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Original Article

Overexpression of vascular endothelial growth factor indicates poor outcomes of glioma: a systematic review and meta-analysis

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Abstract: Background: Accumulated studies have revealed that vascular endothelial growth factor (VEGF) plays an essential role in the progression of glioma, but the prognostic significance of VEGF expression for patients with glioma remains unknown. Method and material: A literature search of public databases (PubMed, ISI Web of Science, Science Direct, Cochrane Central Register of Controlled Trials, Wiley Online Library, China National Knowledge Infrastructure, China Biology Medicine disc, Chongqing VIP and Wan Fang Data) was conducted. A meta-analysis was performed to evaluate the association between the overexpression of VEGF and the survival for the glioma patients. Subsequently we evaluated the impact of VEGF expression on the pathological grade of glioma. Results: A total of 32 articles with 2307 cases contributed to this analysis, of which 31 reported overall survival (OS) and 5 reported progression-free survival (PFS). In this meta-analysis, VEGF overexpression significantly identified the unfavorable outcome on OS (HR = 1.647, 95% CI: 1.324~2.048, P < 0.001, Z = 4.48) but not on PFS (HR = 1.021, 95% CI: 0.974~1.070, P = 0.393). Subgroup analyses also revealed that high level of VEGF was associated with the poor OS for the patients with glioma according to region, case number, specimen type, method to detect VEGF and statistical method. Furthermore, the significant correlation was achieved between VEGF expression and the pathological grade of glioma (r = 0.307, P < 0.001). Conclusion: This study suggests that VEGF expression is significantly correlated with the glioma progression and may be a valuable prognostic factor on OS for the glioma patients.

Keywords: Vascular endothelial growth factor, glioma, prognosis, meta-analysis

Introduction

Glioma, the most prevalent intracranial neoplasia in adults, is classified as grade I to grade IV for its differentiation, based on the World Health Organization (WHO) criteria. Studies have pointed to an increasing incidence of gliomas over the past few decades. Though diagnostic and therapeutic techniques have been improved tremendously in last ten years, the survival of patients with malignant glioma remains still poor. Several prognostic factors are well established for glioma patients, such as isocitrate dehydrogenase 1 (IDH1), P53, epidermal growth factor receptor (EGFR), and Ki-67 [1-4]. Nevertheless, there is a compelling demand to explore more prognostic markers to prolong the survival of glioma patients.

Vascular endothelial growth factor (VEGF) is an endothelial, cell-specific mitogen, which acts as a prime mediator in angiogenesis. As a critical pro-angiogenic factor, VEGF is also involved in carcinogenesis and metastasis in cancers [5, 6]. Increasing evidence suggested that VEGF is a prognostic factor of many cancers, such as lung cancer, hepatocellular carcinoma, gastric cancer, colon cancer and osteosarcoma [7-11], but the predictive value of VEGF on the survival for glioma patients has not been clarified. Recent studies have focused on the interaction between glioblastoma cells and blood vessels. Bevacizumab, an angiogenesis inhibitor, has been observed to increase PFS in patients with glioblastoma multiforme, by inhibiting both VEGF and vascular permeability [12]. Evidence is accumulating that VEGF may play a vital role

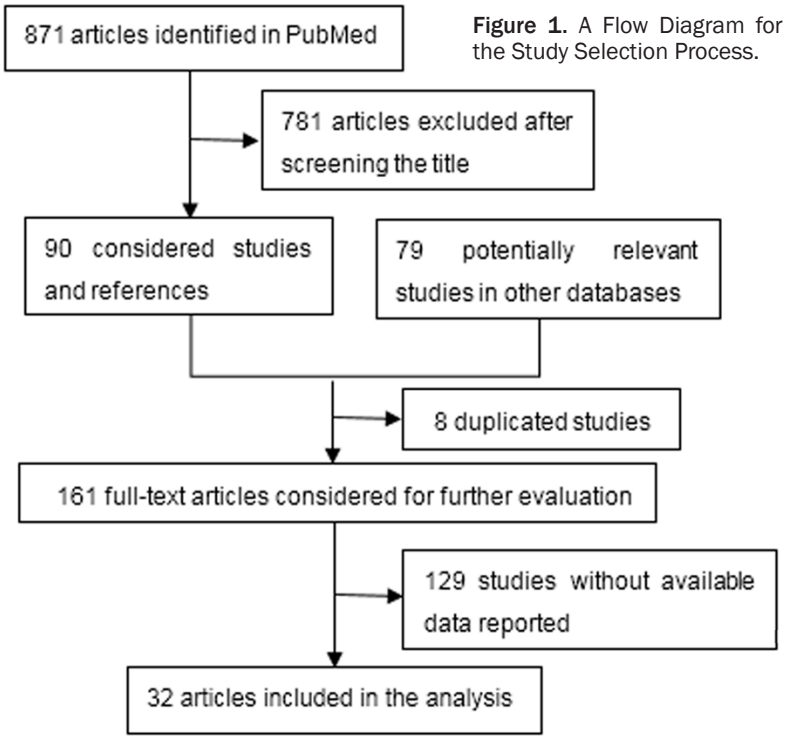

Figure 1. A Flow Diagram for the Study Selection Process.

in the progression of glioma, but the potential of VEGF as a prognostic marker for glioma remains dismal. In the light of the previous studies, we performed a meta-analysis to explore the prognostic value of VEGF for glioma patients.

Materials and methods

Search strategy

An electronic literature search was conducted in PubMed, ISI Web of Science, Science Direct, Cochrane Central Register of Controlled Trials and Wiley Online Library, which are English Databases up to 28th March 2015. For Chinese Databases, the search identified the eligible studies in China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), Chongqing VIP and Wan Fang Data. The search was based on the keywords as follows: ("vascular endothelial growth factor" or "VEGF" or "VEGFA" or "VEGFB" or "VEGFC" or "VEGFD" or "angiogenesis" or "bevacizumab" or "endostatin") and ("glioma" or "astrocytoma" or "oligodendroglioma" or "oligoastrocytoma" or "ependymoma" or "glioblastoma" or "gliomatosis cerebri" or "brain cancer" or "brain neoplasm" or "brain tumor" or "GBM" or "AA" or "AO" or "DIPG") and ("prognos*" or "surviv*" or "follow-up studies" or "mortality" or "incidence" or "predict" or "outcome").

Selection criteria

All eligible studies were included by the following criteria: (1) glioma patients should be affirmed pathologically; (2) the association between VEGF expression and OS or PFS should be evaluated for glioma patients; (3) a hazard ratio (HR) should be provided or the sufficient data should be available to calculate a HR for OS or PFS; (4) it should be the most recent or complete study if the same patient cohort were reported more than once by the same authors or research group; (5) it should be written in either Chinese or English in full text.

The studies were considered ineligible by the following exclusion criteria: (1) review, experimental studies, conference abstracts, expert opinion or case report; or (2) no sufficient data for calculating the HR.

Data extraction and assessment of study quality

Two authors (WJ Chen and Xin Zhang) reviewed all of the included studies independently and extracted the following data: first author's name, publish year, region, case number, WHO grade, test method, specimen type, survival, HR and statistical method. We labeled the data without reporting the above contents as "not applicable". Each discrepancy was resolved by discussion and consensus among the authors. Newcastle-Ottawa quality assessment scale was used to assess the quality of each study.

Statistical analysis

The relationship of VEGF expression with the pathological grade of glioma was analyzed by using a two-sided Chi-square test and spearman's rank correlation. HRs and 95% CIs were used to estimate overall effects for survival out-

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

Author and year	Region	Case	Grade	Specimen type	Assay	HR (95% CI)	Out-come	Sur-vival	Method	quality score
Bian 2000	China	48	I-IV	Tumor tissues	IHC	6.625 (0.875, 50.230)	NS*	OS	Survival Curve	6
Zhong 2001	China	94	I-IV	Tumor tissues	IHC	3.876 (1.408, 10.750)	Poor	OS	HR (multivariate)	7
Hara 2004	Japan	100	II-IV	Tumor tissues	IHC	0.904 (0.463, 1.765)	NS	OS	HR (multivariate)	7
Liu 2004	China	50	I-IV	Tumor tissues	IHC	4.275 (0.816, 22.390)	NS	OS	HR (univariate)	6
Nam 2004	Korea	26	IV	Tumor tissues	RT-PCR	3.175 (0.858, 11.740)	NS	OS	Original Data	7
Zhou 2005	China	87	III-IV	Tumor tissues	qRT-PCR	1.226 (0.390, 3.595)	NS	OS	HR (multivariate)	3
Buccoliero 2006	Italy	43	IV	Tumor tissues	IHC	1.562 (0.717, 3.405)	NS	OS	Original Data	7
Cheng 2006	China	60	I-IV	Tumor tissues	IHC	2.114 (1.054, 4.255)	Poor	OS	HR (univariate)	6
Carlson 2007	USA	71	III-IV	Tumor tissues	RT-PCR	4.340 (2.240, 8.430)	Poor	OS	HR (univariate)	6
Sathornsumetee 2008	USA	68	III-IV	Tumor tissues	IHC	1.180 (0.500, 2.830)	NS	OS	HR (multivariate)	7
Flynn 2008	USA	62	IV	Tumor tissues	IHC	1.840 (1.060, 3.210)	Poor	OS	HR (multivariate)	7
Zeng 2009	China	56	I-IV	Tumor tissues	IHC	1.070 (0.540, 1.770	NS	OS	Survival Curve	6
Yoo 2010	Korea	76	I-IV	Tumor tissues	IHC	1.021 (0.574, 1.815)	NS	OS	HR (multivariate)	6
Piperi 2011	Greece	97	II-IV	Tumor tissues	IHC	0.974 (0.543, 1.749)	NS	OS	HR (multivariate)	7
Saetta 2011	Greece	60	II-IV	Tumor tissues	IHC	1.007 (0.991, 1.023)	NS	OS	HR (multivariate)	5
El-Sayed 2011	Egypt	26	I-IV	Tumor tissues	IHC	17.074 (3.491, 83.520)	Poor	OS	Original Data	7
BeriNAan-Neagoe 2012	Romania	14	IV	Tumor tissues	RT-PCR	0.910 (0.180, 4.640)	NS	OS	HR (NA*)	6
Castells 2012	Spain	71	IV	Tumor tissues	RT-PCR	1.631 (0.955, 1.663)	NS	OS	HR (multivariate)	6
Fan 2012	China	62	II-IV	Tumor tissues	IHC	1.710 (0.770, 3.783)	NS	OS	Survival Curve	6
Smith 2012	UK	79	III-IV	Tumor tissues	IHC	0.559 (0.291, 1.077)	NS	OS	HR (multivariate)	7
Cao 2013	Japan	22	I-IV	Tumor tissues	IHC	2.748 (0.321, 23.560)	NS	OS	Original Data	7
Shin 2013	Korea	67	IV	Tumor tissues	IHC	1.010 (0.500, 2.040)	NS	OS	HR (multivariate)	6
Xu 2013	China	88	I-IV	Tumor tissues	IHC	0.560 (0.191, 1.641)	NS	OS	HR (multivariate)	6
Xu 2013	China	80	NA	Tumor tissues	IHC	1.830 (0.903, 3.713)	NS	OS	Survival Curve	6
Xu 2013	China	36	NA	Tumor tissues	IHC	3.310 (0.560, 19.500)	NS	OS	Survival Curve	6
Jensen 2013	USA	18	III-IV	Tumor tissues	ELISA	8.727 (1.375,55.350)	Poor	OS	HR (univariate)	6
Tabouret 2013	France	26	II-IV	Blood	ELISA	3.170 (1.193, 8.422)	Poor	OS	HR (multivariate)	7
Jensen 2013	USA	18	III-IV	Tumor tissues	ELISA	0.460 (0.160, 1.373)	NS	PFS	HR (univariate)	6
Krauze 2013	USA	202	IV	Urine	ELISA	1.001 (0.998, 1.005)	NS	PFS	HR (multivariate)	3
Shin 2013	Korea	67	IV	Tumor tissues	IHC	1.550 (0.790, 3.020)	NS	PFS	HR (multivariate)	5
Tabouret 2013	France	26	II-IV	Blood	ELISA	2.822 (1.088, 7.321)	Poor	PFS	HR (multivariate)	5
Chinorean 2014	Romania	14	IV	Blood	ELISA	2.340 (0.580, 9.440)	NS	OS	HR (NA)	6
Nambirajan 2014	India	126	I-III	Tumor tissues	IHC	1.200 (0.300, 4.200)	NS	OS	HR (multivariate)	6
Clara 2014	Brazil	208	IV	Tumor tissues	IHC	1.940 (1.223, 3.078)	Poor	OS	HR (multivariate)	7
Takano 2014	Japan	37	III-IV	Blood	ELISA	3.480 (1.546, 7.840)	Poor	OS	Survival Curve	6
McLeNAon 2015	USA	22	I-III	Tumor tissues	IHC	1.038 (1.010, 1.068)	Poor	PFS	HR (univariate)	4

*NA for not applicable, NS for not significant.

comes. Study region, case number, specimen type, VEGF test method, statistical method were analyzed for subgroup analyses. HR greater than 1 with 95% CI not overlapping 1 indicates a poor prognosis for the VEGF-positive group. The Z test was used to determine the significance of the combined HR ($P < 0.05$ was considered as statistically significant).We used the methods described by Parmar et al. and the software Engauge Digitizer Version4.1 (http://digitizer.sourceforge.net/) when the studies provided Kaplan-Meier survival curves but no HRs with 95% CIs [13]. Moreover, the multivariate HRs and 95% CIs were combined when multivariate and univariate analyses of OS and/or PFS were available in the same study, which could better reveal the influence of multiple factors on the survival response. The Q-statistic was selected to test the statistical heterogeneity. The random-effects model was used when the Q-test reported a *P* value < 0.05 by using the method described previously [14]. Otherwise, the fixed-effects model (Mantel-Haenszel method) [15] was selected. We also used the I^2-statistic to calculate heterogeneity (I^2 less than 25%, no heterogeneity; I^2 = 25-50%, moderate heterogeneity; and I^2 greater than 50%, large or extreme heterogeneity).

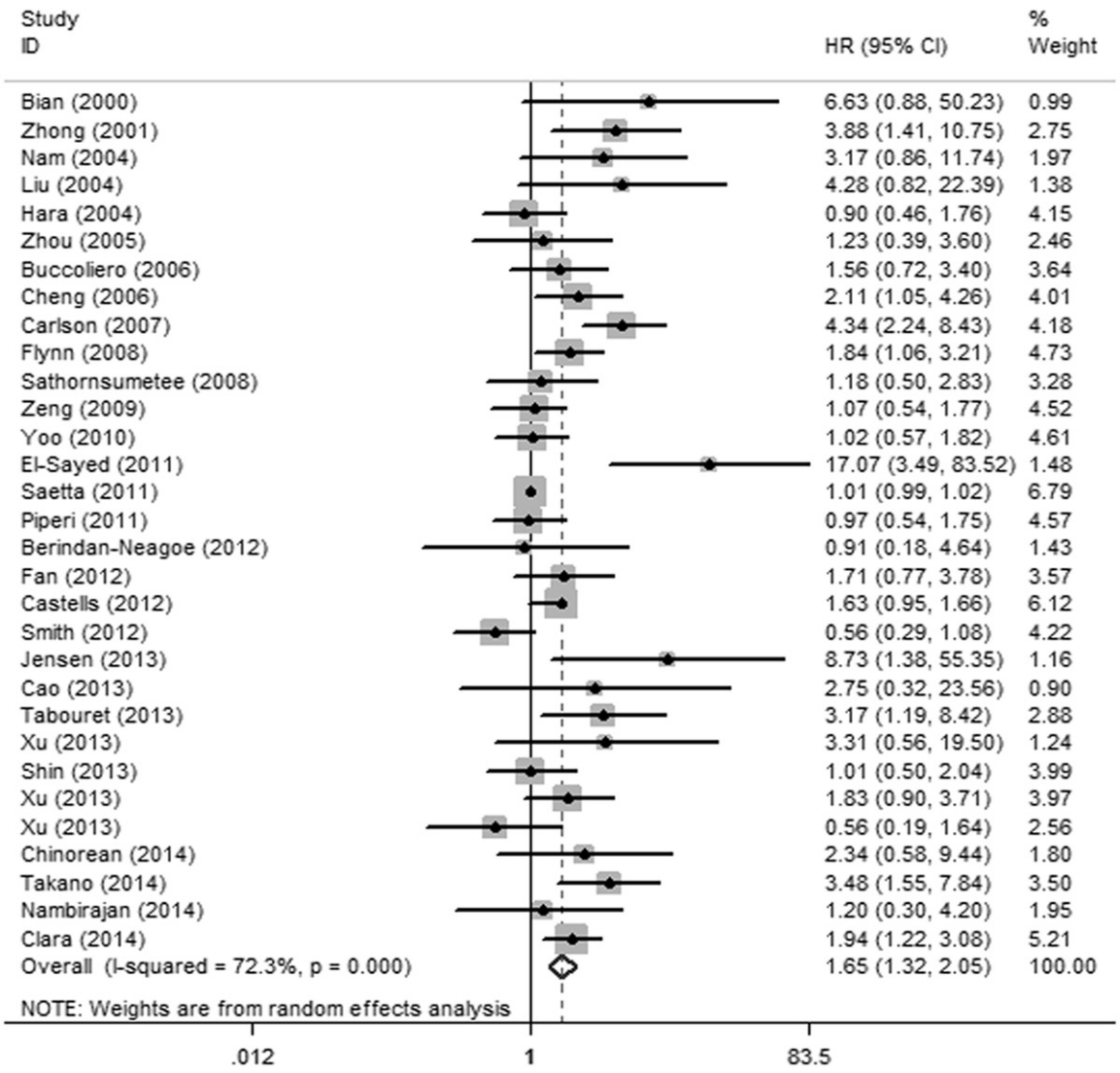

Figure 2. A Forest Plot of the Combined Relative HR form Random-effect OS.

Publication bias was estimated by a funnel plot and Egger' test [16, 17]. All two-sided *P* values less than 0.05 were considered to be significant. SPSS20 and STATA version 12.0 software were used for the statistical calculation.

Results

Literature search and characteristics of included studies

The flow diagram for the study selection process was depicted in **Figure 1**. In total, 32 studies were included in the analysis, of which 31 reported the OS and 5 reported the PFS for glioma patients [18-49]. These 32 studies published between 2000 and 2015 include 2307 cases, among which 5 studies [19, 22, 25, 36, 49] were in Chinese. In the included studies, ten studies [19, 25, 29, 30, 36, 40, 41, 45, 46, 49] with 713 cases reported the of VEGF overexpression with the pathological grade of gliomas. In total, 17 Asian studies, 8 European studies, 5 American studies and 1 African study were included in the current meta-analysis. The characteristics of included studies were presented in **Table 1**.

Meta-analysis

Thirty-one studies provided the sufficient data evaluable for OS in this meta-analysis. VEGF positive expression conferred the poor OS for glioma patients with HR = 1.647 (Z=4.48;

Table 2. Summarized HRs of subgroup analyses for OS in the meta-analysis

Stratified analysis	Study (N)	HR (95% CI)	P	Z	Heterogeneity		
					I^2	P	Statistical model
Region							
Asia	17	1.492 (1.206, 1.844)	0.000	3.690	34.9%	0.077	Fixed-effects model
Europe	8	1.218 (0.893, 1.663)	0.213	1.250	69.0%	0.002	Random-effects model
America	5	2.191 (1.638, 2.929)	0.000	5.290	54.8%	0.065	Fixed-effects model
Case number							
Small	15	2.398 (1.547, 3.716)	0.000	3.910	72.2%	0.000	Random-effects model
Large	16	1.395 (1.081, 1.799)	0.011	2.560	57.5%	0.002	Random-effects model
Specimen type							
Tumor tissues	28	1.547 (1.242, 1.928)	0.000	3.890	70.9%	0.000	Random-effects model
Blood	3	3.155 (1.784, 5.579)	0.000	3.950	0.0%	0.890	Fixed-effects model
Assay							
IHC	22	1.394 (1.112, 1.747)	2.880	0.004	61.5%	0.000	Random-effects model
RT-PCR	4	2.286 (1.175, 4.446)	2.440	0.015	64.8%	0.037	Random-effects model
ELISA	4	3.447 (1.999, 5.942)	4.450	0.000	0.0%	0.730	Fixed-effects model
Method							
Survival curve	6	1.797 (1.275, 2.533)	0.001	3.350	33.7%	0.183	Fixed-effects model
Original data	4	2.633 (1.455, 4.763)	0.001	3.200	57.9%	0.068	Fixed-effects model
HR (multivariate)	15	1.246 (0.994, 1.562)	0.057	1.910	65.4%	0.000	Random-effects model
HR (univariate)	4	3.359 (2.147, 5.256)	0.000	5.300	11.1%	0.338	Fixed-effects model

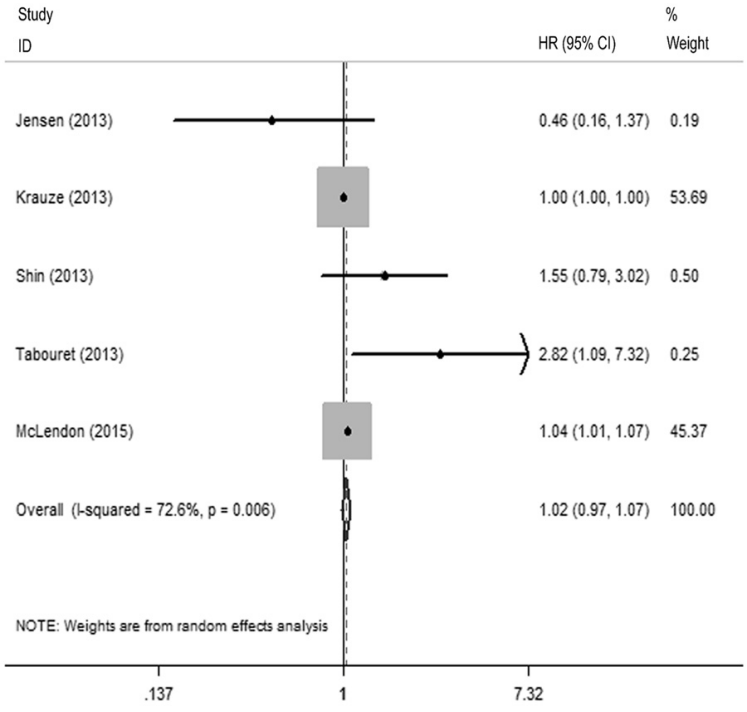

Figure 3. A Forest Plot of the Combined Relative HR form Random-effect PFS.

Figure 2). The heterogeneity was found for the pooled HR for OS (I^2 = 72.3%, P < 0.001). However, the prognostic effect of VEGF positive expression for glioma patients was not significant in PFS analysis group with the pooled HR of 1.021 (95% CI: 0.974~1.070, P = 0.393, Z = 0.860; I^2 = 72.6%, P=0.006; **Figure 3**) with 5 studies included. Additionally, we divided patients into different subgroups for OS classified by region, case number, specimen type, VEGF test method and statistical method. The combined HR was 1.492 (95% CI: 1.206~1.844, P < 0.001) and 2.191 (95% CI: 1.638~2.929, P < 0.001) in the Asian studies and American studies, respectively. Next, we divided the studies into two groups depending on the case number less or more than sixty. VEGF positive expression was a valuable prognostic marker in both small sample sizes (N ≤ 60, HR = 2.398, 95% CI: 1.547~3.716, P < 0.001) and large sample sizes (N > 60, HR = 1.395, 95%

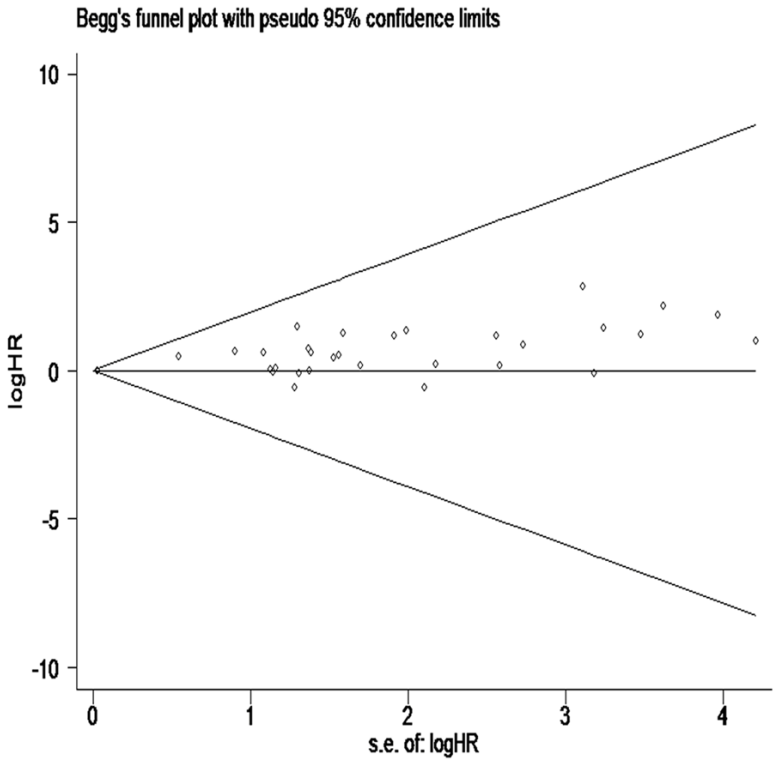

Figure 4. A Funnel Blot for the publication bias test of OS studies.

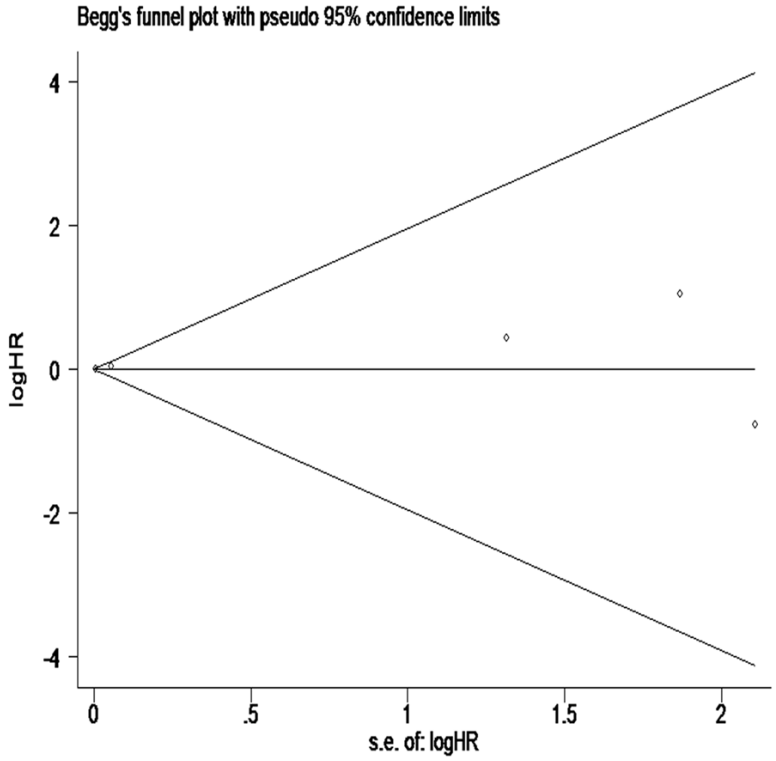

Figure 5. A Funnel Blot for the publication bias test of PFS studies.

CI: 1.081~1.799, P = 0.011). The subgroup analyses were proceeded among the specimen types. In the tumor tissues and blood sample group, the combined HRs were 1.547 (95% CI: 1.242~1.928, P < 0.001) and 3.155 (95% CI: 1.784~5.579, P < 0.001), respectively. VEGF expression was also considered as a prognostic factor according to different VEGF test methods. Significant impacts of VEGF expression were observed in IHC group (HR = 1.394, 95% CI: 1.112~1.747, P = 0.004), RT-PCR group (HR = 2.286, 95% CI: 1.175~4.446, P = 0.015) and ELISA group (HR = 3.447, 95% CI, 1.999~5.942, P < 0.001), respectively. Finally, we also found an inverse effect of VEGF expression on OS according to the statistical methods. The pooled HRs were 1.797 (95% CI: 1.275~2.533, P = 0.001), 2.633 (95% CI: 1.455~4.763, P = 0.001) and 3.359 (95% CI: 2.147~5.256, P < 0.001) in the group providing survival curve, original data and univariate HR, respectively (**Table 2**).

Heterogeneity analysis results

Significant heterogeneities were found in the analysis between VEGF and OS and PFS (I^2 = 72.30%, P < 0.001 and I^2 = 72.60%, P = 0.006, respectively). In the subgroup analyses for OS, the heterogeneities were reduced in the Asian and American studies (I^2 = 34.9%, P = 0.077 and I^2 = 54.8%, P = 0.065). The pooled HR in blood tissue group did not show obvious heterogeneity (I^2 = 0.0%, P = 0.890). The pooled HR also reached low

Table 3. Correlation of VEGF expression with the pathological grade of gliomas from the available included studies

Study	Positive		Negative		Chi-square test	Spearman
	Low-grade	High-grade	Low-grade	High-grade		
Zhong 2001	24	15	11	0		
Cheng 2006	8	37	8	7		
Zeng 2009	2	38	6	10		
Yoo 2010	2	31	12	31		
El-Sayed 2010	8	14	3	1		
Fan 2012	2	27	7	16		
Cao 2013	3	18	2	4		
Xu 2013	36	56	20	4		
Nambirajan 2014	18	25	58	25		
Tabouret 2014	18	25	58	23		
Total	121	286	185	121	Z = -8.199, P < 0.001	r = 0.307, P < 0.001

heterogeneity in ELISA group (I^2 = 0.0%, P = 0.730). Moreover, heterogeneity was not noticeable in the group of survival curve group, original data and univariate HR (I^2 = 33.7%, P = 0.183; I^2 = 57.9%, P = 0.068 and I^2 = 11.1%, P = 0.338) (**Table 2**).

Publication bias

The Funnel plot and Begg's test did not show any evidence of publication bias (P = 0.507 for OS, P = 1 for PFS; **Figures 4** and **5**).

Correlation of VEGF overexpression with the pathological grade of gliomas

The Chi-square test was applied to analyze the relationship between VEGF expression and glioma pathological grade. The results revealed that VEGF positive rate was higher in high-grade glioma (70.27%) than that in low-grade glioma (39.54%, Z = -8.199, P < 0.005). VEGF expression was shown to be positively relevant with pathological grade of gliomas by spearman's rank correlation (r = 0.307, P < 0.005) (**Table 3**).

Discussion

VEGF, with a molecular weight of 38.2 kDa, is involved in triggering the process of angiogenesis in neoplasia. VEGF also stimulates capillary permeability, angiogenesis and endothelial cell growth [50]. Glioma, a highly vascularized tumor, develops with progressive angiogenesis. VEGF has been indicated to be a potential biomarker in serum/plasma and cerebrospinal fluid of glioma patients [51, 52]. VEGF upregulation also increases cell density, leading to the tumor hypoxia [53]. VEGF, induced by hypoxia via HIF-1a, acts as a central proangiogenic factor in blood vessel formation by stimulating VEGFR-2/KDR in glioma [54]. Additionally, the prognostic value of VEGF upregulation for survival in glioma patients was described previously [55, 56]. However, other researchers argued that VEGF could not be an independent prognostic factor for the survival of glioma patients [57, 58]. Hence, well-designed studies with large sample size are still needed to provide strong evidence to explore the prognostic value of VFGF for the glioma patients.

Our study suggested that higher positive rate of VEGF expression was found in the group of high-grade glioma compared to the low-grade glioma. Previous studies also reported that VEGF upregulation was involved in the angiogenesis and progression of glioma, suggesting the participation of VEGF in positive regulation of neoangiogenesis and proliferation during gliomagenesis [59, 60]. Consistent with the previous researches, our study revealed that VEGF expression was significantly related to glioma pathological grade by analyzing the 713 cases available in the included studies.

In this meta-analysis, our result implied that VEGF overexpression was notably associated with OS of glioma patients. Of note, the subgroup analyses also proved the strong prognostic relevance of VEGF overexpression on OS of glioma patients. Contrary to our expectation, no significance was found between VEGF over-

expression and PFS of glioma patients. The main reason might probably be that too few studies were available reporting the relation between VEGF expression and PFS of glioma patients. Hence, larger cohort would be required to investigate the impact of VEGF on PFS of gliomas.

Nevertheless, several limitations did exist in the present meta-analysis. Firstly, we only included English and Chinese studies in this meta-analysis while the coincident studies in other languages were not included. Secondly, another key bias might be extrapolating the HRs and the 95% CI by different methods. When the studies did not provide the HRs, we extrapolated HRs from the survival curves or estimated them from the sufficient data, which might be less reliable than the ones obtained from published statistics. Thirdly, journals often favor studies with positive results, whereas the negative results might not be showed in publications. Fourthly, we did not exclude the studies with limited numbers of cases, which might be an important bias since the small scale probably did not provide reliable evidences for this analysis.

In conclusion, this meta-analysis was the first one to yield the association between VEGF expression and the survival of glioma patients. The VEGF overexpression is significantly associated with the OS of the glioma patients but not with PFS. Moreover, we infer the significant association between VEGF expression and glioma pathological grade in a large number of cases included. Our study suggests that VEGF shows the significant relevance to glioma pathological grade and might be a valuable prognostic factor for the OS of the patients with glioma. Nevertheless, well-designed studies with larger cohort are needed to explore the valuable role of VEGF in glioma.

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Disclosure of conflict of interest

None.

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