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Is CD147 a New Biomarker Reflecting Histological Malignancy of Gliomas?

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Abstract CD147 belongs to immunoglobulin superfamily and can stimulate the surrounding fibroblasts to secret matrix metalloproteinases (MMPs). Studies showed that when compared with their normal counterparts, CD47 expression level increased in lung carcinoma tissue, breast cancer tissue, and bladder cancer tissue. They increase in line with a tumor's malignant progression, invasiveness, and metastasis. However, the precise implications and utility of the presence of CD147 in the WHO grading system for gliomas have rarely been reported; in addition, the signal transduction pathways regarding CD147 remain unclear and controversial. Thus, in performing a meta-analysis, it is essential to reach a reliable conclusion. The related literatures were incorporated into the present meta-analysis after careful assessment, and odds ratios (ORs) with 95 % confidence intervals (95 % CIs) were calculated. Heterogeneity evaluation was estimated. Ten studies involving 615 patients were found to be eligible, nine of which were conducted in China and the remaining one in Japan. Analysis of eight studies involving dichotomous data revealed that CD147 overexpression in glioma tissue was related to higher WHO grading (III + IV; OR, 9.900; 95 % CI, 5.943, 16.491; $P = 0.000$) closely, whereas analysis of three studies of continuous data type indicated that there were no statistical associations (standard mean difference, −1.894; 95 % CI, −4.081, 0.293; $P = 0.090$). In accordance with funnel plot, Egger test, and Begg test, there was no publication bias. Considering that the continuous data make up only a small proportion of the overall analysis, we believe that our study indicates that CD147 overexpression is potentially related to higher WHO grade. Certainly, more data compiled based on evidence-based medicine are required to further support this conclusion.

Keywords CD147 · Glioma · Grade · Prognosis · Meta-analysis

Introduction

Histopathologically, gliomas have four WHO grades [1]. Grade I and II gliomas are regarded as low-grade gliomas, and grades III and IV gliomas are high-grade gliomas [2]. The higher the grades, the poorer the prognosis will be. Glioblastoma (grade IV) is the deadliest one. It is important to find more effective biomarkers for the prediction of a glioma's WHO grade.

CD147, also called tumor cell-derived collagenase stimulatory factor (TCSF), extracellular matrix metalloproteinase inducer (EMMPRIN), or basigin, is a type of neoplasm cell surface molecule that is able to stimulate the surrounding fibroblasts to produce metalloproteinase (MMP) [3]. MMP can degrade extracellular matrix, which is essential for tissue reorganization, tumor's metastasis, and invasiveness. Previous studies revealed that the expression levels of MMP were much higher during tumor invasion, and CD147 overexpression correlates closely with tumor progression and invasive activity [4]. The role of CD147 in guiding neoplasms' diagnosis, treatment, and prognosis (such as pancreatic cancer [5], gastric cancer [6], prostate cancer [4], breast cancer [7], and lung cancer [8]), has been widely discussed in recent years. A few studies have also observed its roles in gliomas. They

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Table 1 Inclusion criteria for study selection in this meta-analysis

Number	Inclusion criteria
1	The patients were confirmed with the diagnosis of glioma by pathologists.
2	The main outcome of the study was glioma WHO classification.
3	A CD147 expression model was identified using immunohistochemistry (IHC), reverse transcription PCR (RT-PCR), real-time quantitative PCR (qPCR), or other reliable molecular biological methods.
4	The OR with a 95 % confidence interval (95 % CI), the mean value with standard deviation (SD) between CD147 expression, and WHO classification could be obtained from articles directly or calculated based on the figures or tables given in articles or through contacting the authors.
5	For the duplicate articles, only the most complete or the most newly published one was included.

found the CD147 expression might be associated with a glioma's malignant progression [3, 9–11]. However, the precise role of CD147 in glioma WHO grading is still unclear and remains under discussion. To eliminate the between-study heterogeneity and elucidate a more precise implication of CD147 in gliomas, a meta-analysis was carried out.

Methods

Search Strategy, Study Selection, and Data Extraction

A literature search was performed with Embase, Google Scholar, PubMed, Wanfang, and Cnki databases up to April 2015. Search terms involved "Extracellular Matrix Metalloproteinase (EMMPRIN/CD147)" or "CD147," "gliomas [MeSH]," "expression," "grade," and others. Two reviewers independently selected eligible studies. Disagreement between the two reviewers was settled by discussion with a third reviewer. Inclusion criteria were listed in Table 1. Two reviewers collected the following information independently using a purpose-designed form: author, publication year, country, mean age, patient number, histopathology, test means, WHO grading, and the positive percentage of CD147 in surgical specimen. Disagreement between the two reviewers was resolved by a third one.

Quality Assessment, Data Synthesis, and Analysis

We performed quality assessment of the included studies using European Lung Cancer Working Party (ELCWP) scale [12] (Table 2). Two independent investigators compared their

Table 2 The statistical methods used in this meta-analysis and their explanation

Statistic means	Goals and usages	Explanation
ELCWP scale	Literature quality assessment	Assessing literature quality by reading and scoring each article based on the quality scale for biologically prognostic factors established by the European Lung Cancer Working Party (ELCWP). This scale system evaluates a study's scientific design, laboratory methodology, generalizability, and result analysis. Each category can reach up to 10 points, so the maximum score is 40 points. The final scores represented the percentage of the maximum of achievable scores, ranging from 0 to 100 %. Therefore, the higher the values, the better the methodological quality.
Galbraith plot	To evaluate heterogeneity between the included studies	In the Galbraith plot, if the circles are all distributed within the region bounded by the upper line and lower line, this can be taken as evidence of no significant heterogeneity.
Cochran's Q test	To evaluate heterogeneity between the included studies	Cochran's Q test is an extension to the McNemar test for related samples that provides a method for testing for differences between three or more matched sets of frequencies or proportions. Heterogeneity was also considered significant if $P < 0.05$ using the Cochran's Q test.
I^2 index test	To evaluate heterogeneity between the included studies	The I^2 index measures the extent of true heterogeneity dividing the difference between the result of the Q test and its degrees of freedom $(k-1)$ by the Q value itself and multiplied by 100. I^2 values of 25, 50, and 75 % were used as evidence of low, moderate, and high heterogeneity, respectively.
Sensitivity analysis	To examine the stability of the pooled results	A sensitivity analysis was performed using the one-at-a-time method, which involved omitting one study at a time and repeating the meta-analysis. If the omission of one study significantly changed the result, it implied that the result was sensitive to the studies included.
Funnel plot	Publication bias test	Potential publication bias was assessed by visual inspection of the funnel plot; if the plot was asymmetric, possible publication bias was indicated.

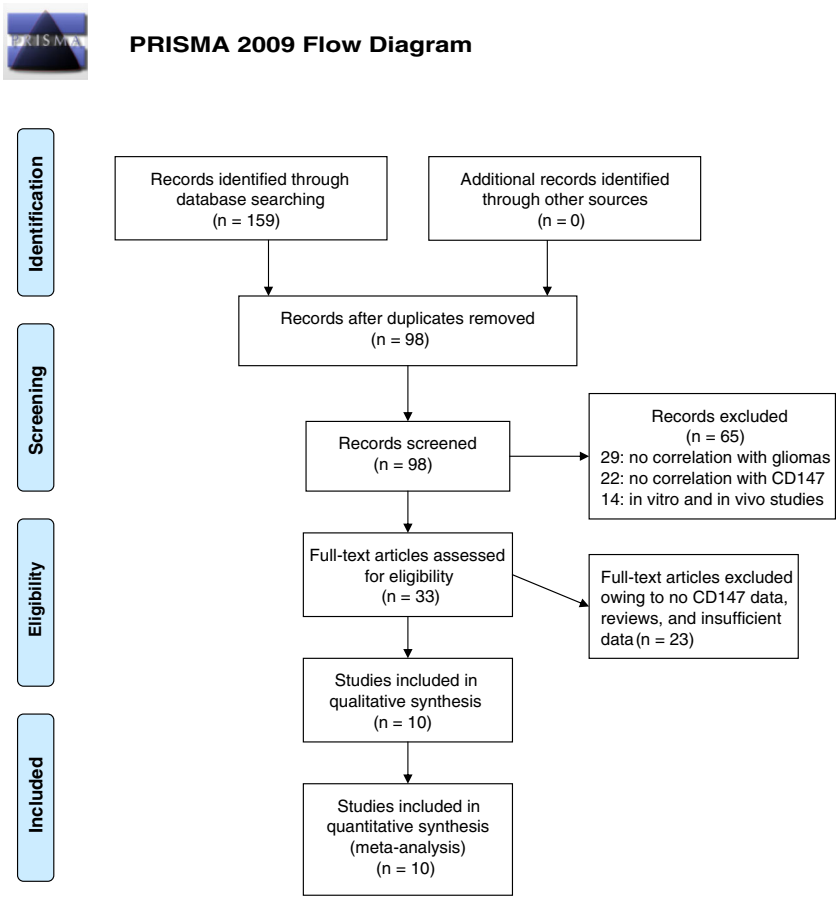

Fig. 1 Literature search and selection of articles

calculated scores and, if necessary, achieved a consensus score for each category during a meeting. Differences were expressed as odds ratios (ORs) or standard mean differences (SMDs) with 95 % confidence intervals (CIs). The Galbraith plot, Cochran's Q test, and I^2 test (variation in OR attributable to heterogeneity) were all performed to evaluate the heterogeneity between the included studies [13, 14] (Table 2). If there was no evidence of statistical heterogeneity between the studies, then a fixed effect model was used. Otherwise, the random effect model of DerSimonian and Laird was adopted [15]. A sensitivity analysis was performed to examine the stability of the pooled results (Table 2). Potential publication bias was assessed by funnel plot (Table 2) [16] and Egger linear regression test ($P < 0.05$ indicates publication bias) [17]. Since there

Table 3 Baseline characteristics of the 10 included studies

Year	Study ID	Country	Number	Mean age (year)	Male	Grade (I + II)	Method	Cutoff (%)	Positive (%)	Data type
2000	Sameshima T	Japan	18	NA	NA	5	IHC	10	61.11	Dichotomous
			20	NA	NA	3	Northern blot	NA	NA	Continuous
2006	Wang XS	China	60	58.2	34	28	IHC	5	71.67	Dichotomous
2006	Shi QH	China	46	42.5	26	21	IHC	POS	56.52	Dichotomous
2007	Liang QC	China	61	32.56	39	30	IHC	POS	78.69	Dichotomous
2007	Li H	China	50	48.2	28	23	IHC	20	72.00	Dichotomous
2008	Gu J	China	45	3 months~12 years	29	18	IHC	5	73.33	Dichotomous
2010	Ju HG	China	78	42.4	48	43	IHC	10	61.54	Dichotomous
2011	Ju HG	China	78	42.4	48	43	RT-PCR	NA	NA	Continuous
2013	Ye H	China	69	46	29	32	IHC	5	37.68	Dichotomous
2014	Han S	China	90	NA	NA	34	qPCR	NA	NA	Continuous

Table 4 Results of the included studies focusing on the relationship between CD147 expression and glioma WHO gradings

Study or subgroup		Publishing year	Low-grade gliomas			High-grade gliomas			% Weight	OR	95 % CI
			Negative stained	Positive stained	Total	Negative stained	Positive stained	Total			
Dichotomous studies	Sameshima et al.	2000	5	0	5	2	11	13	1.18	50.600	[2.059, 1243.673]
	Wang et al.	2006	14	14	28	3	29	32	13.26	9.667	[2.382, 39.224]
	Shi et al.	2006	14	7	21	6	19	25	17.30	6.333	[1.742, 23.021]
	Liang et al.	2007	13	17	30	0	31	31	2.63	48.600	[2.72, 867.960]
	Li et al.	2007	12	11	23	2	25	27	8.34	13.636	[2.602, 71.462]
	Gu et al.	2008	12	6	18	0	27	27	1.31	105.769	[5.519, 2027.137]
	Ju et al.	2010	23	20	43	7	28	35	34.01	4.600	[1.655, 12.786]
	Ye et al.	2013	27	5	32	16	21	37	21.97	7.088	[2.233, 22.492]
	Integrated/pooled	–	120	80	200	36	191	227	100	9.9	[5.943, 16.491]
Study or subgroup		Publishing year	Low-grade gliomas			High-grade gliomas			% Weight	SMD	95 % CI
			*n*1	Mean1	SD1	*n*2	Mean2	SD2			
Continuous studies	Sameshima et al.	2000	3	0.060	0.007	17	0.291	0.098	30.57	−2.506	[−3.981, −1.030]
	Ju et al.	2011	43	0.211	0.066	35	0.597	0.173	34.39	−3.075	[−3.737, −2.413]
	Han et al.	2014	34	6.860	1.060	56	7.110	1.340	35.04	−0.201	[−0.628, 0.226]
	Integrated/pooled	–	80	–	–	108	–	–	100	−1.894	[−4.081, 0.293]

were only 10 included studies, meta-regression was not conducted.

$P < 0.05$ was regarded statistically significant. Data analyses were conducted by means of STATA 12.0 (StataCorp LP, College Station, TX, USA) and Review Manager 5.3 software.

Results

Search Results and Characteristics of the Studies

The article searches were performed as presented in Fig. 1. A total of 10 articles eventually met the inclusion criteria. All 10 studies were done in Asia: 9 were carried out in China and 1 in Japan. The basic characteristics and statistical result of the 10 studies are seen in Tables 3 and 4. The positive rate of CD147 expression varied from 37.68 to 78.69 %. CD147 protein or mRNA in glioma tissues was investigated using immunohistochemistry (IHC; eight studies), RT-PCR (one study), qPCR (one study), and Northern blot (one study). When cytoplasm or nucleus was stained, CD147 was defined as positive.

Study Quality

The detailed ELCWP scores are shown in Table 5. Result analysis achieved the highest mean score of 8.31, followed by designs (8.07), methods (8.06), and generalizability (7.95). The mean global scores for articles in terms of whether only using IHC test methods, countries, whether dichotomous data type or continuous data type showed no significant differences detected by Student's *t* test ($P > 0.05$); this indicated that the baseline characteristics of the various studies did not cause heterogeneity.

Meta-Analysis of CD147 and the WHO Grading System

The WHO grading system for glioma was divided into low (I + II) and high grade (III + IV) for data merging. Information on WHO grading was available in eight studies with dichotomous data and three studies with continuous data (Tables 3 and 4). In the Galbraith plot analysis of dichotomous studies (Fig. 2a), all points fell within the appointed region, which can be taken as evidence of no significant heterogeneity across all of these studies ($Q = 7.73$, degrees of freedom = 7, $I^2 = 9.4$ %). As revealed in Fig. 3a, using a fixed effect model, pooled OR indicated a significant association between CD147 expression and high WHO grade (OR, 9.900; 95 % CI, 5.943, 16.491; $P = 0.000$). This suggested that high CD147 expression in postoperative glioma tissues can predict a high-grade glioma. Conversely, in the Galbraith plot analysis of the continuous studies (Fig. 2b), two points fell outside the region, suggesting relatively high heterogeneity. As shown in Fig. 3b, using a

Table 5 Clinical and methodological characteristics of the 10 included studies

Items		Number of studies	Design	Method	Generalizability	Results analysis	Global score (%)
All studies		10	8.07	8.06	7.95	8.31	80.98
Test methods	Only IHC	8	8.20	8.05	7.94	8.34	81.31
	Others	3	7.83	8.17	8.07	8.37	81.08
	P value	–	0.119	0.494	0.513	0.895	0.876
Countries	China	9	8.03	8.03	7.92	8.27	80.64
	Japan	1	8.4	8.3	8.2	8.7	84
	P value	–	0.185	0.157	0.207	0.060	0.052
Data type	Dichotomous	8	8.20	8.05	7.94	8.34	81.31
	Continuous	3	7.83	8.17	8.07	8.37	81.08
	P value	–	0.119	0.494	0.513	0.895	0.876

random effect model, the SMDs of the three studies did not indicate that CD147 expression intensity was potently correlated with high-grade gliomas (SMD, −1.894; 95 % CI, −4.081, 0.293; $P = 0.090$).

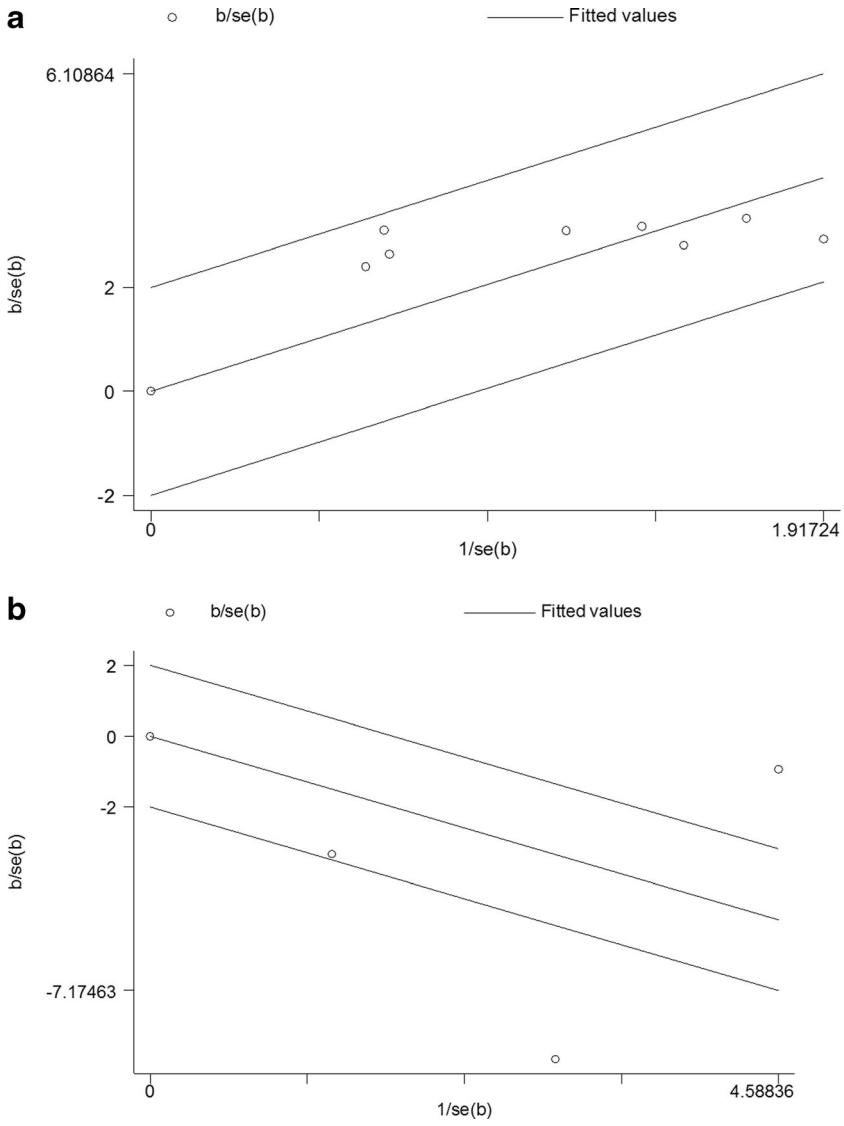

Fig. 2 Galbraith plot of the included studies focusing on the correlation between CD147 and WHO grade. **a** The eight studies with dichotomous data. **b** The three studies with continuous data. If the circles are all distributed within the region bounded by the upper and lower line, it can be taken as evidence of homogeneity. The farther away from the region, the more obvious the heterogeneity

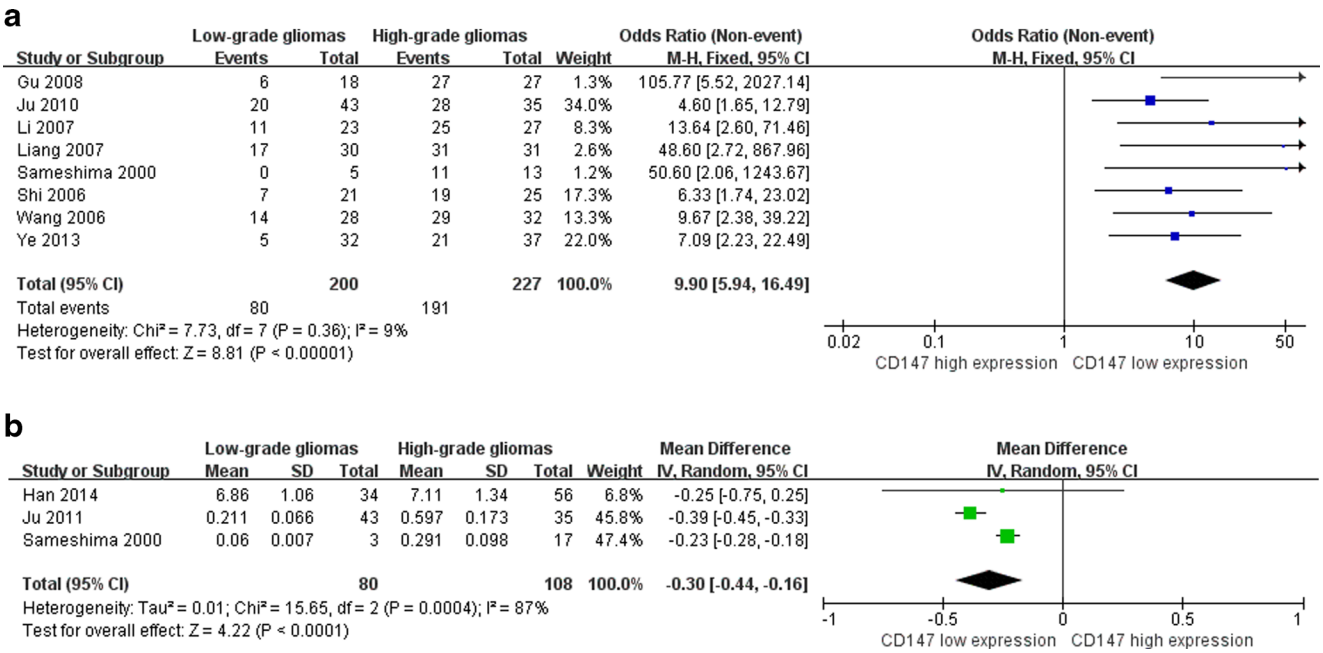

Fig. 3 Individual and pooled effects with 95 % CI regarding CD147 and WHO grade. **a** Using a fixed effect model, an association between CD147 and WHO grade was revealed in 10 studies with dichotomous data (OR, 9.900; 95 % CI, 5.943, 16.491; $P = 0.000$). **b** Using a random effect model, analysis of three studies with continuous data indicated that the association between CD147 and WHO grade was not statistically significant (SMD, −1.894; 95 % CI, −4.081, 0.293; $P = 0.090$)

Sensitivity Analysis and Publication Bias

The results of sensitivity analysis indicated there are not any individual studies statistically affecting the integrated OR of CD147 and the WHO grade, suggesting that the results were robust (Fig. 4). With Egger test and Begg test, no publication bias was detected among the eight studies that used only IHC in their analyses ($P = 0.178$; 95 % CI, −0.191, 0.824); similarly, studies using other methods also did not reveal statistical bias ($P = 0.560$; 95 % CI, −108.60, 95.34). In addition, a funnel plot was overally symmetric (Fig. 5), revealing no significant publication bias.

Discussion

CD147, also known as EMMPRIN, TCSF, or basigin, is a member of the immunoglobulin superfamily. Its structure is related to the putative primordial form of this family [18]; it has been implicated in a variety of physiological and pathological

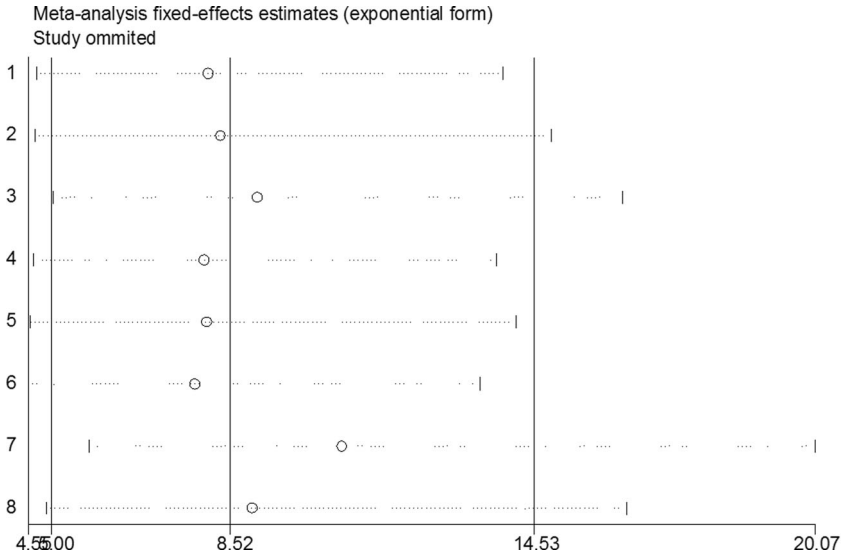

Fig. 4 Sensitivity analysis of the included articles regarding only IHC data. Results were computed by omitting each study in turn. Meta-analysis fixed effect estimates (exponential form) were used. The *two ends of the dotted lines* represent the 95 % CI

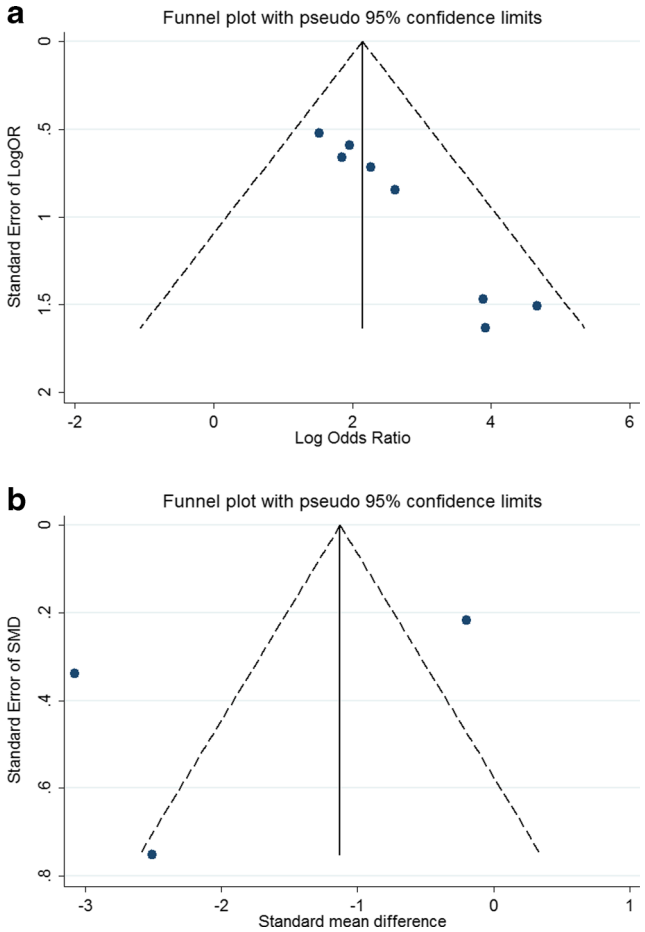

Fig. 5 Funnel plots (designed to visualize a potential publication bias). The shape of the funnel plot in all studies did not reveal obvious evidence of asymmetry regardless of the dichotomous studies (**a**) or the continuous studies (**b**), suggesting that publication bias was also not observed among studies with pathological indicators

activities. In recent years, studies have demonstrated that CD147 overexpression plays a significant role in the biology of tumors and has an influence on prognosis [5, 18]. One possible explanation for this is its role in producing MMPs, which is a crucial step in tissue remodeling and tumor invasion and metastasis [19]. The number of literatures in relation to CD147 each year shows a general tendency to increase over time. A timeline of the related publications is available as Fig. 6. On the basis of a world map with the global distribution of CD147-related publications based on the analysis of their geolocational data, the countries that the publications are from are mainly concentrated in Europe, North America, and East Asia (Fig. 7). Some studies have reported that CD147 levels were correlated with the progression of malignant glioma. Sameshima proposed that CD147 overexpression in glioma tissues can lead to increased secretion of ECM through interacting with endotheliocytes and fibroblasts, then facilitating cancer cells' invasiveness and local tissue angiogenesis [3]. Nevertheless, few studies have systematically described the precise clinical implications of CD147 in gliomas and its precise roles in WHO grading. As such, whether CD147 can be used as a biomarker for WHO grading of gliomas remains unclear. In view of this, we combined Embase, Google Scholar, PubMed, Wanfang, and Cnki databases to analyze the clinical significance and practical implications regarding CD147 systematically.

We explored CD147 in 10 glioma literatures and its relation to WHO grading in 615 cases. The analysis of eight dichotomous studies revealed that higher CD147 level was closely correlated with higher pathological grade (III + IV; OR, 9.900; 95 % CI, 5.943, 16.491; $P = 0.000$), but analysis of the three continuous studies did not detect any statistically associations (SMD, −1.894; 95 % CI, −4.081, 0.293; $P = 0.090$). However, the later three studies only make up a small part of the overall analysis, so we consider that the present meta-analysis still suggests a potential association between CD147 overexpression and high-grade glioma.

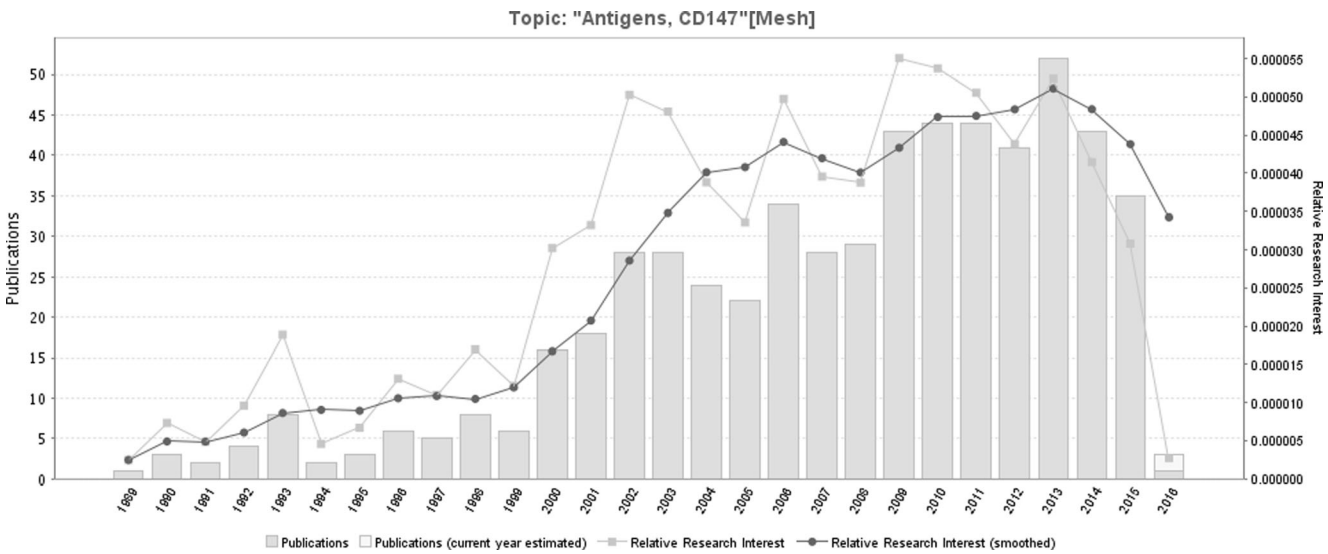

Fig. 6 A timeline of the publications related to CD147

Fig. 7 A world map with the global distribution of CD147-related publications based on the analysis of their geolocational data

Because there were no significant heterogeneities across the eight literatures with dichotomous data confirmed by Galbraith plot, I^2 test, and Cochran's Q test, a fixed effect model was chosen. As heterogeneity was detected across the three continuous studies, we adopted a random effect model to conduct the pooled SMD estimates. However, there were still several limitations that should be noted. Publication bias is a major concern in systematic meta-analysis [20]. Most of the journal only published the reports with positive research results. In the "gray literature," such as meeting monographs, dissertation, etc., there may be potentially "unpublished" negative research results. Unfortunately, although everything possible had been done for searching for these data, nothing gained. Secondly, in this meta-analysis, all the studies are from China and Japan. Frankly, it could lead to selection bias in this regard. But after searching PubMed, Google Scholar, Medline, Cnki, and Wanfang databases, we did only find useable studies from China and Japan. Thirdly, the languages of published eligible articles in this meta-analysis were limited to English and Chinese, which may have caused publication bias because of the absence of studies published in other languages that met our inclusion criteria. It is worth noting here, however, that in the present meta-analysis, neither the Egger's and Begger's P value tests ($P = 0.178$; 95 % CI, −0.191, 0.824) nor the funnel plot indicated publication bias. Thus, at least in statistical terms, this analysis is robust and reasonable.

Conclusions

In conclusion, the present meta-analysis suggests that CD147 is potentially associated with high WHO grading of glioma patients and may be assumed to be an essentially prognostic factor. Most importantly, the pathological CD147 gene or protein detection would facilitate new insights regarding the accurate prediction of tumor grade and early treatment regimens of patients undergoing surgical resection. However, to achieve a more robust conclusion, more data compiled on the basis of evidence-based medicine are required to definitively prove the correlation.

Compliance with Ethical Standards

Conflict of Interest The authors state that there are no conflicts of interest to disclose.

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