Original Article
CD133 expression may be useful as a prognostic indicator in stomach cancer: a meta-analysis

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Abstract: Objective: CD133 has been recognized as a marker of cancer stem-like cells in stomach cancer. However, its predictive value in stomach cancer still remains controversial. In this study, we aimed to evaluate the association between the expression of CD133 and clinicopathological features and outcome of stomach cancer patients by performing a meta-analysis. Methods: A systematic literature search for relevant articles published from 2010 to 2015 was conducted in PubMed, Embase and Cochrane databases. Publication bias was assessed by the funnel plots, and heterogeneity and sensitivity were analyzed as well. Results: In present study, 8 articles with a total of 603 patients were subjected to the final analysis. Compared with normal tissue, CD133 expression was higher in stomach cancer tissue (OR = 2.24, 95% CI 1.63-3.08). And high expression of CD133 much likely associated with lymph node metastasis, distant metastasis and III-IV stage cases, leading to a risk difference of 1.86 (95% CI 1.38-2.50), 1.55 (95% CI 1.05-2.31) and 1.85 (95% CI 1.43-2.39), respectively. In addition, survival analysis demonstrated a significant association between overexpression CD133 and poor 5-year overall survival (OR = 0.41, 95% CI 0.29-0.58). Conclusion: Based on the results of this study, we conclude that CD133 serves as a predictive marker of poor prognosis. Higher CD133 expression is significantly associated with lymph node metastasis, distant metastasis and advanced clinical stage.

**Keywords:** Cancer stem cell, CD133, stomach cancer, meta-analysis

Introduction

Stomach cancer is the fourth most common cancer worldwide with 930,000 cases diagnosed in 2002 [1]. It is more common in men and in developing countries. In 2012 number of deaths were 700,000 having decreased slightly from 774,000 in 1990 making it the third leading cause of cancer death after lung cancer and liver cancer [2]. Surgical resection is considered to be one of the standard treatments of stomach cancer, providing the long-term survival. Although there has been significant progress in diagnostic studies and therapeutic options, its incidence and mortality rates remain high; therefore, new therapies are urgently needed.

Cancer stem cells (CSCs) are cancer cells that possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. CSCs were first identified by John Dick in acute myeloid leukemia in the late 1990s. And CSCs have the capacity for self-renewal, driving tumorigenicity, recurrence, metastasis, and the capacity to differentiate, albeit aberrantly, giving rise to a heterogeneous population of cancer cells [3, 4]. Furthermore, CSCs are believed to play a key role in resistance to chemotherapy and radiotherapy [5, 6]. 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 [7, 8]. In other words, identification and characterization of CSCs could lead to development of directed and more effective treatments for cancer.

Reliable markers that identify CSCs will pave the way to better understanding of signaling pathways [9]. Several molecular biomarkers have been used in clinical trials to define the existence of CSCs, including CD133, CD44 and CD166. CD133 (prominin1) is a
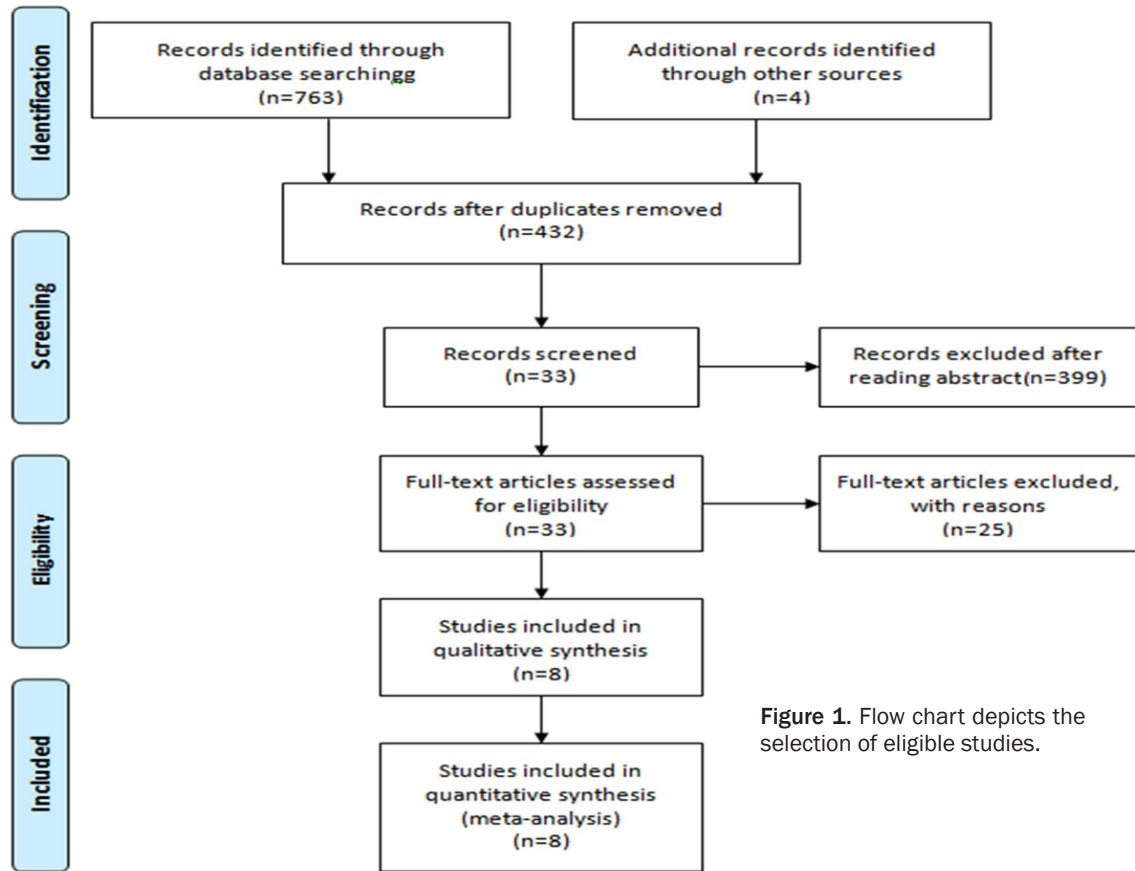
Figure 1. Flow chart depicts the selection of eligible studies.

five-transmembrane domain glycoprotein expressed on CD34+ stem and progenitor cells, in endothelial precursors and fetal neural stem cells. And CD133 is one of the most important stem cell markers in many solid cancers such as brain tumors [10], colon cancer [11], lung cancer [12], liver cancer [13] and prostate cancer [14]. Additionally, CD133 may participate in tumor initiation, cellular migration, and vasculogenic mimicry [15].

Thus, we did a meta-analysis to evaluate the CSC maker CD133, and correlated their expression with clinicopathologic characteristics and stomach cancer, using a large collection of high quality data.

Methods

Literature search

The protocol for this systematic review was based on the PRISMA statement. We performed systematic literature searches of PubMed, Embase and Cochrane databases for

possible publications. Reports cited the references identified in this systematic review and relevant reviews were also searched to include potentially missed studies. The following terms were used in the search procedure: ('stomach cancer' or 'gastric cancer' or 'cancer' or 'stomach adenocarcinoma' or 'gastric adenocarcinoma') AND ('cancer stem cell' or 'neoplastic Stem Cells) AND ('CD133' or 'prominin-1' or 'AC133'). The retrieved studies were carefully examined to exclude potential duplicates or overlapping data. Titles and abstracts of articles selected from the initial search were first scanned, and then full papers of potential eligible studies were reviewed.

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) The study must be a case control design or a cohort design concerning the correlation between CSCs and clinical outcomes of stomach cancer. (2) Diagnosis

Table 1. Characteristics of studies

First author	Year	Country	Cases (n)	Gender (M/F)	Age	Method	Expression	Group
Hashimoto	2013	Japan	189	133/56	55~77	IHC	29.6	(2) (3) (4) (5)
Chen	2013	China	152	101/51	23~84	IHC	42.1	(1) (3) (4) (5)
Wakamatsu	2012	Japan	190	-	-	IHC	9.5	(2) (3)
Lu	2012	China	20	-	-	IHC	65.0	(1)
Wang	2011	Singapore	112	76/36	-	IHC	17.0	(2) (3) (4) (5)
Zhang	2011	China	99	69/30	29~83	IHC	29.3	(1) (2) (3)
Ishigami	2010	Japan	97	69/28	40~85	IHC	27.8	(2) (3) (4)
Zhao	2010	China	336	274/62	18~85	IHC	57.4	(3) (5)
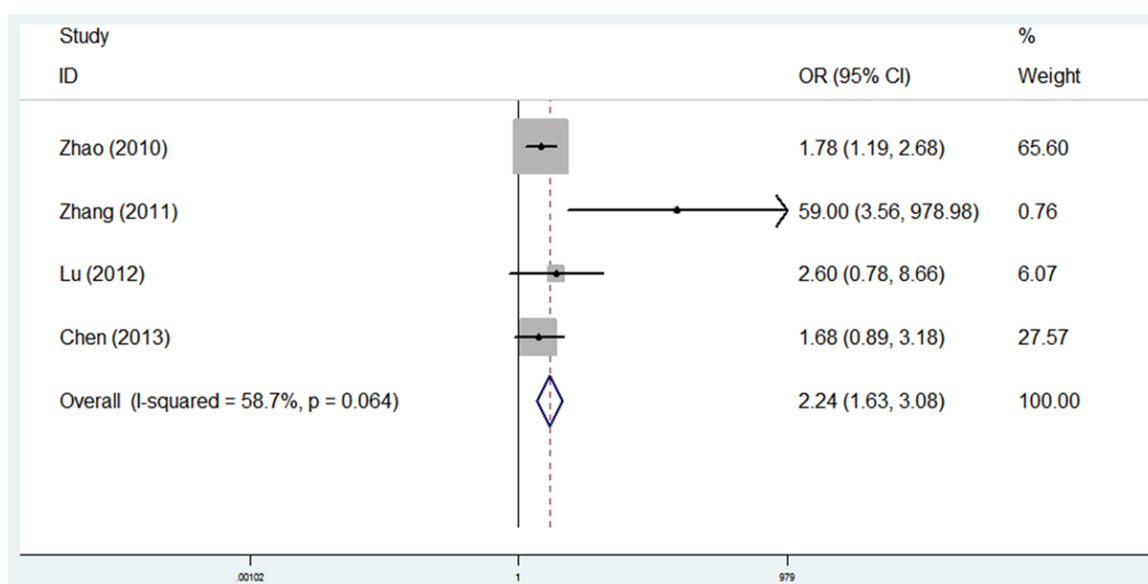
Figure 2. Meta-analysis of high expression of CD133 in stomach cancer group and control group.

of stomach cancer was proven by histopathologic analysis. (3) CD133 expression should be evaluated in primary stomach cancer tissue. (4) The data provided must be sufficient to estimate either disease free survival (DFS) or overall survival (OS).

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, and CD133 expression. 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 stomach cancer only by Kaplan-Meier curve, the software Engauge Digitizer 4.1 (http://sourceforge.net/projects/digitizer/) was utilized to extract the relevant data.

Statistical analysis

All statistical tests were two-sided, and all statistical analyses were carried out with SPSS 16.0 and Stata Statistical Software 13.0. A random effects model was used to estimate pooled ORs in order to take into account the heterogeneity of the risk estimates and to provide more conservative estimates compared with the fixed effects model. 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. A significant heterogeneity was defined as a P value <0.10. To investigate potential sourc-
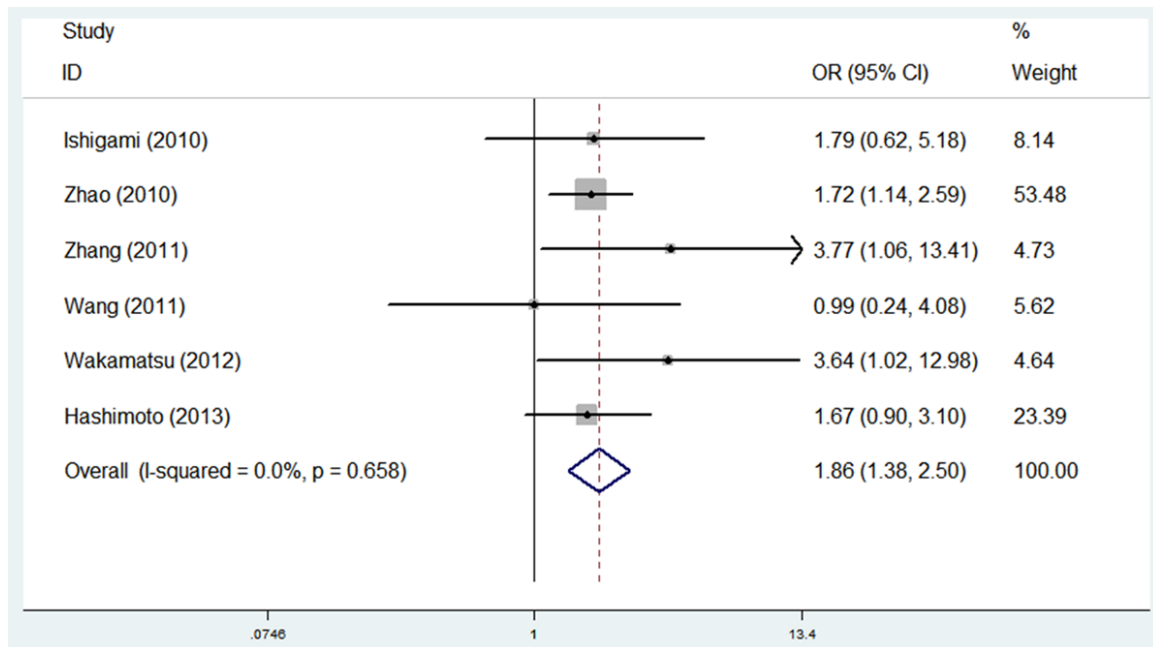
Figure 3. Meta-analysis of high expression of CD133 in positive and negative lymph node metastasis stomach cancer group.
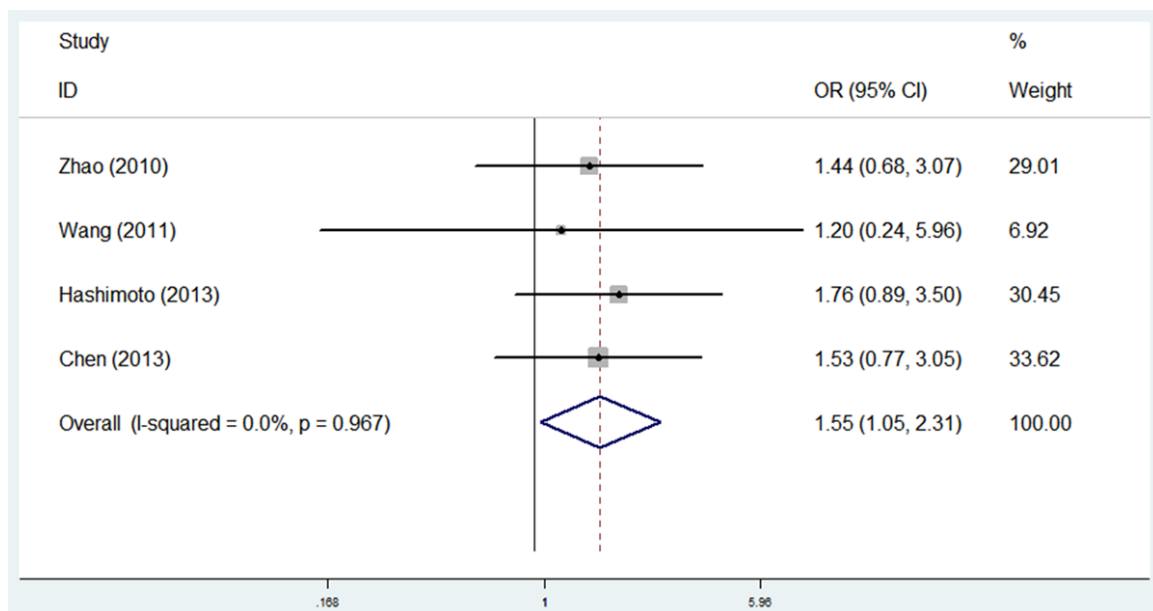
Figure 4. Meta-analysis of high expression of CD133 in positive and negative distant metastasis stomach cancer group.

es of between studies heterogeneity, subgroup analyses was conducted. Also, sensitivity analyses were carried out to assess whether the summary estimates are robust to inclusion of studies. Bias was assessed using the tests by Egger, and Begg, and the contour enhanced funnel plots.
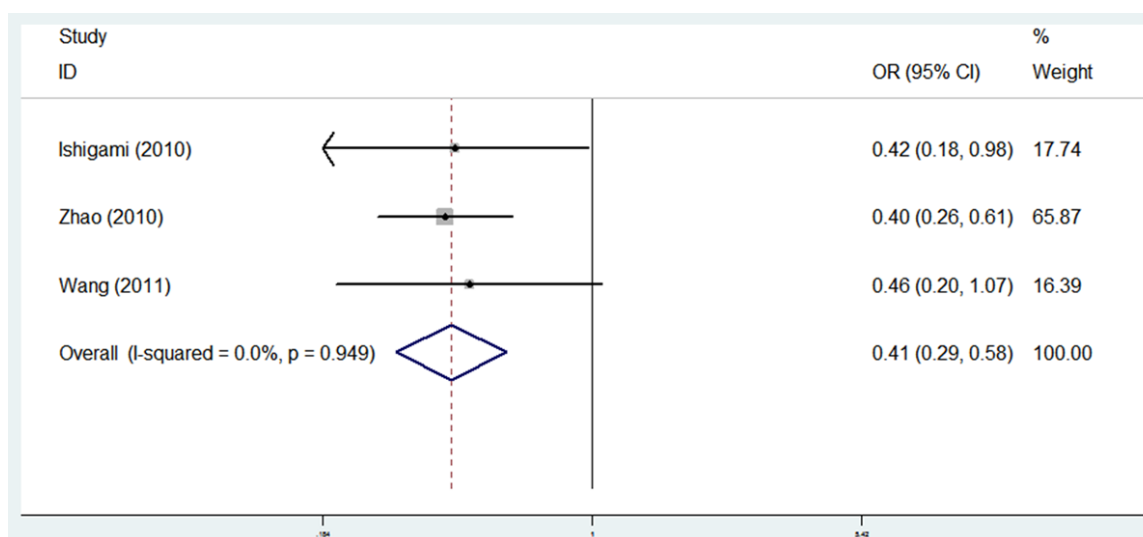
Results

Study selection and characteristics

Figure 1 summarizes the process of study identification, exclusion, and inclusion. After the removal of all studies that did not meet our crite-
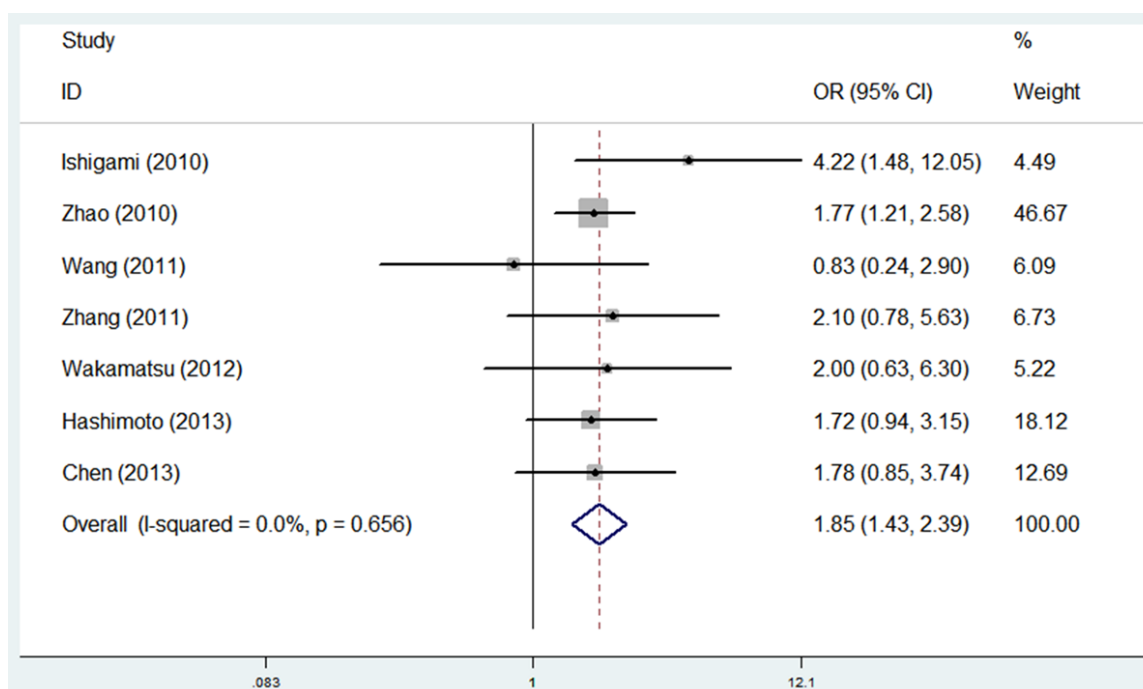
Figure 5. Meta-analysis of high expression of CD133 in III-IV stage group and I-II stage group.

Figure 6. Meta-analysis of 5-year overall survival between positive and negative CD133 group.

ria, eight studies [16-23] from 767 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 2010-2013. All the studies were conducted in Asian population, four from China, three from Japan, and one from Singapore. A total of 1195 patients were included, the majority of the patients were male.

Correlation of CD133 with clinicopathological parameters

The association between CD133 and several clinicopathological parameters was illustrated in **Figures 2-5**. High expression of CD133 correlated with stomach cancer group (OR = 2.24, 95% CI 1.63-3.08). Moreover, High expression of CD133 was also associated with positive lymph node metastasis, positive distant metas-

tasis and III-IV stage cases, leading to a risk difference of 1.86 (95% CI 1.38-2.50), 1.55 (95% CI 1.05-2.31) and 1.85 (95% CI 1.43-2.39), respectively.

Correlation of CD133 with 5-year overall survival

The relationship between CD133 expression and the risk of CRC was illustrated in **Figure 6**. Three reports [20, 22, 23] in regard to the association of CD133 and 5-year OS rate could be obtained from published information. High expression of CD133 was statistically significantly associated with poor 5-year OS (OR = 0.41, 95% CI 0.29-0.58).

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, S4, S5), suggesting that the results of the meta-analysis were robust.

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

Summary

At present, CSCs have drawn widespread attention because of their potential roles in tumorigenesis, tumor maintenance, spread and relapse. Such cells are hypothesized to persist in tumors as a distinct population and cause relapse and metastasis by giving rise to new tumors. Therefore, development of specific therapies targeted at CSCs holds hope for improvement of survival and quality of life of stomach cancer patients. CD133 is also considered a useful marker to identify the CSCs and its expression has been shown to have prognostic significance in stomach cancer patients.

Many medical centers have evaluated the association between CD133 expression and the clinical and pathological features of stomach cancer patients. A study [24] from Shanghai Jiaotong University School of Medicine in China suggested that CD133 may contribute to the resistance of stomach cancer cells to chemotherapy drug through P-gp, Bcl-2 and Bax, suggesting PI3K/Akt signal pathway involved in this process. Subsequently, a case-control study [25] genotyped four selected, potentially functional CD133 SNPs (rs2240688A>C, rs7686732C>G, rs10022537T>A, and rs3130C>T), and found that compared with the miRNA binding site rs2240688 AA genotype, AC + CC genotypes were associated with significantly increased stomach cancer risk (OR = 1.52, 95% CI = 1.09-2.13); for another miRNA binding site rs3130C>T SNP, the TT genotype was associated with significantly reduced stomach cancer risk (OR = 0.68, 95% CI = 0.48-0.97), compared with CC + CT genotypes. These results proposed that CD133 miRNA binding site variants could be potential biomarkers for genetic susceptibility to stomach cancer and predictors for prognosis of stomach cancer patients. Later the results [26] from College of Medicine, The Catholic University of Koreac revealed that CD133-positive patients had a significantly worse 5-year disease-free (28.1% vs. 65.8%) and overall (47.5% vs. 74.0%) survival rate than those who were CD133-negative. A multivariate analysis suggested that CD133 expression significantly affected the 5-year disease-free and overall survival. In contrast, a study [27] from Tokyo Medical and Dental University in Japan revealed that CD133(+) cell lines formed well-differentiated tumors while CD133(-) formed poorly differentiated ones. And CD133(+) was never found on poorly differentiated diffuse-type cells. Thus, loss of expression of CD133 might be related to gastric tumor progression. Such conflicting options made it difficult to establish CD133 as a significant marker to predict the clinical outcomes and prognosis for stomach cancer patients.

So based on the previous literatures, we systematically reviewed the correlation between levels of CD133 expression and stomach cancer. This present study demonstrates that high expression of CD133 is significant associated with lower 5-year overall survival (OS). Besides,

high expression of CD133 also relates with positive lymph node metastasis, positive distant metastasis, III-IV stage. Thus, these results suggest that level of CD133 expression is correlated with a number of adverse parameters that are traditionally associated with poor prognosis and may be useful as a novel independent prognostic factor.

Recently, some other cell surface molecules such as CD44, CD24, CD166 and EpCAM have been verified as putative CSC markers in CRC (colorectal cancer). Undoubtedly, the combination of these markers could provide a better selection of CSCs. Horst D, et al. [28] 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 CRC. 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. [29] 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 [30], 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. [31] 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. [32] 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 stud-

ies 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 stomach cancer 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 poor prognosis, including lymph node metastasis, distant metastasis, advanced clinical stage. Thus, CD133 may have a predictive role and be helpful tool in the management of patients with stomach 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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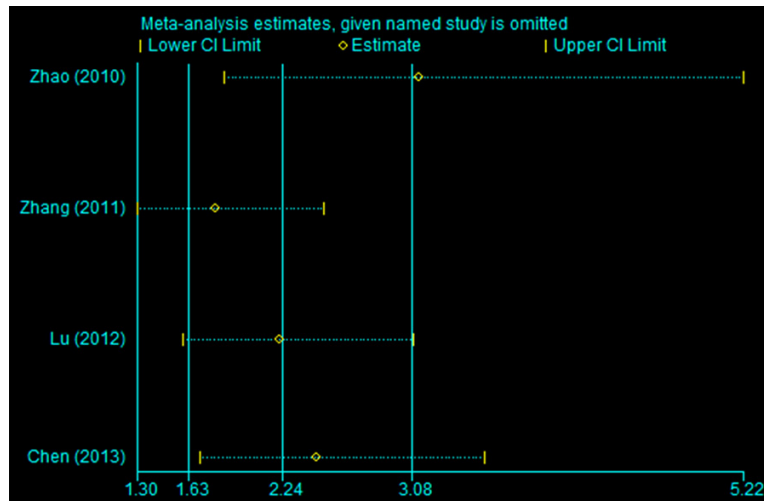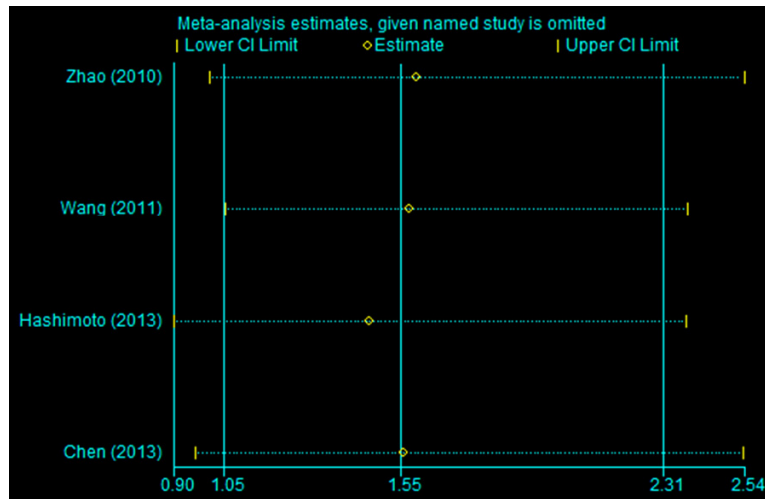
Figure S1. Sensitivity analysis of high expression of CD133 in stomach cancer group and control group.
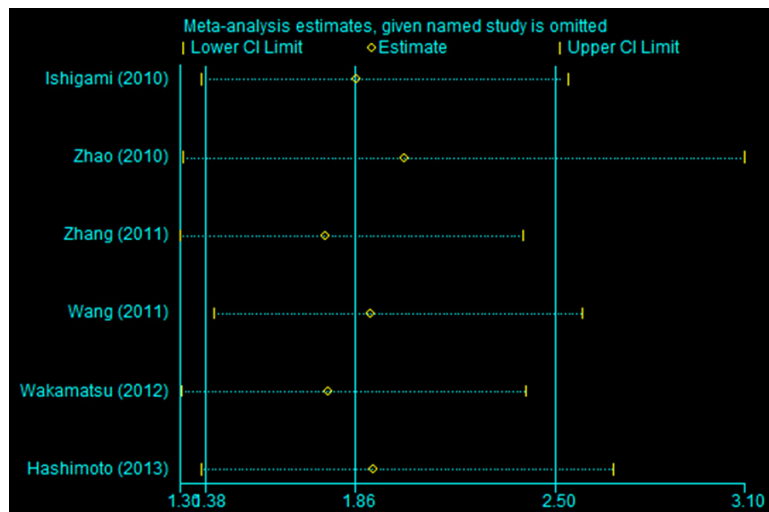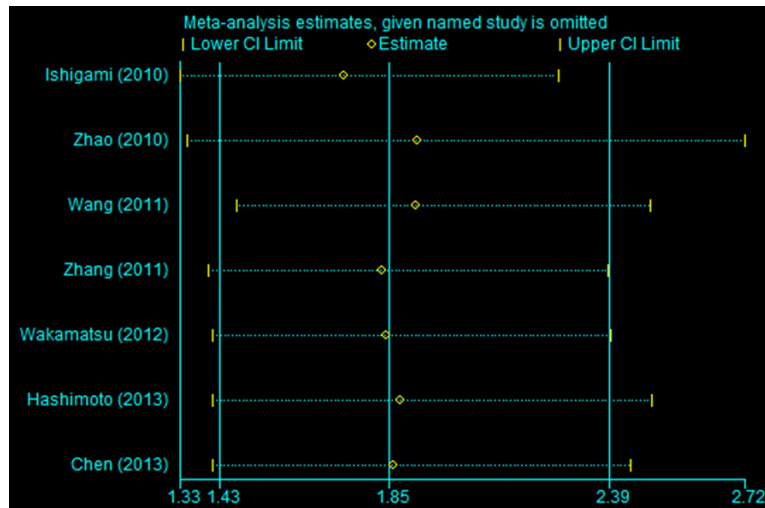

Figure S2. Sensitivity analysis of high expression of CD133 in positive and negative lymph node metastasis stomach cancer group.

Figure S3. Sensitivity analysis of high expression of CD133 in positive and negative distant metastasis stomach cancer group.

Figure S4. Sensitivity analysis of high expression of CD133 in III-IV stage group and I-II stage group.
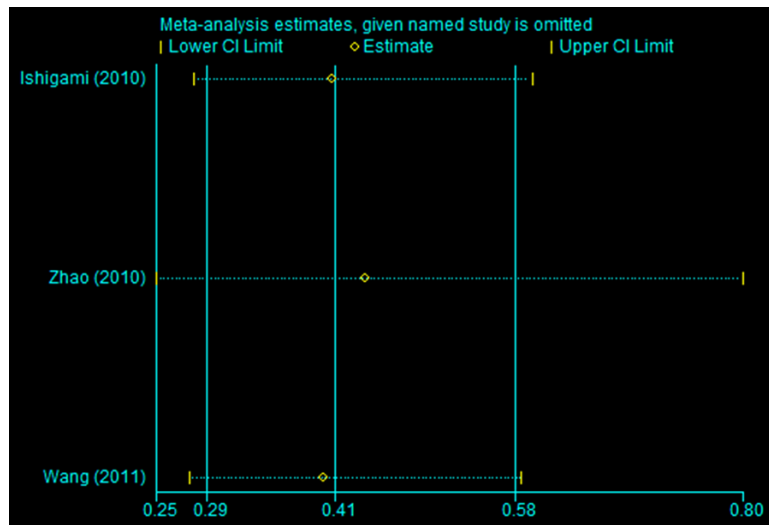
Figure S5. Sensitivity analysis of 5-year overall survival between positive and negative CD133 group.