Int J Clin Exp Med 2017;10(2):2285-2295
www.ijcem.com /ISSN:1940-5901/IJCEM0031681

Original Article

The prognostic value of C-X-C chemokine receptor 4 in non-small cell lung cancer: a meta-analysis

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Received May 4, 2016; Accepted July 26, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: This study aims to better define the roles of CXCR4 in mediating and/or modulating and prognosis of CXCR4 in NSCLC. 10 publications were included by searching PubMed, Scopus, EMBASE, and CENTRAL databases. Primary outcomes were overall survival (OS) and disease-free survival (DFS). Effect sizes were summarized using Hazard ratios (HRs) and their 95% confidence intervals (CIs). The results revealed CXCR4 expression did not significantly correlate with prognosis according to OS and DFS in NSCLC patients. However, high CXCR4 expression was significantly associated with poor prognosis of OS in ≤ 70% stage I NSCLC (HR, 1.79; 95% CI, 1.36-2.37; P=0.000), while that was reverse in > 70% stage I (HR, 0.49; 95% CI, 0.32-0.75; P=0.001). Additionally, high CXCR4 expression was significantly correlated with poor OS in Asian subgroup (HR, 2.11; 95% CI, 1.57-2.85; P=0.000), and was significantly associated with poor OS in less male group (≤ 70% male; HR, 1.88; 95% CI, 1.28-2.77; P=0.001), but no significant association between high CXCR4 expression and OS was found in follow-up period subgroups. High CXCR4 expression might potentially allow for prediction of OS in ≤ 70% stage I NSCLC, since it was associated with increased survival for > 70% stage I NSCLC. Besides, Asian was a much worse factor for prognosis of advanced NSCLC patients, whose CXCR4 was overexpressed, and gender might be an important factor for the correlation between high CXCR4 expression and prognosis of NSCLC patients. However, larger scale trials with strict design, varied subpopulations, and long-term outcomes are needed.

Keywords: C-X-C chemokine receptor 4, non-small cell lung cancer, outcomes, prognosis, overall survival, disease-free survival

Introduction

Primary lung cancer, one of the most common tumors worldwide, is the leading cause of cancer deaths in males, and nearly 85% of lung cancer cases are represented by non-small cell lung cancer (NSCLC) [1, 2]. As we all know, metastatic spread to the regional lymph nodes, liver, bone and brain, which is characteristic of NSCLC, constitutes the primary source of morbidity and mortality [3, 4]. With the improved understanding of molecular mechanisms and processes related to metastasis of NSCLC, newer developed therapies which target specific receptors are being studied. These therapies represent opportunistic targets for engineering vehicles which localize in primary and distal lung tumors, and therefore, the search for prognostic biomarkers is becoming increasingly clinically relevant [5].

C-X-C chemokine receptors (CXCR) are G protein-linked receptors involved in cytoskeletal rearrangement, cell adhesion, and directional migration [6-9]. CXCR respond to cytokines and are integral membrane proteins from which 20 different ones have been previously identified [6]. Currently, C-X-C chemokine receptor 4 (CXCR4), a specific receptor in the chemokine receptors family, has been identified to serve as a prognostic factor which is required for cancer cells to proliferate and to migrate, and in modulation of cancer progression in solid tumors [6]. Accumulative evidence has demonstrated that CXCR4 not only induces migration of various cell types directionally, but also par-

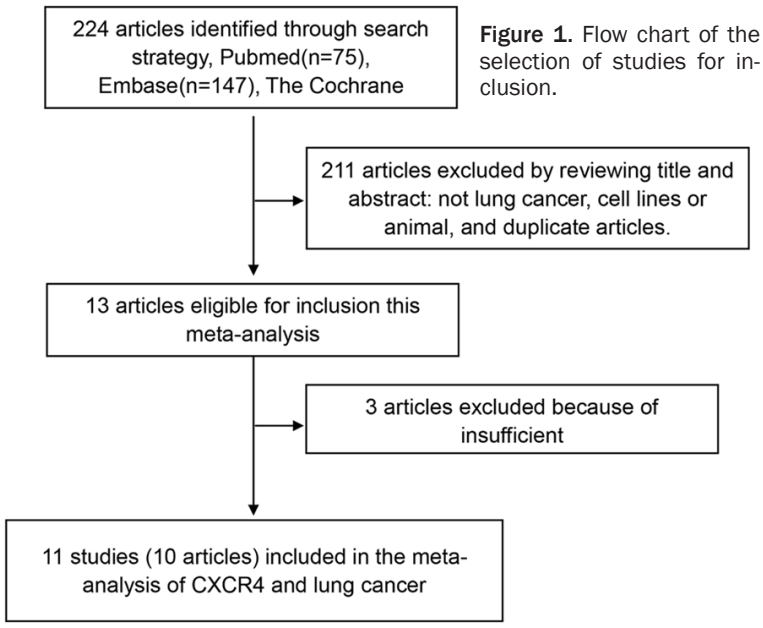

Figure 1. Flow chart of the selection of studies for inclusion.

ticipates in the growth and metastasis of tumors; however, considerable controversies remain with regard to the role of CXCR4 in NSCLC prognosis [10-12].

It has been reported that high expression of CXCR4 in cytoplasm significantly correlates with metastasis and increased morbidity in NSCLC patients [13]; on the contrary, high expression in nucleus correlates with favorable prognosis and prolonged survival [14]. Therefore, the present investigation was undertaken to ascertain whether independent predictors of prognosis, including nationality, gender, and follow-up, might have contributed to the differences in these studies. Further, we performed a current systematic review and meta-analysis focused on OS and DFS to clarify whether CXCR4 is a predictor of prognosis in patients with NSCLC.

Methods

A meta-analysis was performed based on the QUORUM (Quality of Reporting of Meta-analyses) guidelines and the recommendations of the PRISMA [15], in addition, it was registered in PROSPERO (Registration No: CRD4201501-5745).

Literature search

Primary relevant published articles were searched from PubMed (1990 to Oct. 2015), Scopus (1988 to Oct. 2015), EMBASE (1990 to Oct. 2015), and the Cochrane Library (Issue 12 of 12, Oct. 2015), including the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessments (HTA). The search phrases were lung cancer *OR* lung carcinoma *OR* non-small cell lung cancer *OR* NSCLC *OR* lung adenocarcinoma *OR* ACC *OR* lung squamous cell carcinoma *OR* SCC *OR* lung large cell carcinoma *OR* LCC *AND* C-X-C chemokine receptor 4 *OR* CXCR4 *OR* chemokine receptor(s). The searching lists of trials, published meta-analysis, and relevant review articles were also screened manually in order to identify additional articles of this meta-analysis and to exclude any irrelevant reports.

Study inclusion and exclusion

Eligible studies met the following criteria: (1) studies included the association between the CXCR4 expression and the prognosis of NSCLC patients with OS and/or DFS; (2) all the cases were medically confirmed of NSCLC clearly; (3) all the research of outcome measured with sufficient data on survival rate or Kaplan-Meier curves. However, the following studies were excluded: (1) review articles without primary data; (2) research about cell lines or animal model trials; (3) insufficient information or unavailable data of the survival rate.

Data extraction

All the following data were independently extracted from each article using a standard data collection forms by two authors: first author name, year of publication, country, number of patients, age, gender, tumor stage, staining pattern, follow-up, and histological subtype. Primary outcomes were assigned to the overall survival (OS) and disease-free survival (DFS) during the follow-up according to the hazard ratio (HR) with 95% confidence intervals (CIs).

Table 1. Characteristics of the included studies

Studies	No. of patients	Age mean (Range)	Gender M/F	Methods	Staining patterns	High/ Low	Stage	Histologic subtype	OS/DFS	NOS score
Al Zobair, *et al*. 2013 (China)	125	59 (37-80)	87/38	IHC	Mainly cytoplasm	62/63	I: 16; II: 23; III: 55; IV: 31	ADC:64 SCC:61	OS	8
Osuka, *et al*. 2012 (Canada)	170	67 (32-88)	86/84	IHC	Cytoplasm	29/141	IV: 170	ADC:91 SCC:49 Other:30	OS	7
Wang M, *et al*. 2011 (China)	208	59.8 (35-76)	128/80	IHC	Cytoplasm	117/91	I: 88; II: 70; III: 50	ADC: 90 SCC: 106 LCC:12	OS	8
Minamiya, *et al*. 2010 (Japan)	79	62.3 (NA)	43/36	PCR	Cytoplasm and nucleus	37/42	I: 57; II: 7; III: 15	ADC:79	OS, DFS	7
Yurdakul, *et al*. 2010 (Turkey)	50	59.9 (NA)	46/4	IHC	Cytoplasm	23/27	III: 24; IV: 26	SCC:40 ADC:5 Other:5	OS	6
Iwakiri, *et al*. 2009 (Japan)	79	NA	47/32	PCR	Cytoplasm and nucleus	40/39	I: 79	ADC:53 SCC:21 Other:5	OS, DFS	8
Karen, *et al*. 2009 (USA)	16	69 (NA)	8/8	FACS analysis	Cytoplasm and nucleus	5/11	I: 2; III: 2; IV: 12	ADC:6 SCC:2 Other:8	OS	6
Wagner, *et al*. 2008 (USA)	154	67±8	46/108	IHC	Cytoplasm	47/107	I: 90; II: 19; III: 39; IV: 6	ADC:132 SCC:20 Other:2	DFS	9
Wagner, *et al*. 2008 (USA)	154	67±8	46/108	IHC	Nucleus	62/92	I: 90; II: 19; III: 39; IV: 6	ADC:132 SCC:20 Other:2	DFS	9
Suzuki, *et al*. 2008 (Japan)	90	NA	NA	IHC	NA	22/68	I: 31; II+III+IV: 59	NA	OS	6
Spano, *et al*. 2004 (France)	61	60.6 (38-84)	48/13	IHC	Nucleus	17/44	I: 61	ADC:32 SCC:22 Other:7	OS	7

Abbreviations: IHC: Immunohistochemistry; PCR: Polymerase chain reaction; FACS: Fluorescence-activated cell sorting; NA: Not applicable; SCLC: Small cell lung cancer; ADC: Adenocarcinoma; SCC: Squamous cell carcinoma; LCC: Large cell carcinoma; OS: Overall survival; DFS: Disease-free survival; NOS: Newcastle-Ottawa scale.

Table 2. Summary of bias assessment

Study	Selection			Comparability		Outcome			Quality assessment star
	Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Based on the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Al Zobair, *et al*. 2013 (China)	1	1	1	1	1	1	1	1	8
Osuka, *et al*. 2012 (Canada)	0	1	1	1	1	1	1	1	7
Wang M, *et al*. 2011 (China)	1	1	1	1	1	1	1	1	8
Minamiya, *et al*. 2010 (Japan)	0	1	1	1	1	1	1	1	7
Yurdakul, *et al*. 2010 (Turkey)	0	1	0	1	1	1	1	1	6
Iwakiri, *et al*. 2009 (Japan)	1	1	1	1	1	1	1	1	8
Karen, *et al*. 2009 (USA)	1	1	1	1	1	1	0	0	6
Wagner, *et al*. 2008 (USA)	1	1	1	1	2	1	1	1	9
Wagner, *et al*. 2008 (USA)	1	1	1	1	2	1	1	1	9
Suzuki, *et al*. 2008 (Japan)	1	1	0	1	1	0	1	1	6
Spano, *et al*. 2004 (France)	0	1	1	1	1	1	1	1	7

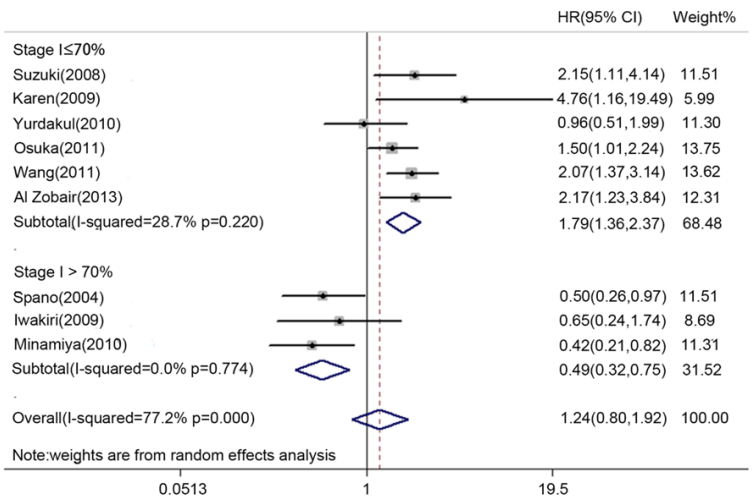

Figure 2. Forest plot: the association between CXCR4 expression and OS of NSCLC patients in group with clinical stage (stage I > 70% *vs* stage I ≤ 70%). The pooled HR for OS showed that high CXCR4 expression was significantly associated with worse survival in stage I ≤ 70% subgroup in NSCLC (HR=1.81, 95% CI, 1.38-2.37, P=0.000), while in stage I < 70% it was opposite (HR=0.49, 95% CI,0.32-0.75, P=0.001).

Quality assessment

Two reviewers assessed the quality of included studies based on the Newcastle-Ottawa scale (NOS, available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) [16]. Briefly, the quality of the studies assessment included three main categories as follows: (1) selection of cohort, (2) comparability of cohort, and (3) ascertainment of outcome. If a study mentioned one of these key points, a star mark was utilized, and the highest quality of assessment for those included studies was 9 stars (range from 0 to 9 stars). Any discrepancies were resolved by discussion among the author group.

Statistical analysis

The effect size was pooled by using HR with 95% CIs, and used as to assess the association between CXCR4 expression and survival in patients with NSCLC. Statistical analyses were performed using STATA 12.0 software (Stata Corporation, College Station, Texas). The HR and 95% CIs were extracted directly if the publications reported them originally and estimated them by using methods reported by Tierney *et al.* [17]. If the 95% CIs covered the value of 1, we considered that the difference between CXCR4 expression and survival rate in patients with NSCLC was not statistically significant. Heterogeneity was measured by both the Q statistic and I^2 statistic (I^2=0-50% represents no or moderate heterogeneity; I^2 > 50% represents significant heterogeneity), and Chi-squared test was used to calculate the effect size according to Peto's method. When the heterogeneity was not significant, fixed-effect model (Mantel-Haenszel, P > 0.1 and I^2 < 50%) was used, otherwise the random-effect model (Der Simonian and Laird, P ≤ 0.1 or I^2 ≥ 50%) was employed. Sensitivity analysis was used to assess the robustness of the pooled results. Publication bias was evaluated by the Begg rank correlation method and the Egger weighted regression method [18, 19]. All the *P*-values were two sided, and P < 0.05 was considered statistically significant.

Results

Study selection

A total of 224 citations were identified. Initially, 211 records were removed after detailed review. The remaining publications that did not provide available data between CXCR4 expression and OS/DFS were further excluded. Finally, 11 studies from 10 publications were deemed eligible for meta-analysis (**Figure 1**).

Characteristics and methodological quality of included studies

All 10 included publications and their baseline demographics, clinical characteristics, and staining patterns in a total of 1186 participants from 11 trials [13, 14, 20-27] were outlined in **Table 1**. OS was evaluated in 9 and DFS was reported in 4 publications.

The NOS score of each included study was presented in **Table 1**. The median quality score was 7.4 (range from 6 to 9). The details of quality assessment results of each included studies were listed in **Table 2**.

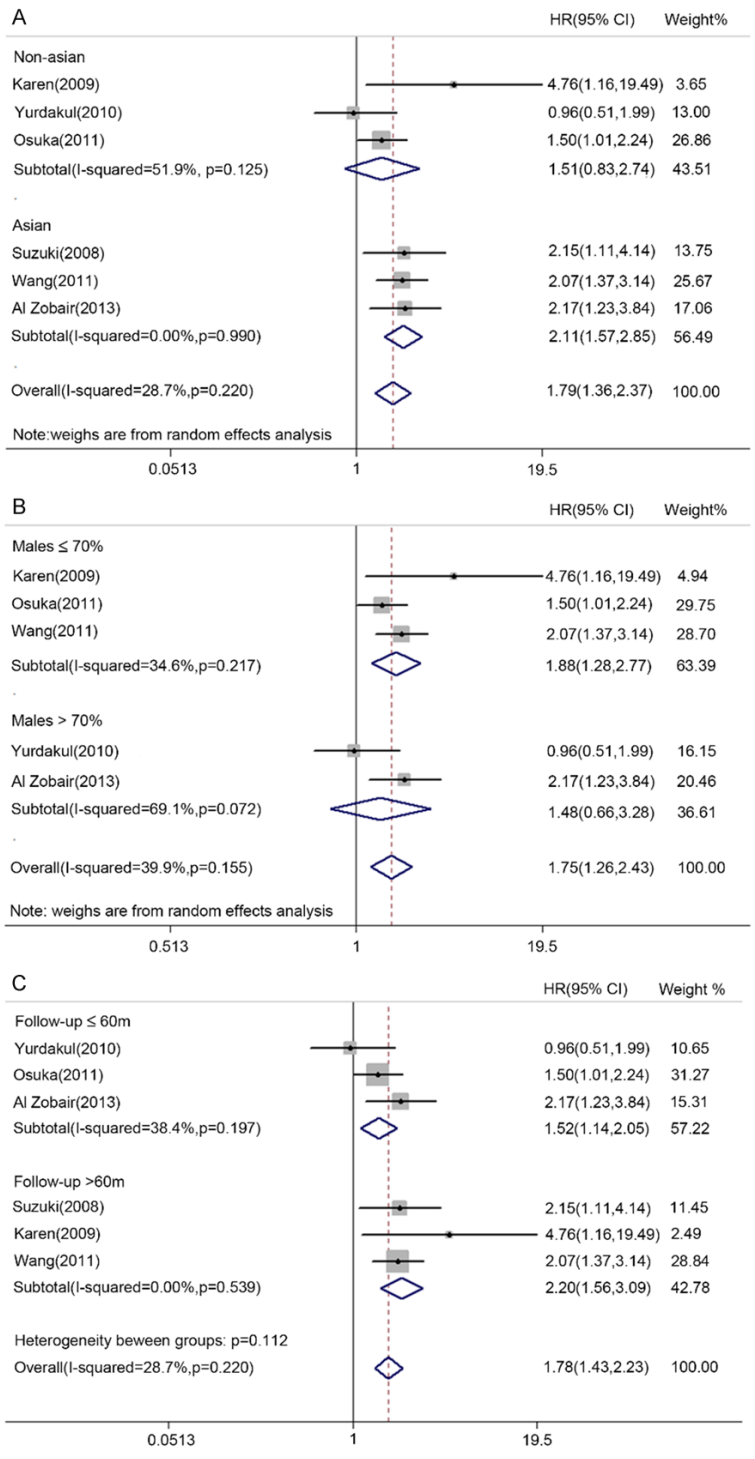

Figure 3. Forest plot: the association between CXCR4 expression and OS of NSCLC patients. Group A, nationality: non-Asian *vs* Asian; Group B, gender: male > 70% *vs* male ≤ 70%; Group C, follow-up period: > 60 m *vs* ≤ 60 m. The pooled HR for OS showed these results: A. High CXCR4 expression indicated poor prognosis in Asian NSCLC patients (HR, 2.21; 95% CI, 1.57-2.85; P=0.000; I^2=0.0%), but non-Asians did not (HR, 1.51; 95% CI, 0.83-2.74; P=0.178; I^2=51.9%). B. High expression of CXCR4 was a poor prognosis for ≤ 70% male patients (70% male; HR, 1.88; 95% CI, 1.28-2.77; P=0.001; I^2=34.6%), but not seen in > 70% male patients (HR, 1.49; 95% CI, 0.67-3.31; P=0.339; I^2=66.3%). C. The follow-up periods didn't affect the pooled results.

CXCR4 expression and OS

Nine studies reported OS results and summary effect sizes were presented in **Figure 2**. High expression of CXCR4 did not significantly correlate with poor OS (HR, 1.24; 95% CI, 0.80-1.92; P=0.346) with significant heterogeneity (I^2=77.2%). The heterogeneity most likely originated from distinct experiment results between > 70% stage I and ≤ 70% stage I, according to the included publications (> 70% stage I: number of stage I patients > 70%; ≤ 70% stage I: number of stage I patients ≤ 70%, mainly stage II+III+IV patients). Subgroup analysis according to the clinical stage revealed that high CXCR4 expression indicated poor prognosis for OS in patients with NSCLC in ≤ 70% stage I (HR, 1.79; 95% CI, 1.36-2.37; P=0.000; I^2=28.7%), while that in > 70% stage I was opposite (HR, 0.49; 95% CI, 0.32-0.75; P=0.001; I^2=0.0%).

Further subgroup analysis was performed on nationality, gender, and follow-up periods for ≤ 70% stage I NSCLC and these data were presented in **Figure 3** and **Table 3**. In nationality subgroups, high CXCR4 expression significantly correlated with poor OS in Asian group (HR, 2.11; 95% CI, 1.57-2.85; P=0.000) with less heterogeneity (I^2=0.0%), however, there was no correlation in non-Asian group (HR, 1.51; 95% CI, 0.83-2.74; P=0.178; I^2=51.9%). When grouped by gender, high CXCR4 expression was significantly associated with poor OS in less male group (≤70% male; HR, 1.88; 95% CI, 1.28-2.77; P=0.001) with less heterogene-

Table 3. Summary of subgroup analysis

Variables	No. of studies	No. of patients	Effect size	95% CI	I^2
Nationality					
Non-Asian	3	236	1.51	0.83-2.74	51.9%
Asian	3	423	2.11	1.57-2.85	0.0%
Gender					
Males > 70%	2	175	1.48	0.66-3.28	66.3%
Males < 70%	3	394	1.88	1.28-2.77	34.6%
Follow-up period (m)					
> 60 m	3	314	2.20	1.56-3.09	0.0%
≤ 60 m	3	345	1.52	1.14-2.05	38.4%

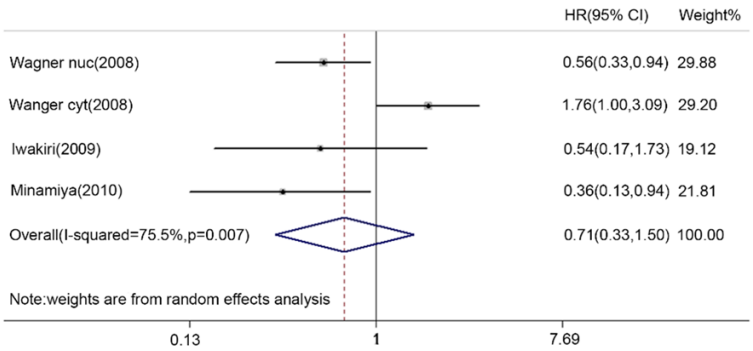

Figure 4. Forest plot: the association between CXCR4 expression and DFS of NSCLC patients. The pooled HR for DFS showed that high CXCR4 expression wasn't significant correlation with DFS (HR, 0.71; 95% CI, 0.33-1.50; P=0.365).

ity (I^2=34.6%), but the similar results didn't found in more male group (> 70% male; HR, 1.48; 95% CI, 0.66-3.28; P=0.339; I^2=69.1%). The follow-up periods didn't affect the pooled results. (> 60 m follow up periods; HR, 2.20; ≤ 60 m follow up periods; HR, 1.54).

CXCR4 expression and DFS

Four studies reported DFS results and the effect sizes were presented in **Figure 4**. There was no significant correlation between high CXCR4 expression and DFS (HR, 0.71; 95% CI, 0.33-1.50; P=0.365) with significant heterogeneity (I^2=75.5%). No further subgroup analysis was performed because of the limited number of publications.

Sensitivity analysis

Sensitivity analysis indicated the robustness of our results and it was presented in **Figure 5A**. The studies with low quality did not significantly affect the results of the present meta-analysis.

Publication bias

Both Egger's and Begg's tests revealed that there was no evidence of significant publication bias which might influence our meta-analysis results (**Figure 6**, OS: Egger's test, P=0.500; Begg's test, P=0.466; DFS: Egger's test, P=0.576; Begg's test, P=0.734).

Discussion

Although several different approaches towards NSCLC therapies, including surgical therapy, immunotherapy, radiotherapy and chemotherapy, have improved in recent years, the 5-year mortality and morbidity rescue are still limited [28]. Currently, advances in molecular biology have enabled researchers to focus on biological molecular markers. Increasing understanding from preliminary experiments has indicated that high expression of CXCR4 by tumor cells and activation of the CXCL12/CXCR4 axis are involved in the progression and metastasis of various kinds of solid tumors, including NSCLC and might contribute to unfavorable outcomes [29].

Currently, the relationship between CXCR4 and the prognosis in patients with NSCLC was uncertain because of the limited and contradictory clinical evidence. Some trials reported that high expression of CXCR4 was significantly correlated with poor prognosis in advanced stage NSCLC [20, 25], while others demonstrated it was an improved outcome in early stage NSCLC [14, 22]. Besides, many potential factors, such as nationality, gender, and follow-up periods, sub-cellular localization of CXCR4 are all important prognostic factors and contribute to clinical heterogeneity.

We attempted to access the prognostic value of CXCR4 in NSCLC and to explore the possible

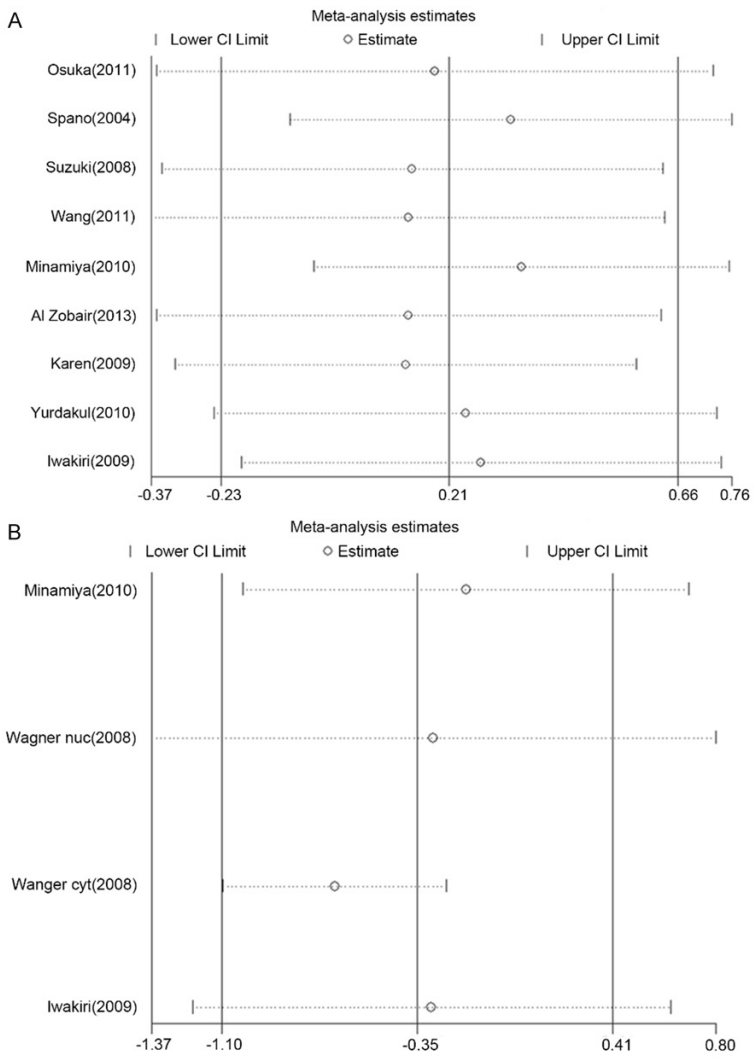

Figure 5. Sensitivity analysis of all the studies assessing OS (A) and DFS (B). Sensitivity analysis verified the robustness of our results. (A) Sensitivity analysis of 9 the studies assessing OS. (B) Sensitivity analysis of 4 the studies assessing DFS.

heterogeneity in all available clinical evidences in the current meta-analysis. To the best of our knowledge, this was the first investigation in which there was a synthesis attempted of evidence as to the relationship of CXCR4 and OS and DFS. Our meta-analysis demonstrated that neither a high expression of CXCR4 correlated with poor OS nor DFS. In further subgroup analysis, it was found that heterogeneity was likely derived from the different proportions of stage I NSCLC patients. The high CXCR4 level was correlated with poor OS in less stage I patients (≤ 70% stage I patients); while, interestingly, it showed significant association with increased survival in more stage I patients which mainly consisted of > 70% stage I NSCLC patients. The underlying reason might be that high expression of CXCR4 indicated poor prognosis in advanced NSCLC patients which contained more stage II, III, IV NSCLC patients than the early stage I. It was summarized that the theory, high CXCR4 expression indicated longer OS for early stage of NSCLC patients, should be treated with caution, and large sample randomized controlled trials (RCTs) are urgent needed.

No superiority of CXCR4 in predicting the prognosis was demonstrated according to DFS with significant heterogeneity, which might be influenced by the different sub-cellular localizations of CXCR4. And we didn't perform the further subgroup analysis due to the limited number of included studies and sample size. The different sub-cellular localizations of CXCR4, including nucleus and cytoplasm, remains considerable controversies as to its precise mediation or modulation in many cancers [25]. High CXCR4 expression of colorectal cancer cells nucleus was demonstrated to have significant impact on poor survival [30], and in breast cancer patients, high expression of CXCR4 in cytoplasm has been closely associated with poor prognosis [31]. So the different functions of CXCR4 in different staining types of NSCLC patients should be further explored when more clinical data are available.

In subgroup analysis of nationality, high CXCR4 expression indicated poor prognosis in Asian NSCLC patients, but not in non-Asians. This result illustrated that the geographic or ethnicity settings could be involved in the relationship between CXCR4 expression and the disease prognosis. In subgroup analysis of gender, it

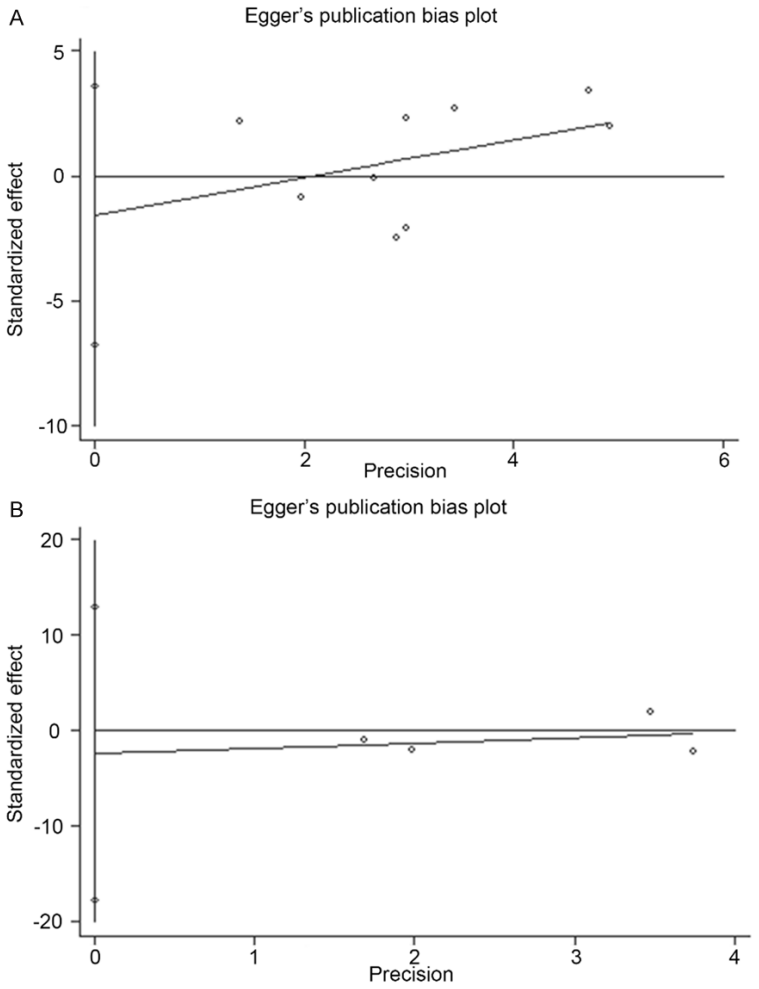

Figure 6. Egger's plot: the OS rate (A) and DFS rate (B). The assessing of Egger's publication bias plot of the studies showed that there were no publication biases in the meta-analysis. (A) Egger's plot from 9 studies in determining the relationship between CXCR4 expression and OS in NSCLC. (B) Egger's plot from 4 studies in determining the relationship between CXCR4 expression and DFS in NSCLC.

was found that high expression of CXCR4 was a poor prognosis for ≤ 70% male patients, but that was not found in > 70% male patients. Similarly, Otsuka *et al.* found that female patients whose tumor overexpressed CXCR4 seemed to have a significantly worse prognosis in stage IV NSCLC [21]. This phenomenon cannot be clearly explained by both the previous and our studies. However, a gender-based difference of CXCR4 expression in outcomes of NSCLC is not improbable, like our research, many studies associated male with better outcomes and longer survival than female [32]. Besides, other baseline clinical demographics, such as histology, site of primary disease, extent of metastases, smoke-exposure, current treatment, among the included trials were unavailable.

In the current meta-analysis, we made our best effort to minimize the potential bias by conducting comprehensive searches and thorough systematic review methods following recognized guidelines through multiple databases, and were confident that we had not omitted any major relevant studies or systematic reviews. Moderate to high quality publications with primary OS and/or DFS outcomes were included in the present investigation. However, some limitations were inevitable, and they were from the internal validity of the included trials. Firstly, we relied on study level systematic reviews in which person years of follow-up were not accurately ascertainable. Secondly, different detecting antibodies and immunohistochemistry methods in the included studies might potentially affect prognostic value. Thirdly, the cut-off values for high CXCR4 level were different in many of the studies, which could contribute to heterogeneity in the pooled results. Fourthly, no meta-analysis on identifying the potential role of different sub-cellular localization of CXCR4 with OS and DFS because of limited publication. Finally, it was a challenge to perform such pragmatic trials that need to be large enough to detect small treatment effects. Thus, important strategies, such as designing with large-scale sample size and analyzing with intend-to-treat (ITT) principle to avoid large loss to follow-up, will represent a research frontier in investigation of CXCR4 in OS and DFS in the future.

Moving forward, investigation is needed as to the impact of specific prognostic factors on ITT sample and long-term end-point outcomes, such as mortality and morbidity, by using re-

gression method. Further investigation in specific subgroups stratified according to reliable risk assessment tools is warranted. Expanding results to the fullest extent from pooling data from publicly funded international investigations and undertaking competing risks analysis is also needed.

In summary, the current systematic review with meta-analysis suggests that high level of CXCR4 might be a candidate for predicting poor OS in advanced NSCLC, while it was associated with increased survival in early stage of NSCLC patients. Besides, Asian was a much worse factor for prognosis of advanced NSCLC patients, whose CXCR4 was overexpressed; and gender might be an important factor for the relationship between high CXCR4 expression and prognosis of NSCLC patients. But this conclusion should be considered with cautions. Better designed studies with large sample and long-term morbidity and mortality are needed to confirm the current results. Further evaluation concerning the prognostic value of CXCR4 in a more homogenous population of patients with advanced NSCLC is important to eliminate the interference of any other treatment factors.

Acknowledgments

This work is partly supported by the Public Science and Technology Research Funds Projects of National Health and Family Planning Commission of China (No. 201402013) and Natural Science Foundation of China (No. 81471710).

Disclosure of conflict of interest

None.

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