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RESEARCH ARTICLE

Clinicopathological significance and prognostic value of the expression of the cancer stem cell marker CD133 in hepatocellular carcinoma: a meta-analysis

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Abstract To conduct a meta-analysis to assess the association between CD133 expression and clinicopathological significance and prognostic value in hepatocellular carcinoma patients. Studies were identified via an electronic comprehensive literature search through the Pubmed, Chinese CNKI, and Wanfang databases. This meta-analysis was performed using Stata statistical software version 12.0. The outcomes included various clinicopathological and survival parameters ($P<0.05$ was consider to indicate a statistical significance). A total of 21 studies comprising 2592 patients were included in this meta-analysis. CD133 overexpression was significantly associated with a series of clinicopathological parameters, such as low tumor differentiation (pooled odds ratio (OR)=2.26, 95% CI: 1.59–3.21, $P<0.00001$), advanced tumor stage (pooled OR=2.17, 95% CI: 1.70–2.77, $P<0.00001$), vascular invasion (pooled OR=2.06, 95% CI: 1.25–3.39, $P=0.005$), and vascular thrombosis (pooled OR=1.47, 95% CI: 1.08–1.99, $P=0.015$). However, CD133 expression was not correlated with hepatitis, cirrhosis, α-fetoprotein level, tumor number, tumor size, encapsulation, or metastasis. Regarding survival outcome, CD133 overexpression was significantly correlated with poor overall survival (pooled hazard ratio (HR)=2.01, 95% CI: 1.45–2.80, $P=0.00002$) and poor disease-free survival (pooled HR=1.82, 95% CI: 1.45–2.29, $P<0.00001$). This meta-analysis indicated that CD133 overexpression is significantly associated with clinicopathological factors and poorer survival outcome.

Keywords Cancer stem cells · CD133 · Hepatocellular carcinoma · Meta-analysis · Prognosis · Clinicopathological features

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of death worldwide, with nearly one million new cases diagnosed every year worldwide [1, 2]. Previous researches have indicated that hepatic resection is the most practical and effective treatment for HCC, and 5-year survival rates of up to 50 % can be achieved [3–5]. However, the prognosis for HCC patients remains unpredictable and unsatisfactory due to high rates of recurrence and metastasis, which can be as high as 45 % within 2 years of surgery [6–9]. The cellular and molecular mechanisms involved in the initiation and progression of HCC are still unclear. In recent studies, stem/progenitor cells have been associated with hepatocarcinogenesis in rodents and activated in HCC patients [10, 11]. Increasing evidence suggests that tumors can be initiated and maintained by cancer stem cells (CSCs) [12–14]. The cell surface marker CD133, also known as prominin-1, is widely used as a CSC marker in various tumors, including liver cancer, lung cancer, colon cancer, and gastric cancer [2,

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15–18]. To our knowledge, many recent studies have attempted to determine whether CD133 overexpression is associated with clinicopathological factors and prognosis in different malignant tumors. However, the relationship between high CD133 expression and clinical outcome in HCC patients remains a controversial issue. Here, we performed a meta-analysis to assess whether CD133 overexpression was correlated with the clinicopathological factors and prognosis of HCC patients and provide a new insight into the potential treatment of HCC and molecular mechanisms involved in HCC.

Materials and methods

Literature search strategy

Studies were identified via an electronic comprehensive literature search using the Pubmed, Chinese CNKI, and Wanfang databases with the key words "CD133" OR "AC133" OR "prominin-1" AND "liver cancer" OR "liver carcinoma" OR "liver neoplasm" OR "liver tumor" OR "hepatic cancer" OR "hepatic carcinoma" OR "hepatic neoplasm" OR "hepatic tumor" OR "hepatocellular carcinoma". This search was performed up to February 15, 2015. The title and abstract of each study were identified to exclude any irrelevant studies. The remaining articles were browsed to determine whether they contained information relating to the topic of interest. The reference lists of the relevant articles were also screened to further identify potential studies (Fig. 1).

Selection criteria

The inclusion criteria were showed to select literature as follows: (1) diagnosis of HCC was confirmed by histopathological methods; (2) studies of CD133 expression based on liver cancer tissue rather than serum or any other types of specimen were included; (3) CD133 expression was detected by the immunohistochemical staining method; (4) articles on the association of CD133 levels with overall survival (OS), disease-free survival (DFS) or clinicopathological features of HCC; (5) articles providing sufficient data to allow the estimation of an odds ratio (OR) with 95 % confidence interval (CI) of clinicopathological parameters or a hazard ratio (HR) with 95% CI of OS or DFS. There were no limits of the number of cases, gender ratio, or the cutoff values of immunohistochemical staining in this meta-analysis. If there were multiple articles by the same group based on similar patients in the searching results, only the most recent or most informative article was selected in this meta-analysis (Fig. 1). We assessed the quality of the primary studies by using Newcastle-Ottawa Quality Assessment Scale (case-control studies).

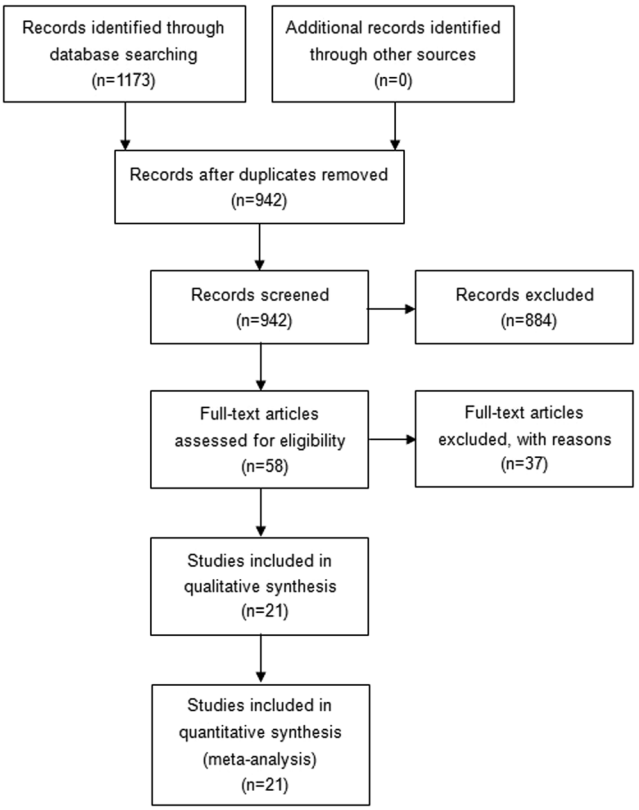

Fig. 1 Flow chart for selection of studies for inclusion in this meta-analysis

Data extraction

To minimize bias and improve reliability, two reviewers independently assessed all potentially relevant studies. The following characteristics were extracted from eligible studies and are illustrated in detail in Table 1: name of first author, year of publication, number of patients, and $CD133^{+}$-group, age (mean/median), gender, cutoff values, tumor differentiation, TNM stage, follow-up (months), treatment, and quality score. ORs with 95% CI were evaluated the correlation between high CD133 expression and general clinicopathological parameters, including hepatitis B virus (HBV, negative vs. positive), hepatitis C virus (HCV, negative vs. positive), cirrhosis (absent vs. present), α-fetoprotein (AFP) level (≤400 vs. >400 ng/ml), tumor differentiation (I+II vs. III+IV) and tumor stage (I+II vs. III+IV), tumor number (single vs. multiple), tumor size (≤5 vs. >5 cm), vascular invasion (absent vs. present), vascular thrombosis (absent vs. present), encapsulation (absent vs. present), and metastasis (absent vs. present). HRs with 95% CI assessed the association

Table 1 General characteristics of included studies

Study	Year	Patients (*n*)	$CD133^+$ (*n*)	Age (mean/median)	Male (%)	Cutoff values	TNF stage	Tumor differentiation	Follow-up (months)	Treatment	NOS
Song WJ [19]	2008	63	26	50.3	82.5	≥1.32 %	I–IV	I–IV	60	NO	6
Tsuchiya A [20]	2009	31	9	67.4	80.6	NR	I–IV	NR	NR	NO	6
Yeh CT [21]	2009	154	24	56.2	74.0	NR	I–IV	NR	125	NO	6
Zhang H [22]	2009	65	50	NR	81.5	>0 %	I–IV	I–IV	NR	NO	6
Lingala S [23]	2010	25	10	56.4	80.0	NR	I–IV	I–IV	NR	NO	6
Sasaki A [24]	2010	136	30	61.0	82.4	NR	I–IV	I–IV	90	NO	6
Yang XR [25]	2010	314	NR	NR	NR	NR	I–IV	I–IV	130	NO	5
Guo XD [26]	2011	84	36	45.8	79.8	>10 %	I–IV	I–IV	NR	NO	6
Wu XH [27]	2011	54	39	54.0	74.1	≥Score3	I–IV	I–IV	36	NR	6
Zen C [28]	2011	40	14	55.0	82.5	≥5 %	I–IV	NR	78	LT/TACE	5
Pan QX [29]	2012	70	49	55.0	57.1	≥10 %	I–IV	NR	62	NO	5
Zeng XC [30]	2012	109	44	58.0	94.5	≥Score2	I–IV	NR	77	NO	5
Liu LL [31]	2013	245	45	48.0	84.1	≥Score3	I–IV	NR	80	NO	6
Tian J [32]	2013	100	51	51.0	79.0	≥Score2	I–IV	NR	NR	NO	6
Wu LM [33]	2013	190	42	59.0	92.6	Strong staining	I–IV	I–III	128	NO	6
Chan AW [34]	2014	282	38	55.4	84.4	≥Score1	I–IV	I–IV	240	NR	5
Chen K [35]	2014	387	216	47.0	87.6	Strong staining	I–IV	I–IV	96	NR	6
Guo Z [36]	2014	50	42	46.2	NR	≥5 %	I–IV	NR	NR	NR	6
Ye F [37]	2014	120	29	50.1	90.0	NR	I–IV	I–III	36	NR	5
Yilmaz G [38]	2014	35	25	64.3	85.7	Strong staining	I–IV	I–IIIC	NR	NR	6
Zhao MY [39]	2014	38	26	47	84.2	≥Score3	I–IV	I–IV	24	NO	6

LT liver transplantation, *TACE* transcatheter arterial chemoembolization, *NR* not reported, *NO* not treated before liver resection, *NOS* Newcastle-Ottawa Scale

between high CD133 expression and survival outcome, including OS and DFS (5 years of follow-up).

Statistical analysis

ORs with 95% CI were used to estimate the association between high CD133 expression and general clinicopathological parameters ($P<0.05$ was considered to indicate a statistical significance). HRs with 95% CI were used to assess the correlation between high CD133 expression and survival outcome ($P<0.05$ was representative of statistical significance). For articles that did not directly provide HR with 95% CI of OS and DFS, Engauge Digitizer 4.1 (Boston, USA) software was applied to digitize and extract the data from Kaplan-Meier curves. The lnHR and variance were calculated by the methods described by Tierney et al. [40]. Statistical heterogeneity within studies was tested with the chi-squared-based Q-test and I^2 test ($P<0.10$ or $I^2>50$ %, indicated the existence of heterogeneity among studies). The fixed-effects (Mantel–Haenszel method) model or random-effects (DerSimonian and Laird method) model was used depending on the heterogeneity analysis. Publication bias was estimated by the Begg's and Egger's funnel plot ($P<0.05$ was considered of significant publication bias). In the sensitivity analyses, $P<0.05$ was representative of significant differences. All statistics were calculated by Stata statistical software version 12.0 (StataCorp, College Station, TX, USA).

Results

Description of studies and quality assessment

A total of 21 studies comprising 2592 patients met our selection criteria in this meta-analysis. The sample sizes of the studies included ranged from 25 to 387, with a mean of 123.4. Most patients were male (83.4 % from 19 studies). No preoperative therapy was performed on patients in 14 studies. One study reported that preoperative therapy (transcatheter arterial chemoembolization or liver transplantation) was performed in some HCC patients. All these studies evaluated CD133 expression by immunohistochemical staining methods in liver cancer tissues. All patients were divided into either $CD133^+$ or $CD133^-$ groups. Tumor differentiation was graded by Edmondson and Steiner, and tumor stage was classified by the International Union Against Cancer (UICC) 2002 issue of the TNM stage. Nine studies did not report tumor stage. All studies were graded by using Newcastle-Ottawa

Quality Assessment Scale (case-control studies). More than five points meant a better quality. More detailed information was showed in Table 1.

CD133 overexpression and clinicopathological features in HCC patients

In our analyses, CD133 overexpression in HCC patients was associated with several clinicopathological parameters (Table 2), such as low tumor differentiation (pooled OR=2.26, 95% CI: 1.59–3.21, $P<0.00001$, random effect), advanced tumor stage (pooled OR=2.17, 95% CI: 1.70–2.77, $P<0.00001$, fixed effect), vascular invasion (pooled OR=2.06, 95% CI: 1.25–3.39, $P=0.005$, random effect), and vascular thrombosis (pooled OR=1.47, 95% CI: 1.08–1.99, $P=0.015$, fixed effect). However, as shown in Table 2, no correlations were observed between CD133 expression and HBV (pooled OR=1.10, 95% CI: 0.86–1.42, $P=0.447$, fixed effect), HCV (pooled OR=0.80, 95% CI: 0.48–1.33, $P=0.379$, fixed effect), cirrhosis (pooled OR=1.28, 95% CI: 0.99–1.67, $P=0.059$, fixed effect), elevated serum AFP level (pooled OR=1.17, 95% CI: 0.95–1.44, $P=0.129$, fixed effect), tumor number (pooled OR=1.43, 95% CI: 0.80–2.54, $P=0.230$, random effect), tumor size (pooled OR=0.99, 95% CI: 0.81–1.20, $P=0.899$, fixed effect), encapsulation (pooled OR=0.80, 95% CI: 0.61–1.05, $P=0.110$, fixed effect), or metastasis (pooled OR=1.47, 95% CI: 0.90–2.39, $P=0.121$, fixed effect). The results of the heterogeneity analyses indicated no statistically significant difference ($P>0.10$ for Q-test, $I^2<50$ % for I^2 test), except tumor differentiation ($P=0.001$, $I^2>56.7$ %), tumor number ($P<0.010$, $I^2>70.1$ %), and vascular invasion ($P=0.059$, $I^2>48.6$ %) (Table 2).

CD133 overexpression and survival outcome in HCC patients

Ten studies (1950 patients) that had assessed the correlation between CD133 overexpression and OS and five studies (949 patients) containing information regarding the association between high CD133 expression and DFS could be obtained from published articles. The unadjusted HRs with 95% CI, which were not directly mentioned, were gained the assessment by the Kaplan-Meier method [19, 21, 24, 29–31, 33–35]. It showed that CD133 overexpression was significantly associated with poor OS (pooled HR=2.01, 95% CI: 1.45–2.80, $P=0.00002$, random effect) for a heterogeneity ($P=0.001$ for Q-test, $I^2=67.4$ % for I^2 test) (Fig. 2) and poor DFS (pooled HR=1.82 95% CI: 1.45–2.29, $P<0.00001$, fixed effect) for no heterogeneity ($P=0.566$ for Q-test, $I^2=0.0$ % for I^2 test) (Fig. 3). These results indicated that CD133 is an important influencing factor of prognosis in HCC patients.

Table 2 Meta-analysis of CD133 overexpression and clinicopathological features in HCC patients

Clinicopathological features	Studies (*n*)	Patients (*n*)	Analytical model	Pooled OR (95% CI)	*P* value	Heterogeneity		Publication bias	
						Q Chi^2 (*P* value)	I^2 (%)	Begg's test (*P* value)	Egger's test (*P* value)
HBV (negative vs. positive)	7	959	FEM	1.10 (0.86, 1.42)	0.447	3.22 (0.781)	0.0	0.368	0.396
HCV (negative vs. positive)	5	791	FEM	0.80 (0.48, 1.33)	0.379	0.80 (0.938)	0.0	0.221	0.134
Cirrhosis (absent vs. present)	6	966	FEM	1.28 (0.99, 1.67)	0.059	4.84 (0.436)	0.0	1.000	0.692
AFP (≤400 vs. >400 ng/ml)	13	1191	FEM	1.17 (0.95, 1.44)	0.129	4.59 (0.970)	0.0	0.855	0.512
Tumor differentiation (I+II vs. III+IV)	20	2260	REM	2.26 (1.59, 3.21)	<0.00001	43.84 (0.001)	56.7	0.581	0.855
Tumor stage (I+II vs. III+IV)	10	1308	FEM	2.17 (1.70, 2.77)	<0.00001	14.10 (0.119)	36.2	0.210	0.329
Tumor number (single vs. multiple)	5	778	REM	1.43 (0.80, 2.54)	0.230	13.37 (0.010)	70.1	0.462	0.389
Tumor size (≤5 vs. >5 cm)	12	1327	FEM	0.99 (0.81, 1.20)	0.634	4.67 (0.946)	0.0	0.945	0.094
Vascular invasion (absent vs. present)	8	1161	REM	2.06 (1.25, 3.39)	0.005	13.61 (0.059)	48.6	0.902	0.973
Vascular thrombosis (absent vs. present)	5	935	FEM	1.47 (1.08, 1.99)	0.015	2.76 (0.599)	0.0	0.806	0.680
Encapsulation (absent vs. present)	9	875	FEM	0.80 (0.61, 1.05)	0.110	10.70 (0.219)	25.2	0.466	0.029
Metastasis (absent vs. present)	4	671	FEM	1.47 (0.90, 2.39)	0.121	3.02 (0.388)	0.7	0.308	0.131

$P<0.05$ was considered to indicate statistically significant differences between CD133 expression and clinicopathological features; $P>0.10$ or $I^2>50$ % indicated the existence of heterogeneity; $P<0.05$ was representative of the significant publication bias

HBV hepatitis B virus, *HCV* hepatitis C virus, *AFP* α-fetoprotein, *OR* odds ratio, *CI* confidence interval, *FEM* fixed-effects model, *REM* random-effects model

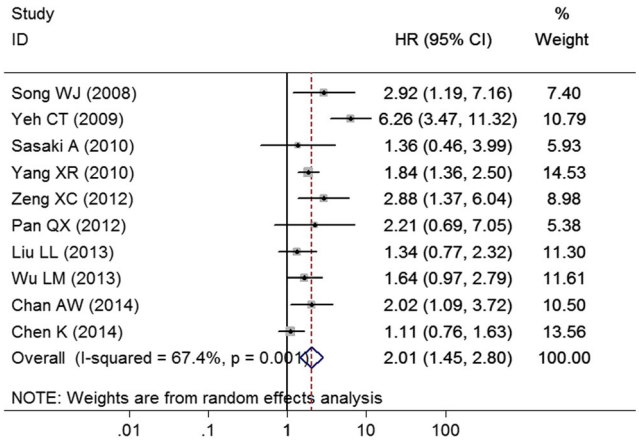

Fig. 2 Meta-analysis of correlation between CD133 expression and OS in HCC patients

Publication bias and sensitivity analyses

The meta-analysis of observational studies has their inherent limitations. Several factors may influence the publication bias, such as the selection of materials, the methods of technique, and the ways of data extraction. Additionally, one of the important limitations is publication bias caused by failing to balance unknown confounders. In this meta-analysis, inclusion criteria were strictly formulated, and funnel plots (Begg's and Egger's test) were used to identify bias. In order to minimize publication bias, two reviewers independently estimated all potentially relevant studies. As to clinicopathological factors, there was no significant publication bias (Table 2, $P>0.05$), except encapsulation ($P=0.466$ and $P=0.029$ in Begg's and Egger's test, respectively). As to survival outcome, the shapes of Begg's and Egger's funnel plots had no evidence of obviously asymmetrical patterns in the results of meta-analyses of OS ($P=0.371$ and $P=0.362$ in Begg's and Egger's test, respectively) and DFS ($P=0.462$ and $P=0.201$ in Begg's and Egger's test, respectively) (Fig. 4). In order to explain the stability of these results in this meta-analysis, we performed sensitivity analyses regarding of all sub-groups of clinicopathological features and survival outcome (Table 3).

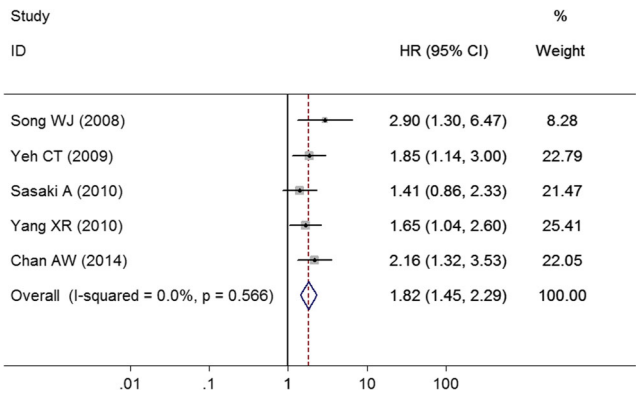

Fig. 3 Meta-analysis of correlation between CD133 expression and DFS in HCC patients

We found that OS, tumor differentiation, and tumor number had significant differences ($P<0.05$). However, these differences had no effect on the final results of meta-analysis. Therefore, we did not exclude these studies from the comprehensive consideration.

Discussion

Recent studies have shown that some functional molecules could be an attractive inhibitor of the target gene CD133, which reactive anticancer mechanisms in targeted CSC therapy in HCC patients [41]. Therefore, the expression of CD133 has played an increasing important role of the evaluation of prognosis and may aid the improvement of diagnosis, treatments, and prevention of HCC. So, we did a comprehensive meta-analysis to systematically evaluate the correlation between the CD133 overexpression and clinical and prognostic outcome.

CD133 is expressed in normal fetal livers and cancerous livers but not in normal adult livers. Generally, chronic viral hepatitis leads to the regeneration of hepatocytes due to the chronic and continuous inflammatory stimulation caused by HBV or HCV. Gradually, cirrhosis and carcinogenesis can occur. However, our study showed that CD133 overexpression had no connection with hepatitis and cirrhosis. These results were the same as those reported by Ma et al. [2] and were against a CSC origin of hepatitis virus-related HCC. Meanwhile, elevated levels of AFP were no correlation with CD133 overexpression which differ from Ma et al. [2]. There were several reasons for this. First, we included more studies in this meta-analysis, both in English and in Chinese. Second, we established more stringent criteria for selecting articles, such as immunohistochemical staining methods. However, higher-quality studies and further researches are needed to clarify this problem.

CD133 is believed to play a key role in the occurrence of cancer, including promoting tumor angiogenesis and growth, activating self-renewal through the neurotensin/IL-8/CXCL1 signal pathway, initiating metastasis and recurrence of cancer, and influencing the prognosis of HCC patients [42]. Here, the $CD133^+$ group had an increased incidence of vessel invasion and generation of embolism. However, no correlation was observed with tumor number, tumor size, encapsulation, or metastasis. Suetsugu et al. demonstrated that $CD133^+$ cells from Huh-7 had a higher tumorigenic potential, greater proliferative ability, and lower differentiation status than $CD133^-$ cells [43]. This meta-analysis demonstrated significant differences between the $CD133^+$ and $CD133^-$ groups in terms of tumor differentiation and tumor stage. Additionally, CD133 overexpression was significantly associated with poor OS and DFS. Thus, CD133 overexpression may be an important marker as the accurate assessment of clinical and prognostic

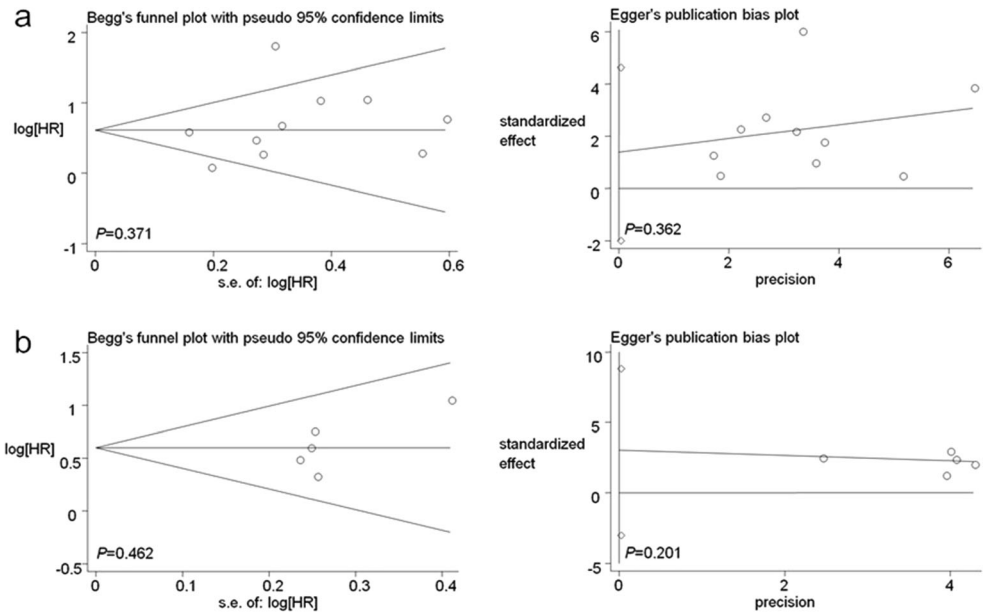

Fig. 4 Begg's and Egger's funnel plot estimated the publication bias for OS (**a**) and DFS (**b**)

outcome and a potential target to deeply explore the cellular and molecular mechanism for the treatment of HCC patients.

However, the results from our study should be interpreted cautiously due to some limitations that might have influenced the conclusions of this meta-analysis. First, the number of included articles was relatively small and included HCC patients from single studies. Second, although CD133 expression was uniformly detected by immunohistochemical staining method in all studies, the cutoff values of positive CD133 expression were not unified in each study. Third, the HRs of OS and DFS were indirectly extracted from Kaplan-Meier curves and calculated by the methods described by Tierney et al. [40]. Accordingly, the HRs with 95% CI may be less reliable that those obtained directly from assessing analysis of variance. These limitations might have partly influenced the significance of high CD133 expression in clinicopathological features and survival outcome observed in this study.

Table 3 Results of sensitivity analyses

Items	Studies (*n*)	Pooled OR/HR (95% CI)	*P* value	Analytical model
Clinicopathological features				
HBV (negative vs. positive)	7	1.11 (0.86, 1.43)	0.781	FEM
HCV (negative vs. positive)	5	0.81 (0.49, 1.36)	0.939	FEM
Cirrhosis (absent vs. present)	6	1.28 (0.99, 1.67)	0.436	FEM
AFP (≤400 vs. >400 ng/ml)	13	1.16 (0.95. 1.43)	0.976	FEM
Tumor differentiation (I+II vs. III+IV)	20	2.26 (1.59, 3.21)	0.001	REM
Tumor stage (I+II vs. III+IV)	10	2.15 (1.67, 2.78)	0.119	FEM
Tumor number (simple vs. multiple)	5	1.43 (0.80, 2.53)	0.010	REM
Tumor size (≤5 vs. >5 cm)	12	0.99 (0.81, 1.21)	0.946	FEM
Vascular invasion (absent vs. present)	8	2.06 (1.25, 3.38)	0.063	REM
Vascular thrombosis (absent vs. present)	5	1.48 (1.08, 2.02)	0.600	FEM
Encapsulation (absent vs. present)	9	0.80 (0.61, 1.05)	0.219	FEM
Metastasis (absent vs. present)	4	1.53 (0.92, 2.54)	0.392	FEM
Survival outcome				
OS	10	1.57 (1.09, 2.27)	0.000	REM
DFS	5	1.75 (1.40, 2.18)	0.465	FEM

$P<0.05$ was considered to indicate statistically significant differences

HBV hepatitis B virus, *HCV* hepatitis C virus, *AFP* α-fetoprotein, *OS* overall survival, *DFS* disease-free survival, *OR* odds ratio, *HR* hazard ratio, *CI* confidence interval, *FEM* fixed-effects model, *REM* random-effects model

Using CD133 as a biomarker is also limited in terms of predicting clinicopathological significance and prognosis in HCC patients. In addition to CD133, some other cell surface molecules have been considered potential CSC markers in HCC patients, including CD90, CD44, and EpCAM [44, 45]. Ma et al. found that $CD133^{+}ALDH^{+}$ cells were significantly more tumorigenic than $CD133^{+}ALDH^{-}$ or $CD133^{-}ALDH^{-}$ cells both in vitro and in vivo [46]. Zhu et al. suggested that the $CD133^{+}CD44^{+}$ subpopulation might allow a better understanding of HCC initiation and progression and establish a precise target for the development of more effective therapies [47], which was consistent with the conclusion by Zheng et al. [48]. Thus, we speculated that the co-expression of markers for the identification of HCC may be more meaningful and efficient for clinicopathological and prognostic estimation.

In summary, this meta-analysis indicated that CD133 overexpression was significantly associated with several clinicopathological parameters, such as low tumor differentiation, advanced tumor stage, vascular invasion, and vascular thrombosis. However, no correlations were observed between high CD133 expression and hepatitis, cirrhosis, AFP, tumor number, tumor size, encapsulation, or metastasis. Regarding survival outcome, CD133 overexpression was significantly correlated with poor OS and poor DFS. In brief, this meta-analysis indicated that CD133 overexpression is significantly associated with clinicopathological factors and poorer survival outcome. Therefore, CD133 could be considered an important influencing factor of clinical application and prognostic estimation and a potential molecular target for the treatment of HCC patients.

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Conflicts of interest None

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