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Prognostic role of survivin in patients with glioma

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Abstract

Background: The aim of this study was to systematically evaluate the prognostic role of survivin in patients with glioma through performing a meta-analysis.

Methods: PubMed, Web of Science, Cochrane Library, and EMBASE were searched for potentially eligible literature. The study characteristics and relevant data were extracted. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled to estimate the prognostic role of survivin in patients with glioma.

Results: Sixteen studies with 1260 patients were included. The pooled HR of higher survivin expression for overall survival was 1.96 (95% CI, 1.57–2.45). The pooled HRs of higher survivin expression for progression- and disease-free survival were 1.62 (95% CI, 0.91–2.90) and 2.41 (95% CI, 0.98–5.90), respectively. Subgroup analyses were also performed.

Conclusion: Our results suggested that higher survivin expression was associated with worse overall survival in patients with glioma. The findings may assist future exploration on pathogenesis, diagnosis, anti-survivin therapy, and prognosis in glioma. However, due to the limited study number, more studies are warranted to verify our results.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, IHC = immunohistochemistry, OS = overall survival, PFS = progression-free survival.

Keywords: glioma, prognosis, survival, survivin

1. Introduction

Glioma is the most common type of primary brain tumor.[1] The survival of patients with glioma did not improve greatly despite the advances in diagnosis and treatment.[2,3] Some prognostic factors for glioma have been studied.[2,4,5] It is still of value to find new factors for the prediction of prognosis and to explore management for gliomas. Survivin, a member of the inhibitor of apoptosis protein family, normally is only expressed during fetal development with little expression in most of the normal adult differentiated cells.[6,7] Survivin is expressed in most human malignancies, and is implicated in the protection from apoptosis and regulation of mitosis.[8] Overexpression of survivin has been reported to be related with a poor prognosis in various tumors, including renal cell carcinoma,[9] esophageal cancer,[10] and breast cancer.[11] The prognostic role of survivin has also been studied in glioma, but the results were inconclusive. Although most studies demonstrated that overexpression of survivin was

associated with worse prognosis in glioma,[12–14] some researchers found no significant association between survivin and survival.[15,16] Due to the inconsistency, we aimed to systematically evaluate the prognostic role of survivin in patients with glioma through performing a meta-analysis.

2. Methods

2.1. Search strategy

Since this is a meta-analysis, ethical approval was not necessary. We followed the developed guidelines for systematic reviews and meta-analyses in performing our study.[17] PubMed, Web of Science, Cochrane Library, and EMBASE were searched for potentially eligible literature (last update ran on October 10, 2017). The following keywords were used: "glioma" AND ("survivin" OR "baculoviral inhibitor of apoptosis repeat containing 5" OR "BIRC5") AND ("prognosis" OR "outcome" OR "survival" OR "mortality"). Reference lists of relevant studies were also screened for additional studies. Authors were contacted where additional studies or data were needed. Languages were restricted to Chinese and English.

2.2. Study selection

The study selection process was performed by two investigators (SZ and CZ) independently, and disagreements were discussed. The titles and abstracts were screened first, and then potentially eligible studies were evaluated in full text. Studies were considered eligible if they met all of the following inclusion criteria: the patients were diagnosed with glioma by histopathologic examination, and received proper therapy; the expression of survivin in the tumor tissue was measured; patients were followed up for survival outcomes; enough data were reported to estimate the prognostic role of survivin in patients with glioma. Unrelated articles, conference abstracts, case reports, reviews, letters,

animal studies, in vitro studies, and studies without enough data were excluded. If multiple studies were performed at the same institution and the samples overlapped, the study with the largest sample size was included.

2.3. Data extraction

Relevant data of the included studies were extracted by two reviewers independently (SZ and CZ), with any disagreements resolved by consensus. The primary data were hazard ratio (HR) for overall survival (OS)/progression-free survival (PFS)/disease-free survival (DFS) with 95% confidence interval (CI), or the data that could be used to calculate the HR and 95% CI. HRs calculated from multivariate analyses were extracted over those calculated from univariate analyses. The characteristics of the studies and patients were also extracted, including first author, publication year, country, the number of patients, sex of patients, mean or median age of patients, tumor grade, survivin detecting methods, and so on.

2.4. Statistical analysis

The log HR and variance were calculated from the HR and 95% CI, and were used for aggregation. Forest plots were constructed to estimate the pooled prognostic value of survivin in patients with glioma. The pooled HR was considered significant, the P-value was $<.05$, and the 95% CI did not overlap 1. The heterogeneity between the studies was assessed, with $I^2 > 50\%$ or $P < .10$, indicating significant heterogeneity.[18] In pooling the studies together, random effect models were used no matter whether heterogeneity exited, since some heterogeneity among studies may be expected due to the differences in study and patient characteristics across the studies.[19] If the heterogeneity was significant, sensitivity analysis was performed to evaluate the contribution of each study to heterogeneity by excluding individual studies one at a time. Subgroup analyses were also performed according to patient source, tumor grade, survivin detecting methods, survivin location, and other characteristics of the studies. Publication bias was assessed by Begg's test, with $P > .05$, suggesting no significant publication bias. All the above-mentioned statistical analyses were performed by STATA 11.0 (STATA Corporation, College Station, TX).

3. Results

3.1. Literature research

A total of 567 citations were identified during the initial literature search. Among them, 139 were duplicated and were removed. After screening for titles and abstracts, 386 studies were excluded according to the predefined inclusion and exclusion criteria. The rest 42 studies were assessed in full text and 26 were further excluded due to unrelated, overlapped, lacking enough data, or other reasons. Eventually, 16 articles[6,7,12–16,20–28] met the inclusion criteria and were included. The study selection process was shown in Figure 1.

3.2. Study characteristics

The basic characteristics of the 16 included studies were shown in Table 1. The studies were conducted in 9 different countries. A total of 1260 patients were included. Most studies examined different grades of glioma together, with 3 studies focusing on medulloblastoma and 2 studies on glioblastoma. Thirteen studies

used immunohistochemistry (IHC) to examine the expression of survivin, with 2 studies examining the expression of mRNA and 1 study using western blot. Ten studies focused on the expression of survivin in the nuclei, and 6 studies examined both nuclear and cytoplasmic expression. Ten studies reported HRs with 95% CI from multivariate analyses, and the HRs were calculated from survival curves in the rest 6 studies.

3.3. Overall analysis

Among the 16 included studies, 14 examined OS. The pooled HR of higher survivin expression for OS was 1.96 (95% CI, 1.57–2.45) (Fig. 2). Significant between-study heterogeneity was observed ($I^2 = 86.4\%$, $P < .001$). In performing sensitivity analysis, after excluding 1 study at a time, the heterogeneities were still above 80%.

Three studies examined PFS and the pooled HR of higher survivin expression was 1.62 (95% CI, 0.91–2.90). Two studies examined DFS and the pooled HR of higher survivin expression was 2.41 (95% CI, 0.98–5.90).

3.4. Subgroup analysis

As to the 14 studies examining OS, subgroup analyses were performed.

3.4.1. Patient source. Among the 14 studies, 6 were from China and Japan (East-Asia group) and the rest were from western countries (non-East-Asia group). The pooled HR of higher survivin expression for OS was 2.18 (95% CI, 1.44–3.30) in the East-Asia group. In the non-East-Asia group, the pooled HR of higher survivin expression for OS was 1.87 (95% CI, 1.40–2.51).

3.4.2. Tumor grade. Six studies examined medulloblastoma or glioblastoma (grade IV group) and 3 studies examined grades I to III gliomas (grade I–III group). In the grade IV group, the pooled HR of higher survivin expression for OS was 3.10 (95% CI, 1.29–7.44). The pooled HR of higher survivin expression for OS was 1.84 (95% CI, 1.01–3.35) in the grades I to III group.

3.4.3. Detecting method. Eleven studies used IHC to examine the expression of survivin (IHC group), and 2 studies examine the expression of mRNA (mRNA group). The pooled HR of higher survivin expression for OS was 1.79 (95% CI, 1.42–2.26) in the IHC group. In the mRNA group, the pooled HR of higher survivin expression for OS was 2.48 (95% CI, 1.52–4.07).

3.4.4. Survivin location. Eight studies focused on the expression of survivin in the nuclei (nuclear group), and 6 studies examined both nuclear and cytoplasmic expression (nuclear/cytoplasmic group). In the nuclear group, the pooled HR of higher survivin expression for OS was 1.64 (95% CI, 1.29–2.09). The pooled HR of higher survivin expression for OS was 2.96 (95% CI, 1.58–5.53) in the nuclear/cytoplasmic group.

3.4.5. HR adjustment. Eight studies reported HRs from multivariate analyses (multivariate group), and the HRs were from univariate analyses in 6 studies (univariate group). The pooled HR of higher survivin expression for OS was 1.75 (95% CI, 1.36–2.24) in the multivariate group. In the univariate group, the pooled HR of higher survivin expression for OS was 2.26 (95% CI, 1.66–3.07).

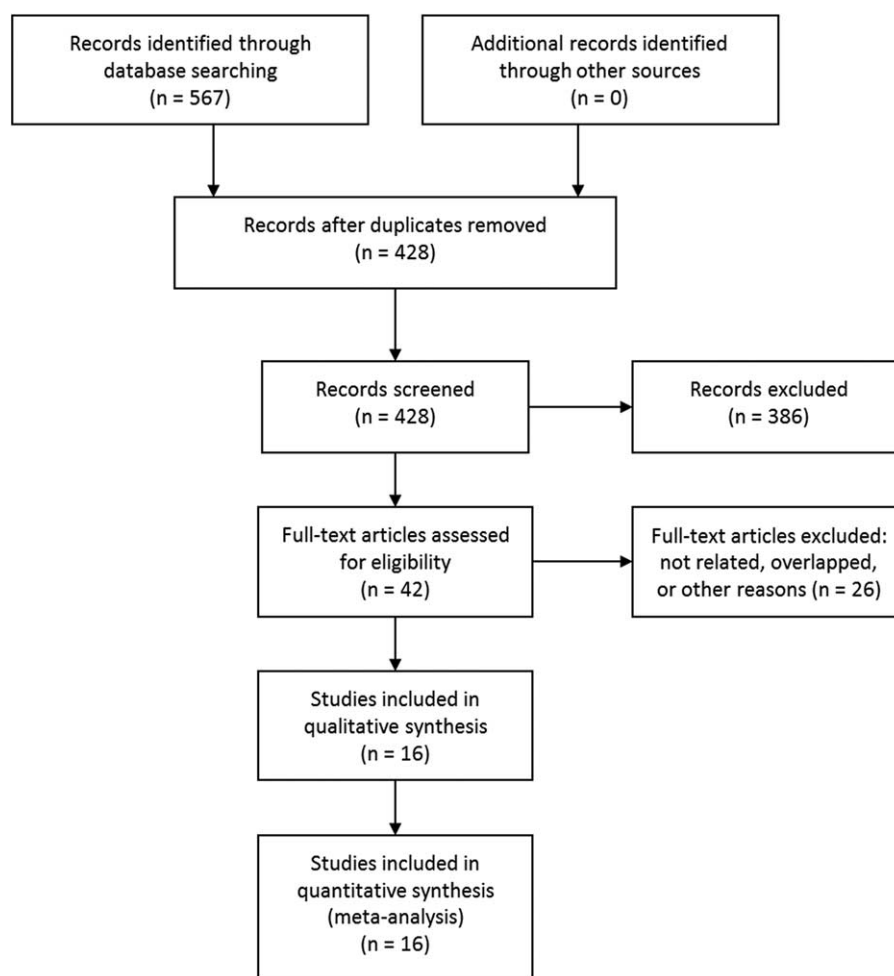All the meta-analyses results were summarized in Table 2.

Figure 1. Selection process of studies.

3.5. Publication bias

No significant publication bias was found in the meta-analysis. The Begg's plot of publication bias of the 14 studies examining OS was shown in Figure 3 ($P=.063$).

4. Discussion

The aim of this study was to evaluate the prognostic role of survivin in patients with glioma. We systematically summarized the existing evidence through performing a meta-analysis, and 16

Table 1

Characteristics of the included studies.

Author	Year	Country	N (F/M)	Age	Tumor grade	Detecting method	Survivin location	Outcome measure	HR estimation
Zhang	2017	China	70 (28/42)	Median 50	I–IV	IHC	Nuclear	OS	Survival curve
Varughese	2017	Norway	89 (57/32)	—	II–III	IHC	Nuclear	OS/PFS	HR/CI
Tastekin	2016	Turkey	80 (35/45)	Mean 58.55	IV	IHC	Nuclear/cytoplasmic	OS	HR/CI
Doucette	2014	USA	84 (—/—)	—	I–II	mRNA	Nuclear/cytoplasmic	OS	Survival curve
Lin	2012	China	154 (66/88)	Mean 43	I–IV	IHC	Nuclear/cytoplasmic	OS	HR/CI
Huang	2011	China	73 (30/43)	Mean 41	II–IV	IHC	Nuclear	DFS/PFS	HR/CI
Faccion	2011	Brazil	41 (15/26)	Median 7	IV	IHC	Nuclear	OS	Survival curve
Shirai	2009	Japan	66 (26/40)	Mean 55.1	IV	IHC	Nuclear	OS	HR/CI
Ridley	2008	UK	74 (33/41)	Mean 5.4	II–III	IHC	Nuclear	DFS	HR/CI
Kogiku	2008	Japan	99 (44/55)	Mean 53.8	II–IV	IHC	Nuclear/cytoplasmic	OS	HR/CI
Pan	2007	China	94 (43/51)	Median 36	I–IV	IHC	Nuclear	OS	HR/CI
Haberler	2006	Austria	82 (27/55)	Median 7.3	IV	IHC	Nuclear	OS/PFS	HR/CI
Preusser	2005	Austria	63 (—/—)	Median 11.3	II–III	IHC	Nuclear	OS	Survival curve
Pizem	2005	Slovenia	56 (13/43)	—	IV	IHC	Nuclear	OS	HR/CI
Kajiwara	2003	Japan	43 (15/28)	Median 46.7	II–IV	mRNA	Nuclear/cytoplasmic	OS	Survival curve
Chakravarti	2002	USA	92 (—/—)	Mean 48	I–IV	Western blot	Nuclear/cytoplasmic	OS	Survival curve

CI = confidence interval, DFS = disease free survival, HR = hazard ratio, IHC = immunohistochemistry, N (F/M) = number of patients (female/male), OS = overall survival, PFS = progression free survival.
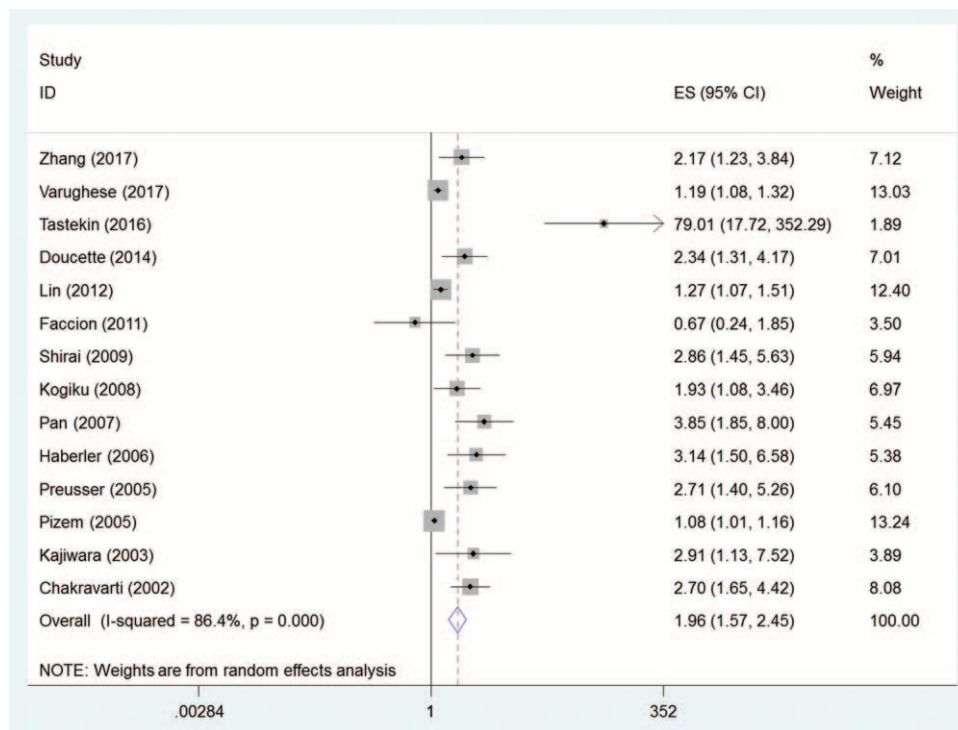
Figure 2. Pooled hazard ratio (HR) of higher survivin expression for overall survival in patients with glioma.

studies were included. Our results suggested that higher survivin expression was associated with poorer overall survival in patients with glioma. Our results also showed that higher survivin expression was associated with a tendency of poorer PFS and DFS, but the number of studies was limited.

Subgroup analyses were performed to further examine the role of survivin in patients with glioma. The pooled HR of higher survivin expression for OS in the East-Asia group was slightly higher compared to that in the non-East-Asia group, suggesting that the prognostic value of survivin may differ among different ethnicities. As to tumor grade, the pooled HR in grade IV glioma was much higher than that in grades I to III glioma, implying

different prognostic roles of survivin in different grades of gliomas. The pooled HR in the mRNA group was higher than that in the IHC group, suggesting that it might be better to examine the expression of mRNA in the prognosis of glioma by survivin. The pooled HR in the nuclear/cytoplasmic group was also higher than that in the nuclear group. The results may suggest the detection of survivin both in the nuclei and the cytoplasm. Besides, the pooled HRs in the multivariate group and the univariate group were both significant, which further validated the prognostic role of survivin in glioma. However, these findings must be interpreted with caution due to the limited number of studies, especially in the grades I to III group and

Table 2
Summary of meta-analysis results.

	N	Pooled HR (95% CI)	P value	Heterogeneity (I^2, P)	Conclusion
OS					
Total	14	1.96 (1.57–2.45)	<.001	86.4%, <.001	Positive
East-Asia	6	2.18 (1.44–3.30)	<.001	71.5%, .004	Positive
Non-East-Asia	8	1.87 (1.40–2.51)	<.001	89.5%, <.001	Positive
Grade IV	6	3.10 (1.29–7.44)	.011	91.8%, <.001	Positive
Grade I–III	3	1.84 (1.01–3.35)	.046	81.1%, .005	Positive
IHC	11	1.79 (1.42–2.26)	<.001	86.7%, <.001	Positive
mRNA	2	2.48 (1.52–4.07)	<.001	0.0%, .699	Positive
Nuclear	8	1.64 (1.29–2.09)	<.001	82.7%, <.001	Positive
Nuclear/cytoplasmic	6	2.96 (1.58–5.53)	.001	87.7%, <.001	Positive
Multivariate	8	1.75 (1.36–2.24)	<0.001	88.9%, <.002	Positive
Univariate	6	2.26 (1.66–3.07)	<0.001	24.3%, .252	Positive
PFS					
Total	3	1.62 (0.91–2.90)	.103	68.2%, .043	Negative
DFS					
Total	2	2.41 (0.98–5.90)	.055	10.9%, .289	Negative

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, IHC = immunohistochemistry, N = number of studies, OS = overall survival, PFS = progression-free survival.
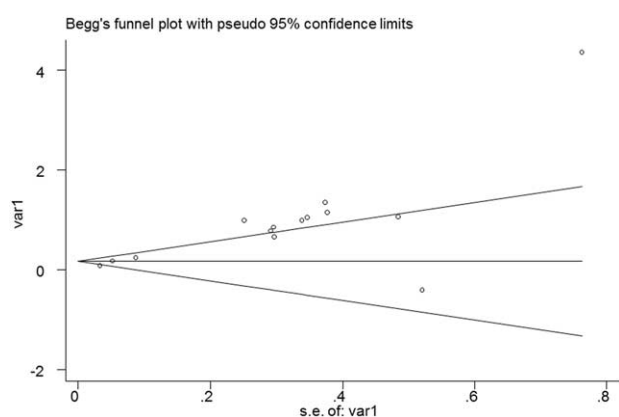
Figure 3. The Begg's plot of publication bias of the 14 studies examining overall survival.

mRNA group. Much more studies are needed to verify our findings.

Survivin is expressed in fetal tissues and tumor cells but is absent in normal adult differentiated cells.[6–8] Survivin is expressed during the G_2/M phase of the cell cycle,[29] and its expression has been detected in both the nuclei and cytoplasm of tumor cells.[15] In the nuclei, it is crucial to promote accurate mitosis progression.[30] In the cytoplasm, it suppresses apoptosis via the direct inhibition of caspase-associated proteins.[31] Taken together, the defects in molecular control of cell growth and apoptosis contribute greatly to tumor pathogenesis, cellular homeostasis, and tumor development, resulting in poor survival.[12,20] Besides, survivin expression was reported to be related with radiation resistance. Chakravarti et al found that survivin could regulate double-strand DNA break repair and tumor cell metabolism, thus suppressing radiation-induced cell death in primary glioblastoma.[32]

Researchers have also investigated different prognostic implications of different localizations of survivin. Saito et al found that, in patients with glioblastomas, nuclear localization of survivin was associated with worse survival compared with cytoplasmic expression.[33] However, Bell et al demonstrated that higher maximum survivin cytoplasm/nuclear ratio was associated with worse survival in patients with glioblastoma.[34] Therefore, more studies are needed to explore this interesting issue.

Despite the prognostic role of survivin, our findings also suggested other implications of survivin in glioma. As we mentioned above, it may help define the tumorigenic mechanism underlying glioma. It may also aid in determining an effective diagnosis.[20] Moreover, survivin is a promising therapeutic target without affecting normal tissue. Preclinical studies have shown that RNA knockdown targeting survivin exerted antitumoral effects in vitro and in vivo.[35,36] Clinical trials evaluating the safety and efficacy of sepantronium bromide (YM155), a small molecule survivin suppressant, suggested that YM155 was generally well tolerated but with modest activity in various malignancies.[37–41] Further evaluation of YM155 in combination with other agents may be warranted. Besides, anti-survivin strategies may improve the radiation response and may be related with the better outcome.[23]

There were some limitations in our study. Firstly, the number of included studies was limited, especially in the subgroups.

Besides, significant between-study heterogeneity was observed in this meta-analysis, and sensitivity analysis did not reveal any study that contributed greatly to heterogeneity. Furthermore, the characteristics of the studies and patients varied. For example, the gender, age, tumor grade, detecting method, and other characteristics differed between the studies. Therefore, the results should be treated with caution. In addition, publication bias was a major concern for all meta-analyses and should not be completely excluded, although it was not significant in our meta-analysis

In conclusion, our results suggested that higher survivin expression was associated with worse overall survival in patients with glioma. The findings may assist future exploration on pathogenesis, diagnosis, anti-survivin therapy, and prognosis in glioma. However, due to the limited study number and heterogeneity among the studies, more studies are warranted to further verify our results.

Author contributions

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Writing – review & editing: Sunfu Zhang, Changwei Zhang, Yanlin Song, Jing Zhang, Jianguo Xu.

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