Neurosurgical Review (2020) 43:1–8
https://doi.org/10.1007/s10143-018-0965-x

REVIEW

Prognostic and clinicopathological significance of long non-coding RNA in glioma

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Received: 19 December 2017 / Revised: 20 February 2018 / Accepted: 7 March 2018 / Published online: 21 March 2018

Abstract

Growing evidence from recent studies have revealed that long non-coding RNA (lncRNA) might be a useful prognostic biomarker for glioma; we therefore conducted the current meta-analysis to evaluate prognostic and clinicopathological predictive value of lncRNA expression for glioma patients. Eligible studies were identified through multiple research strategies in PubMed, EMBASE, Web of Science, and Cochrane Library up to May 2017. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were utilized to calculate patient's survival. Fourteen eligible studies with 1415 patients were ultimately included in this meta-analysis. Our meta-analysis showed a significant association between high lncRNA expression level and OS in glioma patients (HR 2.09, 95% CI 1.68–2.58, $P < 0.001$). Subgroup analysis was conducted to explore the potential heterogeneity. As for clinicopathological parameters, lncRNA expression was significantly associated with tumor diameter (< 3 vs ≥ 3 cm, OR 0.39, 95% CI 0.27–0.56, $P < 0.001$; < 5 vs ≥ 5 cm, OR 0.56, 95% CI 0.34–0.92, $P = 0.02$), tumor grade (OR 0.21, 95% CI 0.13–0.34, $P < 0.001$), and Karnofsky Performance Status Scale (OR 2.52, 95% CI 1.54–4.11, $P < 0.001$). LncRNA may serve as a biomarker for prognosis and clinicopathological features in glioma patients.

Keywords Long non-coding RNA · Glioma · Prognosis · Characteristic features

Introduction

Glioma accounts for the majority of primary tumors in adult central nervous systems. Due to its resistance to current therapies and individualized disease progress, it will result in a poor prognosis and low overall survival. According to the World Health Organization (WHO) grading system, it can be further categorized into four grades: I–IV lesions, low-grade glioma (WHO I and II), and high-grade glioma (WHO III and IV) [1]. The most aggressive malignant gliomas, anaplastic astrocytoma and glioblastoma multiforme (GMB), have 5-year survival rates of 23 and 5%, respectively [2]. This dismal clinical outcome makes glioma an urgent subject of cancer research, and in the past decades, the molecular mechanisms, genetics, and pathways to treat glioma have been studied.

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Long non-coding RNA (lncRNA), composing of more than 200 nucleotides, is a new class of the non-coding RNA that contributes to cancer development and progression [3]. LncRNAs appear to comprise a hidden layer of internal signals that control various levels of gene expression in physiology and development, including chromatin architecture/epigenetic memory, transcription, RNA splicing, editing, translation, and turnover [4]. Recent studies have revealed that numerous long non-coding RNAs play extensive regulating role in different levels of gene expression and crucial biological roles in cellular development and metabolism [5]. Molecular profiling of normal and tumor tissues has revealed that lncRNA is dysregulated in a great number of human malignancies, including prostate, colorectal, breast, bladder, liver, lung, and brain cancers [6]. For example, lncRNA H19, generated by imprinted genes H19, has been consider as an oncogenic lncRNA in hepatocellular and bladder carcinoma [7]; HOX transcript antisense intergenic RNA (HOTAIR) is frequently upregulated in various types of cancers, including breast, esophageal, lung, and gastric cancers [8]. Colon cancer-associated transcript 2 (CCAT2), mapping to the 8q24 gene desert region, is identified as an oncogenic lncRNA in microsatellite-stable colorectal cancer [9]. LncRNAs are emerging as novel members in cancer paradigm.

Recent studies have indicated that aberrant expression of lncRNAs may affect glioma initiation and progression [10]; microarray studies also have shown significant changes in the expression patterns of many lncRNAs between glioma and normal brain [11]. It is hypothesized that lncRNAs may be potential diagnostic and prognostic biomarkers of glioma [12–14]. Due to the limitation of sample size and research programs, single study may be inaccurate and insufficient. In the current study, a meta-analysis was conducted to evaluate and predict the overall risk of aberrant lncRNA expression for survival in glioma patients. In addition, we also explored its clinicopathological features in glioma.

Materials and methods

Retrieval strategy

A comprehensive literature retrieval was conducted using the electronic databases PubMed, EMBASE, Web of Science, and Cochrane Library (up to May 20, 2017). Both MeSH terms and free-text words were adopted to increase the retrieval's accuracy. Following key words were searched in combinations: "RNA, Long Noncoding" [Mesh]; "Noncoding RNA, Long"; "lncRNAs"; "Long ncRNA"; "RNA, Long Non-Translated"; "Long Non-Protein-Coding RNA"; "Long Intergenic Non-Protein Coding RNA"; "LincRNAs"; "Glioma"[Mesh], astrocytoma, ependymoblastoma, ependymoma, glioblastoma, gliosarcoma, medulloblastoma, oligodendroglima, optic nerve glioma, pontine glioma, subependymoma; and prognositic, survival, predictive, and clinicopathalogical. Meanwhile, the references of retrieved articles were also screened for potentially eligible literatures.

Inclusion and exclusion criteria

Inclusion criteria were (1) studies investigated the expression of lncRNAs in gliomas of humans; (2) studies included survival data such as overall survival (OS), progression-free survival (PFS), and other sufficient data to estimate hazard ratio (HR) and its 95% confidence interval; (3) studies published in English; (4) detection methods of lncRNAs were restricted to reverse transcription quantitative real-time polymerase chain reaction (RT-qPCR), fluorescence in situ hybridization (FISH), and RNA sequencing (RNA-Seq); and (5)retrospective or prospective studies.

Exclusion criteria were (1) experiments performed in vitro or vivo; (2) duplicated publications; (3) letters, reviews, case reports, and expert opinions; and (4) unable to extract survival data.

Data extraction and quality assessment

All data were extracted independently by two authors, and any disagreements were resolved by consensus with a third investigator. The following data were extracted: last name of the first author, publication year, country, type of lncRNAs, study design, detection method, sample size and types, cutoff point, hazard ratio and its 95% confident interval, follow-up months, and clinicopathological parameters.

HRs and its 95% confident interval were extracted directly from the publications. If HRs and 95% confidence intervals (CIs) were not available directly, HRs were calculated from available numerical data using Parmar's method [15] or from Kaplan-Meier curves by using Tierney's method [16]. For the eligible studies that provided both the univariate and multivariate analyses, survival data from multivariate analyses were selected preferentially.

The quality of eligible papers was assessed by Newcastle-Ottawa Quality Assessment Scale (NOS). The NOS scores ranged from 0 to 9, and a study with an NOS score more than 6 was regarded as high quality. Three authors evaluated each study independently and compared the results afterwards; disagreements about quality were resolved with a fourth investigator.

Statistical analysis

HR and its 95% CIs were used to assess the association between lncRNAs and survival in glioma; meanwhile, odds ratio (OR) and its 95% CI were used to evaluate the relationship between lncRNAs and clinicopathological features in these eligible studies. An observed HR > 1 implied a worse survival for the group with elevated lncRNA expression. Conversely, an observed HR < 1 implied a worse survival for the group with decreased lncRNA expression (). Statistical heterogeneity of each study was assessed by a standard chi-squared test and I^2 statistics, with I^2 value > 50% or $P_{\text{heterogeneity}} < 0.05$ for substantial heterogeneity. If heterogeneity was significant, the random-effect model was used to estimate the pooled HR and OR; conversely, the fixed-effect model was applied [17].A P value of less than 0.05 was considered to be statistically significant. Sensitivity analysis was also conducted to evaluate the stability of the results. Publication bias was evaluated using funnel plot and Egger' test. STATA 12.0 (STATA Corp., LP, College Station, TX, USA) was applied to perform statistical analysis.

Results

Characteristics of included studies

As shown in the flow diagram (Fig. Fig. 1), 350 articles were screened from the databases, and finally, 14 eligible articles covering 1415 patients were included in the current analysis. The detailed selection process was performed in the flow diagram. All of these eligible studies involved OS, but not referred to PFS or disease-free survival (DFS).

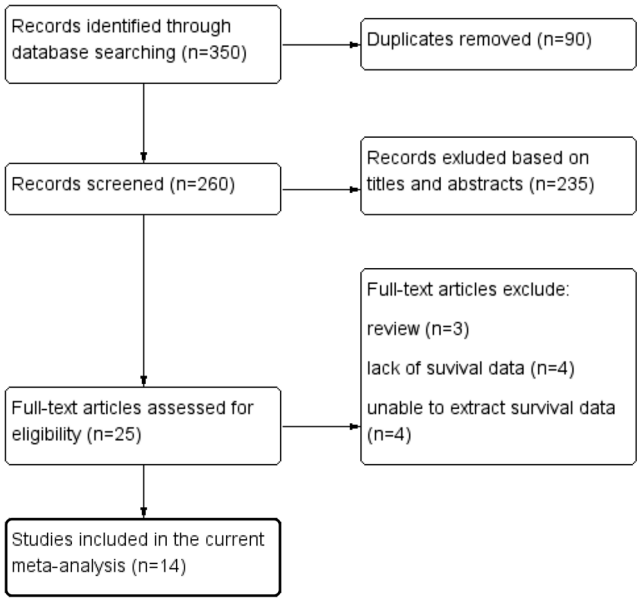

Fig. 1 Flow diagram of study selection process

Table 1 summarized the main characteristics of the included 14 studies ranging from 2013 to 2017, with a maximum sample size of 220 and a minimum sample of 35 patients. The follow-up duration ranged from 30 to 60 months. The included studies were retrospective in design. All of these studies were conducted by Chinese researchers, and experimental data originated from Chinese glioma tissues. A total of 14 lncRNAs were displayed in the table: urothelial carcinoembryonic antigen 1 (UCA1) [18], ZEB1 antisense 1 (ZEB1-AS1) [19], HOXA11-AS [20], NEAT1 [21], cancer susceptibility candidate 2 (CASC2) [22], FOXD3 antisense RNA 1 (FOXD3-AS1) [23], CRNDE [24], highly upregulated in liver cancer (HULC) [25], Hox transcript antisense intergenic RNA (HOTAIR) [26], H19 [27], metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) [28], microvascular invasion in HCC (MVIH) [29], SPRY4-IT1 [30], and AB073614 [31]. Thirteen studies had available HR and 95% CI data, while the remaining one study had the available Kaplan-Meier curve from which useful survival data could be extracted. Among these studies, five studies had a NOS quality sore of 6, while nine studies had 7. Meanwhile, in the 14 studies, 10 studies explored the relationship between the expression of lncRNAs and age, 13 studies with gender, 8 studies with tumor diameter, 8 studies with the tumor location, 3 studies with Karnofsky Performance Status Scale (KPS), 12 studies with tumor grade, and additional features. All of the clinicopathological parameters were summarized in Table 2.

Prognosis

All 14 studies were retrospective and published over the recent 4 years. We conducted an analysis to explore the relationship between lncRNAs and OS of glioma patients.

Table 1 The main characteristics of the included 14 studies in the meta-analysis

First author	Year	Country	lncRNAs	Study design	Tumor type	Detected sample	Method	Total number		Internal reference	Cutoff value	Outcome	Analysis type	Hazard ratio (95% CI)	Follow-up months	Quality score
								Low (I + II)	High (III + IV)					High vs low expression		
Zhao	2017	China	UCA1	Retrospective	Glioma	Tumor tissue	qRT-PCR	22	42	GAPDH	Median	OS	Univariate	Reported	48	6
Lv	2016	China	ZEB1-AS1	Retrospective	Glioma	Tumor tissue	qRT-PCR	37	45	GAPDH	NA	OS	Multivariate	Reported	48	7
Wang	2016	China	HOXA11-AS	Retrospective	Glioma	Tumor tissue	qRT-PCR	97	123	GAPDH	Median	OS	Multivariate	Reported	NA	7
He	2016	China	NEAT1	Retrospective	Glioma	Tumor tissue	qRT-PCR	23	71	GAPDH	Median	OS	Multivariate	Reported	48	6
Liu	2017	China	CASC2c	Retrospective	Astrocytoma	Tumor tissue	qRT-PCR	42	38	GAPDH	Median	OS	Multivariate	Reported	30	7
Chen	2016	China	FOXD3-AS1	Retrospective	Glioma	Tumor tissue	qRT-PCR	13	31	GAPDH	Median	OS	Multivariate	Reported	60	7
Jing	2016	China	CRNDE	Retrospective	Glioma	Tumor tissue	qRT-PCR	46	118	GAPDH	Median	OS	Multivariate	Reported	NA	7
Yan	2017	China	HULC	Retrospective	Glioma	Tumor tissue	qRT-PCR	10	60	GAPDH	NA	OS	Multivariate	Reported	40–58	6
Zhang	2013	China	HOTAIR	Retrospective	GBM	Tumor tissue	qRT-PCR	0	89	GAPDH	Median	OS	Multivariate	Reported	36	7
Zhang	2016	China	H19	Retrospective	Glioma	Tumor tissue	qRT-PCR	15	20	GAPDH	NA	OS	Univariate	K-M curve	36	6
Ma	2015	China	MALAT1	Retrospective	Glioma	Tumor tissue	qRT-PCR	42	76	GAPDH	Median	OS	Multivariate	Reported	60	7
Zhuang	2016	China	MVIH	Retrospective	Glioma	Tumor tissue	qRT-PCR	57	70	GAPDH	Median	OS	Multivariate	Reported	60	7
Zhou	2016	China	SPRY4-IT1	Retrospective	Glioma	Tumor tissue	qRT-PCR	73	90	GAPDH	Median	OS	Multivariate	Reported	60	7
Hu	2016	China	AB073614	Retrospective	Glioma	Tumor tissue	qRT-PCR	30	35	GAPDH	Median	OS	Multivariate	Reported	48	6

GAPDH glyceraldehyde-3-phosphate dehydrogenase, *OS* overall survival, *K-M curve* Kaplan-Meier curve, *NA* not available, *qRT-PCR* quantitative real-time polymerase chain reaction

Table 2 Meta-analysis results of the associations of lncRNAs with OS according to subgroup analysis

Subgroup analysis		Number of studies	HR (95% CI)	*P* value	Model	Heterogeneity	
						I^2	P_h
OS		14	2.09 (1.68–2.58)	< 0.001	Random	87.4%	< 0.001
Analysis type	Multivariate	12	2.07 (1.64–2.61)	< 0.001	Random	87.1%	< 0.001
	Univariate	2	3.01 (0.59–15.49)	0.187	Random	92.2%	< 0.001
Cutoff value	Median	11	2.20 (1.70–2.84)	< 0.001	Random	89.2%	< 0.001
	NA	3	1.81 (1.17,2.78)	0.007	Random	60.3%	0.08
Sample size	< 100	9	2.18 (1.74,2.73)	< 0.001	Random	63.3%	0.005
	> 100	5	1.87 (1.27,2.76)	0.002	Random	81.9%	< 0.001
Tumor type	Glioma	12	2.11 (1.63,2.74)	< 0.001	Random	78.8%	< 0.001
	Astrocytoma and GBM	2	1.98 (1.94,2.02)	< 0.001	Fixed	3.9%	0.308
Quality score	≤ 6	5	2.57 (1.52,4.33)	< 0.001	Random	78.9%	0.001
	> 6	9	1.97 (1.50,2.57)	< 0.001	Random	90.4%	< 0.001

Quantitative real-time polymerase chain reaction (qRT-PCR) was performed to evaluate lncRNAs in 1415 glioma tissues. The detailed characteristics of these 14 eligible studies were presented in Table 2. The estimated polled HR for 14 studies (Fig. 2) showed a significant association between high expression of lncRNA and OS in glioma patients (HR 2.09, 95% CI 1.68–2.58, $P < 0.001$, random effect); meanwhile, a significant heterogeneity ($I^2 = 87.4\%$, $P_h < 0.001$) was observed among the included studies.

In consideration of the inter-study heterogeneity, the prognostic significance was ulteriorly evaluated via subgroup analysis based on the analysis type, cutoff value, sample size,

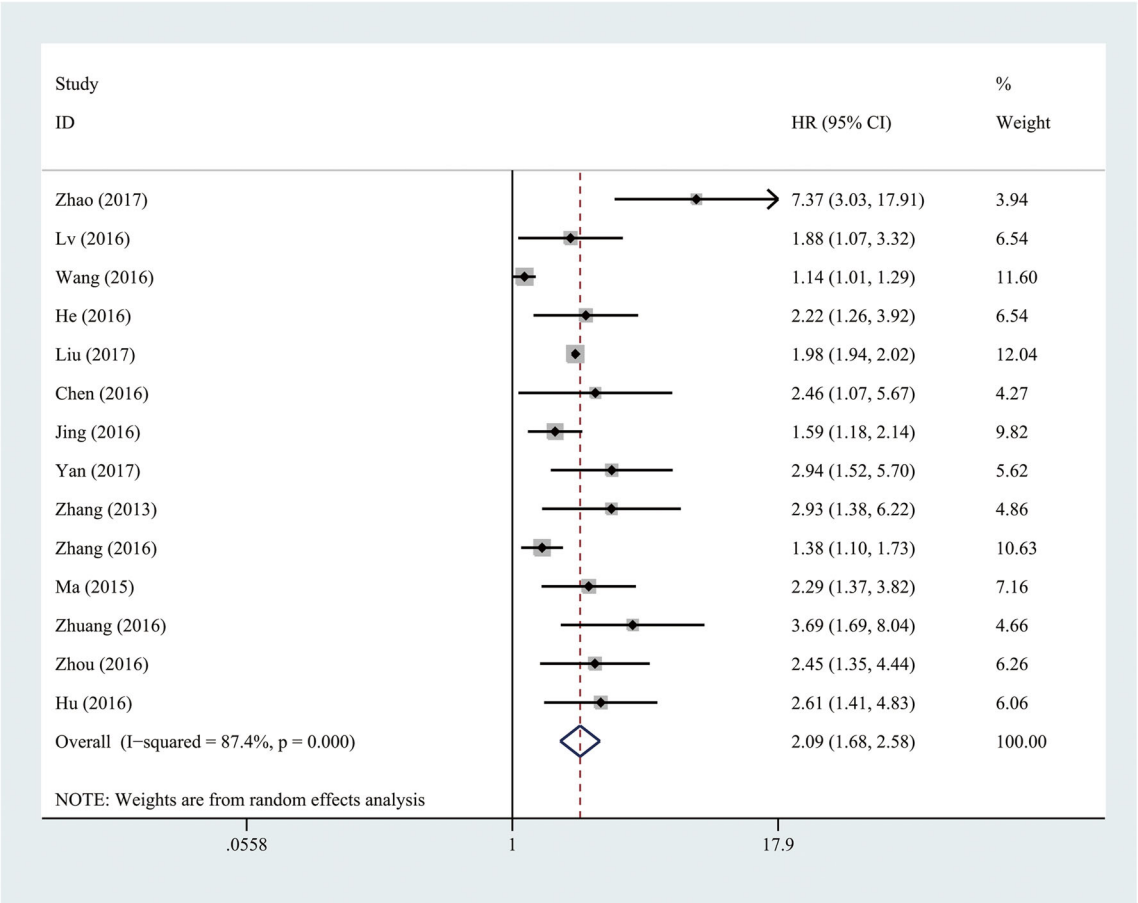

Fig. 2 Meta-analysis of the pooled HRs of OS in glioma

Table 3 Meta-analysis results for the associations of lncRNA expression with clinicopathological parameters

Clinicopathological parameters		Studies (*n*)	Patients (*n*)	OR (95% CI)	*P* value	Heterogeneity		
						I^2	P_h	Model
Tumor grade	I + II vs III + IV	12	1106	0.21 (0.13–0.34)	< 0.001	58%	0.005	Random
Age (year)	< 45 vs ≥ 45	7	712	1.26 (0.93–1.70)	0.13	8%	0.366	Fixed
	< 50 vs ≥ 50	3	226	1.08 (0.30–3.91)	0.9	76%	0.9	Random
Gender	Male vs female	13	1195	0.85 (0.67–1.07)	0.16	0%	0.91	Fixed
Tumor diameter (cm)	< 3 vs ≥ 3	4	539	0.39 (0.27–0.56)	< 0.001	0%	0.99	Fixed
	< 5 vs ≥ 5	4	270	0.56 (0.34–0.92)	0.02	0%	0.54	Fixed
KPS	≤ 80 vs > 80	3	280	2.52 (1.54–4.11)	< 0.001	0%	0.53	Fixed
Tumor location	Frontal vs others	4	281	1.18 (0.71–1.98)	0.53	35%	0.21	Fixed
	Supra vs infra	4	249	1.07 (0.70–1.64)	0.75	49%	0.12	Fixed
Recurrence	Yes vs no	3	375	1.79 (0.84–3.80)	0.13	65%	0.06	Random
Family history of cancer	Yes vs no	3	316	0.69 (0.30–1.56)	0.37	55%	0.11	Random

KPS Karnofsky Performance Status Scale, *supra* supratentorial, *infra* infrarentorial, P_h $P_{\text{heterogeneity}}$

tumor type, and quality score. In subgroup analysis, single tumor type (I^2 = 3.9%, P_h = 0.308) showed extremely low heterogeneity, and cutoff value that is not available (I^2 = 60.3%, P_h = 0.08) and sample size < 100 (I^2 = 63.3%, P_h = 0.005) showed slightly low heterogeneity; other items indicated high heterogeneity. In all the items, only univariate analysis type (HR 3.01, 95% CI 0.59–15.49, P < 0.187) indicated that lncRNA expression was not significantly related to reduced OS, and other items all suggested that high expression of lncRNA predicted poor prognosis.

Clinicopathological features

We analyzed the relationships between lncRNA expression and clinicopathological characteristics, and the pooled ORs and 95% CIs were presented in Table 3. The results of pooled OR indicated that lncRNA expression was significantly associated with tumor grade (OR 0.21, 95% CI 0.13–0.34, P < 0.001), tumor diameter (< 3 vs ≥ 3 cm, OR 0.39, 95% CI 0.27–0.56, P < 0.001; < 5 vs ≥ 5 cm, OR 0.56, 95% CI 0.34–0.92, P = 0.02), and Karnofsky Performance Status Scale (OR 2.52, 95% CI 1.54–4.11, P < 0.001). However, no significant correlation was detected between lncRNA expression and age, gender, tumor location, recurrence, and family history of cancer (P > 0.05).

Sensitivity analysis and publication bias

A sensitivity analysis was conducted to test the stability and reliability of the HR estimates by removing studies individually and sequentially and analyzing the effects on the remaining studies (Fig. 3). The results demonstrated that the pooled HRs were not significantly influenced by any individual study for OS.

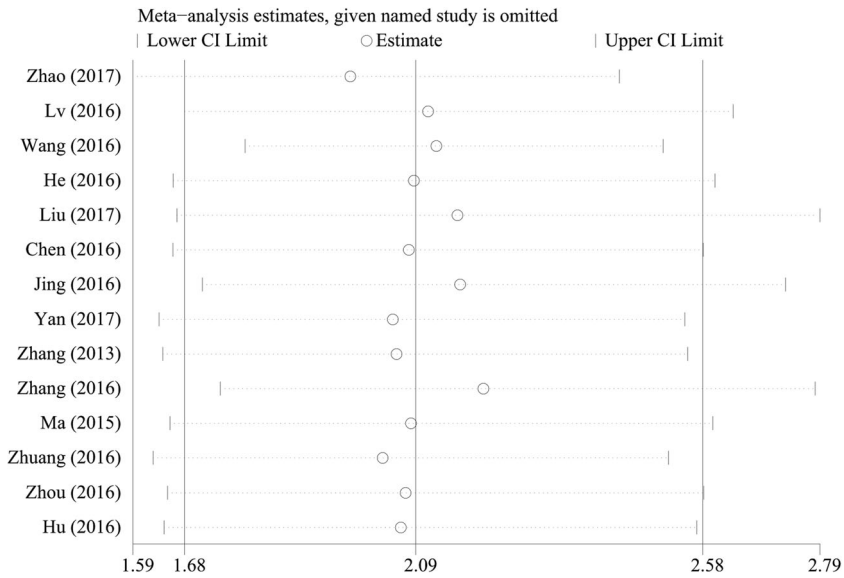

Fig. 3 Sensitivity analysis on the relationship between lncRNA expression and OS

The publication bias for OS in glioma was evaluated with funnel plot (Fig. 4) and Egger's test. No obvious asymmetry was found in funnel plot, and Egger's test ($t = -0.15$, $P > |t| = 0.886$) also indicated that there was no publication bias that existed in the current meta-analysis.

Discussion

It is clear now that lncRNA transcript > 200 nucleotides long with no evidence of protein coding potential can have critical biological functions and play a role in human diseases [32]. Aberrant expression of lncRNAs may potentially alter basic cellular biological processes and contribute to tumorigenesis [33]. Several studies suggest that lncRNAs have the potential to act as prognostic factors and therapeutic target for glioma patients [12–14, 34]. Certain lncRNAs are associated with the initiation, differentiation, progression, recurrence, and stem-like characteristics in glioma, and may be explored for the purposes of diagnosis and prognosis [35]. Considering the limited sample size and the unconvincing result of single study, a meta-analysis was therefore carried out to explore the impact of lncRNA expression on prognosis and clinicopathological parameters of glioma.

Survival data of 1415 glioma patients in 14 eligible studies were systematically evaluated. Due to the high malignancy and rapid progression, it was difficult to obtain PFS or DFS, and OS was the only available prognostic factor to exploring the impact of lncRNA expression on prognosis. The result indicated that lncRNA expression was a poor prognostic factor in glioma with result of poor OS (pooled HR 2.09, 95% CI 1.68–2.58, $P < 0.001$). With regard to clinicopathological features, lncRNAs were significantly related to tumor diameter, tumor grade, and Karnofsky Performance Status Scale. Our quantitative results supported the mainstream viewpoint that lncRNAs predicted a poor prognosis in glioma.

Meta-analysis on the included studies found that heterogeneity was common, especially in the analysis results of survival data. In case of larger heterogeneity ($I^2 = 87.4\%$), subgroup analysis was carried out on OS. According to the changes of I^2 value and P_h, we speculated that the tumor type was the direct source of the heterogeneity, while cutoff value and sample size were the potential sources of the heterogeneity. Many other confounding factors can also result in the existing heterogeneity. At first, most included studies did not grade the glioma; thus, there lacked survival data of the corresponding level. However, there was a significant difference in the survival data of gliomas at different WHO grades, and survival analysis on the mixture of gliomas at different WHO grades will greatly affect the validity of the data. Second, non-uniform factors including the types and extraction of HR (HR obtained from the literatures directly was usually more precise than HR extracted from the survival curve), different cutoff values, and quantity of included literatures would greatly deviate our final analysis results from the truth. Third, 14 different types of LncRNAs were included in 14 studies. The retrieved results of this article are obtained from PubMed, EMBASE, Web of Science, Cochrane Library, and other mainstream databases through standard medical keyword retrieval, and it is not aimed at specific regions and populations. Data come from merely one country cannot powerfully represent the entire human race, so the final results may incur bias and then lead to heterogeneity to some extent that cannot be accurately quantified. At the same time, publication bias also needs to be taken into account. In view of its important research value, we believe that more similar studies dedicated to lncRNA in other regions will continue to emerge.

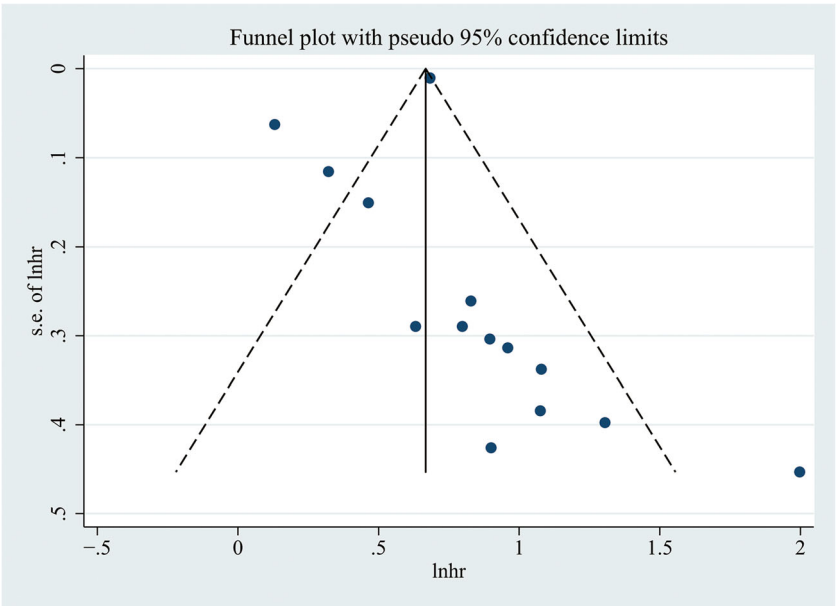

Fig. 4 Funnel plots of publication bias on the correlation between lncRNA expression and OS

As a special type of RNA, they have things in common in molecular structure, signal pathway, and the functional pattern, so we merged them for meta-analysis. This was also an important factor for the increasing heterogeneity, causing the final results unable to reliably and accurately reflect the fact. However, there is no doubt that the final result (HR 2.09, 95% CI 1.68–2.58, $P < 0.001$) is of good reference significance.

For many of the identified lncRNA genes in glioma, information regarding their intrinsic mechanisms and possible functional pathways has not been fully understood [14]. In vitro studies, knockdown of lncRNA OIP5 [36], AB073614 [37], CCAT2 [38], HOTAIR [39], SPRY4-IT1 [40], and XIST [41] inhibited proliferation, migration, and invasion of glioma cells, and the results were corresponded to vivo studies. Among them, knockdown of CCAT2 inhibited the activity of Wnt/β-catenin signal pathway, while the knockdown of HOTAIR blocked the activity of PI3K/AKT and MEK1/2 pathways. The above-mentioned lncRNAs also have a potential as therapeutic targets on count of the underlying mechanism, and the detailed mechanism of function of lncRNAs, especially in tumorigenesis, is waiting to be explored. Technical advances are already paving the way for the promise of better understanding the functional role of lncRNAs [14].

Apart from the inspiring outcomes, there are some limitations in the current study. First, 14 included studies presented 14 different types of lncRNAs, and lacking of vertical comparison on single lncRNA may result in clinic heterogeneity; second, the diverse definition of cutoff values among the studies could also lead to potential bias; third, all of the included studies were conducted in Chinese population, and patients in other regions are not involved; and fourth, due to the diversity of pathological patterns in glioma, different tumor subtypes may cause heterogeneity. Moreover, all of the eligible studies are retrospective studies.

In conclusion, the current meta-analysis firstly evaluated the expression of lncRNAs and clinicopathologic parameters of glioma patients. The results suggest that lncRNA may serve as a biomarker for prognosis and clinicopathological features in glioma patients. It is likely that specific lncRNAs have the potential to be translated into clinical applications for diagnosis, prognosis, or therapeutic target. Further researches including large sample size, more regions, and detailed experiment information are needed.

Author's contribution Study design: Yanhui Liu, Junhong Li, Ruofei Liang.
Literature search: Ruofei Liang, Chen Song, Yufan Xiang.
Data collection: Junhong Li, Ruofei Liang.
Statistical analysis: Junhong Li, Yufan Xiang.
Result interpretation: Yanhui Liu, Junhong Li, Ruofei Liang.
Manuscript preparation: Junhong Li, Ruofei Liang.

Funding This study was supported by the Key Research and Development Project from the Department of Science and Technology of Sichuan Province, China (grant number 2017SZ0006). The sponsor had no role in the design or conduct of this research.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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