of miR-155-5p and miR-155-3p, two key derivatives of miR-155, with different prognosis data [18]. Another article analyzed three separate batches downloaded from TCGA datasets which reported findings on a group of patients with gliomas of GBM, WHO III, and WHOI-IV [25]. There was no overlap between the batches enrolled in the article. Thus, 9 studies (from 6 articles) involving 1259 patients were available for this meta-analysis. Four studies examined glioblastoma, two investigated glioma with grade III, and the remaining two involved glioma with different grades. Microarray (n = 2) and q-PCR (n = 3) were used to assess miR-155 expression, but the rest of the studies did not clarify the test methods used. The cutoff value varied among studies, with the median expression of miR-155 the most widely used. 5 HRs were reported in the present analysis, with the other 4 HRs estimated by analyzing K–M curves. Four of the studies conducted multivariate analysis of OS, while the remaining five performed univariate analysis. All studies provided data on OS, while only 2 studies provided findings on PFS with respect to outcomes.

3.3. Correlation of miR-155 expression with OS and PFS in gliomas

A total of nine studies were used for OS analysis (I^2 = 52.4%, P = 0.032) (Fig. 2; Table 1) using a random-effects model due to significant inter-study heterogeneity. The pooled HR (HR = 1.40, 95%CI [1.19–1.63], $P < 0.001$) suggested that a higher expression level of miR-155 significantly predicted poorer OS in patients with gliomas.

Furthermore, sensitivity analysis did not indicate alterations in the results (HR) by sequentially eliminating individual studies, suggesting that no single study significantly contributed to the heterogeneity for OS (Fig. 3).

Table 1
Characteristics of the included articles.

Author	Year	Country	Type	No. of patients	Disease stage	Material	Method	Cut-off	Survival analysis	Follow-up (month)	Extraction method	Multivariate method	NOS
Wu, Xuechao [18]	2017	China	miR-155-5p miR-155-3p	64	GBM	Tissue(CGGA)	Microarray	Median	OS	> 30	K-M	No	7
Yang, L [16]	2017	China	miR-155	43	I-IV	Tissue	qPCR	NM	OS	60	K-M	No	6
Schliesser, M G [17]	2016	Germany	miR-155	107	III	Tissue(TCGA)	qPCR	NM	OS	> 192	Reported	Yes	8
Sun, J [23]	2014	China	miR-155	131	I-IV	Tissue	qPCR	Mean	OS/PFS	> 60	K-M	Yes	8
Qiu, S [24]	2013	China	miR-155	480	GBM	Tissue(TCGA)	Microarray	Median	OS/PFS	> 100	Reported	Yes	8
Barbano, R [25]	2014	Italy	miR-155	191	GBM	Tissue(TCGA)	Microarray	Median	OS	> 110	Reported	No	8
				58	III	Tissue(TCGA)	Microarray	Median	OS	> 110	Reported	No	8
				185	I-IV	Tissue(TCGA)	Microarray	Median	OS	> 110	Reported	Yes	7

Abbreviations: GBM, glioblastoma multiforme; CGGA, the Chinese Glioma GenomeAtlas; TCGA, The Cancer Genome Atlas; qPCR, quantitative real-time PCR; NM, not mentioned; OS, overall survival; PFS, progression-free survival; K–M, Kaplan-Meier curves; NOS, Newcastle-Ottawa scores.

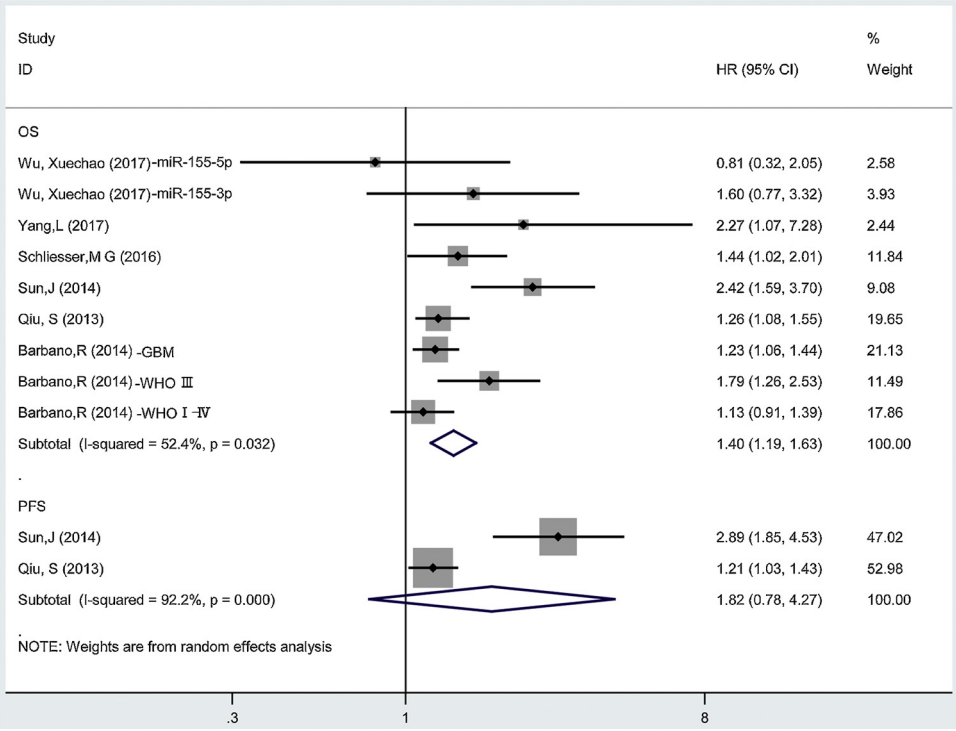

Fig. 2. Forest plot of the relationship between miR-155 and OS/PFS in glioma patients.

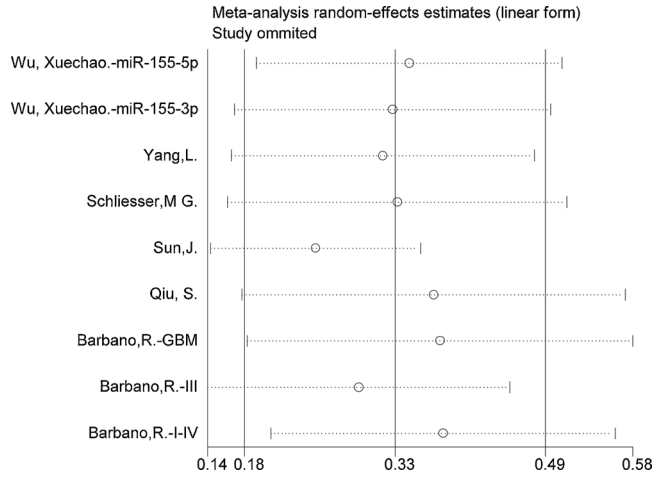

Fig. 3. Sensitivity analysis of miRNA-155 expression and OS among gliomas.

As two [23,24] of the nine studies provided progression-free survival-related data, a meta-analysis of PFS was conducted using the random-effects model (Fig. 2). However, no significant HR (HR = 1.82, 95%CI [0.78–4.27], P = 0.167) and high heterogeneity were found (I^2 = 92.2%, P < 0.001). As a result, we did not perform the sub-group analysis of PFS and miR-155. Despite the lack of significant differences, a similar correlated trend was observed for PFS and miR-155.

3.4. Subgroup analysis

Given that the substantial heterogeneity exhibited in the studies with respect to the OS, we performed subgroup analysis to explore the heterogeneity of covariates including country, tumor grade, test method, cutoff, extraction method, and multivariate analysis (Table 2, Supplementary material). Subgroups analysis by country revealed that the expression of miR-155 significantly correlated with OS both in the China group (HR = 1.95, 95%Cl [1.41–2.68], P < 0.001) and the non-China group (HR = 1.27, 95%Cl [1.15–1.39], P < 0.001). With respect to subgroups by tumor grade, results from both WHO IV (HR = 1.24,95%CI [1.11–1.39, P < 0.001) and WHO III (HR = 1.60, 95% CI [1.26–2.04], P < 0.001) groups suggested poor prognosis with high miR-155 expression levels, meanwhile the WHOI-IV (HR = 1.73, 95%CI [0.94–3.21], P = 0.08) group showed no significant HR. According to subgroups by different test methods, significant HR was found both in the q-PCR group (HR = 1.797,95%CI [1.392–2.318], P < 0.001) and the Other group (HR = 1.252, 95%CI [1.135–1.381], P < 0.001), whereas, no significant HR was reported in the Microarray group (HR = 1.233, 95%CI [0.695–2.190], P = 0.474). Subgroup analysis by Cutoff indicated that both the Median (HR = 1.25, 95% CI [1.14–1.38], P < 0.001) and the Other (HR = 1.51, 95% CI [1.10–2.09], P = 0.011) marked poor prognosis with higher miR-155 expression status. Both the Reported group (HR = 1.27, 95%CI [1.15–1.39], P < 0.001) and the K–M group (HR = 1.95, 95%CI [1.41–2.68], P < 0.001), based on the extraction methods, showed significant HRs. Similarly, significant HRs were attained in both the Yes group (HR = 1.41,95%CI [1.10–1.81], P = 0.007) and the No group (HR = 1.32, 95%CI [1.15–1.51], P < 0.001) in the subgroup analysis of multivariate analysis.

3.5. Publication bias

Finally, publication bias in our study of OS was assessed using the Begg's funnel plots, Egger's test, and Begg's test. Although the funnel plot revealed a substantial publication bias (Fig. 4), the P-value of Begg's and Egger's tests were 0.348 and 0.167, respectively, suggesting that there was no significant publication bias in the entire study.

4. Discussion

In previous studies, patients with differing miRNA expressions had different prognoses and responded to different treatments. Therefore, miRNAs may help classify, diagnose, and predict the clinical course for patients with brain tumors [26–29]. It has been reported that microRNAs plays crucial roles in various physiological and pathological

Table 2
Pooled HRs for OS according to subgroup analysis.

Subgroup analysis		No. of studies	No. of patients	Model	HR (95% CI)	P value	Heterogeneity	
							(I^2)	P value
Country								
	China	4	718	Fixed	1.95(1.41-2.86)	< 0.001	37.8%	0.185
	Non-China	5	541	Fixed	1.27(1.15-1.39)	< 0.001	28.5%	0.231
Grade								
	GBM	4	735	Fixed	1.24(1.11-1.39)	< 0.001	0	0.728
	III	2	165	Fixed	1.60(1.26-2.04)	< 0.001	0	0.381
	I-IV	3	359	Random	1.73(0.94-3.21)	0.08	82.1%	0.004
Test method								
	Microarry	2	64	Fixed	1.23(0.69-2.19)	0.474	21.6%	0.259
	qPCR	3	281	Fixed	1.80(1.39-2.32)	< 0.001	47.0%	0.151
	Other	4	914	Fixed	1.25(1.14-1.38)	< 0.001	39.9%	0.172
Cutoff								
	Median	6	978	Fixed	1.25(1.14-1.38)	< 0.001	20.3%	0.281
	Mean	1	131		2.42(1.59-3.70)	< 0.001		
	Other	2	150	Fixed	1.51(1.10-2.09)	0.011	0	0.38
Extraction method								
	K-M	4	718	Fixed	1.95(1.41-2.68)	< 0.001	37.8%	0.185
	Reported	5	441	Fixed	1.27(1.15-1.39)	< 0.001	28.5%	0.231
Multivariate method								
	Yes	4	772	Random	1.41(1.10-1.81)	0.007	71.4%	0.015
	No	5	387	Random	1.32(1.15-1.51)	< 0.001	36.6%	0.177

processes, such as cell differentiation, proliferation, and apoptosis, as well as in oncogenesis and immune responses [30]. MicroRNAs regulate pathway networks in tumors by targeting various oncogenes and tumor suppressors [31]. MiR-155, located on chromosome 21, is reportedly present in many tumors; it is shown as promoting tumor migration and invasion in hepatocellular carcinoma by suppressing PTEN via the PI3K/Akt pathway [32], while as a tumor promoter in bladder cancer, it functions directly by reducing the expression of the tumor suppressor DMTF1 [33]. MiR-155 promotes the progression of glioma by enhancing the activation of the Wnt pathway [34]. The downregulation of miR-155 in ovarian cancer-initiating cells correlates with CLDN1 overexpression and the suppression of tumor invasion in ovarian cancer [35]. Although miR-155 typically functions as an oncomiR in many tumors, its role as a suppressor has also been reported [35,36].

In recent years, many studies have shown that miR-155 is a potential prognostic factor for various cancers. One report [37] has high miR-155 expression as a predictor of poor OS in cervical cancer patients (HR = 2.320, 95%CI [1.259–4.276], P = 0.007), another [38] revealed that miR-155 expression was an unfavorable prognostic factor of OS (HR = 2.311, 95%CI [1.479–3.611], P < 0.001) in lung cancer, while yet another [39] showed that miR-155 expression level was an independent prognostic factor for overall survival (HR = 2.394, 95%CI [1.568–10.034], P = 0.009) in gallbladder carcinoma after surgical resection. In contrast, Wu et al. [18] reported that there was no significant association between miR-155-5p expression and OS in glioma patients. In light of these inconsistent results on the prognostic value of miR-155 in gliomas, a comprehensive study is highly needed.

4.1. Summary and explanation of the main results

In this meta-analysis, our quantitative results strongly supported the current mainstream viewpoint that miR-155's high expression is linked to poor OS. No publication bias was observed and sensitivity analysis showed that the stability of the entire study was not influenced by any individual study. In subgroup analysis, no obvious heterogeneity occurred in most subgroups but in the subgroup with various tumor grades (I^2 = 82.1%, P = 0.004) and the subgroup using the multivariate analysis method (I^2 = 71.4%, P = 0.015) (Table 2). No significant HR was found in the WHOI-IV(HR = 1.73,95%CI [0.94–3.21], P = 0.08) subgroup, which indicated that the result should only be applied for OS estimated in high grade gliomas and need further elucidation. Apart from that, the subgroup with the test method of microarray also showed no significant difference (HR = 1.233, 95%CI [0.695–2.190], P = 0.474) which may partly attribute to a small number of patients (n = 64). AS for the source of the data, some HRs were extracted from K–M survival curves of 4 studies, and others, from the remaining studies, were directly reported, but no obvious heterogeneity was shown in the two subgroups (Table 2), implying that the data extracted from K–M survival curves were reliable.

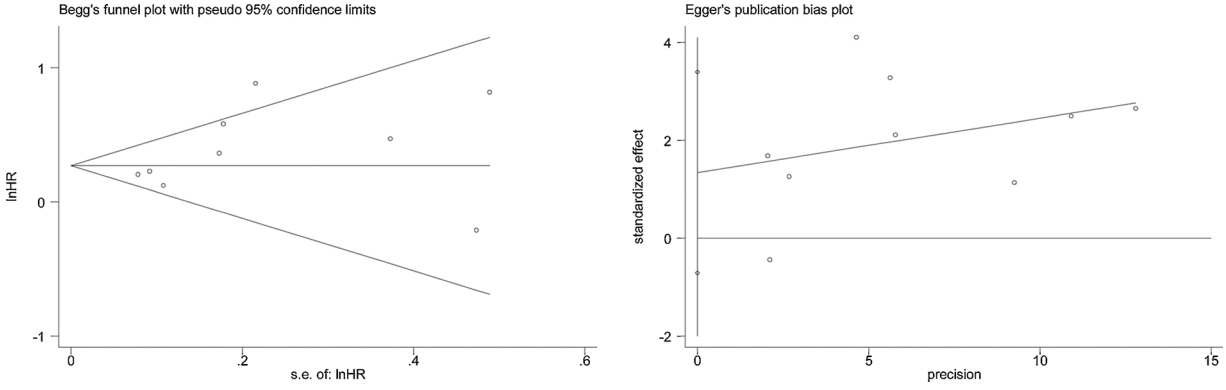

Fig. 4. Publication bias of studies for OS by Begg's test and Egger's test.

4.2. Limitations of the study

Several important limitations should be considered when interpreting our analysis. Firstly, in order to get a more comprehensive result, we pooled HRs for both OS and PFS. However, further analysis for PFS and miR-155 was not conducted for only two eligible studies. Secondly, to date, few studies have analyzed the prognostic value of miR-155 in LGG (Lower Grade Glioma) patients. Barbano et al. [25] showed that miR-155 had a significant higher expression level in grade III + IV than in grade II, but none of the miRNAs they had selected was associated with prognosis in grade II gliomas from the LGG dataset (n = 57). Reports from Wu et al. [18] and Sun et al. [23] present miR-155 as being significantly associated with tumor grade with their expression levels higher in GBM than in LGG. However, both these studies lacked prognostic data. Therefore, we cannot investigate the differences of overall survival between WHO I and IV glioma patients and must recommend that further investigations are performed. Thirdly, Wu et al. [18] reported that the MIR155 host gene (MIR155HG) encoding miR-155 correlated with the overall survival in gliomas (HR = 2.082, P = 0.023) and Schliesser et al. [17] found that miR-155 promoter methylation and miR-155 expression correlated negatively, with the methylation, in particular, showing superior correlation with patient survival. However, due to limited data, we were unable to perform meta-analysis on the relationship between these miR-155 associated parameters and prognosis in glioma patients. Moreover, only one [18] of the selected articles studied the derivatives of miR-155. Additionally, it difficult to define the standard cutoff value; most studies used the median value as the expression cutoff, and there was no consensus between these values among the studies selected. Finally, although subgroup analysis was performed, heterogeneity still existed in some groups, and we could hardly explain its source.

5. Conclusion

In summary, our meta-analysis suggests that miR-155 has a prognostic value in glioma patients. In view of the limitation of the current analysis, our findings should be interpreted with caution. Further large-scale, well-designed, and multi-center prospective studies should be conducted to elucidate the exhaustive mechanism of miR-155 overexpression in human glioma and the relationship with poor prognosis.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2018.12.005.

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