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Original Article

Clinicopathological significance of cancer stem cell markers in nasopharyngeal carcinoma: a meta-analysis

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Abstract: It is uncertain between cancer stem cell (CSC) markers and clinical features in nasopharyngeal carcinoma (NPC). In this study, we conducted a meta-analysis to explore the relationship between CSC markers and clinical features. The relevant literatures were searched by PubMed, Web of Science, Wanfang Data and China National Knowledge Infrastructure for CSC markers and clinical features in NPC until May 2016. All results were analyzed with fixed or random-effects model, using odds ratios (OR) with 95% confidence interval (CI). 20 included articles were comprised with 1703 cases in the meta-analysis. Using random-effects model, we found ALDH1 was significantly associated with clinical grading (OR=0.14, 95% CI=0.07-0.31, P<0.00001). Similarly, CSC markers were correlated with metastasis (OR=2.40, 95% CI=1.68-3.41, P<0.00001), including CD44 (OR=2.43, 95% CI=1.44-4.11, P=0.0009), ALDH1 (OR=2.36, 95% CI=1.48-3.75, P=0.0003) and ABCG2 subgroups (OR=8.95, 95% CI=3.06-26.20, P<0.0001). In fixed-effects model, the distinct association between differentiation and CD133 was revealed (OR=2.57, 95% CI=1.37-4.82, P=0.003). However, there was no obvious correlation between CSC markers and gender. The results indicated that CSC markers were associated with clinical grading, metastasis and differentiation, except sexuality in NPC. Therefore, CSC markers might be the accessorial indexes for diagnosis, treatment and prognosis of NPC.

Keywords: Cancer stem cell markers, nasopharyngeal carcinoma, clinic features, meta-analysis, metastasis

Introduction

Nasopharyngeal carcinoma (NPC) is one of the aggressive head and neck carcinomas. Recently in South China, the incidence and mortality of NPC are progressively increased [1]. Radiotherapy and chemotherapy are the main clinic treatments for the early-stage NPC. Nevertheless, recurrence and metastasis are the major reasons for failure treatment [2]. Currently, there are no valuable prognostic and therapeutic biomarkers for NPC metastasis and recurrence.

Cancer stem cell (CSC) is considered as the important role of self-renewal, drug-resistance, metastasis, differentiation and tumorigenesis [3]. Using surface markers, CSC has been detected in different kinds of solid tumor, including breast cancer, liver cancer, brain cancer, prostate cancer [4-7]. In NPC, CD44, ALDH1, CD133 and ABCG2 are regarded as the valid CSC markers [8-12]. However, the relationship between these CSC markers and clinical features has not been reported in NPC.

Accordingly, we conduct a meta-analysis for quantitative assessment of the association between CSC markers (CD44, ALDH1, CD133 and ABCG2) and clinical features (clinical grading, metastasis, differentiation and sexuality). These results may not only reveal the clinical significance of CSC markers in NPC, but also benefit for finding the potential targets.

Materials and methods

Search strategy

Initially, we searched the database, including PubMed, Web of Science, Wan Fang Data and China National Knowledge Infrastructure until

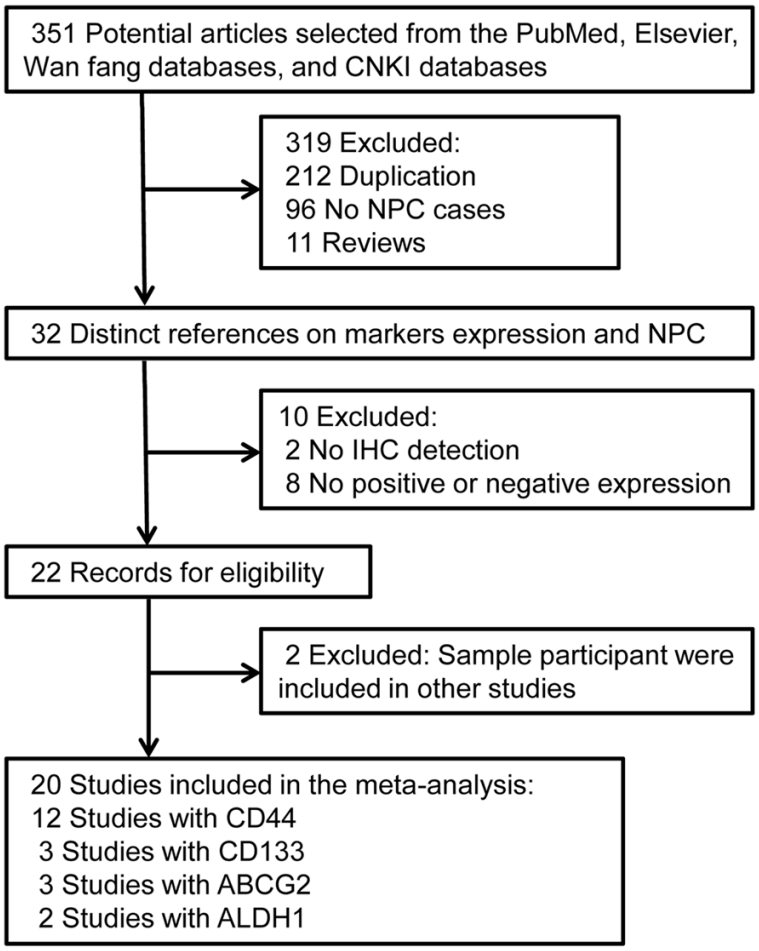

Figure 1. Flow chart for articles included in the meta-analysis.

May 2016. These keywords were combined for searching, such as nasopharyngeal carcinoma ("nasopharyngeal cancer", "NPC"), CD133 ("AC133", "prominin-1"), CD44, ALDH1 ("Aldehyde dehydrogenase"), ABCG2, clinical grading, metastasis, differentiation and sexuality. Overall retrieved studies were published in Chinese and English.

Selection criteria

Studies were included with the following criteria: (1) patients pathologically diagnosed NPC; (2) identification of clinical grading and metastasis according to the tumors node metastasis (TNM) system of the International Union against Cancer and the American Joint Committee on Cancer; (3) involvement of any CSC markers (CD44, ALDH1, CD133 or ABCG2). Accordingly, exclusion criteria were used: (1) repeated papers and reviews; (2) studies in cell lines or animals; (3) mRNA level of CSC markers; (4) unclear numbers or groups. The eligibility of each publication was independently identified by two reviewers, and different opinions were resolved by discussion or a third party.

Data extraction

According to the references' data, we combined moderate and high level of CSC markers as positive expression, while low and negative level as negative expression. Clinical grade I and II were combined as early stage, while grade III and IV as late stage. The following information were extracted from included studies: first author, publication year, research technique, cases' age and number, number of CSC markers positive expression in clinical grading, metastasis, differentiation and sexuality.

Statistical analysis

We evaluated the association between positive expression of CSC markers and clinic features, including clinical grading (I+II vs III+IV), metastasis (metastasis vs no-metastasis), differentiation (differentiation vs undifferentiation), gender (male vs female). OR with 95% CI were calculated, and $P<0.05$ was regarded as a statistical significance. Using chi-squared-based Q test and I^2 statistics, heterogeneity among studies were evaluated with *P* and I^2 value ($P<0.10$ or $I^2>50\%$). If I^2 value was more than 50%, a random-effects model was applied for the analysis, otherwise a fixed-model was used. Publication bias of study was evaluated by the funnel plot ($P<0.05$ was regarded of significant publication bias). Sensitivity analysis was performed by excluding 1 study each time to assess its affection on the overall analysis. The meta-analysis was performed using Review Manager version 5.3 (The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark) and sensitivity analysis was

Table 1. Characteristics of the studies

References	Age	Case (n)	Markers	Marker +/Male	Marker +/Female	Marker +/I, II	Marker +/III, IV	Marker +/ Metastasis	Marker +/ Non-metastasis	Technology
Li et al., 199914	44.5	50	CD44	NS	NS	11/21	6/19	12/30	5/10	IHC
Sun et al., 201119	46.8	73	CD44	NS	NS	NS	NS	18/25	9/25	IHC
Liu et al., 199917	43.9	65	CD44v6	NS	NS	12/17	46/56	40/45	18/28	IHC
Su et al., 200023	46.5	229	CD44v6	NS	NS	82/102	109/127	64/74	109/137	IHC
Zhuo et al., 200121	44.5	56	CD44v6	NS	NS	NS	NS	35/37	11/19	IHC
Zhou et al., 200222	43	116	CD44v6	29/85	13/31	NS	NS	40/60	22/56	IHC
Gu et al., 200213	43.9	40	CD44v6	NS	NS	NS	NS	27/47	7/18	IHC
Ma et al., 200318	45	96	CD44v6	NS	NS	7/12	27/47	27/49	7/10	IHC
Li et al., 200415	45	59	CD44v6	19/77	5/19	5/19	19/77	43/74	17/22	IHC
Wang et al., 200620	56.5	45	CD44v6	NS	NS	NS	NS	10/34	9/14	IHC
Li et al., 201016	43	48	CD44v6	NS	NS	NS	NS	22/25	4/20	IHC
Cai et al., 201024	43	62	CD44v6	NS	NS	NS	NS	34/38	14/24	IHC
Luo et al., 201225	NS	105	ALDH1	32/82	9/23	3/28	38/77	24/48	17/57	IHC
Wu et al., 201327	NS	122	ALDH1	37/92	11/30	5/33	43/89	12/15	40/107	IHC
Luo & Yao., 201426	NS	122	ALDH1	19/92	7/30	0/33	26/89	14/52	12/70	IHC and IF
Wang, 201230	50	135	CD133	16/38	8/18	7/24	17/32	17/30	7/26	IHC
Fu et al., 201428	49.9	112	CD133	37/89	10/23	NS	NS	9/28	21/68	IHC
Tan et al., 201529	49	56	CD133	31/96	17/39	NS	NS	12/37	23/75	IHC
Shen et al., 201232	50.7	34	ABCG2	NS	NS	NS	NS	20/29	0/5	IHC
Huang et al., 201531	46	63	ABCG2	23/38	16/25	12/27	27/36	12/39	2/24	IHC

IHC, immunohistochemistry; IF, immunofluorescence; NS, not specified.

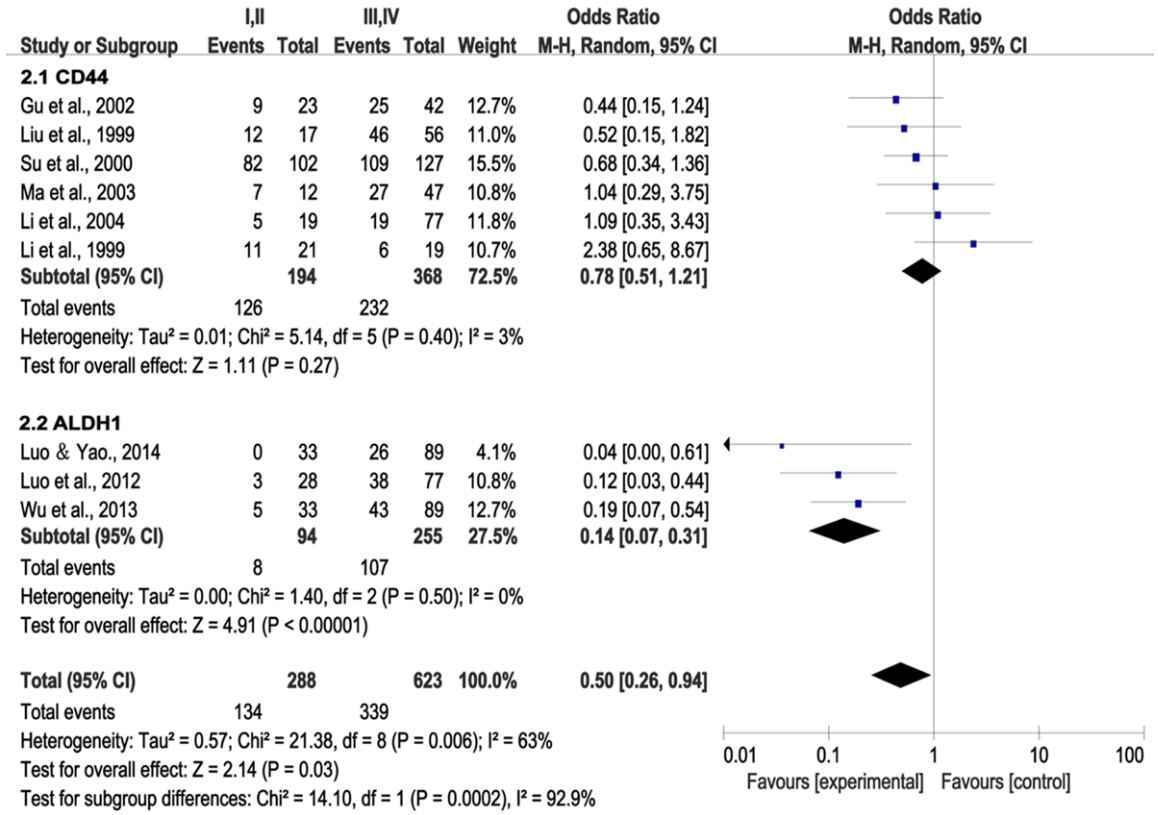

Figure 2. The forest plot between CSC markers and clinical grading I, II versus III, IV in random-effects model.

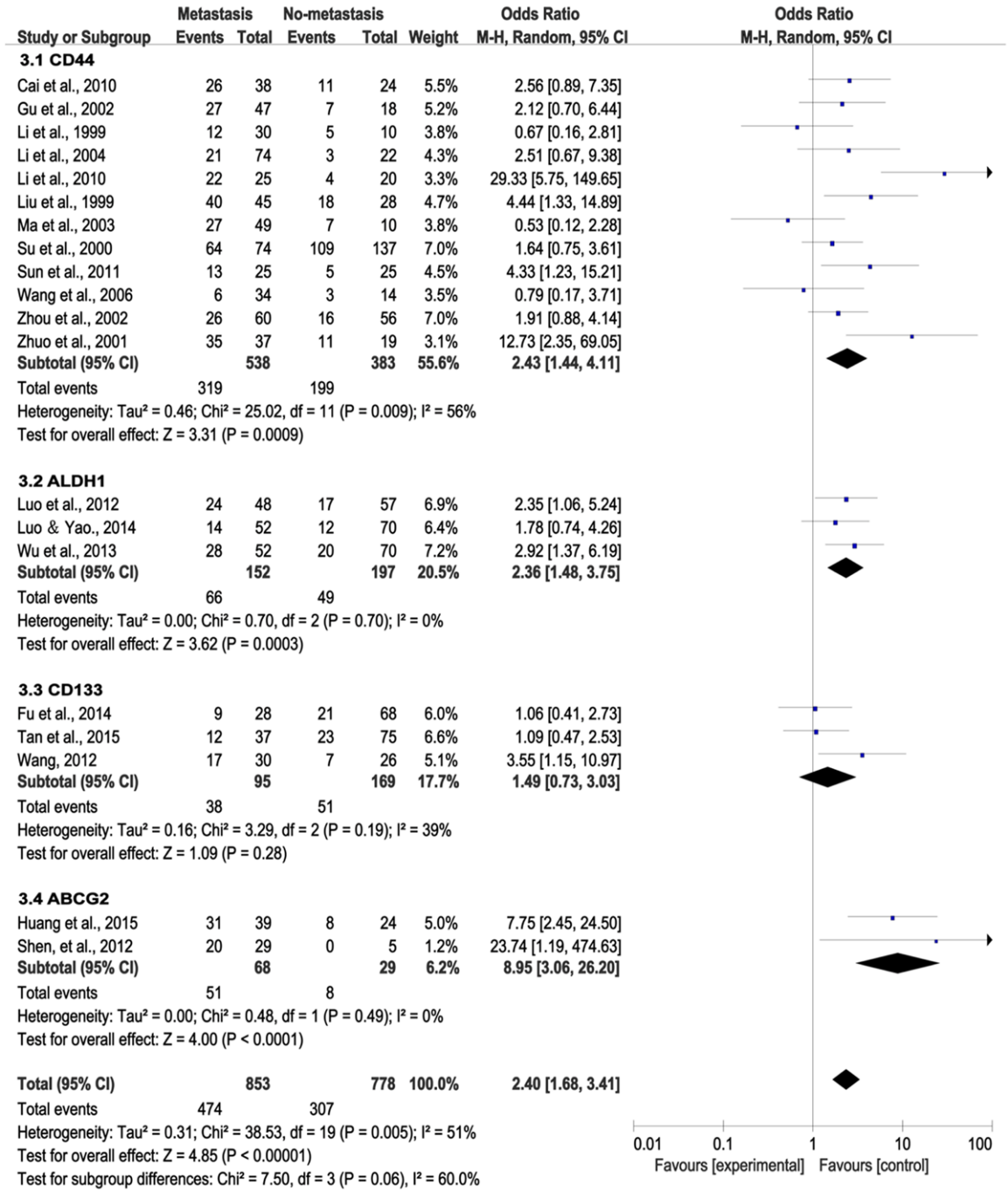

Figure 3. The forest plot between CSC markers and metastatic versus non-metastatic NPC in random-effects model.

done by STATA version 10.0 (Stata Corporation, College Station, TX) software.

Results

Characteristics of studies

Based on the search criteria, 351 publications were retrieved. A flow chart illustrating the study selection process was presented in **Figure 1**. Finally, 20 articles were included through inspecting each article. Among them, there were 12 articles about CD44 [13-24], 3 publications about ALDH1 [25-27], 3 papers related to CD133 [28-30], and 2 literatures associated with ABCG2 [31, 32]. In the aggregate, there were 1703 patients (**Table 1**).

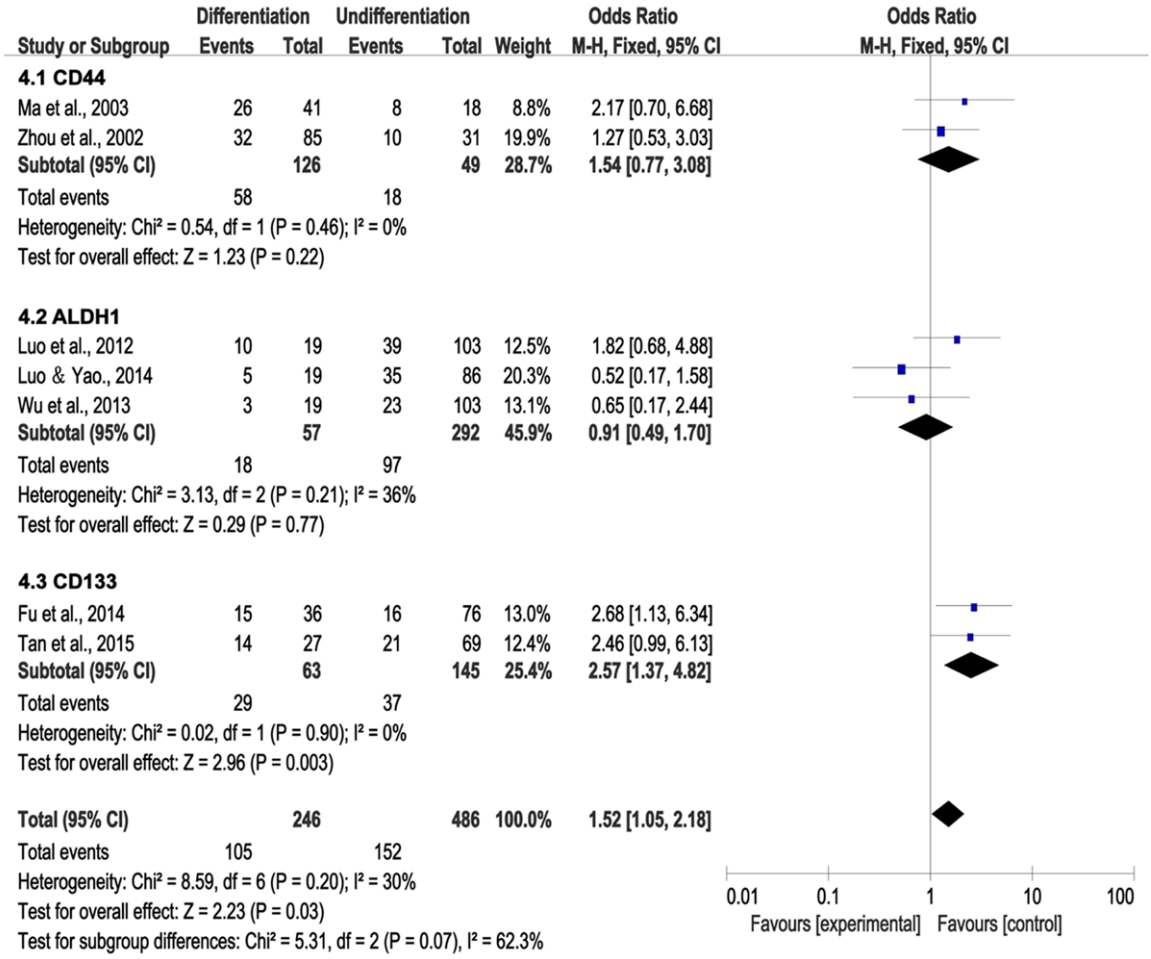

Figure 4. The forest plot between CSC markers and differentiation versus undifferentiation in fixed-effects model.

CSC markers with clinical grading

At first, we used fixed-effects model. But total I^2 was 67% more than 50% (Date not shown). So random-effect model was applied. Overall analysis reflected that CSC markers were related with clinical grading in NPC (OR=0.5, 95% CI=0.26-0.94, P=0.03), especially in late stage (clinical stage III and IV). ALDH1 was statistically associated with clinical stage (OR=0.14, 95% CI=0.07-0.31, P<0.00001), not CD44 (OR=0.78, 95% CI=0.51-1.21, P=0.27) (**Figure 2**).

Association of CSC markers with metastasis

Random-effects model was used because total I^2 of fixed-effects model was 51% (Date not shown). The overall analysis showed that expression of CSC markers was associated with metastasis of NPC (OR=2.40, 95% CI=1.68-3.41, P<0.00001). Further analyzing, the subgroups' data indicated significant relation between CD44 (OR=2.43, 95% CI=1.44-4.11, P=0.0009), ALDH1 (OR=2.36, 95% CI=1.48-3.75, P=0.0003), ABCG2 (OR=8.95, 95% CI=3.06-26.20, P<0.0001) and metastasis. Contrarily, no conspicuous correlation was detected between CD133 and metastasis (OR=1.49, 95% CI=0.73-3.03 P=0.28) (**Figure 3**).

Correlation between CSC markers and differentiation

The results of fixed-effects model analysis revealed that CSC markers were associated with differentiation (OR=1.52, 95% CI=1.05-2.18, P=0.03). In subgroups' analyses, significant association between CD133 and differentiation was detected (OR=2.57, 95% CI=1.37-4.82, P=0.003), not CD44 (OR=1.54 95%

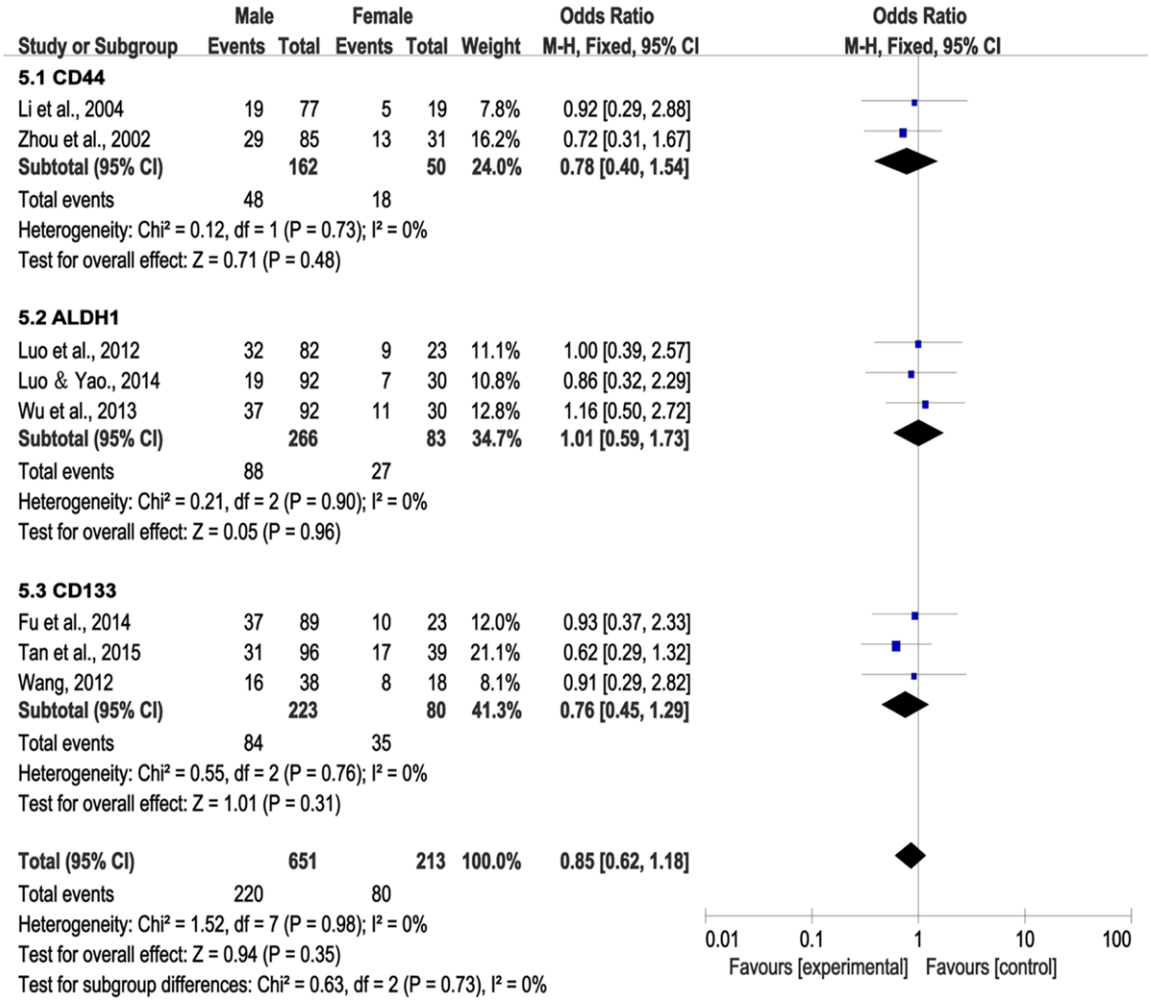

Figure 5. The forest plot between CSC markers and gender in fixed-effects model.

CI=0.77-3.08, P=0.22) and ALDH1 (OR=0.91, 95% CI=0.49-1.70, P=0.77) (**Figure 4**).

CSC markers with gender in NPC

There were 8 studies about CSC markers and gender, involving 2 essays about CD44, 3 articles about ALDH1 and 3 manuscripts about CD133. The results suggested that CSC markers were not obviously correlated with gender (OR=0.85, 95% CI=0.62-1.18, P=0.35), even in CD44 (OR=0.78, 95% CI=0.40-1.54, P=0.48), ALDH1 (OR=1.01, 95% CI=0.59-1.73, P=0.96) or CD133 subgroup (OR=0.76, 95% CI=0.45-1.29, P=0.31) (**Figure 5**).

Publication bias and sensitivity analysis

Publication bias was identified by the funnel plot (**Figure 6**). Because the I^2 of CD44 subgroup was 56% in **Figure 3**, we conducted a sensitivity analysis to check the influence of individual study on the overall effect, especially in CD44. The meta-analysis was not dominated by any single study, and exclusion of any study at a time made no difference (Date not shown).

Discussion

NPC is a high incidence of squamous cell carcinoma with high metastasis and low cure rate [1]. CSC has been regarded as the crucial role of tumor growth, differentiation and metastasis in NPC [25, 33-36]. Hence CSC markers combining with clinicopathologic features would provide the valid way for diagnosis, classification and prognosis. In this study, we designed the meta-analysis to reveal the relation between CD44, ALDH1, CD133, ABCG2 and

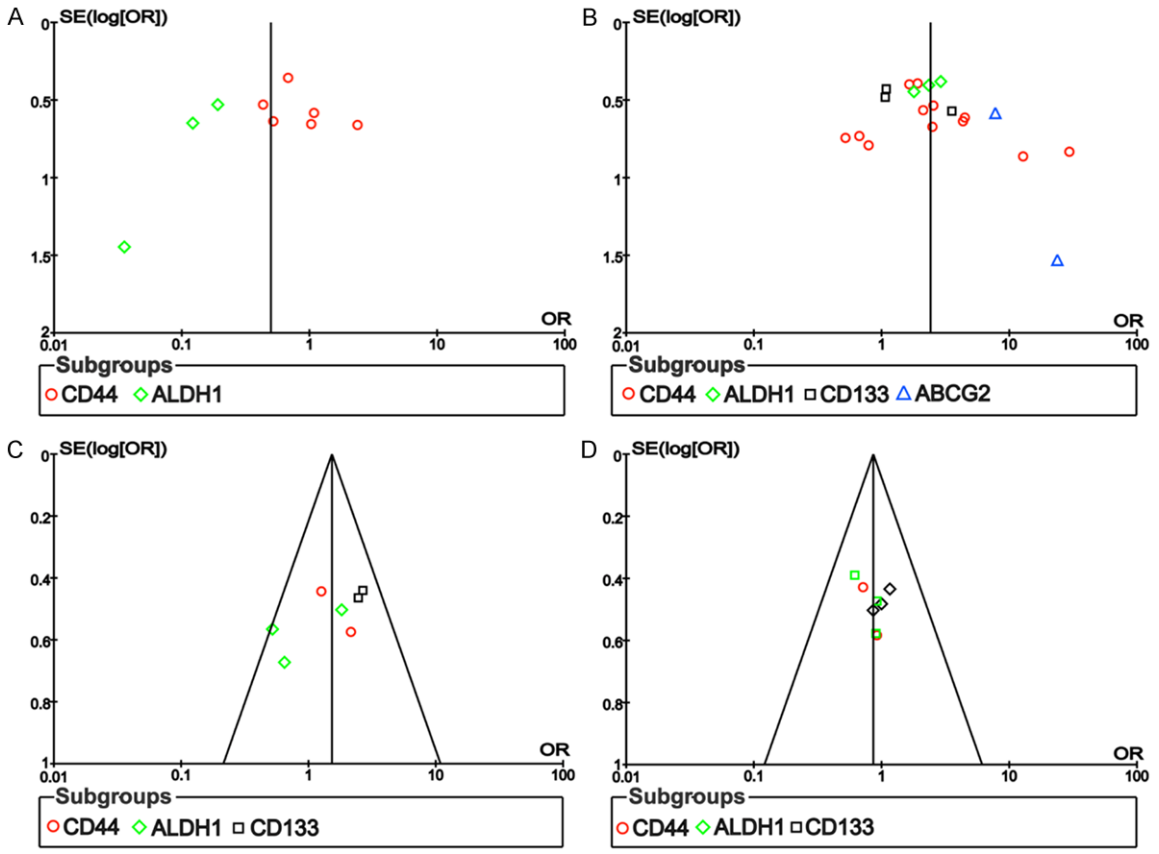

Figure 6. Funnel plot of the logarithm of the odds ratio (OR). A: Clinical grading; B: Metastasis; C: Differentiation; D: Sexuality.

clinical grading, metastasis, differentiation, sexuality in NPC. We found that ALDH1 was associated with clinical grading and metastasis. CD44 and ABCG2 were related to metastasis. CD133 was only connected with differentiation. There was no correlation between 4 markers and sexuality.

Metastasis is accompanied with the structural change of cell-extracellular matrix (ECM) [37]. CD44 can modify ECM structure through regulating the major receptor. Effect of CD44 on tumor metastasis has been confirmed in different kinds of cancer [38-41]. Consistent with previous studies, we also found CD44 had affiliation with metastasis in NPC. However, there are no correlation between CD44 and metastasis in colorectal cancer [42] and laryngeal squamous cell carcinomas [43]. These confusing results suggest the different effect of CD44 in various tumors. While, anti-CD44 antibodies in preclinical and clinical trial imply that CD44 would be potential therapy target in sensitive cancer [44, 45].

The clinic value of ALDH1 remains uncertain. On one hand, the results indicate that ALDH1 is significantly correlated with differentiation, metastasis and tumor stage [46, 47]. On the other hand, from the pooled analyses, there is significant association between ALDH1 and histological grade, not tumor size, metastasis, chemotherapy, and overall survival [48, 49]. Partly confirmed, we found the relation between ALDH1 and clinical grading and metastasis in NPC. These different results may be caused by the heterogeneity of tumor types.

In spite of the unknown function, CD133 has been widely considered as a CSC marker in many solid tumors [5, 8, 50]. Recently, CD133 is used as an efficient prognostic factor, associated with TNM stage, metastasis, differentiation, local recurrence and survival rate [51, 52]. In NPC, we only detected the relationship

between CD133 and differentiation, not TNM stage, metastasis or sexuality. It may partly due to the limitation of our retrieved papers.

ABCG2 is recognized as a resistance factor. Clinical analysis reveals that ABCG2 is associated with carcinogenesis, progression, metastasis and poor prognosis [47, 53]. In NPC, we investigated the conspicuous connection between ABCG2 and metastasis. However only 2 papers about ABCG2 and metastasis were retrieved. Thus, it is impossible to analyze whether ABCG2 is relevant to other clinical features except metastasis.

Generally, our research still has some shortages. Firstly, only 4 common CSC markers of NPC were selected. Other CSC markers in NPC also need to be analyzed. Secondly, because of the low incidence of NPC in the world, some CSC markers analyses are restricted by the limited articles. For example, there are only 2 papers about ABCG2 and clinical features. Thirdly, clinical features should be expanded more valuable for patients' classification and clinical prognosis, such as chemotherapy outcome, overall survival. Then, updating the data should be necessary. Fourthly, in this study, 1,703 cases are included in 20 papers. In the future, enlargement of cases might be more supportable and reliable. Finally, involved manuscripts are published in English or Chinese from the scientist in South China. Potentially high-quality articles in other languages were ignored due to the difficulties in translation.

Altogether, this research provides credible evidence to support the association between CSC markers and clinical features. This research might help us understand the clinical significance and expand the application of CSC markers in NPC

Acknowledgements

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Disclosure of conflict of interest

None.

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