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Review Article

Clinicopathological and prognostic significance of cd133 in esophageal cancer: a meta-analysis

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Abstract: Objective: CD133 has been recognized as a marker of cancer stem-like cells in esophageal cancer. However, its promising value still remains controversial. Therefore, we performed a meta-analysis to evaluate the association between the expression of CD133 and clinicopathological features and the prognosis of esophageal cancer. Methods: A systematic literature search for relevant articles published from 2010 to 2015 was conducted in PubMed, Embase and Cochrane databases. Electronic searches were conducted by hand searching reference lists, abstracts and conferences. Outcomes included clinicopathological features. Publication bias was assessed by the funnel plots, and heterogeneity and sensitivity were analyzed as well. Results: Seven articles with a total of 538 patients were subjected to the final analysis. High expression of CD133 was associated with lymph node metastasis, clinical stage and histopathological grade cases, leading to a risk difference of 1.75 (95% CI 1.17-2.61), 1.91 (95% CI 1.08-3.38) and 1.55 (95% CI 1.11-2.18), respectively. And there was no statistically significant association of CD133 with depth of invasion (OR=1.24, 95% CI: 0.53-2.92). Conclusion: This study indicated that CD133 could be recommended as a useful prognostic factor in esophageal cancer. Higher CD133 expression is significantly associated with lymph node metastasis, distant metastasis and clinical stage. More well-designed prospective studies are needed to confirm the findings.

Keywords: CD133, cancer stem cell, esophageal cancer, meta-analysis

Introduction

As of 2012, esophageal cancer is the eighth-most common cancer globally with 456,000 new cases during the year [1]. It caused about 400,000 deaths that year, up from 345,000 in 1990 [1]. Rates vary widely among countries, with about half of all cases occurring in China. It is around three times more common in men than in women [1]. In the near decades, its incidence, diagnostic options and therapeutic therapies have undergone significant changes, but the prognosis for esophageal cancer patients remains poor, especially in more advanced stages.

Previous work showed that only CSCs could reconstitute tumors with similar histopathological characteristics to the primary cancer, whereas non-stem cancer cells failed to effect tumor initiation. And, CSCs are believed to play a key role in resistance to chemotherapy and radiotherapy [2, 3]. This new paradigm has promising implications for cancer therapy, as our recently available therapies are more successful at eradicating non-cancer stem cells rather than cancer stem cells [4, 5]. In other words, identification and characterization of CSCs could lead to development of directed and more effective treatments for cancer [6].

Recently, several cell surface markers have been identified as stem cell markers in esophageal cancer. Among these markers, CD133 is believed to be the most robust surface marker for cancer stem cells by now. CD133 molecule (also known as prominin-1) is a five transmembrane glycoproteins with a molecular weight of 120 kDa and it is shown to be mainly localized in membrane protrusions [7].

Thus, based on current evidences, we performed a meta-analysis to determine the association between CSCs marker CD133 and the

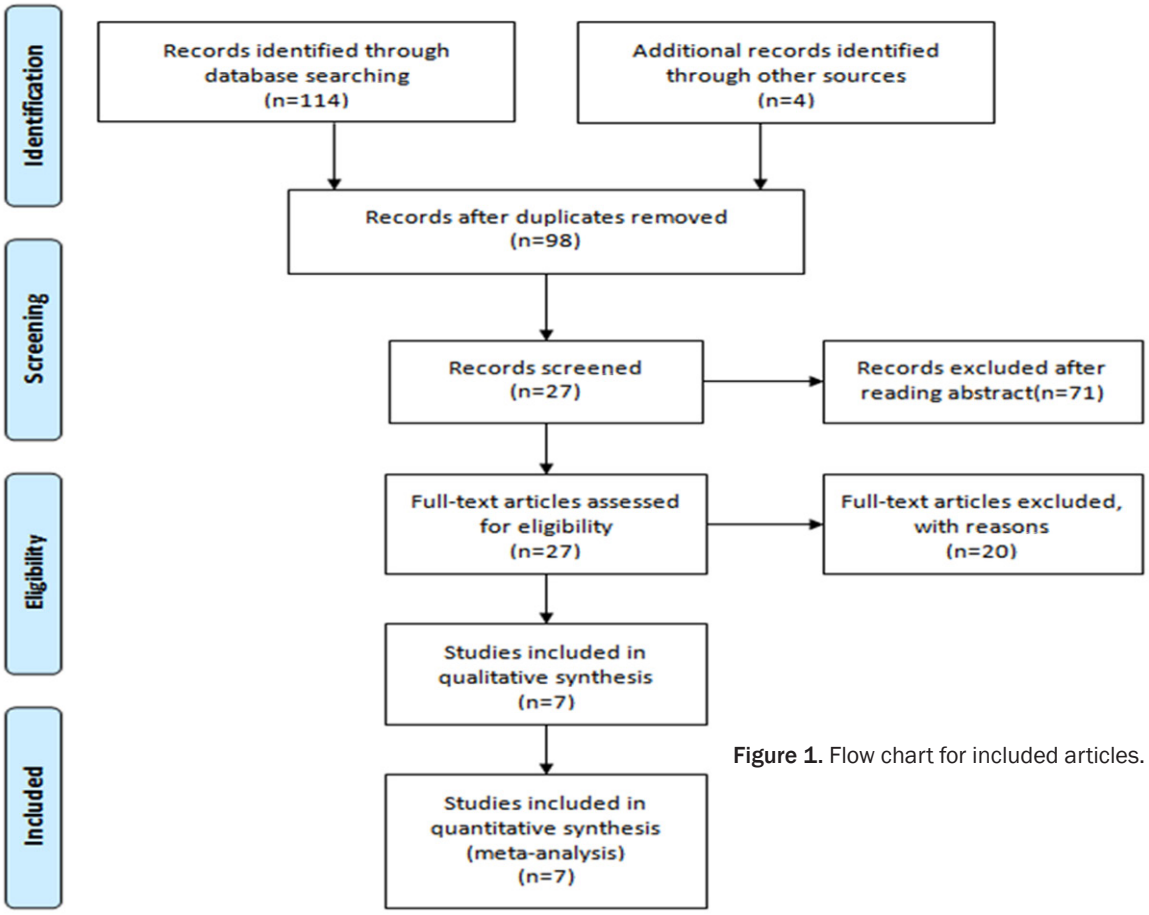

Figure 1. Flow chart for included articles.

clinicopathological characteristics of esophageal cancer and to investigate the roles of CD133 in the prognostic value.

Methods

Literature search

We searched PUBMED, EMBASE and Cochrane Library digital databases for all relevant articles. The search was performed in each database by two independent investigators. The medical subject headings (MeSH) and keywords collected for individually and in combination were as follows: ('esophageal cancer' 'cancer' or 'esophageal adenocarcinoma') AND ('cancer stem cell' or 'neoplastic stem cells) AND ('CD-133' or 'prominin-1' or 'AC133'). No language restrictions were imposed. The reference lists in all identified articles were checked for further relevant articles.

Study selection

Eligibility of studies for inclusion was assessed independently by two investigators. Studies were eligible for inclusion if all the following criteria were fulfilled: (1) Diagnosis of esophageal cancer was proven by histopathologic analysis. (2) CD133 expression should be evaluated in primary esophageal cancer tissue. (3) Articles were published as original research. Reviews, comments, and letters were excluded.

Data extraction

Data was extracted by two of the authors independently using the same standardized form. The fields extracted included first author, year of publication, country of origin, number of patients, research techniques, tumor stage, histopathological type and tumor location. For the articles with the same population resources or overlapping data sets, the paper which included the largest population or contained more useful information was included. If some articles revealed the prognosis of esophageal cancer only by Kaplan-Meier curve, the software Engauge Digitizer 4.1 (http://sourceforge.net/projects/digitizer/) was utilized to extract the relevant data.

Table 1. Characteristics of included studies

First author	Year of publication	Country	Tumor stage (TNM)	Median age (years)	Histopatho-logical type	Tech-nique	No. of patients	Site
Yang [8]	2010	China	I-IV	52.8	SCC	IHC	90	Esophagus or bone
Cao [9]	2009	China	II-III	54.3	SCC	IHC	68	Esophagus or bone
Fei [10]	2011	China	I-IV	55.4	SCC	IHC	90	Esophagus or liver
Feng [11]	2014	China	I-IV	68.8	SCC	IHC	28	Esophagus or bone
Wang [12]	2014	China	I-IV	69	SCC	IHC	40	Esophagus or brain
Okamoto [13]	2013	Japan	I-IV	56.1	SCC	IHC	86	Esophagus or brain
Peng [14]	2012	China	III	58	SCC	IHC	136	Esophagus or liver

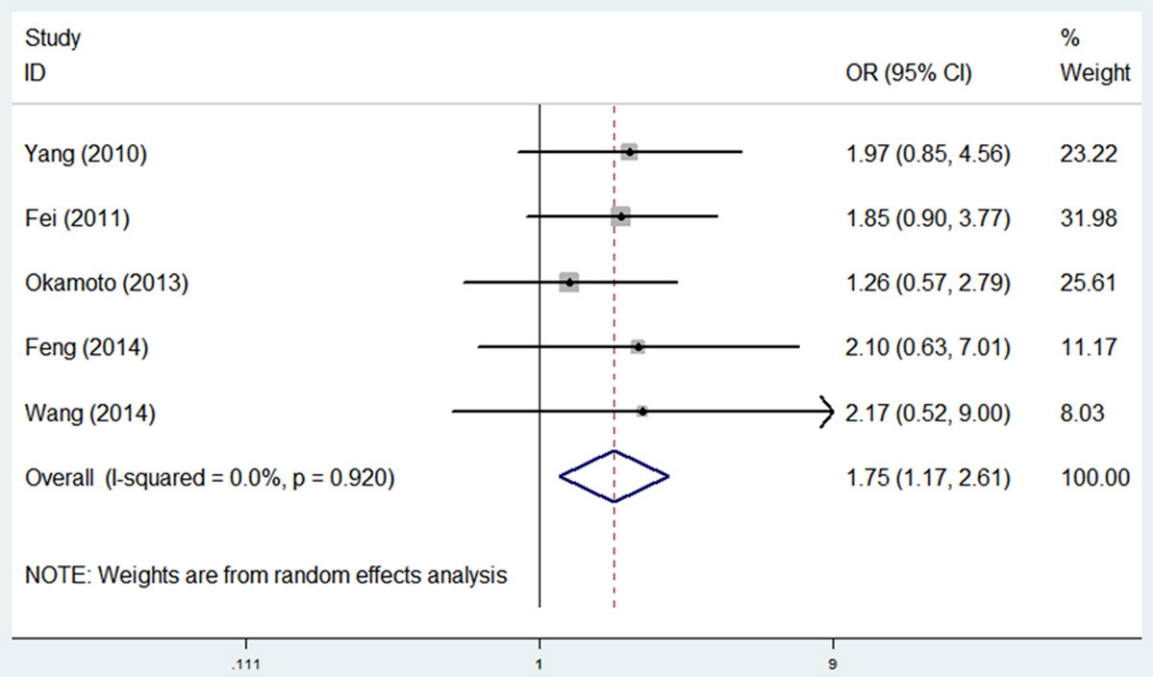

Figure 2. Forest plots of ORs for CD133 and lymph node metastasis.

Statistical analysis

Statistical calculations were all performed using STATA version 13.0. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the association between the expression of the stem cell marker CD133 and the clinicopathological parameters of esophageal carcinoma. Statistical heterogeneity between studies was assessed with the chi-square statistic and quantified by I^2, a statistic that represents the percentage of total variation contributed by between-study variation. If the Q test showed a $P < 0.05$ or the I^2 test exhibited > 50%, indicating significant heterogeneity between studies, the random-effect model was conducted, or the fixed-effect model was used. Publication bias was examined by using the Begg rank correlation method and the Egger weighted regression method.

Results

Study selection and characteristics

Detailed search steps were described in **Figure 1**. The initial search algorithm retrieved a total of 118 studies according to the inclusion criteria stated above. After titles and abstracts were previewed, only 27 identified studies concerning CD133 and the risk of esophageal cancer were further evaluated. After the removal of all studies that did not meet our criteria, 7 studies

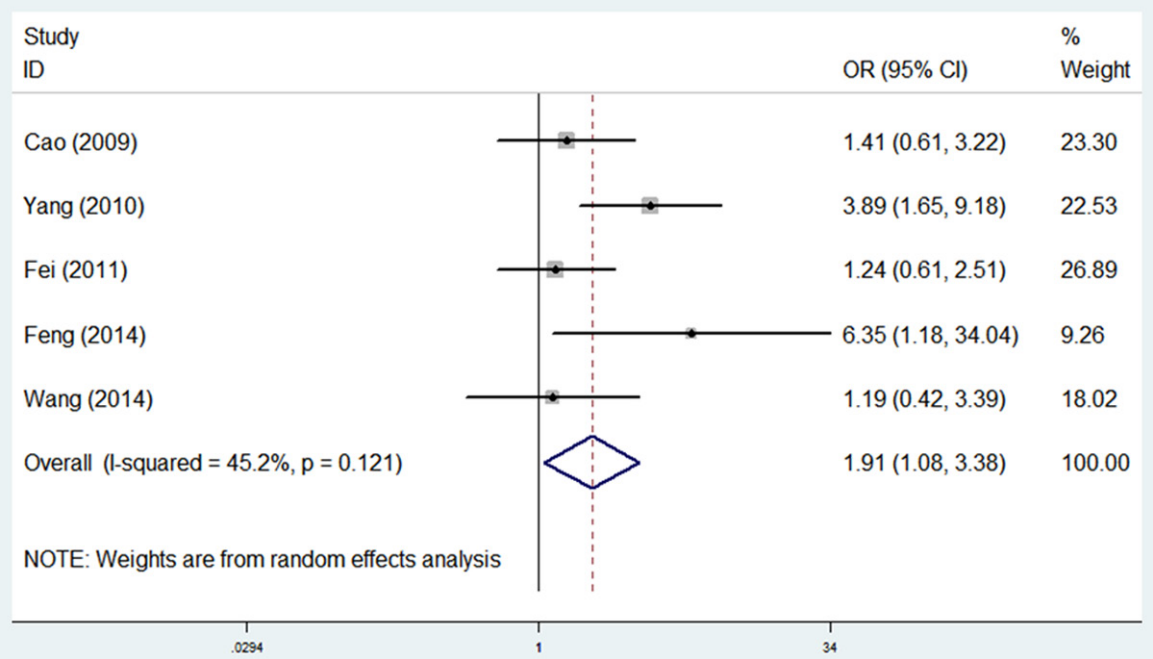

Figure 3. Forest plot of ORs for CD133 and clinical stage.

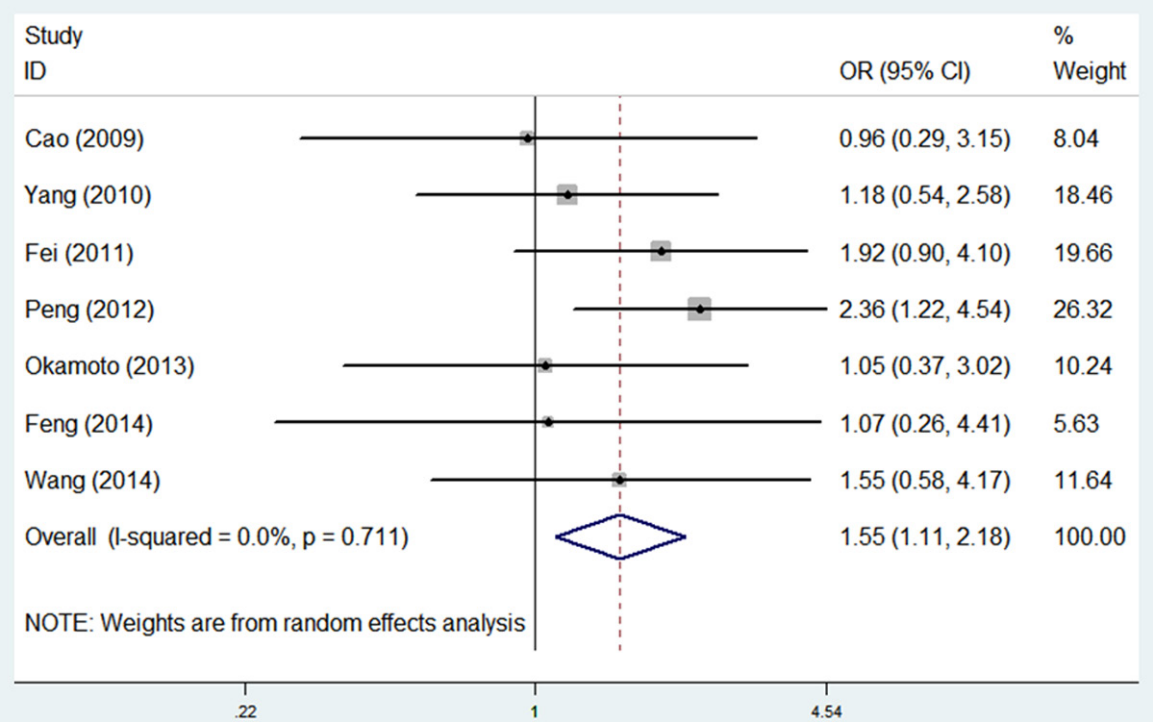

Figure 4. Forest plot of ORs for CD133 and histopathological grade.

[8-14] from 118 publications were finally included in our meta-analysis. The useable data and main characteristics of each article are summarized in **Table 1**. Included articles were published in the period 2010-2014. All the studies were conducted in Asian population, 6 from China, and 1 from Japan. A total of 538 patients were included.

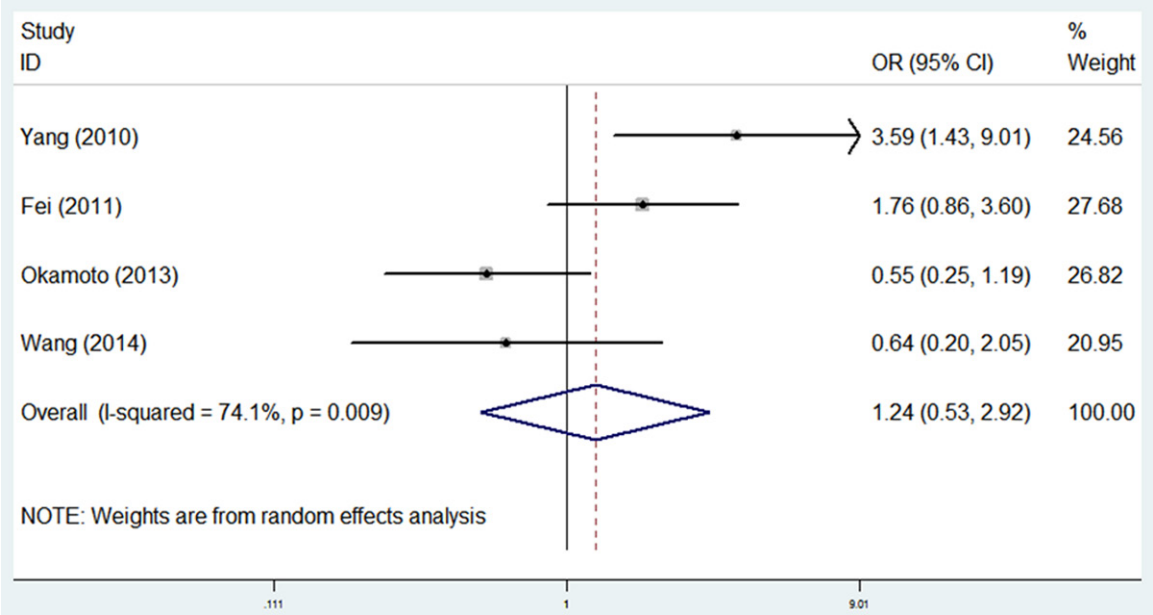

Figure 5. Forest plot of ORs for CD133 and depth of invasion.

Correlation of CD133 with clinicopathological parameters

The association between CD133 and several clinicopathological parameters was illustrated in **Figures 2**-**5**. High expression of CD133 was also associated with lymph node metastasis, clinical stage and histopathological grade, leading to a risk difference of 1.75 (95% CI 1.17-2.61), 1.91 (95% CI 1.08-3.38) and 1.55 (95% CI 1.11-2.18), respectively. And there was no statistically significant association of CD133 with depth of invasion (OR=1.24, 95% CI: 0.53-2.92).

Sensitivity analyses

Sensitivity analysis was subsequently performed to detect the influence of individual study on the pooled estimate by omitting one study from the pooled analysis each time. The exclusion of each single study did not significantly change the pooled OR (Figures S1, S2, S3 and S4), suggesting that the results of the meta-analysis were robust and credible.

Publication bias

Begg's funnel plot was used to check the existence of publication bias. The plot was symmetric, suggesting that the publication bias was little. There was no evidence of publication bias for asymmetrical shapes existed in neither two groups analyses (data not showed).

Discussion

Esophageal cancer is the eighth most frequently diagnosed cancer worldwide, and because of its poor prognosis it is the sixth most common cause of cancer-related death [15]. It caused about 400,000 deaths in 2012, accounting for about 5% of all cancer deaths (about 456,000 new cases were diagnosed, representing about 3% of all cancers) [1]. In general, the prognosis of esophageal cancer is quite poor, because most patients present with advanced disease. By the time the first symptoms (such as difficulty swallowing) appear, the cancer has already well progressed.

Concerning the biological properties of CSCs, many research trials reported that level of CD133 expression in esophageal cancer may be useful as a novel predictive factor of prognosis. However, no consensus of results has been approached. So based on the previous literatures, this meta-analysis demonstrated that high expression of CD133 is significant associated with lymph node metastasis, clinical stage, and histopathological grade. Thus, these results suggested that level of CD133 expression is correlated with a number of parameters that are traditionally associated with poor prognosis.

To our knowledge, CD133 has been regarded as a promising molecular marker and therapeutic target in various solid tumors, such as brain tumors [16], colon cancer [17], lung cancer [18], liver cancer [19] and prostate cancer [20]. Additionally, CD133 may participate in tumor initiation, cellular migration, and vasculogenic mimicry [21]. Moreover, CD133 was associated with tumor differentiations in many cancers. For instance, Ying X, et al. [22] reported that CD133 expression was significantly correlated with tumor differentiation grade in stage II colorectal cancer. Next, Jiang Y, et al. [23] showed that CD133 was higher in the diffuse type than in the intestinal type of gastric cancers and was significantly increased in poorly differentiated gastric cancers. Next, Feng HL et al. [24] proposed that CD133 was negatively correlated with the cellular differentiation of colon cancer. In addition, Fan et al. [25] noted that CD133 expression was correlated with well differentiated or moderately differentiated cholangiocarcinoma. In term of esophageal cancer, Hang D, et al. found that height CD133 expression was linked with well and moderately differentiated tissue compared with poorly differentiated [26]. Our study found that there was a significant difference between the well- and moderately differentiated esophageal carcinoma group and the poorly differentiated esophageal carcinoma group (OR=1.55, 95% CI 1.11-2.18).

Recently, some other cell surface molecules such as CD44, CD24, CD166 and EpCAM have been verified as putative CSC markers in CRC. Undoubly, the combination of these markers could provide a better selection of CSCs. Horst D, et al. [27] proposed that CD133 is the best sole marker to predict low patient survival, while the combined analysis of CD133, CD44, and CD166 markers may be superior in identification of low-, intermediate-, and high-risk cases of colorectal cancer. In addition, besides immunohistochemical staining test, some studies have examined CD133 gene or mRNA expression using reverse transcriptase-polymerase chain reaction (RT-PCR) method. And elevated CD133 gene level may predict distant recurrence and poor prognosis of patients with CRC. Lin EH, et al. [28] revealed that increased levels of expression of CD133 messenger RNA (mRNA) in peripheral blood predicted disease recurrence in patients with colon cancer. And Artells R' study [29], measuring CD133 mRNA expression levels by RT-PCR, observed longer relapse-free interval and overall survival in patients with lower levels of CD133, regardless of adjuvant treatment and other clinical characteristics. Similarly, Huh JW, et al. [30] verified that the 5-year disease-free survival rate of patients with a low CD133 mRNA expression was significantly higher than that of those patients with high levels of CD133 mRNA expression. Iinuma H, et al. [31] suggested that OS and DFS of patients who were positive for CD133 (CEA/CK/CD133) mRNA were significantly worse than those of patients who were negative for these markers, further In patients with Dukes' stage B and C CRC who require adjuvant chemotherapy, detection of CD133 (CEA/CK/CD133) mRNA in peripheral blood is a useful tool for determining which patients are at high risk for recurrence and poor prognosis.

Several restrictions of our study also need to be considered. First, the numbers of the studies and patients included in the current meta-analysis are relatively small. Secondly, all the studies are based on Asian population, none from western countries. Due to lack of statistics on other countries, further studies are needed to investigate the role of CSCs in other population. As is known, there are significant differences such as etiology, biology features, clinical types, and prognosis in the risk of CRC in different ethnic groups within a given geographical area. Although in the subgroup analysis, ethnicity, sample size, and research technique did not significantly influence the prognosis value of CD133. Finally, no attempt was made to identify unpublished work and grey literature, for example university theses or conference proceedings. As a result, publication bias may have influenced the results. And only English literatures were included in this study, it was possible that our findings were biased for many non-English literatures were not included.

In conclusion, this meta-analysis showed that a high level of CD133 was significantly correlated with lymph node metastasis, clinical stage and histopathological grade. Thus, CD133 may have a predictive role and be helpful tool in the management of patients with esophageal cancer. Large-scale, prospective clinical trials with advanced methodologies are still required to

verify the findings and provide a higher level of evidence.

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Disclosure of conflict of interest

None.

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References

[1] In: Stewart BW, Wild CP, editors. World Cancer Report 2014.
[2] Croker AK, Allan AL. Cancer stem cells: implications for the progression and treatment of metastatic disease. J Cell Mol Med 2008; 12: 374-390.
[3] Chuthapisith S, Eremin J, El-Sheemey M, Eremin O. Breast cancer chemoresistance: emerging importance of cancer stem cells. Surg Oncol 2010; 19: 27-32.
[4] Lobo NA, Shimono Y, Qian D, Clarke MF. The biology of cancer stem cells. Annu Rev Cell Dev Biol 2007; 23: 675-699.
[5] Vermeulen L, Sprick MR, Kemper K, Stassi G, Medema JP. Cancer stem cells - old concepts, new insights. Cell Death Differ 2008; 15: 947-958.
[6] Tsang JY, Huang YH, Luo MH, Ni YB, Chan SK, Lui PC, Yu AM, Tan PH, Tse GM. Cancer stem cell markers are associated with adverse biomarker profiles and molecular subtypes of breast cancer. Breast Cancer Res Treat 2012; 136: 407-417.
[7] Corbeil D, Roper K, Fargeas CA, Joester A, Huttner WB. Prominin: a story of cholesterol, plasma membrane protrusions and human pathology. Traffic 2001; 2: 82-91.
[8] Yang AP. The expression of marker cancer stem cells CD133 and Musashi-1 in human esophageal carcinoma and its clinical significances. Southeast Univ 2010; 15: 698.
[9] Cao YK. Relationship between CD133 expression and chemoradio therapy response in esophageal squamous cell carcinoma. Zhongshan Univ 2009; 16: 75.
[10] Fei ZH, Chen SX, Chen L. Expression and significance of Bmi-1 and CD133 in esophageal squamous cell carcinoma. Mod Pract Med 2011; 23: 337.
[11] Feng KX, Li SP, Liu XL, Zhou J, Yuan SH, Xie MH, Jing DS, Sun YZ. Expression of NF-κB, CD133 in esophageal cancer and correlation with metastasis. Mod Oncol 2014; 23: 0206.
[12] Wang YW, Zhang J, Feng G. Expression of CD133 in esophageal squamous cell carcinoma and its clinical significance. Shaanxi Med J 2014; 43: 1464.
[13] Okamoto H, Fujishima F, Nakamura Y, Zuguchi M, Ozawa Y, Takahashi Y, Miyata G, Kamei T, Nakano T, Taniyama Y, Teshima J, Watanabe M, Sato A, Ohuchi N, Sasano H. Significance of CD133 expression in esophageal squamous cell carcinoma. World J Surg Oncol 2013; 11: 51.
[14] Peng J, Guo JJ, Ao X, Zhou TJ, Wang M, Li YQ, Zhang HZ. Expression of CDl33 in the tissue of locally advanced esophagus squamous cell cancer patients and its significance. Chin J Exp Surg 2012; 29: 541.
[15] Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol 2013; 19: 5598-5606.
[16] Ong CW, Kim LG, Kong HH, Low LY, Iacopetta B, Soong R, Salto-Tellez M. CD133 expression predicts for non-response to chemotherapy in colorectal cancer. Mod Pathol 2010; 23: 450-457.
[17] Chen YC, Hsu HS, Chen YW, Tsai TH, How CK, Wang CY, Hung SC, Chang YL, Tsai ML, Lee YY, Ku HH, Chiou SH. Oct-4 expression maintained cancer stem-like properties in lung cancer-derived CD133-positive cells. PLoS One 2008; 3: e2637.
[18] Zhou X, Li D, Wang X, Zhang B, Zhu H, Zhao J. Galectin-1 is overexpressed in CD133+ human lung adenocarcinoma cells and promotes their growth and invasiveness. Oncotarget 2015; 6: 3111-3122.
[19] Chai S, Tong M, Ng KY, Kwan PS, Chan YP, Fung TM, Lee TK, Wong N, Xie D, Yuan YF, Guan XY, Ma S. Regulatory role of miR-142-3p on the functional hepatic cancer stem cell marker CD133. Oncotarget 2014; 30: 5725-5735.
[20] Irollo E, Pirozzi G. CD133: to be or not to be, is this the real question? Am J Transl Res 2013; 5: 563-581.
[21] Nadal R, Ortega FG, Salido M, Lorente JA, Rodríguez-Rivera M, Delgado-Rodríguez M, Macià M, Fernández A, Corominas JM, García-Puche JL, Sánchez-Rovira P, Solé F, Serrano MJ. CD133 expression in circulating tumor cells from breast cancer patients: potential role in resistance to chemotherapy. Int J Cancer 2013; 133: 2398-2407.
[22] Ying X, Wu J, Meng X, Zuo Y, Xia Q, Chen J, Feng Y, Liu R, Li L, Huang W. AC133 expression associated with poor prognosis in stage II colorectal cancer. Med Oncol 2013; 30: 356.

[23] Jiang Y, He Y, Li H, Li HN, Zhang L, Hu W, Sun YM, Chen FL, Jin XM. Expressions of putative cancer stem cell markers ABCB1, ABCG2, and CD133 are correlated with the degree of differentiation of gastric cancer. Gastric Cancer 2012; 15: 440-450.
[24] Feng HL, Liu YQ, Yang LJ, Bian XC, Yang ZL, Gu B, Zhang H, Wang CJ, Su XL, Zhao XM. Expression of CD133 correlates with differentiation of human colon cancer cells. Cancer Biol Ther 2010; 9: 216-223.
[25] Fan L, He F, Liu H, Zhu J, Liu Y, Yin Z, Wang L, Guo Y, Wang Z, Yan Q, Huang G. CD133: a potential indicator for differentiation and prognosis of human cholangiocarcinoma. BMC Cancer 2011; 11: 320.
[26] Hang D, Dong HC, Ning T, Dong B, Hou DL, Xu WG. Prognostic value of the stem cell markers CD133 and ABCG2 expression in esophageal squamous cell carcinoma. Dis Esophagus 2012; 25: 638-644.
[27] Horst D, Kriegl L, Engel J, Kirchner T, Jung A. Prognostic significance of the cancer stem cell markers CD133, CD44, and CD166 in colorectal cancer. Cancer Invest 2009; 27: 844-850.
[28] Lin EH, Hassan M, Li Y, Zhao H, Nooka A, Sorenson E, Xie K, Champlin R, Wu X, Li D. Elevated circulating endothelial progenitor marker CD133 messenger RNA levels predict colon cancer recurrence. Cancer 2007; 110: 534-542.
[29] Artells R, Moreno I, Diaz T, Martínez F, Gel B, Navarro A, Ibeas R, Moreno J, Monzó M. Tumour CD133 mRNA expression and clinical outcome in surgically resected colorectal cancer patients. Eur J Cancer 2010; 46: 642-649.
[30] Huh JW, Park YS, Lee JH, Kim HR, Shin MG, Kim YJ. CD133 mRNA expression and microsatellite instability in colorectal carcinoma. J Surg Oncol 2010; 102: 765-770.
[31] Iinuma H, Watanabe T, Mimori K, Adachi M, Hayashi N, Tamura J, Matsuda K, Fukushima R, Okinaga K, Sasako M, Mori M. Clinical significance of circulating tumor cells, including cancer stem-like cells, in peripheral blood for recurrence and prognosis in patients with Dukes' stage B and C colorectal cancer. J Clin Oncol 2011; 29: 1547-1555.

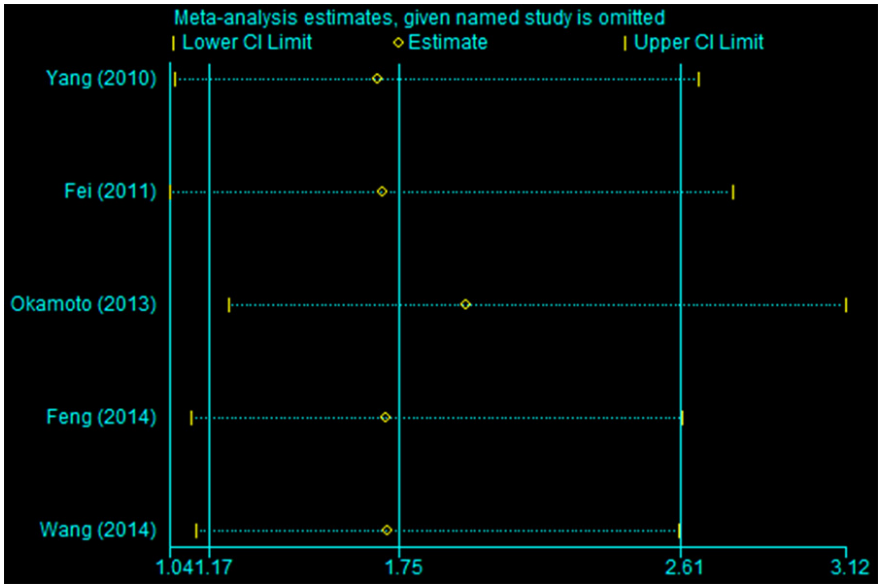

Figure S1. Sensitivity analysis of CD133 and lymph node metastasis.

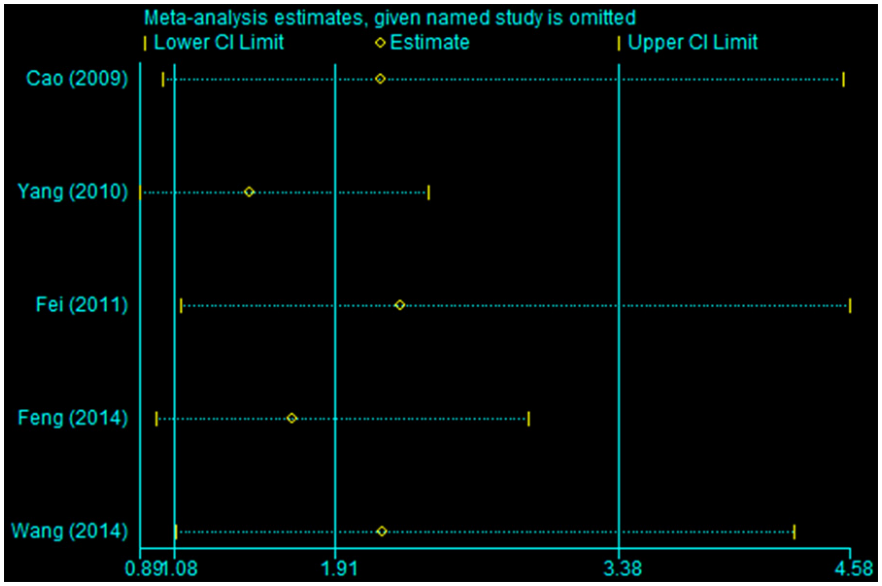

Figure S2. Sensitivity analysis of CD133 and clinical stage.

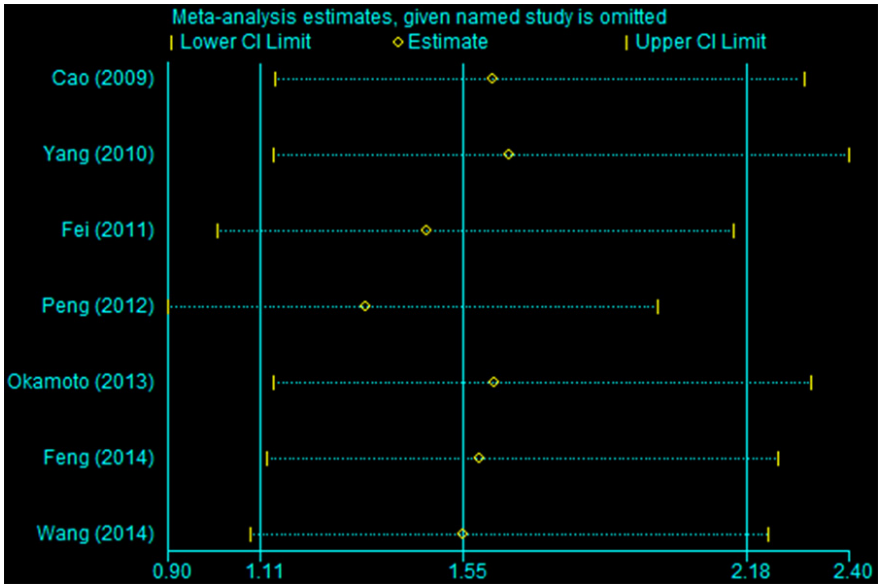

Figure S3. Sensitivity analysis of CD133 and histopathological grade.

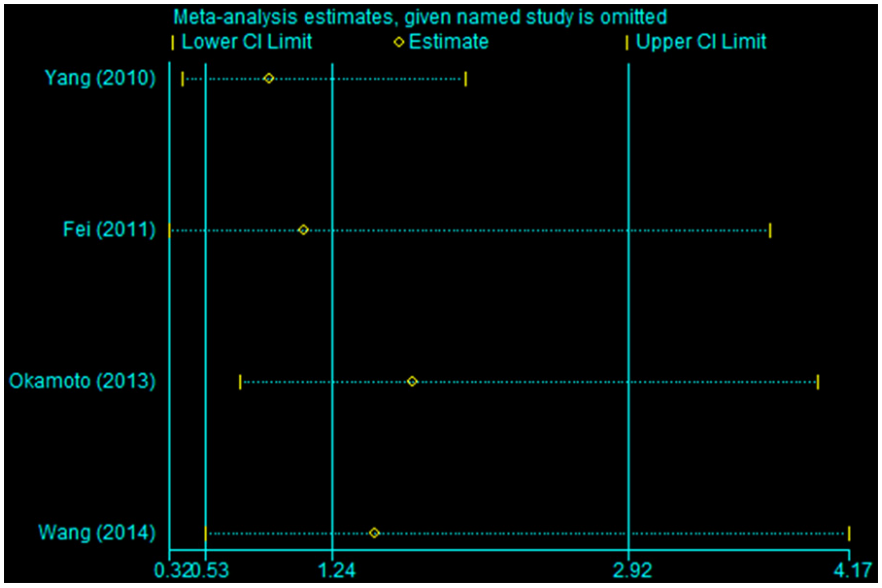

Figure S4. Sensitivity analysis of CD133 and depth of invasion.