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Review Article

Prognostic value of cancer stem cell marker CD133 in ovarian cancer: a meta-analysis

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Abstract: Objective: To investigate the association between CD133 expression and prognosis and clinicopathological features of ovarian cancer. Methods: The electronic and manual searches were performed through the database of PubMed Chinese Wanfang databases (up to September 15, 2014) was performed using the following keywords ovarian cancer, CD133, AC133, prominin-1. Meta-analysis was performed by using Review Manager 5.2 and the outcomes included the overall survival and various clinicopathological features. Results: A total of 1051 ovarian cancer patients from 8 studies were included. Meta-analysis showed that overexpression of CD133 was highly correlated with reduced 2-year overall survival (*OR* = 1.67, 95% *CI*: 1.06-2.63, *P* = 0.03, fixed-effect). With respect to clinicopathological features, CD133 level was positively correlated with tumor stage (*OR* = 0.26, 95% *CI:* 0.12-0.58, *P* = 0.001 random-effect). But not correlated with patients' age (*OR* = 1.12, 95% *CI:* 0.68-1.86, *P* = 0.65 fixed-effect), tumor grade (*OR* = 1.20, 95% *CI*: 0.06-1.62, *P* = 0.17 random-effect), histological type (*OR* = 1.10, 95% *CI*: 0.82-1.47, *P* = 0.54 fixed-effect) and response to treatment (*OR* = 0.84, 95% *CI*: 0.61-1.16, *P* = 0.29 fixed-effect). Conclusion: On the basis of current retrospective evidence, the present meta-analysis indicated that high level of CD133 expression trends to correlate with a worse prognosis in patients with ovarian cancer.

Keywords: Ovarian cancer, cancer stem cells, CD133, prognosis

Introduction

Ovarian cancer is the most lethal of all gynecological malignancies and the fifth leading cause of cancer deaths in women [1]. The prognosis of ovarian cancer is usually poor, due to the lack of either specific symptoms or effective screening and diagnostic methods, in identifying early stage disease. Leading to over 70% of patients being diagnosed with advanced stage disease, in which the 5-year survival rate is only 30%-44% [1, 2]. Several independent prognostic factors including Age, performance status, FIGO stage, grade of tumor, and volume of residual tumor have been established in predicting survival in ovarian cancer patients [3, 4]. However, these macro factors are insufficient to predict the outcomes for the individual patient. Hence, it is necessary to identify new prognostic molecular factors to predict the outcomes of patients, which could be to establish therapeutic strategies and select suitable treatment options for individual ovarian cancer patients.

During the past few years, accumulating evidence supports the cancer stem cell (CSC) hypothesis, according to which CSCs may be responsible for tumor initiation, metastasis, recurrence and therapeutic resistance of cancer, thus indicating poor prognosis [5, 6]. Therefore, it is of major importance to investigate CSCs associated with cancer progression as they may be important factors in determining the clinical outcomes of cancer and the context of potential therapeutic targeting.

Recently, a number of cell surface markers such as CD133, CD44, CD24, ALDH, CD117 and EpCAM are often used to identify and enrich CSCs. Among these markers, CD133 is believed to be the one of robust surface marker for cancer stem cells by now [7]. Its prognostic value for cancer patients has also been found in many cancers such as colorectal cancer [8-10], brain tumors [8], hepatocellular carcinoma [11], gastric cancer [12] and also lung cancer patients [13-16].

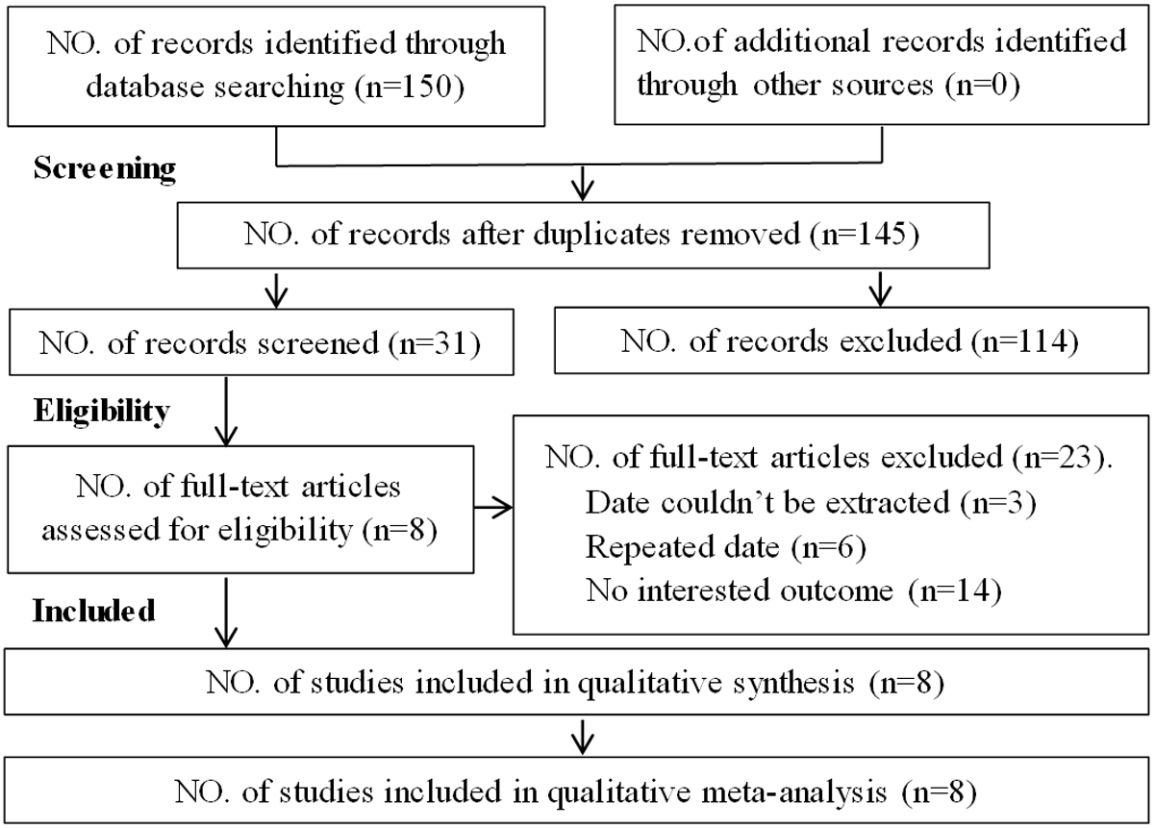


Figure 1. Flow chart for selection of studies.

As for ovarian cancer, insufficient samples and some other factors have resulted in controversial results of different clinical studies, although several studies have assessed the prognostic role of CD133 overexpression for clinical outcomes in ovarian cancer. The present meta-analysis aims to determine the value of CD133 as a prognostic marker for ovarian cancer.

Methods

Literature search strategy

A comprehensive literature search of electronic databases PubMed and Chinese Wanfang was performed up to September 15, 2014. Search strings of PubMed was (AC133 [all fields] OR AC-133 [all fields] OR (AC [all fields] AND 133 [all fields]) OR CD-133 [all fields] OR CD133 [all fields]) OR (CD [all fields] AND 133 [all fields]) OR "AC133 antigen" [supplementary concept] OR "AC 133 antigen" [all fields] OR "prominin1" [all fields] OR PROM1 [all fields] OR PROM-1 [all fields]) AND ("Ovarian neoplasms" [MeSH terms] OR ("Ovary" [all fields] AND "neoplasms" [all fields]) OR "Ovary neoplasms" [all fields] OR ("Ovary" [all fields] AND "cancer" [all fields]) OR "Ovarian Cancer" [all fields] OR "Cancer of Ovary" [MeSH terms]). The reference lists of relative articles were also screened to further identify potential studies.

Selection criteria

Titles and abstracts were evaluated to identify relevant publications, and the full text version scanned. The criteria for inclusion were: (1) articles dealing with CD133 expression and clinicopathological markers, prognostic factors or overall survival (OS) of ovarian cancer were included; (2) articles containing sufficient data to allow the estimation of an odds ratio (OR) or a relative risk (RR) of OS; (3) the expression of CD133 was detected on cancer tissue, rather than in the serum or any other kinds of specimens; (4) articles published as original research. Reviews, comments and articles unrelated to our analysis were excluded. There was no limitation on language as well as the minimum patients of every single study. When there

Table 1. Main characteristics of the eligible studies

References	Year	Country	Study type	Method	TNM grading	Cutoff (IHC)	No. of patients	CD133 (+) N (%)
Ferrandina [17]	2009	Italy	RC	IHC	III~IV	0	160	50 (31.2)
Kim [18]	2014	Korea	RC	TM	I~IV	≥ 1.5	59	33 (55.9)
Li [19]	2012	China	RC	IHC	I~IV	≥ 10%	46	28 (60.9)
Li (2) [20]	2013	China	RC	IHC	I~IV	≥ 2	145	49 (33.8)
Qin [21]	2012	China	RC	IHC	III~IV	≥ 10%	123	43 (35.0)
Ricci [22]	2013	Italy	RC	IHC	I~IV	0	91	24 (26.0)
Zhai [23]	2013	China	RC	IHC	I~IV	0	33	19 (57.5)
Zhang [24]	2012	USA	RC	IHC	I~IV	0	400	123 (31.0)

Note: RC, retrospective cohort; IHC, immunohistochemistry; TM, tissue microarrays.

were multiple articles by the same group based on similar patients and using same detection methods, only the largest or the most recently article was included (**Figure 1**).

Data extraction

All data were independently abstracted by two reviewers (Huamei Song and Aihua Chen) with standardized data abstraction tool. Differences in the extraction of data were assessed by a third investigator (Quan Zhou). The following information was extracted from the included studies: author, publication year, patient's country, detection method, TNM stage, number of patients, cutoff value of CD133, clinicopathological features, positive rates of CD133 overexpression, as well as the expression-related survival. In case the prognosis was only plotted as Kaplan-Meier curve in some articles, the software GetData Graph Digitizer 2.25 (http://getdata- graph-digitizer.com/) was applied to digitize and extract the data.

Statistical analysis

This study was reported in accordance to the PRISMA-statement. Statistical analyses were estimated using Review manager software 5.2 (updated in March 2012 by the Cochrane Collaboration). *P* values were two-sided, with significance at $P < 0.05$. *OR*s with 95% *CI* were used to evaluate the association between the stem cell markers. CD133 and the clinicopathological features for ovarian cancer, including tumor grade and stage, tumor differentiation and lymph node status. The *OR* was used for assessing the association of CD133 and the survival outcome combined over studies. Heterogeneity across studies was evaluated with the *Q* test and *P* values. *OR*s and *RR*s were calculated by a random-effects model when the *P* value was less than 0.05. Otherwise, a fixed-effects model was used. Funnel plots was used to assess publication bias.

Results

Study characteristics

A total of 8 publications (5 in English and 3 in Chinese) between 2009 and 2014 met the criteria for this meta-analysis [17-24] (**Figure 1**). The total number of patients was 1051, ranging from 46 to 400 patients per study. The main features of each eligible study were summarized in **Table 1**. All eligible studies dealt with clinicopathological factors. 4 studies determined with OS [17, 21, 22, 24]. 4 studies only reported the association between CD133 expression and clinicopathological factors without OS analysis [18-20, 23]. Expression of CD133 was evaluated by Immunohistochemistry (IHC) in 7 studies [17, 19-24], by tissue microarrays in 1 study [18]. **Table 1** show all the studies included in the meta-analysis in detail.

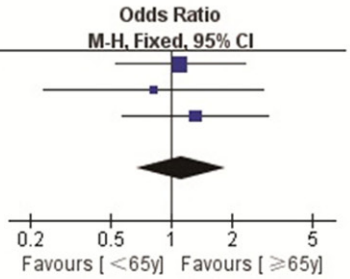
Correlation of stem cell markers with clinicopathological parameters

In the total analyses, the expression of stem cell markers CD133 was not associated with clinical parameters such as patients' age (*OR* = 1.12, 95% *CI*: 0.68-1.86, *P* = 0.65 fixed-effect) (**Figure 2A**), tumor grade (*OR* = 1.20, 95% *CI*: 0.06-1.62, *P* = 0.17 random-effect) (**Figure 2B**), histological type (*OR* = 1.10, 95% *CI*: 0.82-1.47, *P* = 0.54 fixed-effect) (**Figure 2C**) and response to treatment (*OR* = 0.84, 95% *CI*: 0.61-1.16, *P* = 0.29 fixed-effect) (**Figure 2D**), However, the

A

Study or Subgroup	<65y Events	Total	≥65y Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ferrandina2009	36	113	14	47	46.9%	1.10 [0.53, 2.31]
Kim2014	26	46	8	13	18.9%	0.81 [0.23, 2.87]
Qin2012	32	87	11	36	34.2%	1.32 [0.58, 3.04]
Total (95% CI)		**246**		**96**	**100.0%**	**1.12 [0.68, 1.86]**
Total events	94		33			

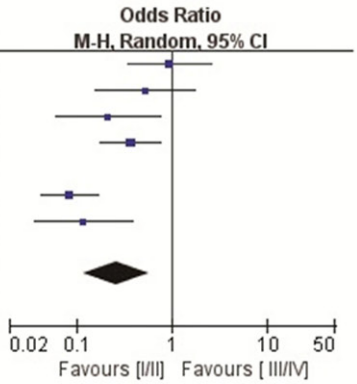
Heterogeneity: Chi² = 0.40, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)



B

Study or Subgroup	I/II Events	Total	III/IV Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ferrandina2009	6	20	44	140	16.7%	0.94 [0.34, 2.60]
Kim2014	23	43	11	16	15.0%	0.52 [0.16, 1.76]
Li2012	7	18	21	28	14.4%	0.21 [0.06, 0.76]
Li2013	14	64	35	81	19.2%	0.37 [0.18, 0.77]
Qin2012	0	0	43	123		Not estimable
Ricci2013	20	91	70	91	19.6%	0.08 [0.04, 0.17]
Zhang2012	3	52	120	348	15.2%	0.12 [0.04, 0.38]
Total (95% CI)		**288**		**827**	**100.0%**	**0.26 [0.12, 0.58]**
Total events	73		344			

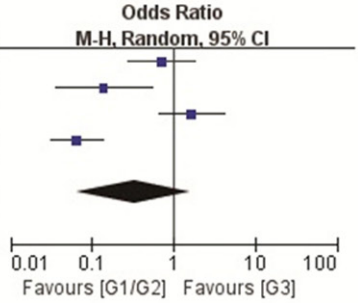
Heterogeneity: Tau² = 0.71; Chi² = 19.83, df = 5 (P = 0.001); I² = 75%
Test for overall effect: Z = 3.29 (P = 0.0010)



C

Study or Subgroup	G1/G2 Events	Total	G3 Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ferrandina2009	7	28	34	107	25.3%	0.72 [0.28, 1.85]
Li2012	5	16	23	30	23.2%	0.14 [0.04, 0.54]
Qin2012	35	93	8	30	25.4%	1.66 [0.67, 4.13]
Ricci2013	14	91	67	91	26.2%	0.07 [0.03, 0.14]
Total (95% CI)		**228**		**258**	**100.0%**	**0.32 [0.06, 1.62]**
Total events	61		132			

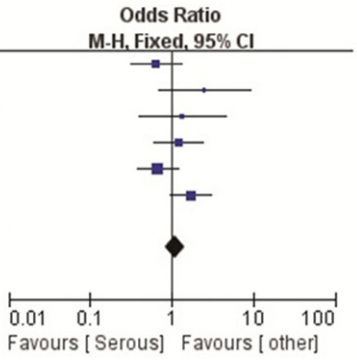
Heterogeneity: Tau² = 2.45; Chi² = 34.54, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 1.37 (P = 0.17)



D

Study or Subgroup	Serous Events	Total	other Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ferrandina2009	33	117	17	45	20.4%	0.65 [0.31, 1.34]
Kim2014	11	15	23	44	3.6%	2.51 [0.69, 9.11]
Li2012	19	30	9	16	5.0%	1.34 [0.39, 4.62]
Li2013	28	78	21	67	16.8%	1.23 [0.61, 2.45]
Ricci2013	41	91	50	91	31.8%	0.67 [0.37, 1.21]
Zhang2012	104	318	18	82	22.3%	1.73 [0.97, 3.06]
Total (95% CI)		**649**		**345**	**100.0%**	**1.10 [0.82, 1.47]**
Total events	236		138			

Heterogeneity: Chi² = 8.94, df = 5 (P = 0.11); I² = 44%
Test for overall effect: Z = 0.61 (P = 0.54)



E

Study or Subgroup	Yes Events	Total	No Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ferrandina2009	40	130	7	30	10.0%	1.46 [0.58, 3.68]
Li2013	30	83	19	62	17.6%	1.28 [0.64, 2.58]
Qin2012	27	84	16	39	18.8%	0.68 [0.31, 1.49]
Zhang2012	83	295	40	105	53.7%	0.64 [0.40, 1.02]
Total (95% CI)		**592**		**236**	**100.0%**	**0.84 [0.61, 1.16]**
Total events	180		82			

Heterogeneity: Chi² = 4.39, df = 3 (P = 0.22); I² = 32%
Test for overall effect: Z = 1.05 (P = 0.29)

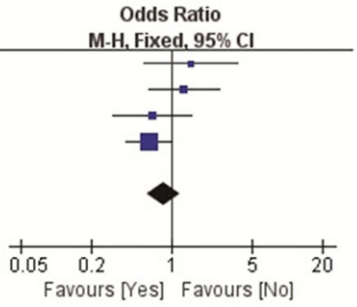


Figure 2. Meta-analysis of correlation between CD133 expression and clinicpathological Parameters in ovarian cancer patients, such as patients' age (A), tumor stage (B), tumor grade (D), tissue histotype (E) and response to clinical treatment (F).

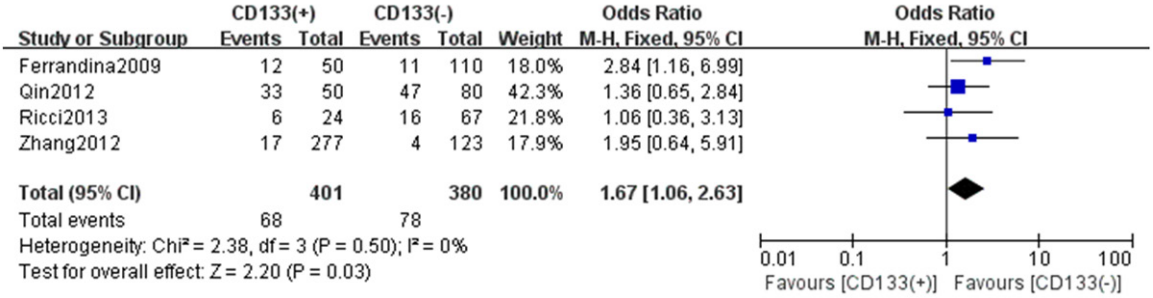


Figure 3. Meta-analysis of correlation between CD133 expression and 2-year overall survival (OS) in ovarian cancer patients.

Table 2. Associations between CD133 and 2-year OS grouped by selected factors

Subgroup	Sample size		Test of association			Test of heterogeneity			model
	CD133 (+)	CD133 (-)	OR	95% *CI*	*P value*	χ^2	*P value*	I^2	
Overall	401	380	1.67	1.06-2.63	0.03	2.38	0.50	0%	fixed
Caucasian	351	300	1.89	1.06-3.38	0.03	1.88	0.39	0%	fixed
Asian	50	80	1.36	0.65-2.84	0.83	-	-	-	fixed
Cutoff ≥ 10%	50	80	1.36	0.65-2.84	0.83	-	-	-	fixed
Cutoff < 10%	351	300	1.89	1.06-3.38	0.03	1.88	0.39	0%	fixed
TNM (I~IV)	301	190	1.46	0.69-3.10	0.32	0.59	0.44	0%	fixed
TNM (III~IV)	100	190	1.80	1.02-3.19	0.04	1.54	0.21	35%	fixed

expression of CD133 was associated with tumor stage (*OR* = 0.26, 95% *CI*: 0.12-0.58, *P* = 0.001 random-effect) (**Figure 2E**).

Impact of CD133 on overall survival (OS) of ovarian cancer

The meta-analysis was performed on 4 studies investigating the association of CD133 expression and 2-year overall survival rate (OS). Since the heterogeneity was not significant (I^2 = 0%, *P* = 0.50), a fixed-effect model was used to calculate the OR of OS in ovarian cancer patients. Meta-analysis found that the presence of stem cell markers CD133 expression was highly correlated with poor 2-year OS (*OR* = 1.67, 95% *CI:* 1.06-2.63, *P* = 0.03, fixed-effect), suggesting that CD133 could be an independent prognostic factor in ovarian cancer patients (**Figure 3**). Then, we assessed the source of heterogeneity for additive model by population (Asian vs. Caucasian), CD133 cutoff value (Cutoff ≥ 10% vs. Cutoff < 10%) and TNM grading [(I~IV) vs. (III~ IV)]. The results were shown in **Table 2**. For the OS, cutoff values, population and TNM grading were not contributed to substantial heterogeneity. Moreover, The subgroup meta-analysis of studies with Caucasian population, cutoff level < 10% and TNM (III~IV) showed high CD133 expression was associated with poor OS of ovarian cancer patients. Nevertheless, these significant difference were not found in Asian population, cutoff level ≥ 10% and TNM (I~IV) in ovarian cancer patients.

Publication bias

The shapes of Begg's funnel plots seemed to have no evidence of obviously asymmetrical in results of meta-analyses of CD133 expression for above clinicopathological parameters and 2-year OS (**Figure 4**).

Sensitivity analysis

In order to gauge results stability, a sensitivity analysis, in which one study was deleted at a time, was performed to determine the influence

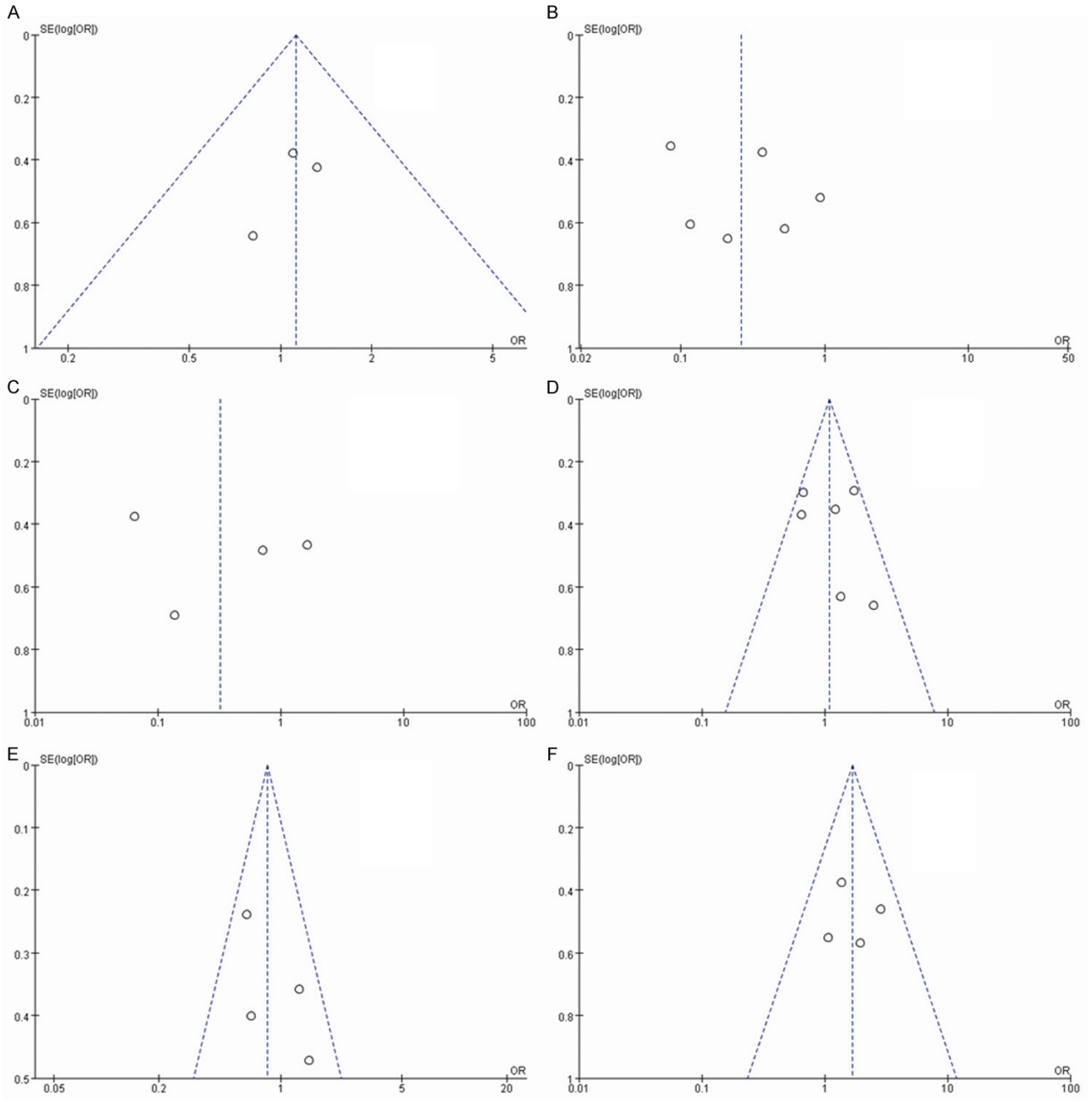

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Figure 4. Funnel plots was assessed for association between CD133 and clinical pathologic features and 2-year OS, such as patients' age (A), tumor stage (B), tumor grade (C), tissue histotype (D), response to clinical treatment (E) and 2-year OS (F).

of individual studies on the summary effect. The meta-analysis was not dominated by any single study, and exclusion of any study made no difference, suggesting the robustness of our results.

Discussion

Up to date, clinically approved biomarkers have been found to the improvement of diagnosis, treatment, and prevention of malignancies, and CD133 is one of the most extensively used markers in solid cancer. Several recent studies have demonstrated that CD133 expression may serve as a promising biomarker in prognosis of colorectal, gastric cancers and non-small cell lung cancer [8-16]. However, it remains controversial whether CD133 is associated with clinicopathological characteristics and prognosis of ovarian cancer [17-24]. Therefore, we performed this meta-analysis to identify the association between CD133 and clinicopathological outcomes, which showed that positive CD133 expression was significantly associated with tumor stage, although CD133 expression was not associated with the patients' age, tumor grade, tissue histotype, response to clinical treatment. Simultaneously, our analysis indicated that CD133 expression was significantly associated with OS, indicating that it might be a marker for poor prognosis of ovarian cancer.

CD133, also known as prominin-1, is the epitope of a glycosylated form of membrane protein, and the physiological function of CD133 remains unknown [25]. Recent study shows that ovarian cancer contains CD133 expressing cells, which is essential for tumor cell propagation and metastasis [26]. Moreover, several studies reported that CD133 expression was positively associated with poor prognosis [17, 22, 27]. However, the conflicting results were also reported [21, 24]. Though 4 studies in this meta-analysis concluded that high CD133 expression is a predictor for poor prognosis [17, 21, 22, 24]. There are still some disputes. First of all, CD133 is still a candidate but not a definite CSC marker. For example, many studies showed that CD133 (+) cells have stamens properties such as self-renewal, differentiation ability, high proliferation and they are able also to form tumors in xenografts. Although, others investigations demonstrated that also CD133 (-) cells can show the same characteristics of CD133 (+) cell [28]. And many scientists insist on combined markers for the identification of CSC now [19-21, 23, 24, 27]. Secondly, for ovarian cancer and some other cancer patients whose tumor tissue over express a CSC marker, their response to clinical treatment, recurrence rate or overall survival was not always worse than the negative ones [17, 22, 29]. Thus more prospective studies are needed to draw a definite conclusion.

Recently, a significant amount of work has been done to identify CSC markers of malignancies. Besides CD133, some other cell surface molecules such as ALDH, nestin, CD44, CD24, CD166 and EpCAM have been considered as putative CSC markers in solid tumors [7] and the combination of these markers may provide a better selection of CSCs. Several studies have shown that CSC-related factors, including ALDH and VEGF, are associated with ovarian cancer progression [30, 31]. For future studies, co-expression of ovarian cancer CSC markers associated with patient survival may be more meaningful for clinical application in ovarian cancer.

To our knowledge, this meta-analysis is the first study which systematically estimates the association between stem cell marker CD133 and ovarian cancer survival. With more samples, the results of our study are more reliable compared to those of a single study. However, our results should be interpreted cautiously since some limitations exist in this present meta-analysis. First of all, the number of included studies, as well as the included ovarian cancer patients in each study, was relatively small. Second, heterogeneity was found in the main analysis. In the current meta-analysis, despite the fact that we tried to optimize standardization, some remaining variability in definitions was unavoidable. For example, the different characteristics of the subjects, the histological types of ovarian cancer, the detecting antibod-

ies against CD133 and the cutoff values for determining high CD133 levels. Third, we were unable to perform subgroup analysis by FIGO stage, grade, and histological type to evaluate the pooled OR for OS because diverse subjects were included in each study. Finally, the retrospective design of most included studies provides a lower level of evidence.

In summary, the present meta-analysis indicates that CD133 expression is associated with a poor OS and tumor stage, but no correlation exists between CD133 expressions and other common clinicopathological parameters such as patients' age, tumor grade, tissue histotype, response to clinical treatment. CD133 may be a potential prognostic marker in ovarian cancer. However, further studies are required, with larger sample sizes, high quality, unified methods and cut-off levels to detect CD133 expression, classified by tumor stage, therapeutic schedule, follow-up time and survival events, make a more definitive conclusion of the present meta-analysis.

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Disclosure of conflict of interest

None.

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