Mol Neurobiol (2016) 53:720–727
DOI 10.1007/s12035-014-9018-9

Clinicopathological and Prognostic Significance of CD133 in Glioma Patients: A Meta-Analysis

Mingzhi Han · Laixiu Guo · Ya Zhang · Bin Huang · Anjing Chen · Weiliang Chen · Xupeng Liu · Shicheng Sun · Kun Wang · Ao Liu · Xingang Li

Received: 31 August 2014 / Accepted: 18 November 2014 / Published online: 15 January 2015

Abstract In recent years, CD133 has been identified as a cancer stem cell (CSC) marker in gliomas. Nevertheless, the clinical and prognostic value of CD133 in glioma patients remains controversial. Therefore, we conducted a systematic meta-analysis to evaluate the correlation of CD133 with World Health Organization (WHO) grade, age, gender, overall survival (OS), and progression-free survival (PFS) in glioma patients. Eligible studies on this subject were included, and then pooled odd ratios (ORs) and hazard ratios (HRs) with 95 % confidence intervals (95 % CIs) were estimated. Publication bias was assessed by the funnel plots, and heterogeneity and sensitivity were analyzed as well. In the present study, 21 articles with the total number of 1535 patients were included. High expression of CD133 in glioma patients was associated with high WHO grade (III+IV) (n=11, OR 5.10, 95 % CI 2.99–8.69; p=0.000), rather than age (n=4, OR 2.54, 95 % CI 0.68–9.52; p=0.167) and gender (n=4, OR 0.71, 95 % CI 0.21–2.45; p=0.587). In addition, survival analysis demonstrated a significant association between CD133 high expression and poor 2-year OS (n=11, HR 2.18, 95 % CI 1.29–3.7; p=0.004), 5-year OS (n=4, HR 10.39, 95 % CI 2.59–41.63; p=0.001), as well as PFS (n=10, HR 2.34, 95 % CI 1.62–3.37; p=0.000). Taken together, this study suggests that CD133 expression correlates to higher grade of gliomas and worse prognosis in glioma patients. Thus, CD133 could be recommended as a useful pathological and prognostic biomarker in clinical practice.

Keywords CD133 · Gliomas · WHO grade · Prognosis · Meta-analysis

Introduction

Glioma is the most common and deadly type of human brain tumors which exhibits malignant aggressiveness and poor prognosis [1, 2]. Histopathologically, gliomas are divided into four malignancy grades according to the World Health Organization (WHO). However, the underlying molecular mechanism of glioma has not been fully identified. Therefore, more precise biomarkers are investigated to predict prognosis or pathological diagnosis.

Recently, a rare subpopulation of cancer cells, termed cancer stem cells (CSC), has been thought to play crucial roles in the initial, progression, metastasis, and recurrence of cancer, owing to their ability to self-renew and to form the tumor bulk [3]. CD133 (also known as prominin-1), located on chromosome 4p15, is a five-domain transmembrane glycoprotein with a molecular weight of 120 kDa. Previous studies have identified CD133 as a CSC marker related to tumorigenesis and cancer progression in various solid tumors, including gliomas, prostate carcinoma, colorectal cancer, etc. [4–6]. Moreover, its prognostic and clinicopathological roles in different types of cancers have been widely investigated [7–9].

However, there is still insufficient clinical data to determine the clinical value of CD133 in gliomas and there even exists conflicts. Some studies suggested that CD133 expression was

Mingzhi Han and Laixiu Guo contributed equally to this work.

M. Han · B. Huang · A. Chen · W. Chen · X. Li (✉)
Department of Neurosurgery, Qilu Hospital of Shandong University and Brain Science Research Institute, Shandong University, 107 Wen Hua Xi Road, Jinan, Shandong 250012, China
e-mail: lixg@sdu.edu.cn

L. Guo
Jining No.1 People's Hospital, Jining, Shandong, China

Y. Zhang
Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China

M. Han · Y. Zhang · X. Liu · S. Sun · K. Wang · A. Liu
School of Medicine, Shandong University, Jinan, Shandong, China

related to higher grade and worse prognosis [10, 11], whereas Dahlrot RH et al. [12] concluded that neither WHO grade nor overall survival (OS) was associated with CD133 expression status in glioma tissues. Consequently, a meta-analysis of published studies was performed to systematically elucidate whether CD133 expression has a correlation with the clinicopathology and prognosis of gliomas.

Methods

Literature Search

We conducted a literature search up to July 2014 without any limitations of origin and languages in the following databases: Pubmed, MEDLINE, Embase, Google Scholar, Wanfang and CNKI, etc. Search terms were subjected to the following: CD133, prominin-1 or PROM1, gliomas [MeSH], expression, prognosis, or survival, etc. The reference lists in relative articles were also screened to further identify potential applicable reports.

Study Selection

Eligible studies were selected by two observers separately. Inclusion criteria were the following: (1) the patients were confirmed the diagnosis of gliomas without restriction of types; (2) the main outcome of interest focuses on age, gender, WHO grade, and overall survival; (3) CD133 expression was evaluated by immunohistochemistry (IHC), RT-PCR, or Western blot (WB), etc; (4) articles provided sufficient information on the OS, progression-free survival (PFS), and clinicopathological indicators of patients related to the CD133 expression. Articles that did not meet these inclusion criteria were excluded. Additionally, if an eligible study was retrieved in duplication, only the latest published one was included.

Data Extraction and Quality Assessment

In order to reduce the bias and enhance the credibility, relevant data were collected by two observers separately using a standardized form as follows: name of the first author, publication year, country of the included subjects, histology, study methods, WHO grade, number of cases, mean ages, cut-off values, and positive percentage.

Two independent reviewers conducted quality assessment of each eligible study according to the European Lung Cancer Working Party (ELCWP) assessment scale [13]. This scale evaluates mainly four dimensions of methodology: the scientific design, laboratory methodology, generalizability, and results analysis. Each category could add up to 10 points, so the maximum overall score are 40 points. The final scores represent the percentage of the maximum achievable score, ranging from 0 to 100 %.

Statistical Analysis

Statistical calculations were all performed using STATA version 12.0. Pooled HR and their corresponding 95 % CI of 2-year OS, 5-year OS, and PFS were counted. As for the studies where HR and 95 % CI were not given directly, data in tables, text or/and figures of the original papers were extracted by using software Engauge Digitizer (version 4.1, http://digitizer.sourceforge.net/) and the methods introduced by Tierney et al. [14] and Parmar et al. [15].

To assess between study heterogeneity among the studies, we used chi-squared test and Q test. If heterogeneity was significant ($p<0.05$), random effect model would be used, while fixed effects model was applied when no statistical heterogeneity existed. Begg's and Egger's funnel plots and tests were introduced to estimate the publication bias [16].

Sensitivity analysis was introduced in order to evaluate the influence of single studies on the overall estimate. By convention, the effect of CD133 expression on pathological features and survival was considered as statistically significant if the pooled estimates of odd ratio/hazard ratio (OR/HR) with 95 % CI did not overlap 1. All p values were two-sided, and $p<0.05$ was considered as statistically significant.

Results

Search Results and Characteristics of Studies

Detailed search steps were described in a flow chart in Fig. 1. To begin with, 231 papers were selected according to the inclusion criteria stated above. Afterwards, 179 articles were excluded owing to those not relevant to the subject based on the titles and abstracts of the articles. The remaining 52 articles

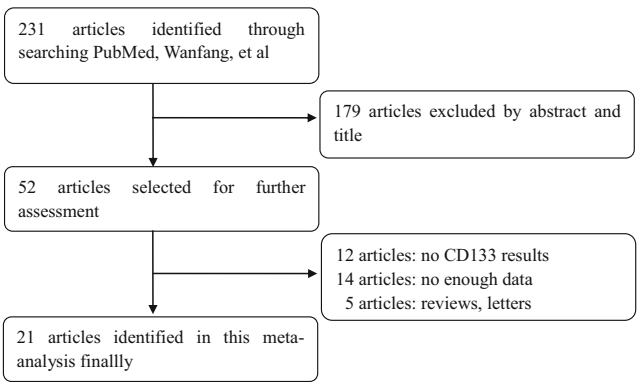

Fig. 1 Literature search and selection of articles. Twenty-one articles were included eventually according to inclusion criteria

were further assessed by two observers, among which 31 articles were excluded: 5 were reviews or letters, 12 were not related to CD133, and 14 did not provide sufficient data. Eventually, 21 eligible articles were included.

All 21 eligible studies were listed in Table 1. The publication years of involved studies range from 2008 to 2014. The total number of patients was 1535. Eight studies were conducted in non-Asian populations and 13 studies in Asian populations, including 1 from Japan, 2 from Korea, and the rest 10 from China. The percentage of positive CD133 expression varies from 17.9 to 80.4 %. Eleven included studies reported OS, and 10 studies indicated PFS. Patients with positive CD133 were evaluated by IHC (18 studies), Western blot (1 study), RT-PCR (1 study), and DNA microarray (1 study). All detected specimens were derived from glioma tissues via surgical resection.

Study Quality

In the present meta-analysis, we estimated the qualities of included study according to ELCWP. As shown in Table 2, the mean global score was 73.5 %. Specifically, study method had a higher score of 7.7, compared with design (7.4), generalizability (7.1), and results analysis (7.2). The global scores in Asian and Non-Asian were 73.8 and 76.3 %, respectively, and no significant difference was observed between them in the global quality score (p=0.075).

Correlation of CD133 with Clinicopathological Features

To identify the value of CD133 in pathological diagnosis, we investigated the association of CD133 expression with clinicopathological features. Data of WHO grade, age, and gender were extracted from included studies, and then pooled OR was calculated. As shown in Fig. 2, a random effect model revealed a relationship between expression of CD133 and WHO grade (III+IV, +) (n=11, OR 5.10, 95 % CI 2.99–8.69; p=0.000). However, no association was observed between CD133 and age (> mean age, +) (n=4, OR 2.54, 95 % CI 0.68–9.52; p=0.167), as well as CD133 and gender (male, +) (n=4, OR 0.71, 95 % CI 0.21–2.45; p=0.587). Taken together, these results suggested that CD133 expression could be recommended as a clinical biomarker for diagnosis in high-grade glioma patients.

Impact of CD133 on 2-year OS, 5-year OS, and PFS of Gliomas

To further evaluate the relationship between CD133 and prognosis in postoperative glioma patients, survival analysis of 2-

Table 1 Characteristics in 21 included studies

Study ID	Country	Number	Histology	Mean age	Male	WHO grade	Method	Cut-off	Positive
2014 Dahlrot RH [12]	Denmark	239	Glioma	64.0	134/239	II, III, IV	IHC	>2 %	149/239
2014 Li SZ [17]	China	54	Glioma	NA	NA	I–IV	IHC	>5 %	31/54
2013 Shin JH [18]	Korea	67	Glioblastoma	55.0	34/67	IV	IHC	>50 %	12/67
2013 Shibahara I [19]	Japan	112	Glioblastoma	57.0	64/112	IV	WB	Ratio >1	31/112
2013 Xing PF [20]	China	58	Glioma	45.2	32/58	I, II, IV	IHC	>25 %	41/58
2013 Pan L [21]	China	46	Glioma	42.0	28/46	I–IV	IHC	>5 %	37/46
2013 Zhu ZW [22]	China	80	Glioma	50.0	34/80	I–IV	IHC	>3 %	28/80
2012 Melguizo C [23]	Spain	78	Glioblastoma	56.0	42/78	IV	IHC	>25 %	34/78
2012 Kong LJ [24]	China	62	Glioma	NA	34/62	I–IV	IHC	>5 %	41/62
2012 Ma QF [25]	China	66	Glioma	42.0	36/66	I–IV	IHC	>25 %	48/66
2011 Pallini R [26]	Italy	37	Glioblastoma	54.2	17/37	IV	IHC	>1 %	15/37
2011 Metellus P [27]	France	48	Glioblastoma	60.1	35/48	IV	RT-PCR	Value >1	19/48
2011 Kim KJ [28]	Korea	88	Glioblastoma	54.9	46/88	IV	IHC	>50 %	52/88
2011 He J [29]	China	59	Glioma	57.0	36/59	III, IV	IHC	>10 %	24/59
2011 Ke J [30]	China	45	Glioma	NA	NA	II–IV	IHC	POS	16/45
2011 Guo CY [31]	China	62	Glioma	NA	NA	I–IV	IHC	POS	39/62
2010 Kappadakunnel M [32]	USA	47	Glioblastoma	NA	NA	IV	DNA Microarray	NA	23/47
2008 Zhang MY [11]	China	125	Glioma	48.1	85/125	II–IV	IHC	>30 %	34/125
2008 Zeppernick F [10]	Germany	95	Glioma	NA	59/95	II–IV	IHC	>1 %	57/95
2008 Rebetz J [33]	Sweden	23	Glioma	47.0	14/23	I–IV	IHC	>30 %	8/23
2008 Pallini R [34]	Italy	44	Glioblastoma	57.5	28/44	IV	IHC	>2 %	19/44

Table 2 Clinical and methodological characteristics of included studies

	Number of studies	Design	Method	Generalizability	Results analysis	Global score (%)
All studies	21	7.4	7.7	7.1	7.2	73.5
WHO grade	11	6.6	7.5	7.2	6.8	70.3
Age	4	6.8	7.3	6.9	7.5	71.3
Gender	4	7.1	7.5	7.3	8.1	75.0
OS	11	7.2	8.0	7.4	7.6	75.5
PFS	10	6.9	7.7	7.3	7.5	73.5
Asian	13	7.5	7.7	7.0	7.3	73.8
Non-Asian	8	7.8	8.0	7.3	7.4	76.3
p value		0.231	0.485	0.308	0.087	0.075

year OS, 5-year OS, and PFS was conducted. As showed in Fig. 3, a random effect model revealed that high CD133 expression was negatively associated with 2-year OS (n=11, HR 2.18, 95 % CI 1.29–3.7; p=0.004) and 5-year OS (n=4, HR 10.39, 95 % CI 2.59–41.63; p=0.001). In addition, our meta-analysis also showed that the patients with positive CD133 expression had a worse PFS than those with negative one (n=10, HR 2.34, 95 % CI 1.62–3.37; p=0.000). Taken together, these results indicated that upregulated expression of CD133 predicted a poor survival prognosis in patients with gliomas.

Publication Bias and Sensitivity Analysis

In the present meta-analysis, Begg's and Egger's test was introduced to examine potential publication bias. Publication bias was observed among 11 studies on WHO grade (p=0.013, 0.013), and 10 studies on PFS (p=0.032, 0.104); while studies on CD133 with 2-year OS, 5-year OS, age, and gender did not reveal any bias (p=0.350, 0.292; p=0.734, 0.959; p=0.308, 0.272; p=0.734, 0.523; respectively). In accordance with these results, Begg's funnel plot also showed the asymmetric distribution of studies on WHO grade (Fig. 4a) and PFS (Fig. 4e).

Sensitivity analysis of our meta-analysis indicated that study of Zeppernick F [10] significantly influenced the pooled OR/HR. In their study, a lower cut-off value (1 %) was used for the detection of CD133 compared with other included studies, which may lead to heterogeneity in this meta-analysis.

Discussion

Up to date, CD133 has been demonstrated as a specific cell surface marker of CSC, and the importance of CD133 in tumorigenesis has been widely documented as well. Due to its crucial roles in cellular biology of cancer, CD133 has been

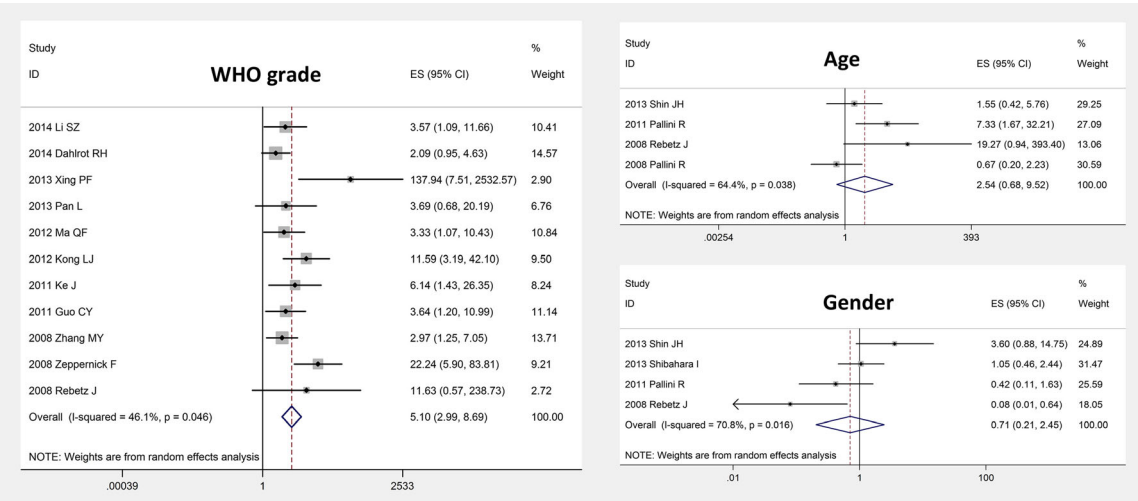

Fig. 2 The individual and pooled OR with 95 % CI about CD133 and WHO grade, age, and gender. A random effect model revealed an association between CD133 and WHO grade (III+IV, +) (n=11, OR 5.10, 95 % CI 2.99–8.69; p=0.000), CD133 and age (> mean age, +) (n=4, OR 2.54, 95 % CI 0.68–9.52; p=0.167), and CD133 and gender (male, +) (n=4, OR 0.71, 95 % CI 0.21–2.45; p=0.587)

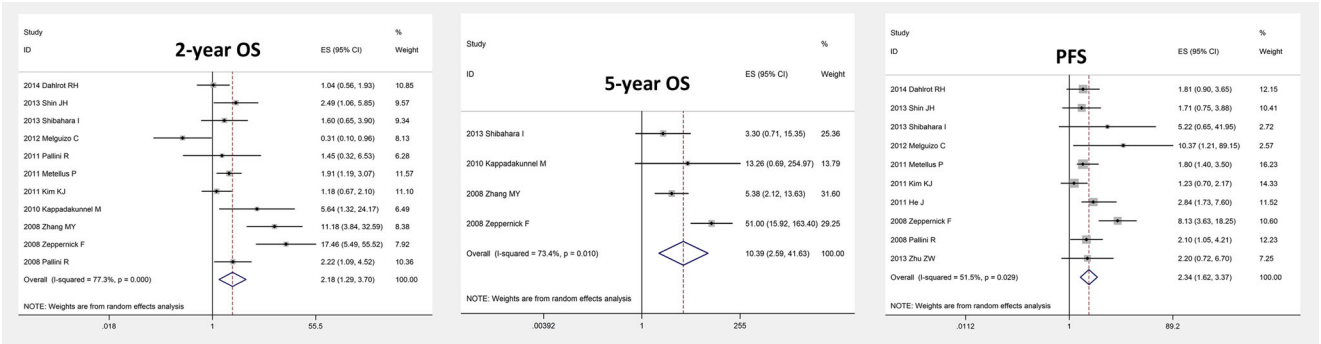

Fig. 3 The individual and pooled HR with 95 % CI about CD133 and 2-year OS, 5-year OS, and PFS in glioma patients. A random effect model revealed an association between CD133 and 2-year OS (n=11, HR 2.18, 95 % CI 1.29–3.7; p=0.004), CD133 and 5-year OS (n=4, HR 10.39, 95 % CI 2.59–41.63; p=0.001), and CD133 and PFS (n=10, HR 2.34, 95 % CI 1.62–3.37; p=0.000)

suggested as a prognostic molecular marker and therapeutic target in various solid tumors. However, the clinical significance of CD133 in diagnosis and treatment is still contradictory and inconclusive in several malignant cancers including gliomas [35]. Most of the studies indicated that CD133 predicted a poor outcome, but studies of Melguizo C et al. [23] and Kim KJ et al. [28] reported that CD133 did not relate to survival of glioma patients; in addition, whether CD133 is significantly associated with WHO grade of gliomas remains to be clarified. Based on these controversial studies, we expected to evaluate the precise impact of CD133 on pathology and prognosis of gliomas.

In this meta-analysis, we summarized the outcomes of total 1535 glioma patients from 21 relevant studies related to CD133, prognosis, and pathology in gliomas. Quality assessment was subjected to the published ELCWP, and there was no significant difference among all the studies. As a result of our analysis, the pooled OR and 95 % CI showed a significant relationship between CD133 and WHO grade (n=11, OR 5.10, 95 % CI 2.99–8.69; p=0.000). While no association was observed between CD133 and age (n=4, OR 2.54, 95 % CI 0.68–9.52; p=0.167) and CD133 and gender (n=4, OR 0.71, 95 % CI 0.21–2.45; p=0.587), which suggested that positive CD133 expression could effectively predict the high grade (III+IV) in glioma patients. With regard to prognosis, the pooled HR and 95 % CI about 2-year OS for all 11 studies were 2.18 (95 % CI 1.29–3.7) compared with 5-year OS at 10.39 (95 % CI 2.59–41.63), both of which revealed a reduced survival in CD133 positive patients. Similarly, a correlation was also observed between CD133 and PFS (n=10, HR 2.34, 95 % CI 1.62–3.37; p=0.000). To conclude, all these results indicated that positive CD133 expression could effectively predict the high grade (III+IV) and worse outcome in glioma patients.

In the present study, we used classical Q statistic to assess heterogeneity, which was considered statistically significant when $p<0.05$ and/or $I^2>50$ %. In this study, there exists heterogeneity in analysis about CD133 and WHO grade, age, gender, OS and PFS, and all p values were <0.05. Therefore, a random effect model, which provides a more conservative standard error and a larger confidence interval, was chosen to determine the pooled OR/HR estimates. In addition, sensitivity analysis plot in this meta-analysis indicated that data from Zeppernick F [10] significantly influenced the pooled OR/HR. In their study, a lower cut-off value (1 %) was used for detection of CD133 compared with other included studies. By multivariate analysis, they combined CD133 expression and other clinical indicators (tumor grade, extent of resection, and patient age) to investigate their clinical significance in glioma patients. To analyze whether their study influenced the stability of pooled estimates, we excluded their study and reanalyzed the remaining data, and there was no heterogeneity with $p>0.05$, which further identified study of Zeppernick F as the main source of heterogeneity in this meta-analysis.

Several restrictions of our study also need to be considered. Firstly, CD133 expression in the included studies was mostly measured by traditional IHC method, which could cause inconsistent CD133 detection when different primary CD133 antibody clones or different antibody concentrations were used. However, it was difficult for us to conduct subgroup analysis by different antibodies to analyze the underlying bias of method on the pooled ORs. Secondly, the definition of cut-off value among the studies also varied, which can lead to potential bias as well. Therefore, we should consider all factors that may affect bias when explaining pooled results in this meta-analysis.

In systematic analysis, publication bias is the main cause of bias. Traditionally, most studies tended to report positive outcomes rather than negative results [36]. In our study, publication bias was observed by either Egger's or Begg's test; meanwhile, the languages of included studies were limited to English and Chinese; thus, other potentially eligible studies which met our inclusion criteria cannot be included, which may cause publication bias as well.

In summary, based on current obtained data, our study clarified the value of CD133 as a significant clinical indicator for glioma patients with worse prognosis and higher WHO grade. Thus, these results could be important for pathological diagnosis and prognostic prediction of glioma patients in

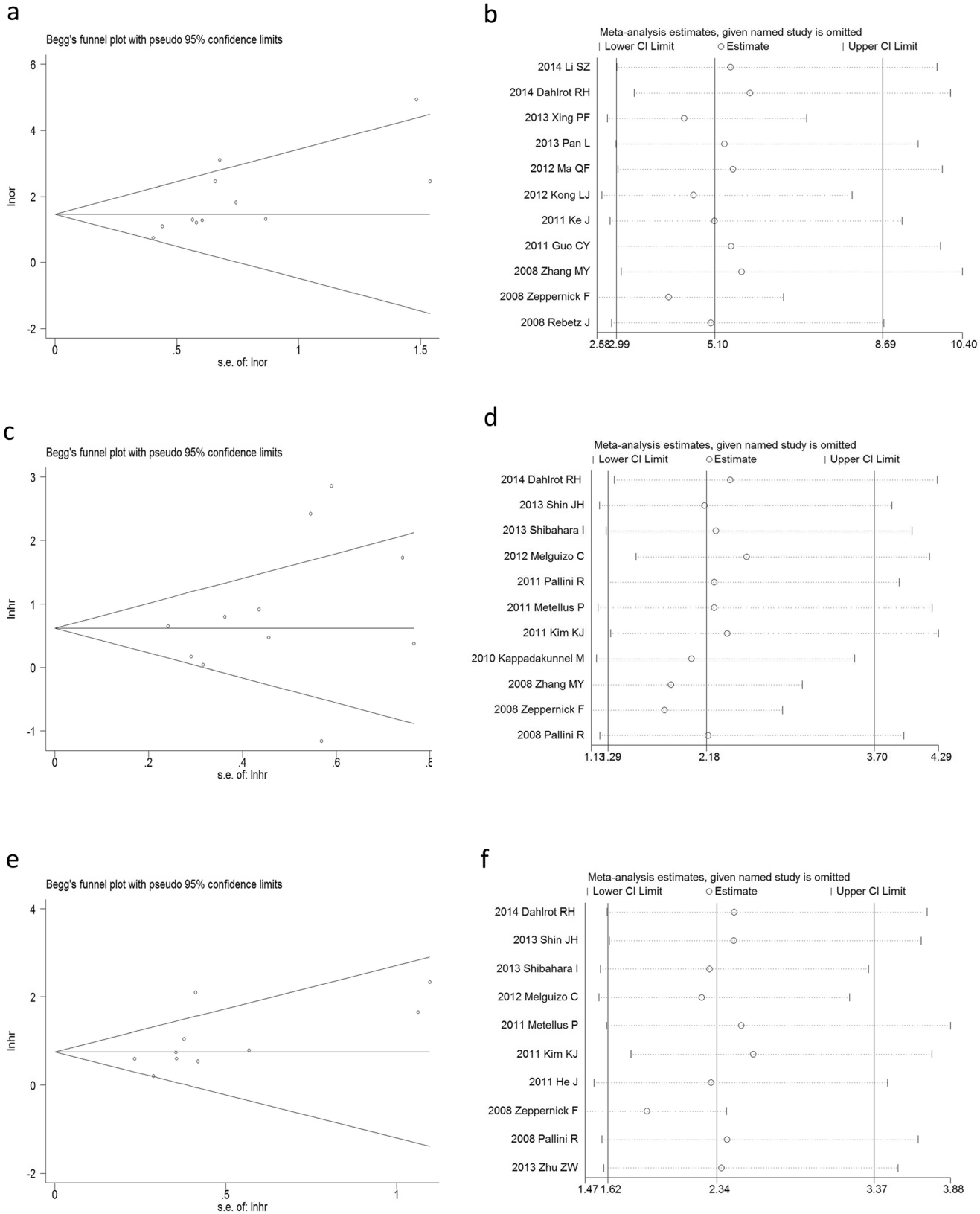

Fig. 4 Begg's funnel blot and sensitivity analysis. Begg's funnel blot was designed to evaluate a potential publication bias. **a** Publication bias of CD133 and WHO grade; **c** CD133 and 2-year OS; **e** CD133 and PFS. Sensitivity analysis indicates that some study affects heterogeneity. **b** Sensitivity analysis of CD133 and WHO grade (2014 Dahlrot RH; 2008 Zeppernick F); **d** CD133 and 2-year OS (2008 Zhang MY; 2008 Zeppernick F); **f** CD133 and PFS (2008 Zeppernick F)

clinical application. In addition, CD133 can lead to a new insight for selecting therapeutic approaches in gliomas.

Acknowledgments This study was supported by the National Natural Science Foundation of China (81172404, 81372720), Special Foundation for Taishan Scholars (TS20110814). We were also very grateful to the help of Yunyun Guo et al. for their valuable advice.

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

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