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Original Article

Clinical and prognostic significance of HIF-1α in glioma patients: a meta-analysis

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Abstract: Gliomas are the most common brain tumors, leading to significant cancer-related mortality worldwide. Hypoxia-inducible factor 1-alpha (HIF-1α) was shown to be involved in the pathophysiology and management of glioma, and might offer a therapeutic target. However, the results remain inconclusive. The purpose of this study was to systematically investigate the clinical and prognostic significance of HIF-1α expression in patients with glioma. Relevant studies published between 2000 and 2015 were searched in the electronic databases. The odds ratio (OR), risk ratio (RR) and mean difference (MD) with their 95% confidence intervals (CI) were employed to calculate the strength of significance. Finally, a total of 24 articles were retrieved, including 1422 glioma patients. No significant heterogeneity was presented between studies (I^2<50%, *P*>0.01). Overall, our results showed that HIF-1α expression was significantly associated with high WHO grade (III+IV) of glioma (OR=8.59, 95% CI=6.56-11.24, P<0.00001). This significant relationship was also found between HIF-1α expression and microvascular density (MD=26.32, 95% CI=14.48-38.16, *P*<0.0001), overall survival (OS) (3-year OS: RR=0.48, 95% CI=0.35-0.66, *P*<0.00001; 2-year OS: RR=0.53, 95% CI=0.38-0.73, *P*<0.0001; 1-year OS: RR=0.79, 95% CI=0.66-0.95, *P*=0.01), and the cumulative survival time. However, HIF-1α expression was not associated with age and gender of glioma patients (*P*>0.05). In conclusions, our results suggested that HIF-1α expression was associated with high grade of glioma and OS, indicating that HIF-1α could predict prognosis and provide clinical insights into the therapeutic strategy for patients with glioma. More studies concerning other populations are also needed in the future research.

Keywords: Glioma, HIF-1α, prognosis, meta-analysis

Introduction

Gliomas, tumors of the neoplastic glial cells, or neuroglia, are the most common primary intracranial and central nervous system tumor [1, 2]. It accounts for 81% of all malignant brain tumors in adults, leading to significant mortality and morbidity worldwide [3]. Glioma incidence rate (RA) have remained stable by region and over time during the last decade [4, 5], but the RA varies by gender, race, age at diagnosis, histologic type and genetics [6, 7]. According to the World Health Organization (WHO) grading system, glioma are divided as astrocytoma, oligodendroglioma, mixed oliogoastrocytoma, and ependymoma based on the degree of malignancy [8]. Although major advances have made, treatment of glioma is still the most challenging problems in oncology and neurosurgery due to resistant to radiation treatment, with the 5-year relative survival less than 5% in patients with the most aggressive glioma histology, glioblastoma [9]. Therefore, there is an urgent need to explore an effective biomarker to predict the grade of gliomas and the overall prognosis so as to enhance patient survival and quality of life.

Hypoxia-inducible factor 1-alpha (HIF-1α), the subunit of HIF-1, is the major transcriptional factor involved in the adaptive response under hypoxic conditions [10]. It controls embryonic and tumorigenic responses to variations in microenvironmental oxygenation [11]. HIF-1α plays a role in hypoxia-mediated apoptosis, tumor angiogenesis and cell proliferation [12]. Its expression was identified in several tumors. Cellular HIF-1α was shown to be an important indicator of prognosis in patients with clear cell renal cell carcinoma, and high HIF-1α expression predicted poor survival [13]. HIF-1 expression was enhanced in meningiomas of higher WHO grade [14]. It was elevated in glioblastoma multiforme as well [15]. Studies have shown

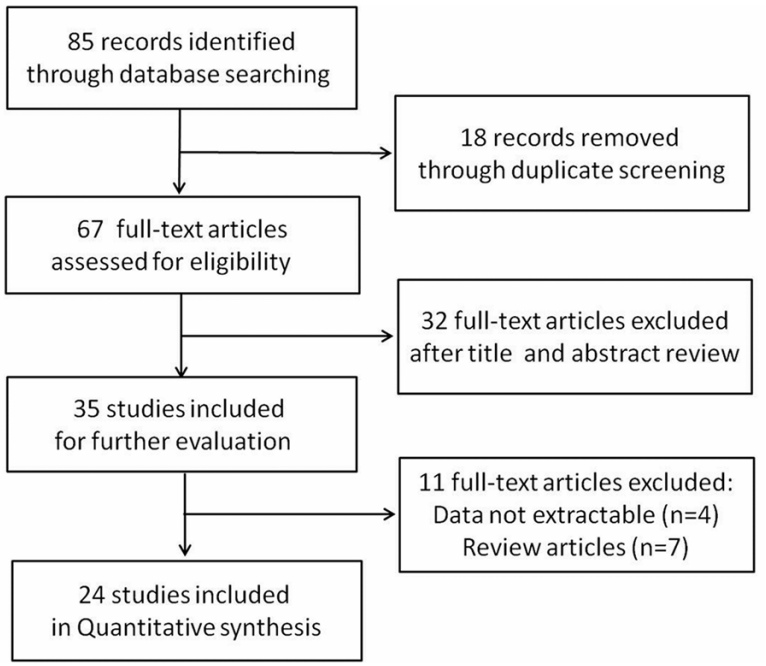

Figure 1. The process of literature selection.

that HIF-1α play a role in the pathophysiology and management of glioblastoma [16]. HIF-1α silencing combined with radiation therapy will increase the therapeutic efficacy of glioma treatment via regulation of cell cycle and apoptosis-related signaling pathways [17]. Furthermore, polymorphisms of HIF-1α gene may be used as a molecular marker for gliomas occurrence, grades and clinical outcome in gliomas patients [18]. Thus, it is crucial to understand the role of HIF-1α in grade and prognosis of gliomas, which can provide clinical insights into the efficacious therapeutic strategy.

Although many researches have been conducted on this issue, the value of HIF-1α in clinical data and prognosis of glioma is still unclear. Therefore, we conducted this meta-analysis to systematically review and evaluate all the published articles on the effect of HIF-α expression in glioma patients and obtain a reliable result.

Materials and methods

Publication search

Eligible articles published between January 2000 and 2015 were searched in online electronic databases of CNKI (China National Knowledge Internet), Wanfang, PubMed, Embase and Medline. The following searching terms: "glioma or glioblastoma", "hypoxia-inducible factor-1 or HIF-1α", "expression", "prognosis" and "clinical significance" as well as their combinations were used. References of related articles were searched manually. Only published articles written in English or in Chinese were included.

Inclusion and exclusion criteria

Eligible studies should meet the following criteria: 1) patients were confirmed with the diagnosis of glioma by the department of pathology, and were classified according to current World Health Organization guidelines [19]; 2) HIF-1α expression was evaluated by using immunohistochemistry (IHC) methods; 3) the main results were focused on WHO grade and overall survival; 4) when the same laboratory or authors reported the same issue twice or more, only the most recent full-test was included.

The exclusion criteria were: 1) reviews or conference papers; 2) data cannot be extracted; 3) duplicate articles; and 4) studies were not conducted in humans or studies with incomplete data.

Data extraction

According to the Newcastle Ottawa Quality Assessment Scale (NOS) criteria [20], two experts independently assessed and scored the quality of the methodology of each study. Any disagreement or discrepancies was resolved by consulting with a third investigator to reach a consensus on NOS scores of each study. The NOS score was ranged from 0 to 10 stars. Studies with NOS score over 6 stars were included in the final analysis. The following information was extracted from each included studies: first author, published year, country, sample size, mean age, cutoff point for protein positivity, WHO grade of patients and positive rate.

Statistic analysis

The clinical significance of HIF-1α expression in glioma patients was estimated by risk ratios (RRs) or odds ratios (ORs) or mean difference

Table 1. Main characteristics of included studies in this meta-analysis

First author	Year	Mean age	Sample size (M/F)	Grade		Cutoff	Positive
				Low (I+II)	High (III+IV)		
Gao WC	2004	35.4	31/32	46	17	>1%	45/63
Fu K	2005	37.63	27/18	22	23	>1%	28/45
Wang GK	2006	43.1±12.54	25/22	13	24	Score =1	26/37
Yin J	2007	46.6	34/26	31	29	>1%	43/60
Li L	2008	49	13/17	21	9	>5%	20/30
Tan YL	2008	4-71	31/23	26	28	Score =1	33/54
Xu X	2008	23-67	31/16	19	28	Score =2	35/47
Zheng KB	2008	40.6	34/28	28	34	Score =3	41/62
Li FC	2009	34	56/30	36	50	-	48/80
Liu QD	2009	40.1	24/16	18	22	Score =2	27/40
Liu Y	2009	36.69±13.47	61/59	60	60	Score =1	62/120
Wu WC	2010	NA	33/25	26	32	Score =1	39/58
Yu G	2010	39	30/22	32	20	>1%	34/52
Zhang L	2010	10-67	41/39	40	40	>1%	49/80
Zhao SP	2010	41.8±18.3	25/20	24	21	Score =2	32/45
Li J	2011	40.1	32/24	34	22	>1%	37/56
Zhang H	2011	37	39/23	30	32	Score =2	40/62
Zhang MY	2011	42.9	35/35	32	38	NA	45/70
Jiang JC	2012	16-68	36/32	34	34	Score =1	46/68
Liu XR	2013	38.81	45/53	50	48	>5%	70/98
Xing PH-a	2013	24-67	35/28	27	36	>1%	42/63
Xing PH-b	2013	27-68	32/26	25	33	>1%	41/58
Cao WD	2014	49.4±19.9	14/13	5	22	Score =2	20/27
Liao CC	2014	-	24/17	17	24	Score =2	27/41

-, not applicable; M/F, male/female; cutoff, cutoff points for HIF-1α expression.

(MD) and their 95% confidence intervals (CI). The statistical significance was determined by Z-test with a *P*-value less than 0.05 considered significant. Extent of heterogeneity between studies was measured by both the Q-test and the I^2 test. The fixed-effect model was employed when the effect were homologous (*P*-value ≥0.01 for the Q-test and I^2≤50% for the I^2 test), while the random-effect model was used in its opposite. All analyses were calculated using the RevMan5.2 program.

Results

Characteristics of included studies

We firstly identified 85 articles through literature search from Jan 1, 2004 to Dec 31, 2014. Among them, 18 articles were duplicated. After screening the titles and abstracts of the remaining 67 articles, 32 articles were excluded for they did not meet our specified criteria. Finally, a total of 24 articles were screened out, including 1422 glioma patients. All the included articles were considered as high quality articles. The selection process was shown in **Figure 1**. Of the 24 studies, 2 were written in English [21, 22] and 22 in Chinese [23-44]; 23 were conducted in Chinese population and 1 in Japanese population [21]. The sample size ranged from 27 to 120. The cutoff points for HIF-1α expression selected in most studies was that 5% or less positive cell percentage was scored as 0, no staining (-); 6%-25% as 1 points, weak intensity (+); 26%-50% as 2 points, moderate intensity (++); 51% or more as 3 points, strong intensity (+++). The main characteristics of included studies were presented in **Table 1**.

Correlation of HIF-1α expression with WHO grade of glioma

Firstly, we divided glioma patients into low (I+II) and high grade (III+IV) according to WHO grade. All the 24 articles contained these data and were available to extract, including 726 high and 696 low grade patients, respectively. No

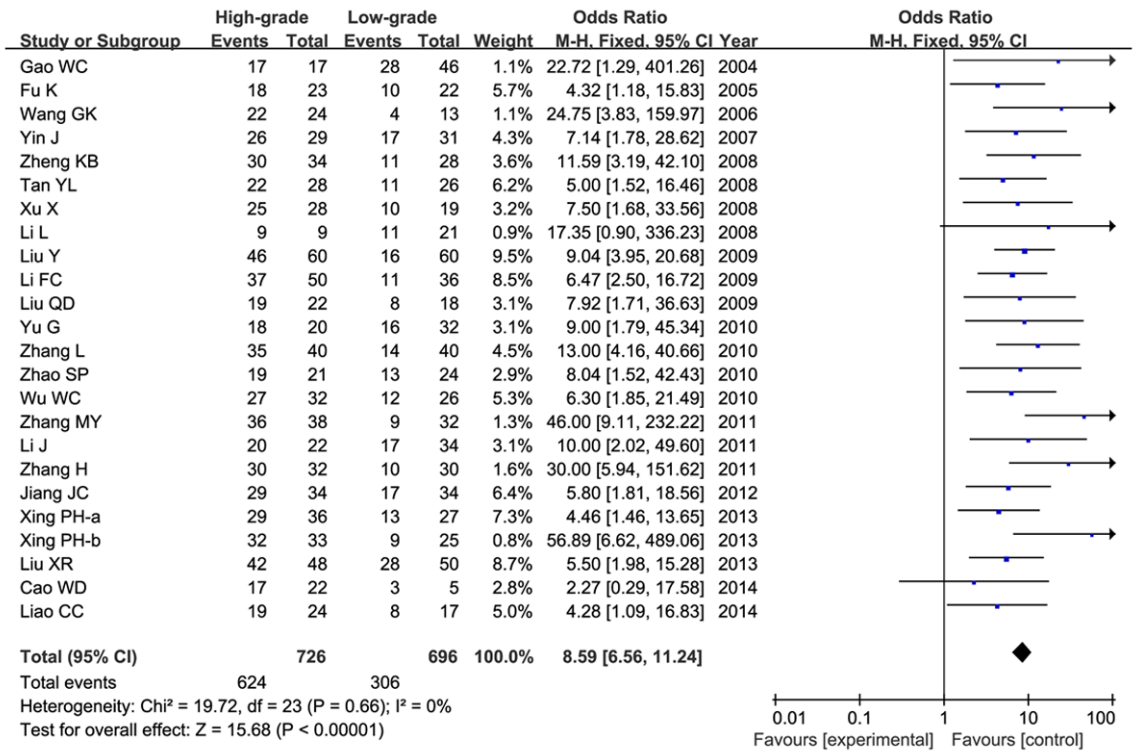

Figure 2. Meta-analysis of HIF-1α expression in high grade (III+IV) and low grade (I+II) gliomas.

significant heterogeneity was found between studies (P>0.01, I^2<50%), and the fixed-effect model was employed. Overall, our results found that HIF-1α was highly expressed in high grade patients compared with that in low grade (86.0% versus 44.0%), indicating HIF-1α expression was significantly associated with high WHO grade of glioma (OR=8.59, 95% CI=6.56-11.24, P<0.00001) as shown in **Figure 2**.

Then we analyzed the relationship between HIF-1α expression and glioma at each grade, respectively. **Table 2** listed the results of each comparison by grade. Our results showed that the HIF-1α expression in patients with higher grade significantly related with glioma when compared with the lower-grade (P<0.00001).

Lastly, we verified the correlation of HIF-1α expression between glioma and normal. Total 11 studies contained 603 glioma patients and 86 controls. This results showed that HIF-1α expression was connected with glioma (OR= 27.16, 95% CI=12.03-61.33, P<0.00001) as shown in **Figure 3**.

Combined effect of HIF-1α expression and gender, age, microvascular density (MVD) in patients with glioma

With respect to the gender issue, six studies included 223 male patients and 210 female patients. Even though the frequency of HIF-1α expression was slightly higher in male patients than that in female patients (68.2% versus 63.8%), our results did not find a significant association between HIF-1α expression and gender (OR=1.23, 95% CI=0.82-1.84, P=0.33) in a fixed-effect model as shown in **Figure 4**.

The same six studies also focused on the age issue. For different age stages were presented, we divided ages into three comparable groups. As shown in **Figure 5**, our results showed no difference between HIF-1α expression and age (P>0.05).

Three articles analyzed the relationship between HIF-1α expression and MVD. Our result demonstrated that there was a significant association between HIF-1α expression and MVD (MD=26.32, 95% CI=14.48-38.16, P< 0.0001) in a random-effect model as shown in **Figure 6**.

Table 2. Meta-analysis of HIF-1α expression in glioma patients by WHO grade

Comparison (WHO Grade)	N	number	Z-test		Between-study heterogeneity		
			OR (95% CI)	P	I^2	Ph	Model
IV+III vs. II+I	24	1422	8.59 (6.56, 11.24)	<0.00001	0%	0.66	F
IV vs. III	14	461	2.51 (1.43, 4.42)	0.001	0%	0.98	F
IV vs. II	11	399	9.18 (5.18, 16.28)	<0.00001	0%	0.82	F
IV vs. I	9	272	24.23 (12.21, 48.09)	<0.00001	0%	0.45	F
III vs. II	12	458	4.59 (2.96, 7.12)	<0.00001	0%	0.74	F
III vs. I	10	304	13.34 (7.53, 23.62)	<0.00001	0%	0.83	F
II vs. I	11	365	4.19 (2.59, 6.77)	<0.00001	10%	0.35	F

N, number of included studies; number, total glioma patients; OR, odds ratio; 95% CI, 95% confidence interval; I^2, Ph, between-study heterogeneity; F, the fixed-effect model.

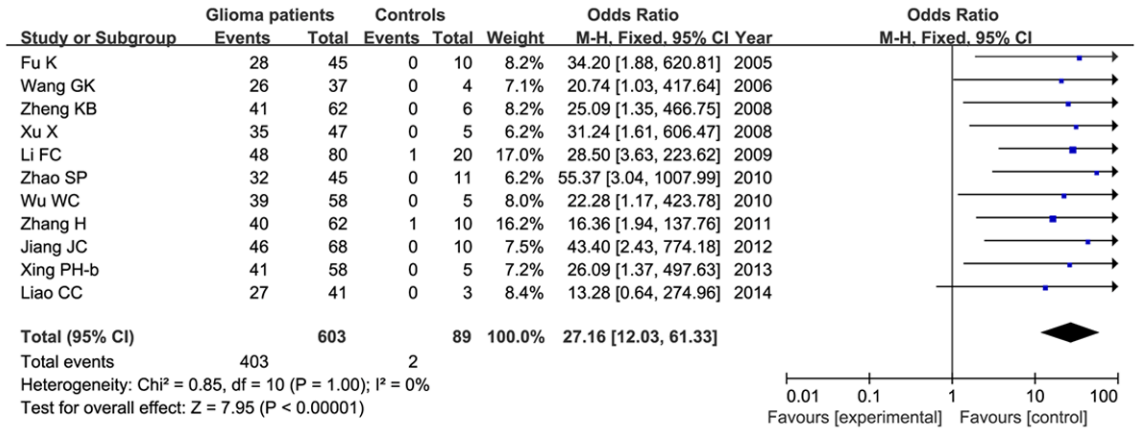

Figure 3. Meta-analysis of HIF-1α expression in patients with gliomas and normal controls.

Correlation of HIF-1α expression with overall survival (OS)

Six articles were obtained, including 310 glioma patients. Two articles concerned the 3-year OS, three in the 2-year OS, two in the 1-year OS, and one in two-month OS. Our result showed that HIF-1α expression was significantly associated with 3-year OS (RR=0.48, 95% CI=0.35-0.66, *P*<0.00001, **Figure 7A**) in a fixed-effect model. This significant association was also found with 2-year OS (RR=0.53, 95% CI=0.38-0.73, *P*<0.0001, **Figure 7B**), and 1-year OS (RR=0.79, 95% CI=0.66-0.95, *P*=0.01, **Figure 7C**).

Three articles concerned the survival times of patients with glioma. The data from the study conducted by Cao et al could not be extracted, and the result revealed a significant effect of HIF-1α expression on the cumulative survival time (*P*<0.05). The meta-analysis of the other two studies also showed HIF-1α expression played a role on survival time.

Sensitivity analysis and publication bias

We deleted each study at a time to reveal single study on the overall effect, and the result indicated that the pooled OR, RR and MD were not significantly influenced by omitting any single study at a given time. The funnel plot also demonstrated no publication bias in this meta-analysis as shown in **Figure 8**.

Discussion

Glioma is a neurological disease with a poor prognosis and a clinical course characterized by progressive functional and cognitive impairment [45]. Heterogeneity between individual patients increasingly limits therapeutic progress for glioma [46]. It is meaningful to investigate biomarkers in each grade of glioma to enhance patient survival and quality of life. In this meta-analysis, we discussed the significance of HIF-1α expression in patients with glioma. Our results found that HIF-1α expression was significantly associated with high WHO

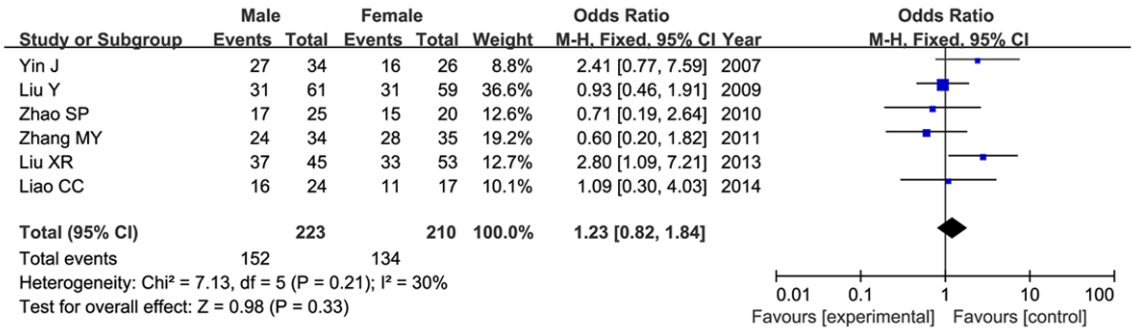

Figure 4. Association between HIF-1α expression and gender in glioma patients in a fixed-effect model.

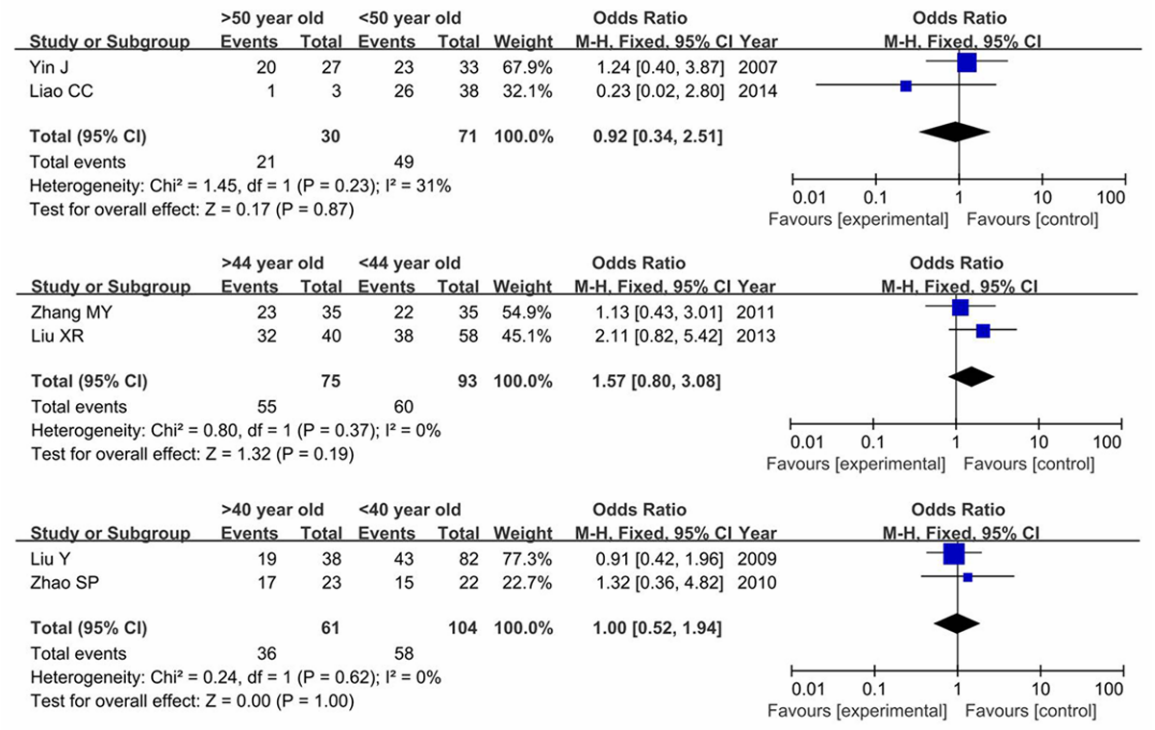

Figure 5. Forest plot of association between HIF-1α expression and age in glioma patients.

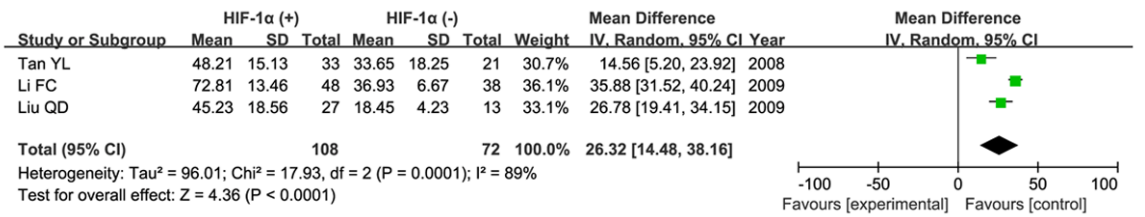

Figure 6. Association between HIF-1α expression and microvascular density (MVD) in patients with glioma.

grade of glioma, MVD, 3 (2 or 1) year overall survival and cumulative survival time (P<0.01). This significant association was not found in age and gender. Our results indicated that HIF-1α expression might predict the prognosis of patients with glioma and provide an insight into

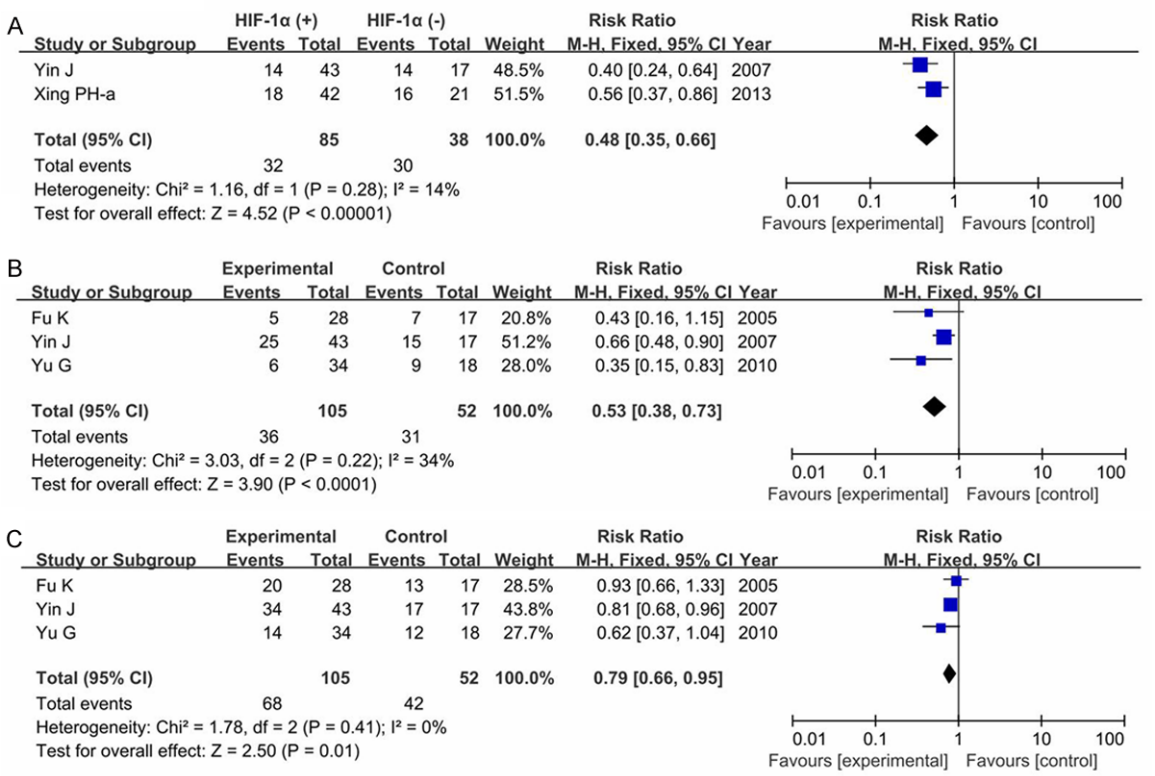

Figure 7. Forest plot of association between HIF-1α expression and overall survive (OS) in glioma patients (A. 3-year OS; B. 2-year OS; C. 1-year OS).

the treatment strategy. Furthermore, this is the first meta-analysis to systematically analyze the role of HIF-1α expression in glioma.

HIF-1α, an O_2-sensitive subunit, is rapidly split by ubiquitination and proteasomal degradation under a normoxic condition, whereas is stabilized and translocates from the cytoplasm to the nucleus under a hypoxic condition [47], which contributes to the regulation of multiple adaptive responses, such as cell proliferation, metabolism, and angiogenesis. It also regulates lymphangiogenic cytokine expression in chronic sterile inflammation [48]. HIF-1α expression is shown to be associated with disease progression. Patients in primary hepatocellular carcinoma who exhibited high HIF-1α expression had significantly poorer overall survival than those with low expression [49]. HIF-1α expression might be a predicative factor of poor prognosis for gastric cancer particularly in Asia [50]. In patients with invasive breast cancer, it correlated with tumor clinicopathological parameters [51].

HIF-1α affected glioma tumor growth, and might play a role in clinical applications for patients with malignant glioma [52]. Studies have exhibited a significant relationship between HIF-1α overexpression and poor prognosis in glioma patients [53]. In majority of glioblastoma, HIF-1α was up-regulated, and the activated regulation of HIF-1α made glioblastoma stem cells more sensitive to hypoxia-mediated maintenance, which provided HIF-1α as an attractive target for glioblastoma therapy [54]. Silencing HIF-1α expression appeared to inhibit the proliferation, invasion, and migration of glioblastoma U87 cells [55]. HIF-1α was shown to be a useful prognostic factor in astrocytic tumor [56].

HIF-1α might play a role in the survival and self-renewal potential of cancer stem cells. It may affect the biology of glioma through regulating or interacting with other proteins. HIF-1 regulated anterior gradient protein 2 expression, which involved in control of glioblastoma growth and vascularity [57]. Positive expression for HIF-1α was correlated with VEGF and PDGF-C

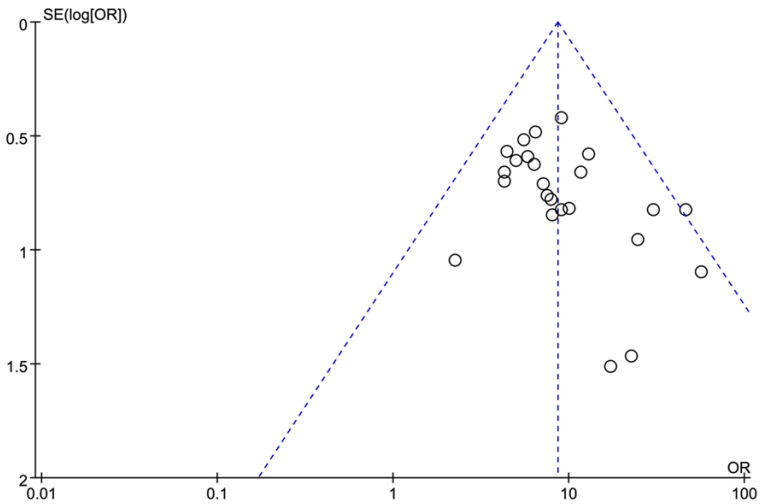

Figure 8. Funnel plot for publication bias in selection of studies.

expression in glioma [58]. Up-regulation of miR-183 in malignant gliomas induced HIF-1α expression and might play a role in glioma biology [59]. Nuclear factor E2-related factor 2 (Nrf2) and HIF-1α were shown to be overexpressed in glioblastoma tissues, and there was significant correlation between HIF-1α level and Nrf2 status overall survive and progression-free survival [60]. HIF-1α and HIF-2α competitively binded to NICD and regulated the activation of Notch signaling, which provided improved therapeutic opportunities for malignant gliomas [61]. Knock down of HIF-1α in human and murine glioma cells might impair the migration in vitro and their invasion in vivo [62].

Several limitations were presented in this meta-analysis. Firstly, most of the included studies were conducted in Chinese population, other populations should be considered. Secondly, the cutoff points for HIF-1a expression were not in unison, which might influence the reliability of results. Thirdly, the included studies for some comparisons were small, such as age, 1-year overall survival. Lastly, other causes, such as genetic polymorphisms of HIF-1α or factors which may interact with HIF-1α expression should be focused on.

In conclusions, our results suggested that HIF-1α expression was significantly associated with high WHO grade of glioma, MVD, 3 (2 or 1) year overall survival and cumulative survival time, indicating that HIF-1α might be a valuable biomarker for glioma grade and therapeutic treatment. However, further studies concerning other non-Asian populations should be included in the future research.

Disclosure of conflict of interest

None.

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