



Research Article

A Meta-Analysis of the Prognostic Value of Abnormally Expressed lncRNAs and Correlation with Clinicopathological Characteristics in Glioma

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Abstract

Objectives: Abnormal expression of lncRNAs are involved in the occurrence and development of glioma. Thus, we conducted a meta-analysis to clarify the prognostic value of lncRNAs in glioma integrally.

Methods: Pubmed, Web of Science, Embase, Cochrane Library, Clinical Trial.gov and Trip database were searched. Hazard ratio (HR) and 95% confidence intervals (CI) were calculated in the analysis of prognostic indicators. Odds ratio (OR) and 95%CI were applied to estimate the association between lncRNAs and clinicopathological features.

Results: The expression level of lncRNA was significantly correlated with the OS rate of glioma patients (HR=1.29, 95%CI: 1.03-1.61, p=0.03). The low expression of CASC2 (HR=0.42, 95%CI: 0.27-0.66, p=0.0001) showed a poor prognosis of glioma patients. MALAT1 (HR=1.42, 95%CI: 0.38-5.29, p=0.60), HOTAIR (HR=1.70, 95%CI: 0.69-4.21, p=0.25) and TUSC7 (HR=1.81, 95%CI: 0.87-3.75, p=0.11) have no statistical significance for the prognosis of glioma patients. The high expression of lncRNA was related to WHO staging (OR=0.31, 95%CI: 0.19-0.50, p<0.00001), EGFR expression (OR=3.14, 95%CI: 1.70-5.77, p=0.0002) and IDH1 status (OR=0.33, 95%CI: 0.12-0.93, p=0.04), while unrelated to age (OR=1.05, 95%CI: 0.78-1.42, p=0.75), gender (OR=1.01, 95%CI: 0.85-1.20, p=0.92), tumor size (OR=0.67, 95%CI: 0.35-1.27, p=0.22), PTEN (OR=0.26, 95%CI: 0.06-1.10, p=0.07), KPS score (OR=1.06, 95%CI: 0.44-2.59, p=0.90), MGMT promoter methylation (OR=2.05, 95%CI: 0.94-4.50, p=0.07) and the recurrence (OR=0.87, 95%CI: 0.42-1.82, p=0.72).

Conclusion: Abnormal expression of lncRNAs were related to survival of glioma patients and may serve as potential prognostic indicators in glioma. The higher expression level of lncRNAs, the worse prognosis of glioma. The expression of lncRNA CASC2 is correlated with the prognosis of glioma patients. The higher the expression level of CASC2, the better prognosis. lncRNAs are related to WHO staging, EGFR expression and IDH1 mutation, while unrelated to age, gender, tumor size, PTEN, KPS score, MGMT gene promoter methylation or tumor recurrence.

Keywords: lncRNAs, clinicopathological features, glioma, prognosis

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Glioma is the most common form of malignant tumor of the central nervous system (CNS), accounting for about 50% to 60% of intracranial primary tumors. Rapid progress, early metastasis, difficult operation, and insen-

sitivity to radiotherapy and chemotherapy are the causes of poor prognosis, which make glioma to be the highest degree of malignancy.^[1]

lncRNAs are located in the nucleus or cytoplasm which

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is a series of RNA with transcripts longer than 200 nucleotides, without functional open reading frame, unable to encode proteins, but related to the genesis and progression of the tumor closely. In recent years, lncRNAs have been reported to play vital roles in various human malignancies via different biological processes such as epigenetic regulation, chromosomal imprinting, cell cycle regulation, transcriptional and translational regulation, differentiation and proliferation and DNA damage repair.

More and more studies have shown that lncRNAs have different transcription level in different types, grade, malignancy and so on. Their value in diagnosis and prognosis is also gradually revealed.^[2] Abnormal expressed lncRNAs could act as potential markers for prognostic evaluation of patients with HCC, lung carcinoma, renal cell carcinoma, pancreatic cancer, cervical cancer, colorectal cancer.^[3-7]

However, varieties of lncRNAs expression in glioma remain controversial. For instance, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was reported inconsistent in transcription level in glioma. It was down-regulated in the studies of Chen et al. and Cao et al., as well as in many other solid tumor.^[8, 9] But Ma et al. claimed it was up-regulated in glioma.^[10] Another example, there also exist differences in the judgement of the prognosis. Cao et al. indicated that over-expression of MALAT1 represented a good prognosis in glioma, which is opposite to Ma et al's and Chen et al's conclusion. Besides, Wang et al. showed down-regulated cancer susceptibility candidate 2 (CASC2) predicted a poorer prognosis while Liao et al showed CASC2 was not statistically significant in survival time by multivariate analysis.^[11, 12] Moreover, there are also different views on the association between lncRNA and clinicopathological features in different articles.

In 2016, a systematic review and meta-analysis about lncRNAs and survival of cancer patients was conducted by Stylianos Serghiou colleagues. It had enrolled 111 eligible studies containing 16,754 participants with 19 tumor types.^[13] But only one article referred to neuroblastoma. Due to absence of raw data, the researchers calculated unavailable HRs from the survival curve which was deficiency of objectivity and scientificity.

The same year, Brian J. Reon et al.^[14] conducted an *in silico* analysis between lncRNAs and low grade glioma (LGG) and glioblastoma multiforme (GBM) using The Cancer Genome Atlas (TCGA) and other databases. They determined that 584 lncRNAs related to a poor prognosis and 282 lncRNAs with a good prognosis in GBM. These were the main limitations of this article: (1) the survival algorithm were accomplished on the same dataset; (2) they verified the changes in the expression of lncRNAs by samples of independent patient.

As far as we know, no similar work has been done yet. Consequently, the meta-analysis was performed to explore relationship between lncRNAs and prognosis and clinicopathological features of patients with glioma.

Methods

Literature search strategies

Six electronic databases including Pubmed, Web of Science, Embase, Cochrane Library, Clinical Trial. gov and Trip database were searched for potentially related articles which reported the association between various lncRNAs expression and clinical value in glioma by following search strategy: "(long non-coding RNA or lncRNA or long ncRNA) and glioma and (prognosis or survival or clinicopathological feature). The publication was limited to human sample and English language, ended in November 1st, 2017. In addition, supplement references were filtered from relevant articles.

Inclusion and exclusion criteria

The studies would be eligible if met the following criteria: (1) patients were confirmed with glioma by pathology after resection; (2) relationship and prognostic value between lncRNAs and glioma were investigated; (3) the study provided clinical features and prognostic index such as overall survival (OS) in the form of hazard ratios (HRs) and 95% confidence intervals (95% CI); (4) patients were divided into high and low groups according to the expression levels of lncRNAs. Exclusion criteria were as follows: duplicate articles; letters; review articles; case reports; lack of original data; non-human studies.

Data extraction and quality assessment

Two independent investigators extracted the data including first author's name, year of publication, country, sample size, numbers of patients in high and low lncRNAs expression groups, the detection method, source of HR from each publication

The data extracted from the literature include the following categories: (1) the basic features, including the name of the first author, country, the year of publication, the sample size. (2) the clinical data, including the expression of lncRNA in glioma, the type of lncRNA, detection method, the sample size of the high and low expression group, tumor type, source of outcome indicators, HR from Cox risk model, and with/without new adjuvant treatment before operation;

Discrepancies between the two investigators were resolved by discussion and consensus with another investigator. For the original articles which HR and 95%CI were not given directly but only Kaplan-Meier survival curves,

Parmar et al proposed that can obtain required survival data from the curve.^[15] After practice, there existed large deviation between the data extracted from curve and the real data. Therefore, such articles were not included in survival analysis to ensure the reliability and stabilization or reproduceable.

Statistical Analysis

Statistical analysis was conducted with Review Manager 5.3 Software for Windows (The Cochrane Collaboration, Software Update, Oxford, UK). HR and 95% CI were calculated to assess to the association between lncRNAs and survival in glioma with a significance level of $\alpha=0.05$. An observed HR >1 indicated that the patients with high level of lncRNAs expression had a worse prognosis. Conversely, HR <1 implied the patients with low level of lncRNAs expression had a worse prognosis. OR and 95% CI were used to estimate the association between lncRNAs and clinical features in patients with glioma. Statistical heterogeneity among the eligible studies was assessed using Cochran Q-test and I² statistic, if I² $>50\%$, a random-effect model (Mantel-Haenszel) was used to calculate HRs or ORs, if not, the fixed-effect model was utilized. A value of $p<0.05$ was considered statistically significant. The Revman 5.3 Software (The Cochrane Collaboration, Oxford, UK) was used to evaluate sensitivity analyses and publication bias of this meta-analysis.

In order to minimize the influence of heterogeneity, the included articles were classified into subgroups according to common features. Funnel plot was performed to estimate the sensitivity and publication bias.

Results

Eligible Studies and Characteristics

As shown in the flow diagram, 257 records were included through screening from Pubmed, Web of Science, Embase, Cochrane Library, Clinical Trial.gov and Trip database. After filtering the titles and abstracts, 219 records were eligibility. Subsequently, the 31 full-text articles were left for further assessed (Fig. 1).

As a result, 33 studies including 33 on OS, one study on disease free survival (DFS), one study on recurrence free survival (RFS) and 27 studies about clinicopathological features were selected for the meta-analysis. It should be mentioned that HR and 95% CI of 9 original articles which reported by survival curves indirectly were eliminated to ensure stabilization and reproduceable in actual survival analysis. They were only listed in the basic information table and used for clinicopathological characteristics analysis. The publication year of the literature range from 2013 to 2017.

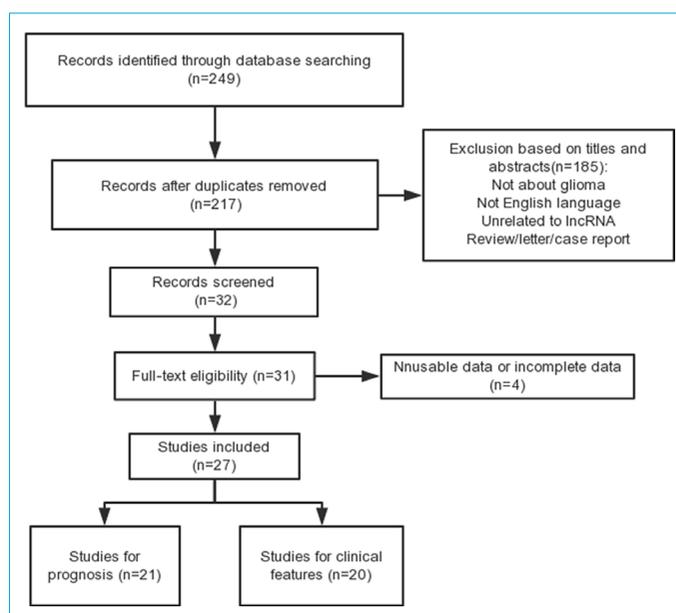


Figure 1. The flow diagram of this meta-analysis.

All case samples were from glioma tissue or cell lines, and the control group was from the non-tumor tissue, adjacent tissue, or sample from trauma. RT-PCR, qRT-PCR, or qPCR was performed to detect lncRNAs expression in glioma tissues or serum. Totally, 25 lncRNAs were described in 33 studies. Twenty-one lncRNAs were up-regulated in glioma. Besides, two lncRNAs were down-regulated. Four kinds of lncRNAs (CASC2, HOTAIR, MALAT1 and TUSC7) were studied more than once. The basic information is shown in Table 1.

Evaluation of the Literature

For the case-control study, the Newcastle Ottawa scale (the NOS scale) was used to evaluate the quality of the literature. The NOS scores ranged from 0 to 9. Three major aspects and 8 items were used to grade 33 case control studies. Two researchers evaluated and proofread the results independently. According to the evaluation, more than half of the articles in the study were scored 6 points and above, so the quality of the study could be considered acceptable (Table 2).

Analysis Between lncRNAs Expression Level and OS of Glioma

Twenty-four studies enrolled 2394 samples from glioma patients reported the high and low expression levels of lncRNAs and OS directly. A maximum sample size of 220 and a minimum size of 39. Twenty-two articles presented multivariate analysis except two articles. Two articles referred to GBM specifically. More than half of the articles claimed that specimens without any preoperative treatment such as chemotherapy or radiotherapy. And the fol-

Table 1. Summary of lncRNAs used as prognostic biomarkers of glioma and GBM

| Expression in glioma | Study ID | Year | LncRNAs | Country | Sample size | Detection method | outcome | Source of HR |
|----------------------|--------------------------------|------|--------------|---------|-------------|------------------|---------|--------------|
| Down-regulated | YW. Liao ^[12] | 2017 | CASC2 | China | 57 | qRT-PCR | OS | Reported&SC |
| | XL. Ma ^[16] | 2017 | TUSC7 | China | 206 | qRT-PCR | OS;DFS | Reported&SC |
| | RL.Wang ^[11] | 2017 | CASC2 | China | 47 | qRT-PCR | OS | Reported&SC |
| | C. Shang ^[17] | 2016 | TUSC7 | China | 39 | qRT-PCR | OS | Reported&SC |
| | W. Chen ^[9] | 2017 | MALAT1 | China | 192 | RT-qPCR | OS;RFS | Reported&SC |
| | SZ. Cao ^[8] | 2016 | MALAT1 | China | 66 | qRT-PCR | OS | Reported&SC |
| | J. Li ^[18] | 2016 | TUG1 | China | 120 | qRT-PCR | OS | SC |
| Up-regulated | QL. Lv ^[19] | 2016 | ZEB1-AS1 | China | 82 | RT-PCR | OS | Reported&SC |
| | XJ.Zhang ^[20] | 2013 | HOTAIR | China | 89 | GSEA | OS | Reported&SC |
| | SY. Jing ^[21] | 2016 | CRNDE | China | 164 | qRT-PCR | OS | Reported&SC |
| | H. Yan ^[22] | 2017 | HULC | China | 70 | qRT-PCR | OS | Reported&SC |
| | R. Zhang ^[23] | 2017 | TP73-AS1 | China | 47 | qRT-PCR | OS | Reported&SC |
| | CB. He ^[24] | 2015 | NEAT1 | China | 94 | qRT-PCR | OS | Reported&SC |
| | Y. Zhou ^[25] | 2016 | SPRY4-IT1 | China | 163 | qRT-PCR | OS | Reported&SC |
| | ZH. Chen ^[26] | 2016 | FOXD3-AS1 | China | 44 | qRT-PCR | OS | Reported&SC |
| | X. Zhou ^[27] | 2015 | HOTAIR | China | 108 | CGGA | OS | Reported&SC |
| | KX. Ma ^[10] | 2015 | MALAT1 | China | 118 | RT-PCR | OS | Reported&SC |
| | JJ.Zhuang ^[28] | 2016 | MVIH | China | 127 | RT-PCR | OS | Reported&SC |
| | L. Hu ^[29] | 2016 | AB073614 | China | 65 | qRT-PCR | OS | Reported&SC |
| | F. Wu ^[30] | 2017 | HOXA-AS3 | China | 129 | qRT-PCR | OS | Reported&SC |
| | QL. Lv ^[31] | 2017 | ZFAS1 | China | 69 | RT-PCR | OS | Reported&SC |
| | W. Zhao ^[32] | 2017 | UCA1 | China | 64 | RT-PCR | OS | Reported&SC |
| | P. Du ^[33] | 2017 | XIST | China | 69 | RT-PCR | OS | Reported&SC |
| | TH. Gao ^[34] | 2017 | HSP90AA1-IT1 | China | 65 | qRT-PCR | OS | Reported&SC |
| | QX.Wang ^[35] | 2016 | HOXA11-AS | China | 220 | qRT-PCR | OS | Reported&SC |
| | CC. Ma ^[36] | 2016 | ATB | China | 79 | qRT-PCR | OS | SC |
| | T. Zhang ^[37] | 2016 | H19 | China | 35 | qPCR | OS | SC |
| | K. Gao ^[38] | 2017 | ZFAS1 | China | 46 | qRT-PCR | OS | SC |
| | Q. Wang ^[39] | 2017 | SNHG1 | China | 78 | qRT-PCR | OS | SC |
| | YQ. Li ^[40] | 2017 | AB073614 | China | 89 | qRT-PCR | OS | SC |
| | F. Ding ^[41] | 2017 | FER1L4 | China | 484 | RT-qPCR | OS | SC |
| | ZZ. He ^[42] | 2017 | UCA1 | China | 80 | qRT-PCR | OS | SC |
| | Shlomit Brodie ^[43] | 2017 | TALNEC2 | Israel | 25 | RT-PCR | OS | SC |

lncRNA: Long-coding RNA; qRT-PCR: Quantities reverse transcription-PCR; RT-PCR: reverse transcription-PCR; qPCR: quantities PCR; OS: Overall survival; RFS: recurrence-free survival; DFS: disease free survival; HR: hazard ratio; SC: survival curve.

low-up times ranged from 30 months to 70 months. Some articles gave lncRNAs with low/high expression, thus appropriate adjustments were made for reliable results accordingly (Table 3).

The high expression level of ZEB1-AS1, CRNDE, HULC, UCA1, TP73-AS1, NEAT1, SPRY4-IT1, FOXD3-AS1, MVIH, AB073614, HOXA-AS3, ZFAS1, HOTAIR, HOXA11-AS, HSP90AA1-IT1, XIST, MALAT1, ATB, H19, SNHG1, FER1L4, TALNEC2 were reported to associate with poor prognosis. On the contrary, TUSC7, TUG1 and CASC2 correlated to good prognosis with the high expression level in glioma. Finally, a significant association between lncRNAs and OS in glioma patients was presented via a random-effect

model assessing the HR and 95% CI (HR=1.29, 95%CI: 1.03-1.61, p=0.03, I²=86%) (Fig. 2a). It could be inferred that the patients with high level of lncRNAs expression may indicate a worse prognosis.

Sensitivity Analysis

Sensitivity analysis was used to judge whether modifying inclusion criteria could affect the final results. The sensitivity analysis did not influence the results excessively by deleting any one study for overall survival no matter in up-regulated or down-regulated groups, which indicated this meta-analysis was relatively stable and credible.

Table 2. Quality assessment based on the NOS scale

| Study | Year | Selection | | | Exposure | | | Score | |
|----------------|------|------------------------------|---------------------------------|-----------------------|--|---------------------------|---|-------|-------------------|
| | | Adequate definition of cases | Representativeness of the cases | Selection of controls | Comparability Control for important factor | Ascertainment of exposure | Same method of ascertainment for cases and controls | | Non response rate |
| F. Ding | 2017 | ☆ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 6 |
| F. Wu | 2017 | ★ | ★ | ☆ | ★ | ★ | ★ | ☆ | 6 |
| H. Yan | 2017 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| K. Gao | 2017 | ★ | ★ | ★ | ★ | ★ | ★ | ☆ | 7 |
| P. Du | 2017 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| Q. Wang | 2017 | ★ | ★ | ☆ | ★ | ★ | ★ | ☆ | 6 |
| QL. Lv | 2017 | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 9 |
| R. Zhang | 2017 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| RL. Wang | 2017 | ★ | ★ | ☆ | ★ | ★ | ★ | ☆ | 6 |
| Shlomit Brodie | 2017 | ☆ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 6 |
| TH. Gao | 2017 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| W. Chen | 2017 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| W. Zhao | 2017 | ★ | ★ | ★ | ★★ | ★ | ★ | ☆ | 8 |
| XL. Ma | 2017 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| YQ. Li | 2017 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| YW. Liao | 2017 | ★ | ★ | ☆ | ★ | ★ | ★ | ☆ | 6 |
| ZZ. He | 2017 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| C. Shang | 2016 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| CC. Ma | 2016 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| J. Li | 2016 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| JJ. Zhuang | 2016 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| L. Hu | 2016 | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 9 |
| QL. Lv | 2016 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| QX. Wang | 2016 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| SY. Jing | 2016 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| SZ. Cao | 2016 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| T. Zhang | 2016 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| Y. Zhou | 2016 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| ZH. Chen | 2016 | ★ | ★ | ★ | ★★ | ★ | ★ | ☆ | 8 |
| CB. He | 2015 | ★ | ★ | ☆ | ★★ | ★ | ★ | ☆ | 7 |
| KX. Ma | 2015 | ★ | ★ | ☆ | ★★ | ★ | ★ | ★ | 8 |
| X. Zhou | 2015 | ☆ | ☆ | ☆ | ★★ | ★ | ★ | ★ | 6 |
| XJ. Zhang | 2013 | ★ | ★ | ☆ | ★ | ★ | ★ | ☆ | 6 |

Table 3. Analysis between lncRNAs expression level and OS of glioma

| Study | Year | LncRNA | Cut off value | Sample size High/low | COX Risk model | OS | | Tumor type | Follow up (months) | Therapy before the operation |
|-----------|------|--------------|-----------------|-------------------------|-------------------|-------------------------|--------|---------------|-----------------------|---------------------------------|
| | | | | | | HR (95%CI) | p | | | |
| YW. Liao | 2017 | CASC2 | Median | 29/28 | MA | 0.571 (0.305–1.069) | 0.08 | glioma | 40 | NA |
| QL. Lv | 2016 | ZEB1-AS1 | NA | 29/53 | MA | 1.885 (1.068–3.326) | 0.029 | glioma | 50 | Not |
| SY. Jing | 2016 | CRNDE | Median | 83/81 | MA | 1.589 (1.034–6.873) | 0.002 | glioma | 70 | Not |
| H. Yan | 2017 | HULC | NA | 46/24 | MA | 2.941 (1.517–5.714)* | 0.001 | glioma | 60 | Not |
| R.Zhang | 2017 | TP73-AS1 | Median | 24/23 | MA | 2.455 (1.126–5.353) | 0.024 | glioma | 40 | NA |
| CB. He | 2015 | NEAT1 | Median | 47/47 | MA | 2.222 (1.261–3.915) | 0.006 | glioma | 80 | Not |
| Y. Zhou | 2016 | SPRY4-IT1 | Median | 81/82 | MA | 0.407 (0.254–0.686)* | 0.003 | glioma | 70 | NA |
| ZH.Chen | 2016 | FOXD3-AS1 | NA | 22/22 | MA | 2.463 (1.068–5.681)* | 0.034 | glioma | 60 | Not |
| X. Zhou | 2015 | HOTAIR | NA | 54/54 | MA | 1.149 (1.008–1.309) | 0.037 | GBM | 70 | NA |
| KX. Ma | 2015 | MALAT1 | Median | 59/59 | MA | 0.437 (0.262–0.729)* | 0.002 | glioma | 60 | Not |
| RL.Wang | 2017 | CASC2 | Median | 22/25 | MA | 0.316 (0.170–0.536)* | 0.023 | glioma | 60 | Not |
| JJ.Zhuang | 2016 | MVIH | Median | 62/65 | MA | 0.271 (0.129–0.529)* | 0.001 | glioma | 70 | Not |
| W. Chen | 2017 | MALAT1 | NA | NA | MA | 2.553 (1.233–5.201) | 0.008 | GBM | 30 | NA |
| L. Hu | 2016 | AB073614 | GAPDH | 28/37 | MA | 0.384 (0.207–0.710)* | 0.002 | glioma | 48 | Not |
| F. Wu | 2017 | HOXA-AS3 | Median | 90/39 | MA | 0.576 (0.356–0.932)* | 0.025 | glioma | 70 | NA |
| QL. Lv | 2017 | ZFAS1 | Median | 27/42 | MA | 1.918 (1.059–3.473) | 0.032 | glioma | 48 | Not |
| QX. Wang | 2016 | HOXA11-AS | Median | 110/110 | MA | 1.140 (1.006–1.292) | 0.04 | glioma | 50 | NA |
| XJ. Zhang | 2013 | HOTAIR | Median | 44/45 | MA | 2.933 (1.384–6.217) | 0.005 | glioma | 30 | NA |
| SZ. Cao | 2016 | MALAT1 | Median | 33/33 | MA | 2.796 (1.157–4.735) | 0.027 | glioma | 50 | NA |
| P. Du | 2017 | XIST | Median | 35/34 | MA | 2.037 (1.083–3.831) | 0.027 | glioma | 36 | NA |
| TH. Gao | 2017 | HSP90AA1-IT1 | at least 2-fold | 32/33 | MA | 2.471 (1.123–5.434) | 0.024 | glioma | 36 | Not |
| XL. Ma | 2017 | TUSC7 | Median | 102/104 | MA | 1.321 (1.023–2.983) | 0.012 | glioma | 60 | Not |
| C. Shang | 2016 | TUSC7 | NA | 19/20 | UA | 2.813 (1.504–6.172) | 0.017 | glioma | 40 | Not |
| W. Zhao | 2017 | UCA1 | median | 32/32 | UA | 7.368 (3.032–17.90) | <0.001 | glioma | 50 | Not |

qRT-PCR: quantities reverse transcription-Polymerase Chain Reaction; SC: survival curve; GSEA: Gene Set Enrichment Analysis.

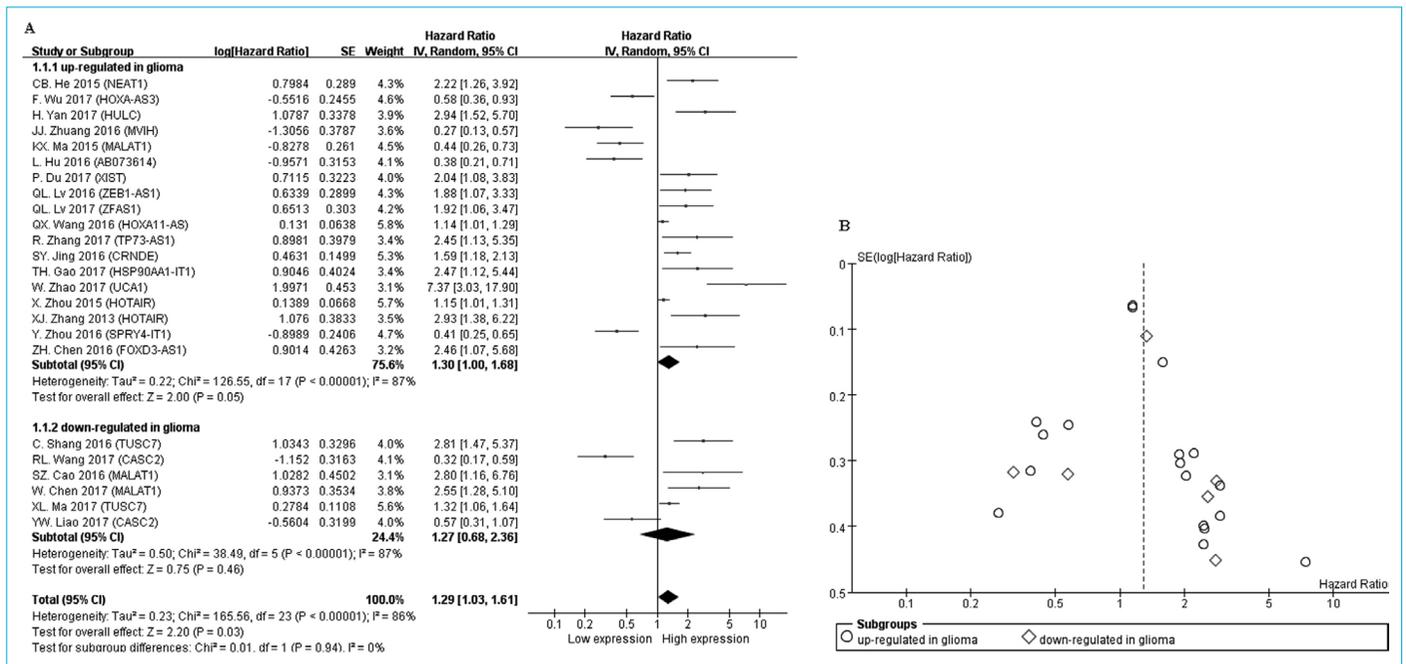


Figure 2. (a) Forest plots of 24 studies evaluating HR of lncRNA expression and OS in glioma. **(b)** Funnel plot of lncRNA expression and overall survival in glioma.

Publication Bias

The funnel plot was applied for assessing publication bias of studies in this meta-analysis. No evident publication bias was observed by visual distribution of funnel plot (Fig. 2B). Due to high heterogeneity (I²=86%, p<0.00001), subgroup

analysis was further conducted to identify the source of heterogeneity of OS by number of samples, analysis type, follow-up time, weight and glioma subtype. However, subgroup analysis seemed to fail to explain heterogeneity source (Table 4).

Table 4. Subgroup meta-analysis of pooled HRs for OS

| Categories | No. of Study | No. of Patients | HR (95%CI) for OS | Heterogeneity | |
|----------------|--------------|-----------------|--------------------|----------------|----------|
| | | | | I ² | p |
| OS | 24 | 2394 | 1.29 (1.03, 1.61) | 86% | 0.03 |
| No. of samples | | | | | |
| <100 | 15 | 967 | 1.78 (1.16, 2.75) | 83% | <0.00001 |
| >100 | 9 | 1427 | 0.89 (0.69, 1.17) | 88% | <0.00001 |
| Analysis type | | | | | |
| Multivariate | 22 | 2291 | 1.17 (0.94, 1.46) | 85% | <0.00001 |
| univariate | 2 | 103 | 4.33 (1.69, 11.07) | 66% | 0.09 |
| Follow-up | | | | | |
| 2 year | 2 | 281 | 2.72 (1.64, 4.53) | 0% | 0.79 |
| 3 year | 5 | 277 | 1.79 (0.97, 3.32) | 75% | 0.003 |
| 4 year | 6 | 566 | 1.67 (0.93, 2.99) | 87% | <0.00001 |
| 5 year | 11 | 1270 | 0.91 (0.65, 1.29) | 89% | <0.00001 |
| Tumor Type | | | | | |
| Glioma | 22 | 2094 | 1.28 (0.97, 1.68) | 87% | <0.00001 |
| GBM special | 2 | 300 | 1.59 (0.74, 3.42) | 80% | 0.03 |
| Weight | | | | | |
| <5% | 20 | 1696 | 1.22 (1.09, 1.37) | 44% | 0.15 |
| >5% | 4 | 698 | 1.34 (0.89, 2.04) | 88% | <0.00001 |

The Relationship Between Four Kinds of lncRNA and the Prognosis of Glioma

Of the 25 lncRNA, 4 lncRNA have been reported more than once. They are CASC2, HOTAIR, MALAT1 and TUSC7. Therefore, we analyzed the expression of these 4 kinds of lncRNA and the overall survival rate of patients with glioma. The results of meta-analysis showed that the prognosis of lncRNA CASC2 was positively correlated with the prognosis of glioma (HR=0.42, 95%CI: 0.27-0.66, $p=0.0001$, $I^2=42%$, fixed effect model), the lower expression of CASC2, the worse the prognosis. But MALAT1 (HR=1.42, 95%CI: 0.38-5.29, $p=0.60$, $I^2=91%$, random effect model), HOTAIR (HR=1.70, 95%CI: 0.69-4.21, $p=0.25$, $I^2=83%$, random effect model) and TUSC7 (HR=1.81, 95%CI: 0.87-3.75, $p=0.11$, $I^2=79%$, random effect model) seemed to have no statistical significance for the prognosis of patients with glioma, but the practical significance needs to be explored further (Fig. 3).

Correlation of lncRNAs with Clinicopathological Characteristics

To explore whether the expression of lncRNAs were related to clinicopathological features, the basic data was summarized for the meta-analysis (Table 5). In the including twenty-seven studies, all the articles estimated the relationship between gender and age with the expression of lncRNAs, nineteen studies revealed the association between lncRNAs and tumor size, twenty-four studies analyzed the association between lncRNAs and clinical stage, four studies reported the association between lncRNAs and MGMT promoter methylation, five studies were about IDH1 mutation,

two were about EGFR expression, nine were about KPS and four were about recurrence. Ten common clinic characteristics including age, gender, tumor size, WHO stage, IDH1 mutation, EGFR, PTEN, KPS, MGMT promoter methylation and recurrence were selected for further analysis.

All of the included studies reported that lncRNAs were not associated with age except one study which carry on lncRNA HULC research.^[16] And one study claimed that HOTAIR expression was associated with gender while the other lncRNAs were irrelevant to gender. MVIH, TUSC7 and FOXD3-AS1 were uncorrelated to tumor size when divide into two groups by 5 cm.^[17-20] Thus, a two-by-two table was formed to calculate the odds ratio (OR) and p value of these clinicopathologic characteristics. If $I^2>50%$, random-effect model was implied; if $I^2<50%$, the fixed-effect model was used. $OR>1$ indicated high level of lncRNAs could be a risk factor of clinicopathological characteristics.

Subgroup analysis suggested that the high expression of lncRNA was related to WHO staging ($OR=0.31$, 95%CI: 0.19-0.50, $p<0.00001$, $I^2=80%$), EGFR expression ($OR=3.14$, 95%CI: 1.70-5.77, $p=0.0002$, $I^2=0%$) and IDH1 status ($OR=0.33$, 95% CI=0.12-0.93, $p=0.04$, $I^2=70%$), whereas age ($OR=1.05$, 95%CI: 0.78-1.42, $p=0.75$, $I^2=29%$), gender ($OR=1.01$, 95%CI: 0.85-1.20, $p=0.92$, $I^2=0%$), tumor size ($OR=0.67$, 95%CI=0.35-1.27, $p=0.22$, $I^2=75%$), PTEN ($OR=0.26$, 95%CI: 0.06-1.10, $p=0.07$, $I^2=0%$), KPS score ($OR=1.06$, 95%CI=0.44-2.59, $p=0.90$, $I^2=84%$), MGMT promoter methylation ($OR=2.05$, 95%CI=0.94-4.50, $p=0.07$, $I^2=62%$) and the recurrence of the tumor ($OR=0.87$, 95%CI=0.42-1.82, $p=0.72$, $I^2=77%$) were irrelevant to expression of lncRNAs (Fig. 4 and Table 6).

lncRNAs and Chemo/Radio-Resistance

Three articles revealed mechanism between lncRNAs and chemo-resistance to temozolomide (TMZ). Liao et al elaborated over-expression of CASC2 could raise the degree of sensibilization of TMZ-resistant glioma cells by inhibiting miR-181a expression.^[12] Chen et al. showed that MALAT1 resulted in chemo-resistance to temozolomide by depressing miR-203 and advancing thymidylate synthase expression.^[9] P Du et al set forth their findings that XIST can restrain the expression of miR-29c by targeting TMZ glioma cells directly.^[21] And O6-methylguanine-DNA methyltransferase (MGMT) and SP1 also occupied important positions in resistance to TMZ. It is worth mentioning that Shlomit Brodie et al discovered that silencing TALNEC2 could inhibit glioma stem cells from renewing it self and enhance the sensitivity to gamma radiation,^[22] which may provide new ideas for the radiotherapy of glioma.

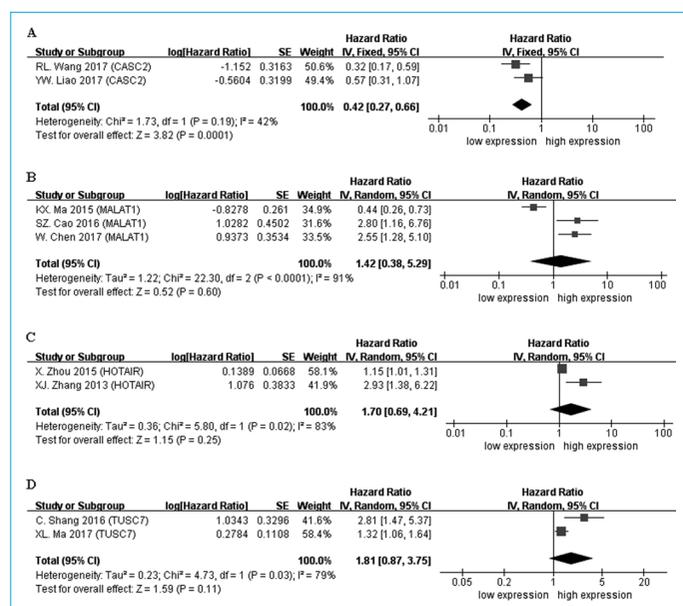


Figure 3. Forest plots of studies evaluating HR of lncRNAs and the OS of glioma patients. (a) CASC2; (b) MALAT1; (c) HOTAIR; (d) TUSC7.

Table 5. The basic clinicopathologic characteristics

| Study | Year | lncRNAs | Clinicopathologic characteristics |
|------------|------|--------------|---|
| YW. Liao | 2017 | CASC2 | Age, Gender, Tumor size, Peritumoral brain edema, WHO stage |
| QL. Lv | 2016 | ZEB1-AS1 | Age, Gender, Clinical Stage, Tumor Location |
| SY. Jing | 2016 | CRNDE | Age, Gender, Onset, Tumor size, Necrosis, WHO grade, Recurrence |
| H. Yan | 2017 | HULC | Age, Gender, Tumor size, Clinical grade, Tumor location, Tumor nodule number |
| R. Zhang | 2017 | TP73-AS1 | Age, Gender, Tumor size, Peritumoral brain edema, WHO stage |
| CB. He | 2015 | NEAT1 | Age, Gender, Onset, Tumor size, Tumor location, Necrosis, WHO grade, Recurrence |
| Y. Zhou | 2016 | SPRY4-IT1 | Age, Gender, Family history of cancer, WHO grade, Tumor size, Tumor location |
| ZH. Chen | 2016 | FOXD3-AS1 | Age, Gender, WHO grade, Tumor size, KPS |
| X. Zhou | 2015 | HOTAIR | Age, Gender, KPS, Resection, IDH1 mutation, MGMT promoter methylation, MGMT, Ki-67, EGFR, PTEN |
| KX. Ma | 2015 | MALAT1 | Age, Gender, Family history of cancer, WHO grade, Tumor size, Tumor location |
| RL. Wang | 2017 | CASC2 | Age, Gender, Tumor grade, KPS, Tumor location, IDH1 mutation |
| JJ. Zhuang | 2016 | MVIH | Age, Gender, Tumor size, Tumor location, KPS, WHO grade, Tumor recurrence, Surgery |
| W. Zhao | 2017 | UCA1 | Age, Gender, Tumor diameter, WHO grade, KPS, Tumor location |
| L. Hu | 2016 | AB073614 | Age, Gender, Tumor grade, Tumor location |
| F. Wu | 2017 | HOXA-AS3 | Age, Gender, Subtype, Grade, IDH1 mutation, MGMT promoter methylation, Radiotherapy, Chemotherapy |
| QL. Lv | 2017 | ZFAS1 | Age, Gender, Clinical stage, Tumor location |
| XJ. Zhang | 2013 | HOTAIR | Age, Gender, KPS, Resection, IDH1, MGMT promoter methylation, MGMT, Ki-67, EGFR, PCNA, PTEN, TOPOII, GST- π |
| QX. Wang | 2016 | HOXA11-AS | Age, Gender, Grade, TCGA, IDH1 mutation |
| SZ. Cao | 2016 | MALAT1 | Age, Gender, Tumor size, WHO grade, KPS |
| P. Du | 2017 | XIST | Age, Gender, Tumor size, PTBE, WHO stage |
| ZZ. He | 2017 | UCA1 | Age, Gender, Differentiation, Tumor size, Invasion depth, Lymphatic metastasis, WHO stage |
| TH. Gao | 2017 | HSP90AA1-IT1 | Age, Gender, Tumor size, WHO grade, Ki-67 |
| XL. Ma | 2017 | TUSC7 | Age, Gender, Tumor size, Tumor location, WHO grade, KPS, Tumor recurrence |
| AQ. Wang | 2017 | lnc00462717 | Age, Gender, Tumor size, WHO grade, KPS |
| WY. Hu | 2017 | PLAC2 | Age, Gender, IDH1 mutation, MGMT promoter methylation, Ki-67 |
| J. Li | 2016 | TUG1 | Age, Gender, extent of resection, radiographic pattern, WHO grade, Tumor size, KPS |
| T. Zhang | 2016 | H19 | Age, Gender, Family history of cancer, WHO grade, Tumor size |

TOPOII: topoisomerase II; PTEN: phosphatase and tensin homolog; IDH1: isocitrate dehydrogenase 1.

Discussion

Up to now, the prognosis of glioma is still extremely poor. Conventional therapy is only suitable for early stage. For WHO III/IV grade, chemotherapy not only has little effect on it, but also brings the side effects that affect the quality of life seriously. Even with the most ideal surgical resection, radiotherapy and/or chemotherapy, the glioblastoma multiform which is most malignant type only have an average lifespan of 14 months.^[23, 24] Thus, predictable biomarkers for prognosis of glioma are strongly needed. This meta-analysis was made to try to clarify the prognostic value of varieties of lncRNAs and correlation with clinicopathological characteristics in glioma.

Totally, thirty-three studies consisting 25 lncRNAs were included in this meta-analysis for OS and clinical features. Pooled analysis demonstrated there existed a significant association between lncRNAs and OS in glioma patients

($p=0.03$). A high heterogeneity ($I^2=86\%$) was emerged in prognosis analysis. Nevertheless, the source of heterogeneity was not found by different subgroup analysis. It could be attributed to that the object of the study is a large class of lncRNA, but they still be essentially different.

Besides, the correlation of lncRNA transcription level with the nine common clinicopathological parameters of glioma were also evaluated. Subgroup analysis suggested that the expression level of lncRNA was significantly associated with WHO stage, EGFR expression, IDH status. No significant association was found in age, gender, tumor size, PTEN, KPS, MGMT promoter methylation and recurrence. Among them, HOTAIR was the unique lncRNA which had been confirmed associating with EGFR expression and was independent of PTEN. HOXA-AS3 and HOTAIR were correlated to IDH1 status while CASC2 and PLAC2^[34] were irrelevant to IDH1 status.^[11, 20, 25, 26] HOXA-AS3 and HOTAIR were also related to MGMT promoter methylation but PLAC2

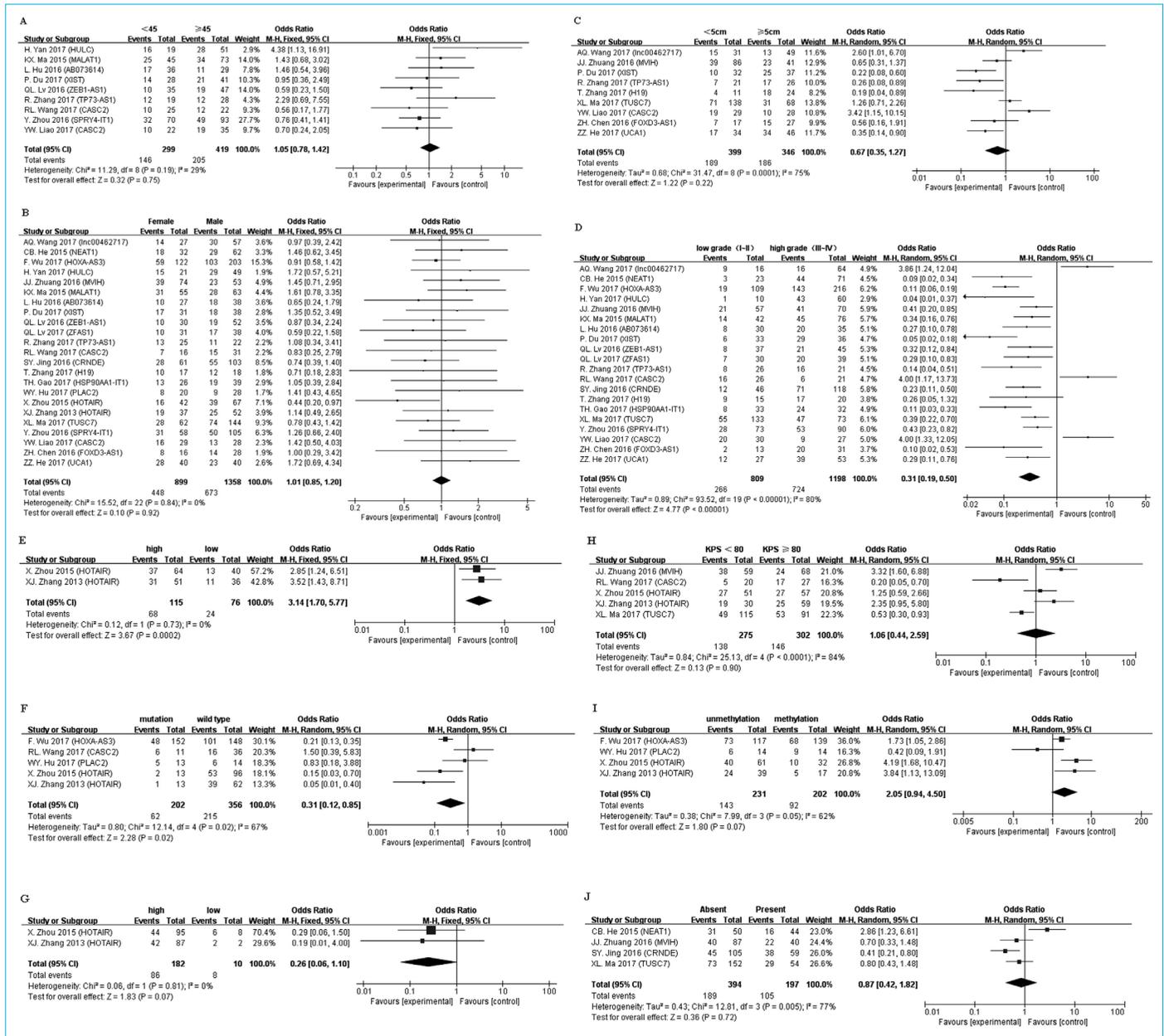


Figure 4. Forest plot of lncRNA expression and clinicopathological parameters in glioma. **(a)** Age; **(b)** Gender; **(c)** Tumor size; **(d)** WHO stage; **(e)** EGFR expression; **(f)** IDH1 status; **(g)** MGMT promoter methylation; **(h)** PTEN; **(i)** KPS; **(j)** Recurrence.

could not affect the process of MGMT promoter methylation. [20, 25-27]

Most articles as well as probed into the mechanism between lncRNAs and glioma from different levels. Firstly, increasing evidences demonstrated that micro-RNA act as an important mediator of the effects on lncRNAs in glioma. lncRNA ATB could promote the malignancy of glioma via regulated mir-200a inversely. [28] CASC2 knockdown lead to the inhibition of PTEN protein level, the partial recovery of miR-181a inhibition and the increase of p-AKT protein level, finally regulated chemo-sensitivity of glioma cells to TMZ. Secondly, several lncRNAs inhibited tumor cell proliferation

by regulating cell cycle. MALAT1, HOTAIR and UCA1 suppresses cell proliferation with G0/G1 cycle arrest while over-expression of PLAC2 resulted in G1/S arrest by modulating RPL36 expression. [9, 26, 27, 29] S-phase was prolonged in HOXA11-AS over-expression cells while FOXD3-AS1 silencing promoted S-phase arrest in glioma cells. And knock-down of ZFAS1 could induced G0/G1 phase cell cycle arrest and then reduced the number of S phase cells. [30, 31] Thirdly, some studies revealed different biological processes might involved in different signaling pathways. ZFAS1 could damage migration and invasion by inhibiting the epithelial mesenchymal transition (EMT) and Notch signaling path-

Table 6. Summarize of the relationship between lncRNA and clinicopathological parameters

| Clinicopathological parameters | Studies | Number of patients | Relative risk of higher lncRNA OR (95% CI) | Significant test | | Heterogeneity test | | Effect model |
|---------------------------------------|---------|--------------------|--|------------------|----------|--------------------|----------|---------------|
| | | | | Z | p | I ² | P | |
| Age (<45 vs. ≥45) | 9 | 718 | 1.05 (0.78-1.42) | 0.32 | 0.75 | 29% | 0.19 | Fixed-effect |
| Gender (female vs. male) | 23 | 2257 | 1.01 (0.85-1.20) | 0.10 | 0.92 | 0% | 0.84 | Fixed-effect |
| Tumor size (<5vs. ≥5cm) | 9 | 745 | 0.67 (0.35-1.27) | 1.22 | 0.22 | 75% | 0.0001 | Random-effect |
| WHO grade (I-II vs. III-IV) | 20 | 2007 | 0.31 (0.19-0.50) | 4.77 | <0.00001 | 80% | <0.00001 | Random-effect |
| EGFR (high vs. low) | 2 | 191 | 3.14 (1.70-5.77) | 3.67 | 0.0002 | 0% | 0.73 | Fixed-effect |
| IDH1 status (mutation vs.wild type) | 5 | 556 | 0.33 (0.12-0.93) | 2.09 | 0.04 | 70% | 0.01 | Random-effect |
| PTEN (high vs.low) | 2 | 192 | 0.26 (0.06-1.10) | 1.83 | 0.07 | 0% | 0.81 | Fixed-effect |
| KPS score (<80 vs. ≥80) | 5 | 577 | 1.06 (0.44-2.59) | 0.13 | 0.90 | 84% | <0.0001 | Random-effect |
| MGMT promotor methylation (no vs.yes) | 4 | 433 | 2.05 (0.94-4.50) | 1.80 | 0.07 | 62% | 0.05 | Random-effect |
| Recurrence (absent vs.present) | 4 | 591 | 0.87 (0.42-1.82) | 0.36 | 0.72 | 77% | 0.005 | Random-effect |

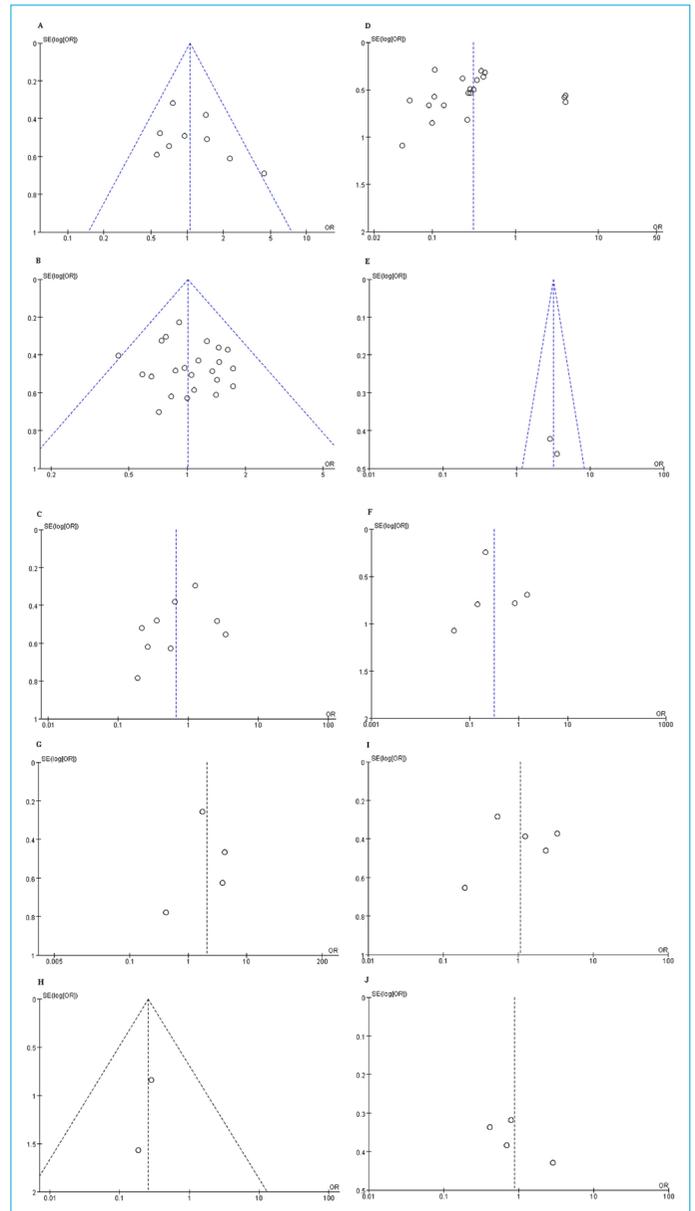


Figure 5. Funnel plot of lncRNA expression and clinicopathological parameters in glioma. (a) Age; (b) Gender; (c) Tumor size; (d) WHO stage; (e) EGFR expression; (f) IDH1 status; (g) MGMT promoter methylation; (h) PTEN; (i) KPS; (j) Recurrence.

way.^[31, 32] CASC2 and AB073614 inhibited glioma cell proliferation, migration, and invasion via oppressing Wnt/ β -catenin signaling pathway.^[11, 33]

In the present study, we first accessed the expression of lncRNAs with the survival and clinicopathological parameters in patient with glioma. There are still some limitations in our meta-analysis. First, all of the eligible studies were non-randomized, and lack of p53, 1p/19q co-deletion, BRAF mutation, deletion of ATRX protein and TERT mutation. Second, different lncRNAs were summarized and collected to estimate the prognosis of glioma, which defi-

ciency of highly specific glioma-related lncRNA. Third, EGFR status, MGMT promoter methylation and PTEN these three clinical features were lack of persuasion because less than 5 articles.

Incidentally, abnormal lncRNAs expression could turn up in other tumor types or nervous system disorders like Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), even non-neoplastic disease.^[34-36] So far we haven't find a molecular indicator with high degree of specificity to assess the prognosis of glioma yet. In the future, there are still a lot of unknowns need to be explored in dept.

Disclosures

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