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Original Article

Prognostic significance of cancer stem cell marker CD133 expression in breast cancer

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Abstract: CD133 has been commonly used as a cancer stem cell (CSC) marker in breast cancer. However, the correlation between CD133 expression, and clinicopathological characteristics and prognosis in breast cancer, remains inconsistent. This study was designed to explore the relationship between CD133 and clinicopathological characteristics, as well as overall survival (OS), through meta-analysis. An electronic search was conducted utilizing the databases of PubMed, Embase, and the Web of Science, up to October 21, 2016. Pooled odds ratios (ORs), and hazard ratios (HRs) with 95% confidence intervals (CIs), were calculated. Publication bias was estimated using Begg's test and Egger's test. A total of 11 studies involving 1447 patients were included in this meta-analysis. The data showed that CD133 expression was correlated with a G3 tumor grade (OR=1.82, 95% CI=1.4-2.36, P<0.001), the presence of lymph node metastasis (OR=2.21, 95% CI=1.75-2.79, P<0.001), negative PR status (OR=0.62, 95% CI=0.47-0.81, P=0.001), negative ER status (OR=0.4, 95% CI=0.19-0.86, P=0.018), advanced TNM stage (OR=2.74, 95% CI=2.05-3.66, P<0.001) and positive HER2 status (OR=2.00, 95% CI=1.04-3.85, P=0.039). Furthermore, CD133 expression was correlated with poor OS (HR=2.04, 95% CI=1.32-3.14, P<0.001). There was no significant publication bias in this meta-analysis. The present meta-analysis demonstrated that CD133 expression was correlated with several clinicopathological characteristics and a poor prognosis. CD133 can be considered as an effective tool for pathological diagnosis and prognostic prediction in breast cancer.

Keywords: Meta-analysis, CD133, breast cancer, risk factors

Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer related death in women worldwide [1]. Breast cancer poses a severe threat to women's health, both in developed countries and in developing countries [1]. Over the past several decades, advances in surgical techniques and targeted therapy for this disease have occurred; however, the prognosis of breast cancer remains unsatisfactory [2]. A variety of prognostic factors, including TNM stage, estrogen receptor (ER) status, and histological grade, are proposed and implemented in clinical practice [3]. Unfortunately, these biomarkers provide limited prognostic value, and lack accuracy. Therefore, more reliable and efficient prognostic factors for breast cancer are required, in order to stratify high-risk populations.

Accumulating evidence demonstrates that cancer stem cells (CSCs) could play important roles in tumor initiation, occurrence, and metastasis [4]. Various markers are commonly used to identify CSCs, such as CD34, CD38, CD44, CD133, and ALDH [4]. CD133, also known as prominin-1, is a trans-membrane glycoprotein expressed in various malignancies, including brain tumors [5], pancreatic cancer [6], non-small cell lung cancer [7], hepatocellular carcinoma [8], and ovarian cancer [9]. In recent years, a number of studies [10-20] also investigated the relationship between CD133 and the prognosis for breast cancer, but the results obtained were inconsistent. Such discrepancies might be due to different research methods, and differences between study populations. Therefore, we performed a quantitative meta-analysis to clarify the relationship between CD133 expression, clinicopathological

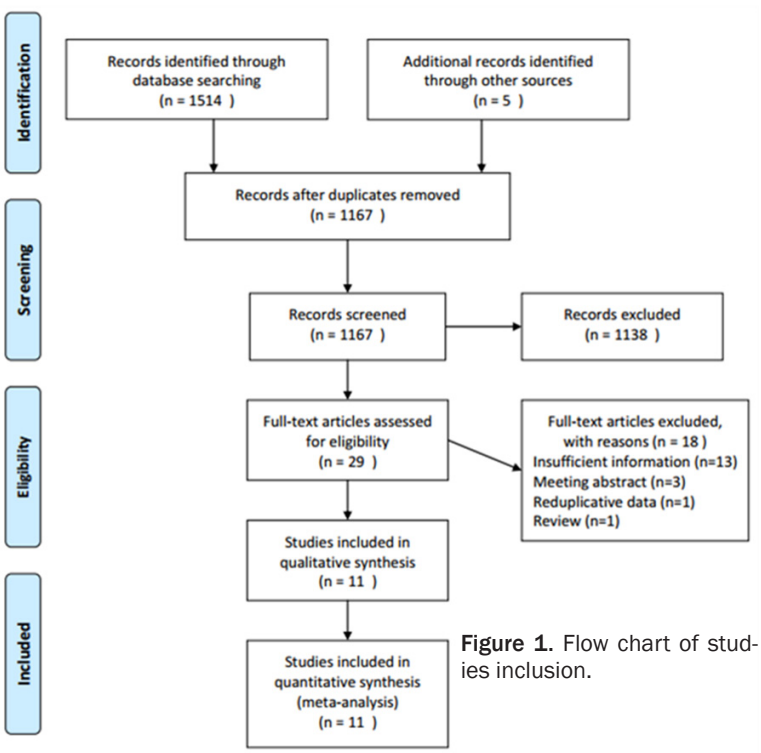


Figure 1. Flow chart of studies inclusion.

characteristics, and the prognosis for breast cancer.

Materials and methods

Literature search

This study was designed and carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21]. The databases of PubMed, Embase, and the Web of Science were thoroughly searched up to October 21, 2016. The following search terms were used: "CD133", "prominin-1", "AC133", "breast cancer", "breast carcinoma", and "breast neoplasms" [MeSH Terms]. Moreover, reference lists of relevant original articles were manually searched for additional studies.

Selection criteria

The inclusion criteria were: (1) the diagnosis of breast cancer was based on pathological examination; (2) CD133 expression was detected using immunohistochemical staining (IHC); (3) studies reported the association between CD133 and overall survival (OS) and/or clinicopathological features, or the data of OS could be calculated using Parmar's method [22]; (4) studies were published in English or Chinese; and (5) if multiple studies were conducted on the same patient population, the most comprehensive study was selected. The exclusion criteria were: (1) studies with insufficient data; (2) reviews, meeting abstracts, case reports, and letters; and (3) duplicated studies.

Quality assessment and data extraction

Quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) [23]. The scale evaluates studies across three dimensions: selection, comparability, and outcome. The maximum score is 9, and studies with a score ≥6 were considered high quality studies. Two researchers (LJH and XBG) independently extracted data from the eligible studies. The extracted data comprised first author, publication year, country, age of patients, sample size, detection method, TNM stage, research period, and percent of samples positive for CD133. Any discrepancies between the two investigators were resolved by discussion with a third investigator (XSG).

Statistical analysis

This meta-analysis was conducted with STATA version 12.0 (StataCorp LP, Texas, USA). $P< 0.05$ was considered as statistically significant. Odds ratios (ORs) with 95% confidence intervals (CIs) were utilized to evaluate the association between CD133 expression and clinicopathological characteristics. The relevant clinicopathological features included tumor grade, lymph node metastasis, tumor size, TNM stage, age, progesterone receptor (PR) status, ER status, and human epidermal growth factor receptor 2 (HER2) status. Hazard ratios (HRs) and 95% CIs of OS were used to evaluate pooled HR. If HR and 95% CI were not reported in the text, then they were calculated from Kaplan-Meier curves, according to the method intro-

Table 1. Characteristics of 11 included studies

Study	Year	Region	Age mean (range)	No. of patients	Detection method	TNM stage	CD133+ (%)	Research period	NOS score
Liu	2009	China	49 (28-71)	74	IHC	I-III	52.7	2004	7
Ieni	2011	Italy	61.8 (41-85)	49	IHC	I-II	34.7	1998-2007	8
Liu	2011	China	NR	121	IHC	I-IV	74.4	2006-2008	7
Zhao	2011	China	47 (25-92)	67	IHC	I-III	43.4	2003-2008	7
Aomatsu	2012	Japan	55 (26-78)	102	IHC	II-III	46.1	2004-2009	8
Currie	2013	New Zealand	NR	89	IHC	NR	25	2003-2005	6
Collina	2015	Italy	57 (24-93)	160	IHC	I-IV	18.8	2003-2009	8
Han	2015	China	45.6 (21-74)	325	IHC	I-IV	48.6	2004-2008	8
Kim	2015	Korea	49 (25-85)	291	IHC	I-III	24.7	2005-2010	7
Lin	2015	Taiwan	52.4	49	IHC	NR	30.6	2001-2013	6
Mansour	2015	Egypt	49.1 (28-70)	120	IHC	I-III	53.3	2006-2013	7

NR: not reported; IHC: immunohistochemical staining; NOS: Newcastle-Ottawa Scale.

duced by Parmar [22]. Heterogeneity between studies was assessed using the I^2 test and Cochran's Q test. If I^2 was >50% or the result of the Q test gave a *P*-value of <0.1, indicating significant heterogeneity, the random-effect model was conducted; otherwise, the fixed-effect model was adopted. Publication bias was assessed using Begg's test and Egger's test.

Results

Search results

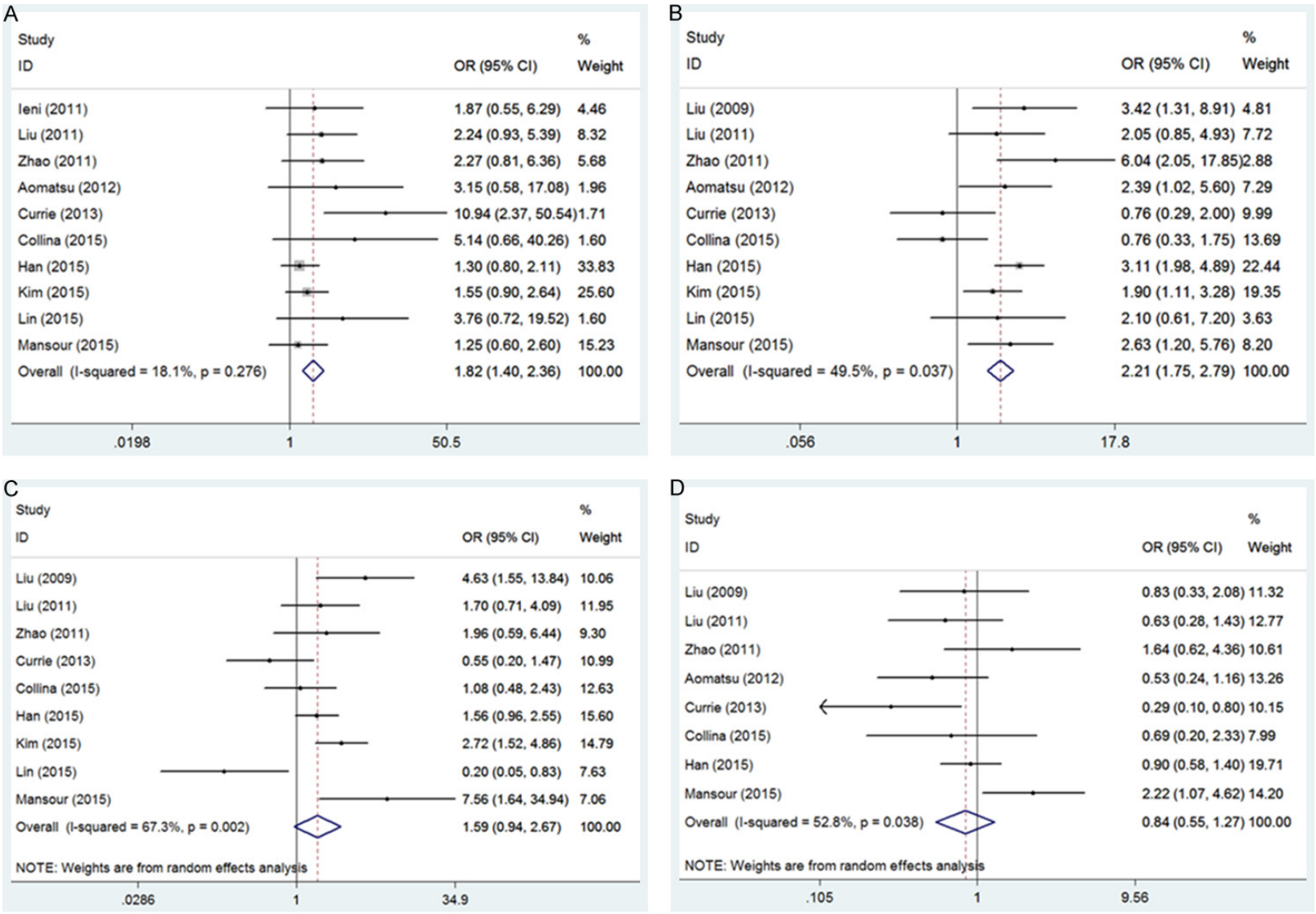
The process of study selection is detailed in **Figure 1**. A total of 1514 records from database searches and 5 records from other sources were identified. After duplicate records were removed, 1167 records were screened by inspection of title and/or abstract. On this basis, 1138 records were excluded, and 29 full-text studies were evaluated for eligibility. Eighteen studies were further excluded for the following reasons: 13 studies provided insufficient data, 3 studies were meeting abstracts, 1 study presented duplicate data, and 1 study was a review. Finally, 11 studies [10-20] were included in the meta-analysis.

Characteristics of included studies

The characteristics of the included studies are shown in **Table 1**. The included studies were published from 2009 to 2015. The total number of samples was 1447, ranging from 49 to 325 per study. Ten studies [10, 11, 13-20] were in English and one [12] was in Chinese. Seven studies [10, 12-14, 17-19] were performed in Asia, two [11, 16] were conducted in Europe, one [15] was carried out in Oceania and one [20] was conducted in Africa. All studies used IHC to detect CD133 expression, and the percentage of positive CD133 expression varied from 18.8% to 74.4%. All 11 studies [10-20] reported an association between CD133 and clinicopathological features, and 4 studies [13, 14, 17, 18] reported a correlation between CD133 and OS. The NOS scores of the included studies ranged from 6 to 8, indicating that all eligible studies were high quality studies.

Correlation of CD133 expression with clinicopathological factors

The relationship between CD133 expression and 8 clinicopathological factors was investigated. These 8 factors were; tumor grade (G3 vs. G1+G2), lymph node metastasis (positive vs. negative), tumor size (≥2 cm vs. <2 cm), age (≥50 years vs. <50 years), PR status (positive vs. negative), ER status (positive vs. negative), TNM stage (III+IV vs. I+II), and HER2 status (positive vs. negative). As shown in **Figure 2** and **Table 2**, CD133 overexpression was associated with G3 tumor grade (OR=1.82, 95% CI=1.4-2.36, P<0.001), presence of lymph node metastasis (OR=2.21, 95% CI=1.75-2.79, P<0.001), negative PR status (OR=0.62, 95% CI=0.47-0.81, P=0.001), negative ER status (OR=0.4, 95% CI=0.19-0.86, P=0.018), advanced TNM stage (OR=2.74, 95% CI=2.05-3.66, P<0.001), and positive HER2 status (OR=2.00, 95% CI=1.04-3.85, P=0.039). However, there was no significant correlation between CD133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Study
ID
OR (95% CI)
%
Weight
Ieni (2011) 1.87 (0.55, 6.29) 4.46
Liu (2011) 2.24 (0.93, 5.39) 8.32
Zhao (2011) 2.27 (0.81, 6.36) 5.68
Aomatsu (2012) 3.15 (0.58, 17.08) 1.96
Currie (2013) 10.94 (2.37, 50.54) 1.71
Collina (2015) 5.14 (0.66, 40.26) 1.60
Han (2015) 1.30 (0.80, 2.11) 33.83
Kim (2015) 1.55 (0.90, 2.64) 25.60
Lin (2015) 3.76 (0.72, 19.52) 1.60
Mansour (2015) 1.25 (0.60, 2.60) 15.23
Overall (I-squared = 18.1%, p = 0.276) 1.82 (1.40, 2.36) 100.00
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1
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Study
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OR (95% CI)
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Weight
Liu (2009) 3.42 (1.31, 8.91) 4.81
Liu (2011) 2.05 (0.85, 4.93) 7.72
Zhao (2011) 6.04 (2.05, 17.85) 2.88
Aomatsu (2012) 2.39 (1.02, 5.60) 7.29
Currie (2013) 0.76 (0.29, 2.00) 9.99
Collina (2015) 0.76 (0.33, 1.75) 13.69
Han (2015) 3.11 (1.98, 4.89) 22.44
Kim (2015) 1.90 (1.11, 3.28) 19.35
Lin (2015) 2.10 (0.61, 7.20) 3.63
Mansour (2015) 2.63 (1.20, 5.76) 8.20
Overall (I-squared = 49.5%, p = 0.037) 2.21 (1.75, 2.79) 100.00
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1
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Study
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OR (95% CI)
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Weight
Liu (2009) 4.63 (1.55, 13.84) 10.06
Liu (2011) 1.70 (0.71, 4.09) 11.95
Zhao (2011) 1.96 (0.59, 6.44) 9.30
Currie (2013) 0.55 (0.20, 1.47) 10.99
Collina (2015) 1.08 (0.48, 2.43) 12.63
Han (2015) 1.56 (0.96, 2.55) 15.60
Kim (2015) 2.72 (1.52, 4.86) 14.79
Lin (2015) 0.20 (0.05, 0.83) 7.63
Mansour (2015) 7.56 (1.64, 34.94) 7.06
Overall (I-squared = 67.3%, p = 0.002) 1.59 (0.94, 2.67) 100.00
NOTE: Weights are from random effects analysis
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Study
ID
OR (95% CI)
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Weight
Liu (2009) 0.83 (0.33, 2.08) 11.32
Liu (2011) 0.63 (0.28, 1.43) 12.77
Zhao (2011) 1.64 (0.62, 4.36) 10.61
Aomatsu (2012) 0.53 (0.24, 1.16) 13.26
Currie (2013) 0.29 (0.10, 0.80) 10.15
Collina (2015) 0.69 (0.20, 2.33) 7.99
Han (2015) 0.90 (0.58, 1.40) 19.71
Mansour (2015) 2.22 (1.07, 4.62) 14.20
Overall (I-squared = 52.8%, p = 0.038) 0.84 (0.55, 1.27) 100.00
NOTE: Weights are from random effects analysis
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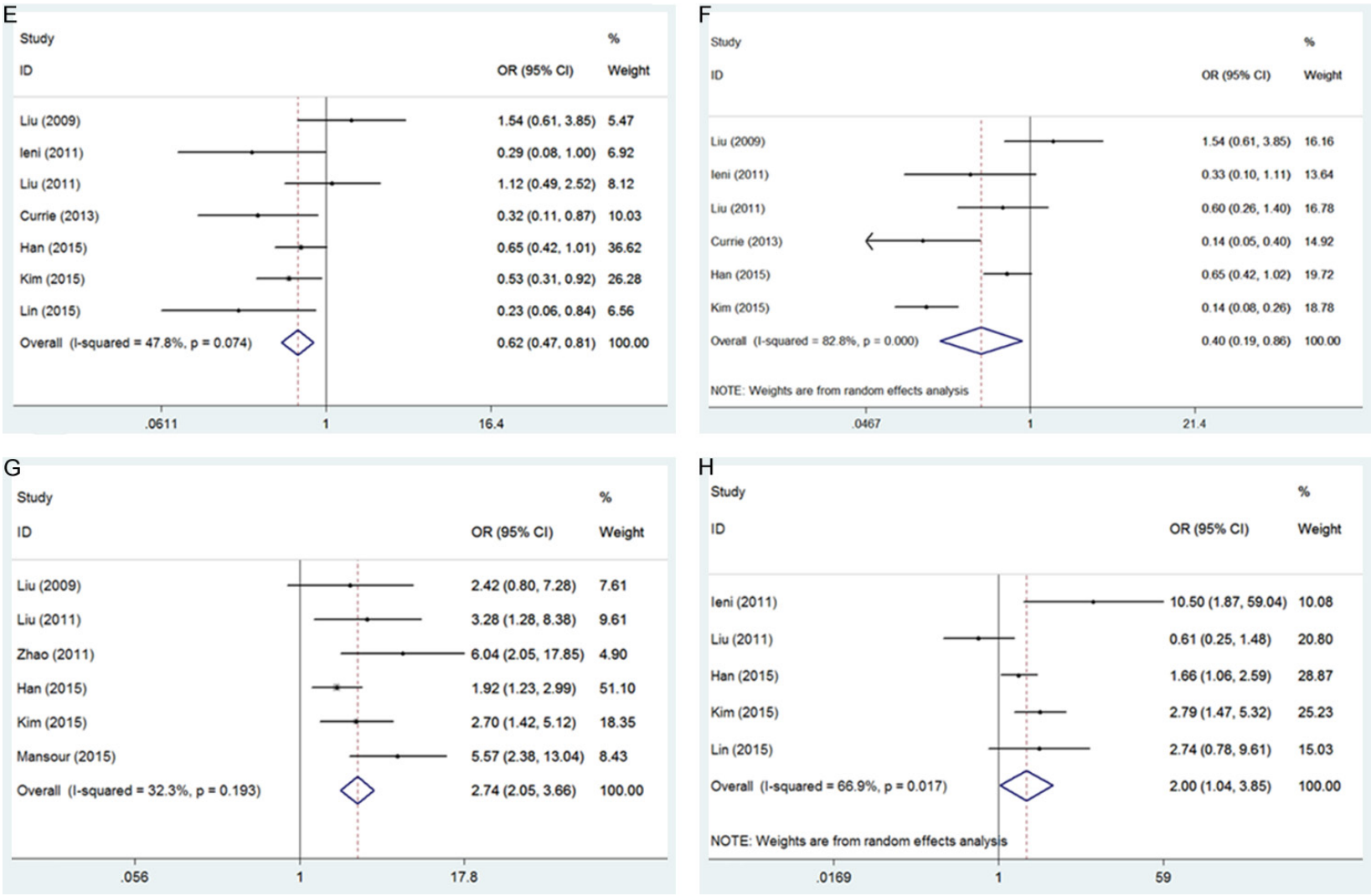

Figure 2. Forrest plot of ORs for the relation of CD133 expression with (A) tumor grade, (B) lymph node metastasis, (C) tumor size, (D) age, (E) PR status, (F) ER status, (G) TNM stage, and (H) HER2 status in breast cancer.

Table 2. Association between CD133 expression and clinicopathological features in breast cancer

Factors	No. of studies	Effects model	OR (95% CI)	p	Heterogeneity	
					I^2 (%)	P_h
Tumor grade (G3 vs. G1+G2)	10	Fixed	1.82 (1.4-2.36)	<0.001	18.1	0.276
Lymph node metastasis (positive vs. negative)	10	Fixed	2.21 (1.75-2.79)	<0.001	49.5	0.037
Tumor size (≥2 cm vs. <2 cm)	9	Random	1.59 (0.94-2.67)	0.083	67.3	0.002
Age (≥50 years vs. <50 years)	8	Random	0.84 (0.55-1.27)	0.41	52.8	0.038
PR status (positive vs. negative)	7	Fixed	0.62 (0.47-0.81)	0.001	47.8	0.074
ER status (positive vs. negative)	6	Random	0.4 (0.19-0.86)	0.018	82.8	<0.001
TNM stage (III+IV vs. I+II)	6	Fixed	2.74 (2.05-3.66)	<0.001	32.3	0.193
HER2 status (positive vs. negative)	5	Random	2.00 (1.04-3.85)	0.039	66.9	0.017

PR: progesterone receptor; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2.

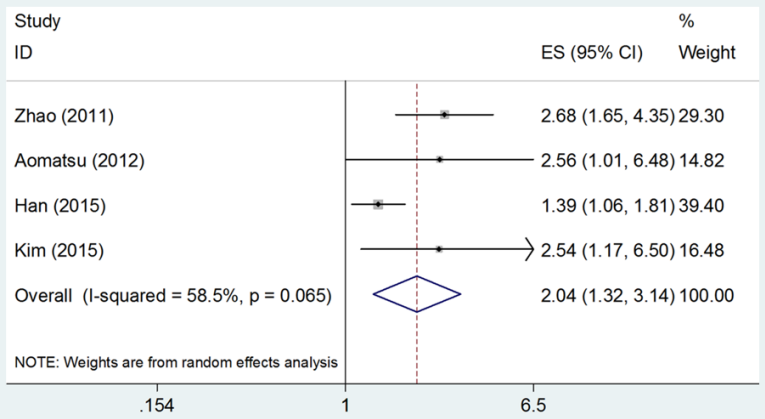

Figure 3. Forrest plot of HR for the relation of CD133 expression with OS in breast cancer.

expression and tumor size (P=0.083) or age (P=0.41).

Relationship between CD133 expression and OS

Four studies [13, 14, 17, 18] investigated the impact of CD133 expression on OS. Since significant heterogeneity was found (I^2=58.5%, P=0.065), a random-effect model was used. The meta-analysis results demonstrated that CD133 overexpression was significantly associated with poor OS (HR=2.04, 95% CI=1.32-3.14, P<0.001) (**Figure 3**).

Publication bias

Begg's rank correlation test and Egger's regression test were used to examine potential publication bias in our meta-analysis. The results were P=1 for Begg's test, and P=0.186 for Egger's test, for OS analysis (**Figure 4**). These results showed that there was no evidence of significant publication bias existing in this meta-analysis.

Discussion

Breast cancer is the most common cancer in women. Breast cancer is complex, and patients often have different responses and clinical outcomes following treatment. CD133 expression was found to be correlated with survival outcomes in breast cancer, but the results were inconsistent. In the current study, we extracted relevant data from 11 eligible studies to perform a meta-analysis. The results showed that CD133 expression was associated with a higher tumor grade, occurrence of lymph node metastasis, negative PR status, negative ER status, advanced TNM stage, and positive HER2 status. With respect to the association between CD133 expression and OS, the data showed that CD133 overexpression was an indicator of a poorer OS (HR=2.04, 95% CI=1.32-3.14, P<0.001). Taken together, this meta-analysis demonstrated that CD133 expression is a potential marker for a panel of clinicopathological factors and linked to a poor prognosis for breast cancer.

CD133 is a commonly used cell surface marker of CSCs in a wide spectrum of cancers [4]. CD133 is expressed in normal tissues, including hematopoietic stem and progenitor cells [24], fetal neural stem cells [25], renal stem cells [26], and prostate stem cells [27]. Furthermore, CD133 is also used as a marker

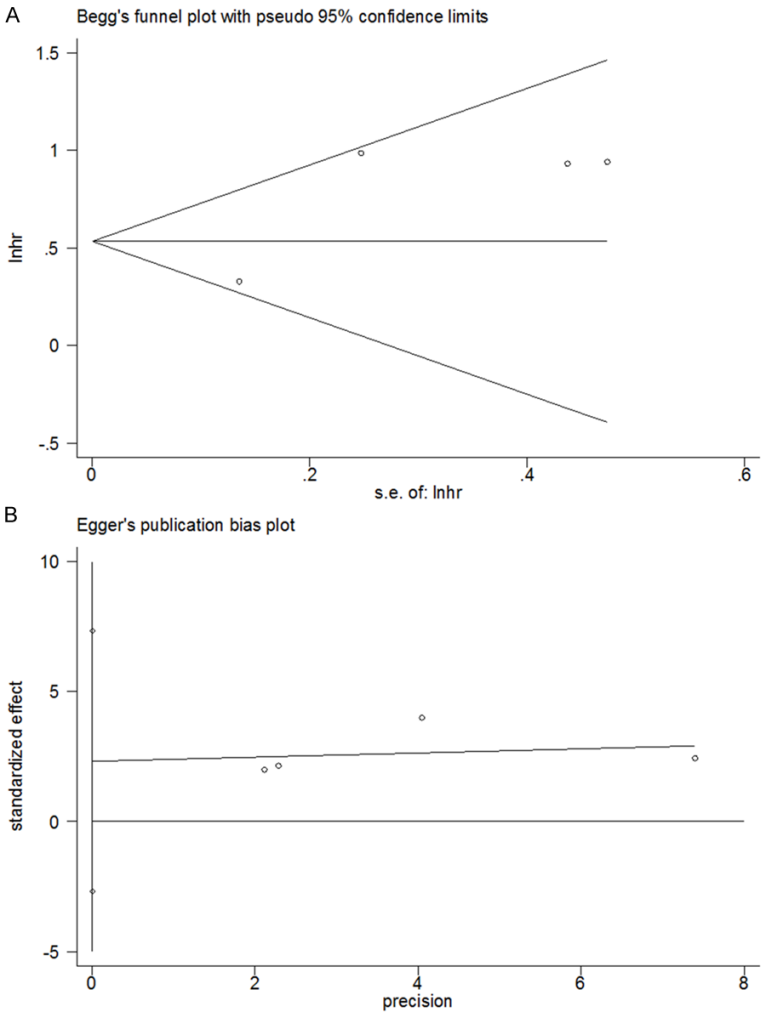

Figure 4. (A) Begg's funnel plot and (B) Egger's regression asymmetry plot for CD133 overexpression and OS.

for CSC isolation in a variety of malignant tumors [28-30]. CD133 is a cell surface glycoprotein whose expression decreases with cellular differentiation. A number of studies have demonstrated that CD133+ cells possess CSC properties, including greater colony-forming efficiency, self-renewal capacity, and higher tumorigenicity in xenografts [31, 32]. Although the normal function of CD133 remains unclear, CD133 has been investigated for use as a prognostic biomarker in a range of different cancers. We also noted that several meta-analysis studies have investigated the prognostic role of CD133 in different cancers, including ovarian cancer [33], glioma [34], gastric cancer [35], esophageal carcinoma [36], colorectal cancer [37], and renal cell carcinoma [38]. The results from other cancer types showed that CD133 overexpression was correlated with poor survival outcomes, which was consistent with our results. Furthermore, there has to date been no meta-analysis investigating the prognostic value of CD133 in breast cancer. To the best of our knowledge, this meta-analysis is the first study to comprehensively and systematically evaluate the association between CD133 expression and prognosis in breast cancer.

Several limitations of this meta-analysis also need to be acknowledged. First, the number of studies included and total sample size were relatively small. Furthermore, only 4 studies were included for OS analysis. Although other studies reported the survival information, HR and 95% CI could not be extracted from the available data. Secondly, most studies (7 of 11) were conducted in Asia, which may introduce selection bias.

In summary, this study demonstrated that CD133 overexpression was associated with higher tumor grade, occurrence of lymph node metastasis, negative PR status, negative ER status, advanced TNM stage, positive HER2 status, and poor OS, in breast cancer. CD133 may be considered a useful tool for pathological diagnosis and prognostic prediction in breast cancer. Owing to the aforementioned limitations, further large-scale studies, recruiting populations of various ethnicities, are needed to confirm our results.

Disclosure of conflict of interest

None.

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References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Lin SX, Chen J, Mazumdar M, Poirier D, Wang C, Azzi A and Zhou M. Molecular therapy of breast cancer: progress and future directions. Nat Rev Endocrinol 2010; 6: 485-493.

[3] Rakha EA, Reis-Filho JS and Ellis IO. Combinatorial biomarker expression in breast cancer. Breast Cancer Res Treat 2010; 120: 293-308.

[4] Pattabiraman DR and Weinberg RA. Tackling the cancer stem cells-what challenges do they pose? Nat Rev Drug Discov 2014; 13: 497-512.

[5] Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkelman RM, Cusimano MD and Dirks PB. Identification of human brain tumour initiating cells. Nature 2004; 432: 396-401.

[6] Chen K, Li Z, Jiang P, Zhang X, Zhang Y, Jiang Y, He Y and Li X. Co-expression of CD133, CD44v6 and human tissue factor is associated with metastasis and poor prognosis in pancreatic carcinoma. Oncol Rep 2014; 32: 755-763.

[7] Herpel E, Jensen K, Muley T, Warth A, Schnabel PA, Meister M, Herth FJ, Dienemann H, Thomas M and Gottschling S. The cancer stem cell antigens CD133, BCRP1/ABCG2 and CD117/c-KIT are not associated with prognosis in resected early-stage non-small cell lung cancer. Anticancer Res 2011; 31: 4491-4500.

[8] Yilmaz G, Akyol G, Cakir A and Ilhan M. Investigation of diagnostic utility and expression profiles of stem cell markers (CD133 and CD90) in hepatocellular carcinoma, small cell dysplasia, and cirrhosis. Pathol Res Pract 2014; 210: 419-425.

[9] Zhang J, Guo X, Chang DY, Rosen DG, Mercado-Uribe I and Liu J. CD133 expression associated with poor prognosis in ovarian cancer. Mod Pathol 2012; 25: 456-464.

[10] Liu Q, Li JG, Zheng XY, Jin F and Dong HT. Expression of CD133, PAX2, ESA, and GPR30 in invasive ductal breast carcinomas. Chin Med J (Engl) 2009; 122: 2763-2769.

[11] Ieni A, Giuffre G, Adamo V and Tuccari G. Prognostic impact of CD133 immunoexpression in node-negative invasive breast carcinomas. Anticancer Res 2011; 31: 1315-1320.

[12] Liu T, Li X, Wang L, Chen Y, Pan X, Song S, Yang L, Cui J and Yang J. Distribution and clinicopathologic significance of CD133+ cells in benign and malignant breast lesions. Chin J Clin Oncol 2011; 38: 1196-1200.

[13] Zhao P, Lu Y, Jiang X and Li X. Clinicopathological significance and prognostic value of CD133 expression in triple-negative breast carcinoma. Cancer Sci 2011; 102: 1107-1111.

[14] Aomatsu N, Yashiro M, Kashiwagi S, Takashima T, Ishikawa T, Ohsawa M, Wakasa K and Hirakawa K. CD133 is a useful surrogate marker for predicting chemosensitivity to neoadjuvant chemotherapy in breast cancer. PLoS One 2012; 7: e45865.

[15] Currie MJ, Beardsley BE, Harris GC, Gunningham SP, Dachs GU, Dijkstra B, Morrin HR, Wells JE and Robinson BA. Immunohistochemical analysis of cancer stem cell markers in invasive breast carcinoma and associated ductal carcinoma in situ: relationships with markers of tumor hypoxia and microvascularity. Hum Pathol 2013; 44: 402-411.

[16] Collina F, Di Bonito M, Li Bergolis V, De Laurentiis M, Vitagliano C, Cerrone M, Nuzzo F, Cantile M and Botti G. Prognostic value of cancer stem cells markers in triple-negative breast cancer. Biomed Res Int 2015; 2015: 158682.

[17] Han Z, Chen Z, Zheng R, Cheng Z, Gong X and Wang D. Clinicopathological significance of CD133 and CD44 expression in infiltrating ductal carcinoma and their relationship to angiogenesis. World J Surg Oncol 2015; 13: 56.

[18] Kim SJ, Kim YS, Jang ED, Seo KJ and Kim JS. Prognostic impact and clinicopathological correlation of CD133 and ALDH1 expression in invasive breast cancer. J Breast Cancer 2015; 18: 347-355.

[19] Lin CH, Liu CH, Wen CH, Ko PL and Chai CY. Differential CD133 expression distinguishes malignant from benign papillary lesions of the breast. Virchows Arch 2015; 466: 177-184.

[20] Mansour SF and Atwa MM. Clinicopathological significance of CD133 and ALDH1 cancer stem cell marker expression in invasive ductal breast carcinoma. Asian Pac J Cancer Prev 2015; 16: 7491-7496.

[21] Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264-269, w264.

[22] Parmar MK, Torri V and Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998; 17: 2815-2834.

[23] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-605.

[24] Buhring HJ, Seiffert M, Bock TA, Scheding S, Thiel A, Scheffold A, Kanz L and Brugger W. Expression of novel surface antigens on early hematopoietic cells. Ann N Y Acad Sci 1999; 872: 25-38; discussion 38-29.

[25] Uchida N, Buck DW, He D, Reitsma MJ, Masek M, Phan TV, Tsukamoto AS, Gage FH and Weissman IL. Direct isolation of human central nervous system stem cells. Proc Natl Acad Sci U S A 2000; 97: 14720-14725.
[26] Bussolati B, Bruno S, Grange C, Buttiglieri S, Deregibus MC, Cantino D and Camussi G. Isolation of renal progenitor cells from adult human kidney. Am J Pathol 2005; 166: 545-555.
[27] Richardson GD, Robson CN, Lang SH, Neal DE, Maitland NJ and Collins AT. CD133, a novel marker for human prostatic epithelial stem cells. J Cell Sci 2004; 117: 3539-3545.
[28] Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, Squire J and Dirks PB. Identification of a cancer stem cell in human brain tumors. Cancer Res 2003; 63: 5821-5828.
[29] Hermann PC, Huber SL, Herrler T, Aicher A, Ellwart JW, Guba M, Bruns CJ and Heeschen C. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. Cell Stem Cell 2007; 1: 313-323.
[30] Collins AT, Berry PA, Hyde C, Stower MJ and Maitland NJ. Prospective identification of tumorigenic prostate cancer stem cells. Cancer Res 2005; 65: 10946-10951.
[31] Wright MH, Calcagno AM, Salcido CD, Carlson MD, Ambudkar SV and Varticovski L. Brca1 breast tumors contain distinct CD44+/CD24- and CD133+ cells with cancer stem cell characteristics. Breast Cancer Res 2008; 10: R10.
[32] Schmitt F, Ricardo S, Vieira AF, Dionisio MR and Paredes J. Cancer stem cell markers in breast neoplasias: their relevance and distribution in distinct molecular subtypes. Virchows Arch 2012; 460: 545-553.
[33] Zhou Q, Chen A, Song H, Tao J, Yang H and Zuo M. Prognostic value of cancer stem cell marker CD133 in ovarian cancer: a meta-analysis. Int J Clin Exp Med 2015; 8: 3080-3088.
[34] Han M, Guo L, Zhang Y, Huang B, Chen A, Chen W, Liu X, Sun S, Wang K, Liu A and Li X. Clinicopathological and prognostic significance of CD133 in glioma patients: a meta-analysis. Mol Neurobiol 2016; 53: 720-727.
[35] Wen L, Chen XZ, Yang K, Chen ZX, Zhang B, Chen JP, Zhou ZG, Mo XM and Hu JK. Prognostic value of cancer stem cell marker CD133 expression in gastric cancer: a systematic review. PLoS One 2013; 8: e59154.
[36] Sui YP, Jian XP, Ma LI, Xu GZ, Liao HW, Liu YP and Wen HC. Prognostic value of cancer stem cell marker CD133 expression in esophageal carcinoma: a meta-analysis. Mol Clin Oncol 2016; 4: 77-82.
[37] Zhao Y, Peng J, Zhang E, Jiang N, Li J, Zhang Q, Zhang X and Niu Y. CD133 expression may be useful as a prognostic indicator in colorectal cancer, a tool for optimizing therapy and supportive evidence for the cancer stem cell hypothesis: a meta-analysis. Oncotarget 2016; 7: 10023-10036.
[38] Cheng B, Yang G, Jiang R, Cheng Y, Yang H, Pei L and Qiu X. Cancer stem cell markers predict a poor prognosis in renal cell carcinoma: a meta-analysis. Oncotarget 2016; 7: 65862-65875.