Review Article
Insulin-like growth factor binding protein 2 expression and prognosis of glioma patients: a systematic review and meta-analysis

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Abstract: Many studies have focused on the prognosis role of insulin-like growth factor binding protein 2 (IGFBP2) in glioma patients, but the results remain inconsistent. Thus, a meta-analysis was carried out to explore the relationship between IGFBP2 and glioma prognosis. Relevant publications were searched in several widely used databases and six articles (seven studies, 766 patients in all) were included in the meta-analysis. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the association between IGFBP2 and glioma prognosis. Significant relationship between IGFBP2 expression and glioma prognosis was not observed in overall meta-analysis for overall survival (HR = 1.044, 95% CI = 0.998-1.093). However, increased IGFBP2 expression is significantly associated with poor overall survival in the multivariate analysis subgroup (HR = 1.036, 95% CI = 1.024-1.047) and glioblastoma multiform subgroup (HR = 1.028, 95% CI = 1.003-1.054). According to the results of our meta-analysis, higher IGFBP2 expression in glioma patients is associated with unfavorable prognosis and has predictive effect on overall survival for glioma patients, especially glioblastoma multiform patients.

Keywords: IGFBP2, expression, glioma, prognosis, meta-analysis

Introduction

Insulin-like growth factor binding protein 2 (IGFBP2) is a member of the IGFBP family. It is a secreted protein that binds insulin-like growth factor (IGF)-I and IGF-II [1, 2]. It also functions by binding other kinds of proteins [3-6]. There is a nuclear localization sequence in IGFBP2 as well [7]. So far, IGFBP2 has been widely studied and implicated in the progression of many cancer types including glioma [4, 8-12]. Glioma is the most common primary tumor of the brain [13]. According to the current WHO classification, glioma can be divided into three grades, including glioblastoma multiform (GBM, grade IV), anaplastic astrocytoma (AA, grade III), anaplastic oligodendroglioma (AO, grade III), and oligodendroglioma (O, grade II) [14, 15], among which GBM patients were reported to have very poor survival [16, 17].

In this study, we investigated the association between IGFBP2 and glioma prognosis in a systematic and statistic way. In the past decade, a series of studies have focused on the relationship between IGFBP2 expression and glioma prognosis [15, 18-24], but the results of those individual studies provided limited information and could not draw a convincible conclusion. Therefore, we performed a meta-analysis with a relatively large sample size of six articles (seven studies, 766 patients in all) to provide a more reliable conclusion of the relationship between IGFBP2 and glioma prognosis.

Materials and methods

Literature search, selection, and data collection

In this study, we searched papers published before Sep 7, 2015 according to the keywords "insulin-like growth factor binding protein 2"/"IGFBP2"/"IGFBP-2"/"IBP2"/"IGF-BP53", "astrocytoma"/"brain neoplasms"/"oligodendroglioma"/"glioblastoma"/"brain tumor"/"glioma", and "survival"/"prognosis"/"mortality"/"death" in PubMed and Web of Science independently.
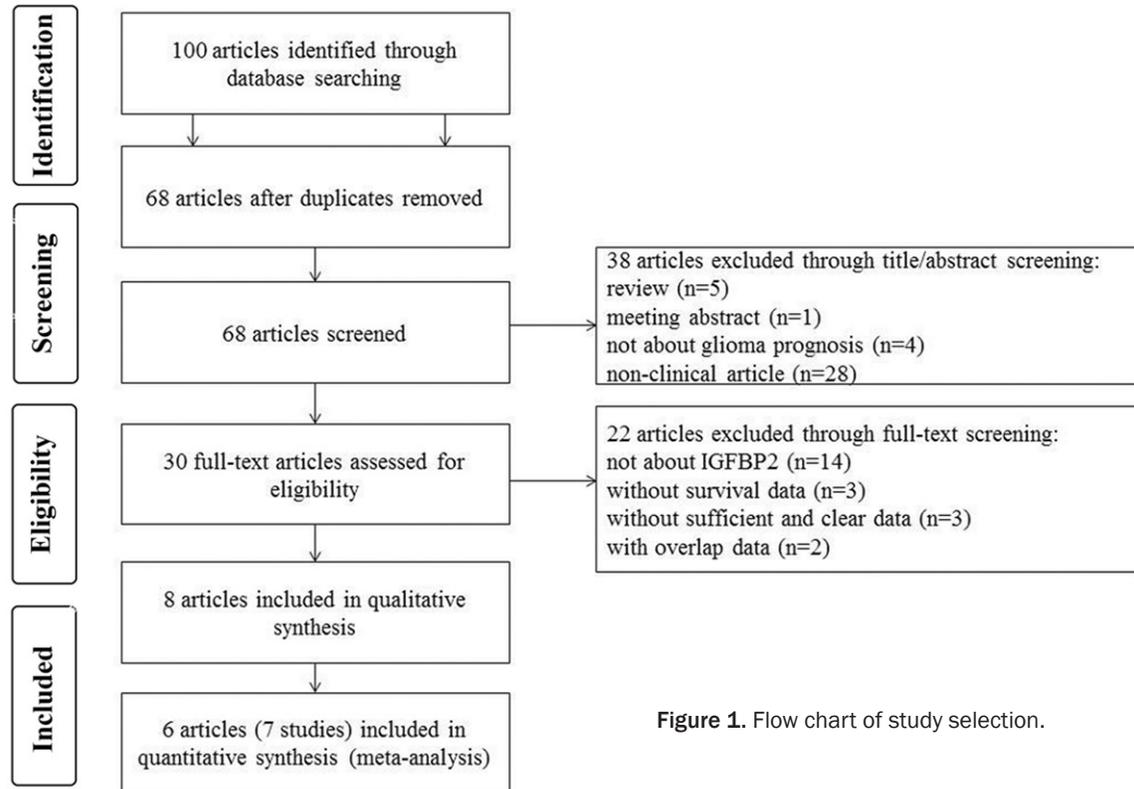
Figure 1. Flow chart of study selection.

The papers obtained were further selected for the meta-analysis and our selection criteria were: (a) full text English-written study; (b) study providing sufficient and clear data for individual hazard ratio (HR) and 95% confidence interval (CI) exaction or calculation; (c) studies sharing the same sample of patients were compared and the most complete study from them was included in our meta-analysis.

In this study, two investigators independently collected data from each eligible paper. The data were composed of first author, published year, patients' country of origin, number of patients, tumor grade, detection method, median follow-up months, outcome endpoints, survival analysis method, HR and 95% CI for IGFBP2 high expression group versus IGFBP2 low expression group. Individual HR and 95% CI were calculated using univariate survival analysis if only IGFBP2 expression data and survival time were available. Multivariate HR and 95% CI were selected if both univariate and multivariate results were reported in an individual study. Through checking between the two investigators, a final data collection was determined.

Meta-analysis methods

According to the data collected from each eligible paper, we performed both the overall meta-analysis and subgroup meta-analysis based on survival analysis method and tumor grade, to evaluate the relationship between IGFBP2 and glioma prognosis. In the overall as well as the subgroup meta-analysis, pooled HRs and 95% CIs for overall survival (OS) were all calculated by fixed effects model or random effects model. The model chosen was based on the heterogeneity test. For the heterogeneity test, we performed the χ^2-based *Q*-test in this study [25]. When *Q*-test reported a *P* value of more than 0.10, fixed effects model was used to calculate the pooled HRs [26], otherwise random effects model was used [27].

Publication bias was also tested using the Begg's funnel plot and the Egger's test [28]. If the funnel plot was asymmetric and the Egger's test reported a *P* value of less than 0.05, the publication bias probably exists.

In this study, we used the software Stata version 14.0 (Stata Corporation, College Station, TX, USA) to carry out the meta-analysis.

Table 1. Studies and data included in this meta-analysis

Author	Year	Patients' country of origin	Study design	No. of patients	Grade	Detection method	Median follow-up months (range)	Outcome	Survival analysis method (adjustment factors)
McDonald[a]	2007	Australia	NA	143	Mixed	IHC	NA (NA)	DSS	M (age, IQGAP1)
Marucci	2008	Italy	NA	36	Mixed	IHC	16.6 (0.4-195.0)	OS	U
Lin[b]	2009	China	R	52	GBM	ELISA	21.1 (NA)	DFS	M (age, gender, KPS, extent of resection)
Santosh	2010	India	P	136	GBM	IHC	17.0 (NA-34.0)	OS	U
Zhou[c]	2010	USA	NA	49	AA	Real-time qRT-PCR	37.0 (NA)	OS	M (age, recur, ABCG2, BMI1, MELK, MSI1, PROM1, PAX6, PTEN, VEGFA, CDK4, EGFR, MMP2, RPS9)
Zhou[c]	2010	USA	NA	45	AO & O	Real-time qRT-PCR	AO: 85.4 (NA); O: 116.0 (NA)	OS	M (age, recur, ABCG2, BMI1, MELK, MSI1, PROM1, PAX6, PTEN, VEGFA, CDK4, EGFR, MMP2, RPS9)
Gállego Pérez-Larraya	2014	France	R	107	GBM	ELISA	19.8 (NA)	OS	M (age, tumor volume)
Han	2014	China	R	83	GBM	ELISA	13.8 (0.9-34.8)	OS	M (age, sex, KPS, tumor size, extent of resection, MGMT)
Martino-Echarri	2014	USA	NA	310	Mixed	Gene expression array	13.0 (0.2-251.7)	OS	U

NA, Not available; R, retrospective; P, Prospective; GBM, Glioblastoma multiforme; AA, Anaplastic astrocytoma; AO, Anaplastic oligodendroglioma; O, Oligodendroglioma; IHC, Immunohistochemistry; ELISA, Enzyme-linked immunosorbent assay; qRT, Quantitative reverse transcription; DSS, Disease-specific survival; OS, Overall survival; DFS, Disease-free survival; M, Multivariate cox proportional hazard regression; U, Univariate survival analysis; KPS, Karnofsky performance status; MGMT, MGMT promoter methylation status. [a]Study was excluded from meta-analysis because disease-specific survival was studied and overall survival data was not available. [b]Study was excluded from meta-analysis because disease-free survival was studied and overall survival data was not available. [c]The article Zhou et al., 2010 investigated more than one tumor grade respectively and was treated as independent studies in the meta-analysis.

Table 2. Detailed results of meta-analysis

Meta-analysis groups	Number of studies	Sample size	Overall survival	
			HR (95% CI)	P^a
Overall analysis	7	766	1.044 (0.998, 1.093)[b]	< 0.01
Tumor grade				
GBM	5	541	1.028 (1.003, 1.054)[b,c]	0.027
Survival analysis method				
Univariate	3	482	2.365 (0.857, 6.528)[b]	< 0.01
Multivariate	4	284	1.036 (1.024, 1.047)[c]	0.103

[a]P values for heterogeneity test. If P > 0.1, HRs were calculated using fixed effects model, otherwise the random effects model was used. [b]HRs calculated using random effects model. [c]Results which are statistically significant.

Results

Studies and data included in this meta-analysis

Through searching and selection, a final list of 8 articles [15, 18-24] was collected for qualitative synthesis (see **Figure 1**). The detailed information of these 8 articles was all presented in **Table 1**. As shown in **Table 1**, All 8 articles collected were studies with various ethnicities (3 studies of Asians, and 5 studies of Caucasians). Of the 8 articles, 6 articles focused on overall survival, 1 study focused on disease-specific survival, and the rest 1 study focused on disease-free survival. Among the 8 articles, the 6 articles (7 studies) which focused on overall survival were included in the quantitative synthesis (meta-analysis). In total, the 7 eligible studies from 6 articles provided 766 samples about the relationship between IGFBP2 and glioma prognosis.

Meta-analysis results

In this study we performed both the overall meta-analysis and subgroup meta-analysis based on survival analysis method and tumor grade. All the meta-analyses were based on the outcome endpoint OS. The detailed results of our meta-analysis are shown in **Table 2**. In overall meta-analysis, random effects model was used to calculate the pooled HR and 95% CI because the heterogeneity test reported a *P* value of less than 0.01. The result did not suggest significant association between IGFBP2 expression and overall survival of glioma patients (pooled HR = 1.044, 95% CI = 0.998-1.093, see **Table 2** and **Figure 2**). In the stratified analysis based on survival analysis meth-

od, no obvious association existed in the univariate analysis subgroup, but significant association between IGFBP2 expression and glioma prognosis was observed in the multivariate analysis subgroup (pooled HR = 1.036, 95% CI = 1.024-1.047, see **Table 2**). In the subgroup meta-analysis based on tumor grade, significant association between increased IGFBP2 expression and poor overall survival was detected in GBM subgroup (pooled HR = 1.028, 95% CI = 1.003-1.054, see **Table 2**). In summary, according to the results of our meta-analysis, the IGFBP2 expression may be a predictive marker of overall survival for glioma patients, especially GBM patients.

Publication bias test results

The results of Begg's funnel plot (see **Figure 3**) and Egger's test showed no publication bias for GBM subgroup (*P* = 0.216) and for univariate analysis subgroup (*P* = 0.070), but publication bias may exist for overall analysis (*P* = 0.024) and for multivariate analysis subgroup (*P* = 0.041) in this meta-analysis.

Discussion

In this study, the results of our meta-analysis suggest that higher IGFBP2 expression in glioma patients was associated with unfavorable prognosis and had predictive effect on OS for glioma patients, especially GBM patients. IGFBP2 is a secreted protein that functions by binding IGF-I, IGF-II and other sorts of proteins [1-6]. It also has a nuclear localization sequence [7]. It is reported that IGFBP2 is overexpressed in 80% of GBMs [29] and IGFBP2 overexpression contributes to the invasive potential of glioma cells [3, 30-32]. Therefore, the prognostic effect of IGFBP2 for glioma patients, especially GBM patients, is biologically reasonable. Furthermore, combined effects of IGFBP2 with other molecular and environmental prognostic factors probably exist in glioma progression. Further research on such combined prognostic effect is required in the future.

In addition, all the results of our meta-analysis should be considered prudently due to the exis-
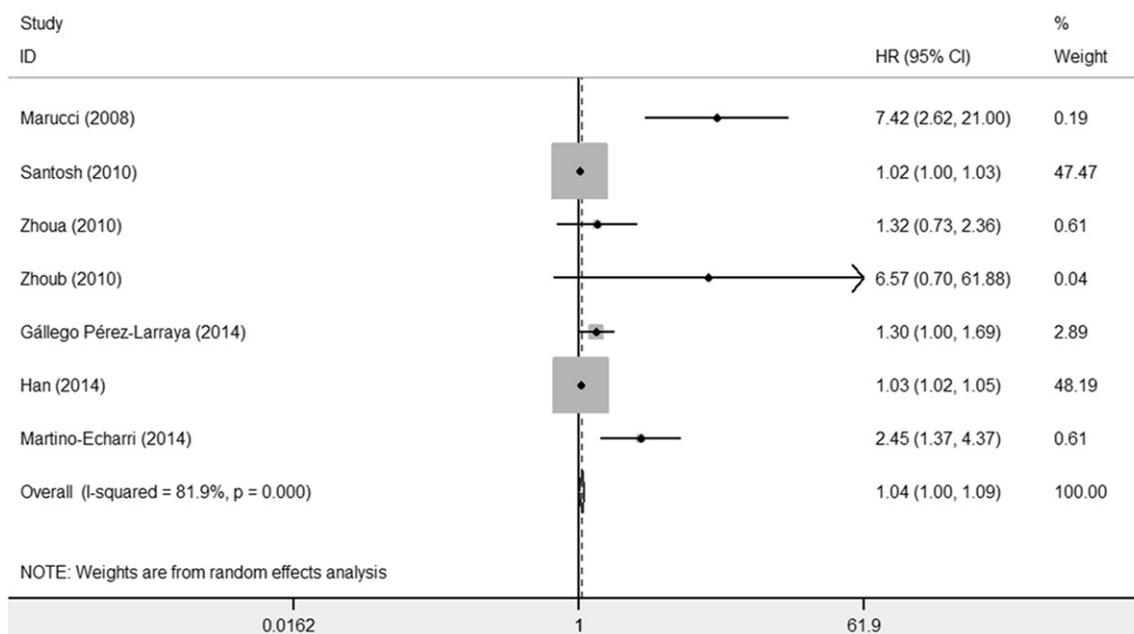
Figure 2. Forest plot for the overall meta-analysis of the association between IGFBP2 expression and glioma prognosis. HR: hazard ratio; CI: confidence interval.
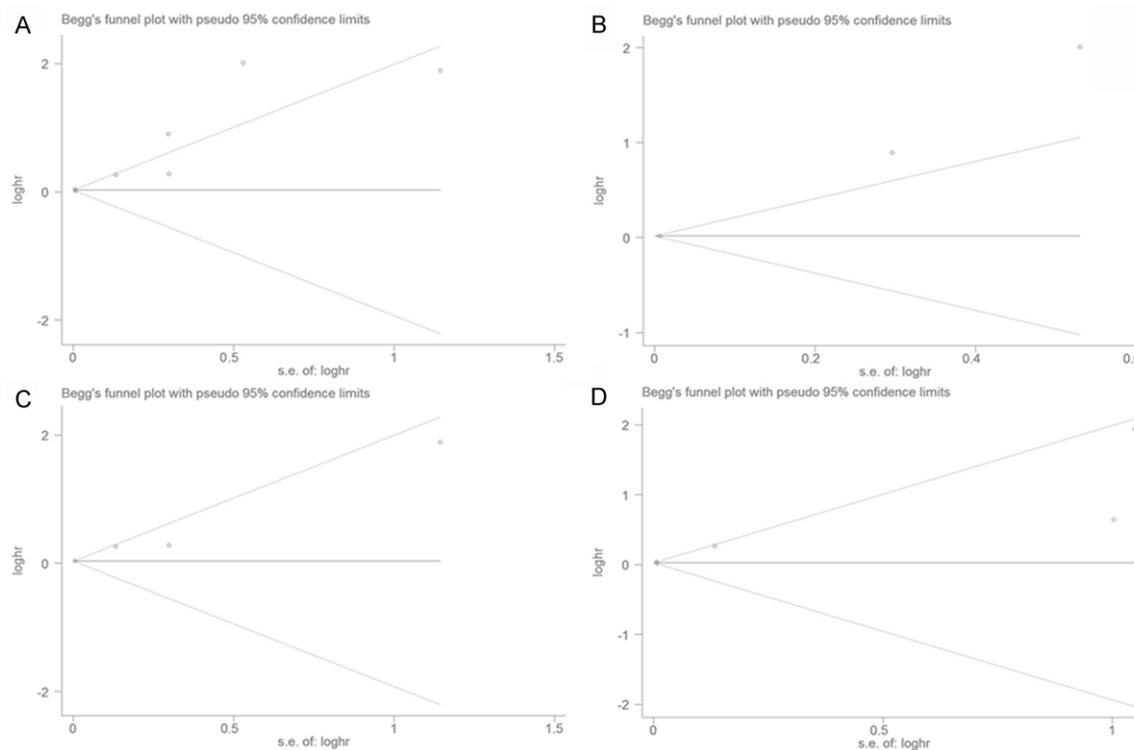

Figure 3. Begg's funnel plots for the studies involved in the meta-analysis of IGFBP2 expression and glioma prognosis. A. Overall analysis. B. Univariate analysis subgroup. C. Multivariate analysis subgroup. D. GBM subgroup. loghr: logarithm of hazard ratios; s.e.: standard error.

tence of several limitations. One limitation is the insufficient sample size used in our meta-

analysis especially in the subgroup analysis based on tumor grade and survival analysis

method. A second limitation is the heterogeneity caused by the diverse detection methods of IGFBP2 expression and cutoff values used in individual studies. The third limitation is the lack of patient data adjustment according to detailed individual information such as age and lifestyle in our meta-analysis. Another limitation is that subgroup meta-analysis based on ethnicity, grades of glioma other than GBM, and outcome endpoints other than OS cannot be carried out in our study due to the limited data. Hence, in order to achieve a more convincible conclusion, further analysis using larger sample size, unified detection method and adjusted individual data is required, and further stratified analysis based on ethnicity, grades of glioma, and outcome endpoints should also be performed.

In conclusion, supported by a meta-analysis with a total of 7 eligible studies from 6 articles (766 samples in all), our study indicates that the IGFBP2 expression is likely to be a predictive marker of overall survival for glioma patients, especially GBM patients, with increased IGFBP2 expression acting as a risk factor for poor prognosis. Although there are some limitations, our meta-analysis can still provide valuable information for studying the relationship between IGFBP2 and glioma prognosis.

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Disclosure of conflict of interest

None.

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