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Original Article

Chemokine receptor CXCR4 expression and lung cancer prognosis: a meta-analysis

Jin-Xiao Liang[1], Wei Gao[2], Yong Liang[3], Xin-Ming Zhou[1]

[1]Department of Thoracic Surgery, Zhejiang Cancer Hospital, Hangzhou, People's Republic of China; [2]Department of Biochemistry and Molecular Biology, Dalian Medical University, Dalian, People's Republic of China; [3]Department of Clinical Medicine, Taizhou University Medical School, Taizhou, People's Republic of China

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Abstract: The chemokine receptor CXCR4 is a G protein-coupled receptor that plays an important role in several biological processes, such as trafficking and homeostasis of immune cells (like T lymphocytes), alteration of cell skeleton rearrangement and cell migration. To investigate whether the CXCR4 protein impacts on lung cancer prognosis, a meta-analysis was performed. Our meta-analysis study involved 2,037 lung cancer patients from 24 studies by a comprehensive search from PubMed, Embase and CNKI databases up to September 2014. Odds ratio (OR) or hazard ratio (HR) with 95% confidence interval (CI) were used to evaluate the relationship. We found that the CXCR4 expression was significantly associated with lymph node metastasis (OR = 3.79, 95% CI: 2.15-6.68), distant metastasis (OR = 3.67, 95% CI: 1.84-7.32), tumor stage (OR = 2.78, 95% CI: 1.77-4.39) and overall survival (HR = 1.63, 95% CI: 1.16-2.30). In conclusion, CXCR4 might be a new prognostic biomarker, and it might become a new diagnosis and therapeutic target in lung cancer.

Keywords: CXCR4, lung cancer, prognosis, meta-analysis

Introduction

Lung cancer is a high malignant carcinoma and it has been reported to be the first leading cause of cancer death in the United States [1]. Despite the advanced diagnostic techniques for early detection of lung cancer, the prognosis of lung cancer patients is still unsatisfactory. Even in early stage lung cancer, many patients developed recurrent disease and died of metastasis [2]. Because of the limited knowledge of lung cancer and technology for treatment, lung cancer can hardly be cured as our expectation. So it is necessary to explore prognostic factors to predict the outcomes of lung cancer patients, which can guide doctors to making effective strategies and increasing survival time for patients.

Chemokines are a small molecules family that adjusts immune responses. They are divided into two types, namely CXC and CC, by the position of the first two cysteines in their sequence [3]. The chemokine receptor CXCR4 is a G protein-coupled receptor (GPCR) that binds its ligand stromal cell-derived factor 1 (SDF-1, also known as CXCL12). CXCR4 has been identified to play an important role in several biological processes, such as trafficking and homeostasis of immune cells (like T lymphocytes) [4], leading to alteration of cell skeleton rearrangement and cell migration [5]. In several types of cancer, CXCR4 also contributes to neoplasia and the development of cancer [6]. Recent studies has reported that CXCR4 was related to cell survival, differentiation, proliferation and metastasis in breast cancer [7], colorectal cancer [8], gastric cancer [9], prostate cancer [10], etc. These studies derived that CXCR4 is merging as attractive targets for developing novel prognostic approaches for cancers.

Since Spano *et al.* first identified the relationship between CXCR4 expression and lung cancer patient's prognosis [11]; several studies have been published to describe this association [12-34]. But each of the studies has failed to provide conclusive results. Our present meta-analysis study was conducted to quantitatively and precisely estimate the potential effect of CXCR4 and lung cancer prognosis.

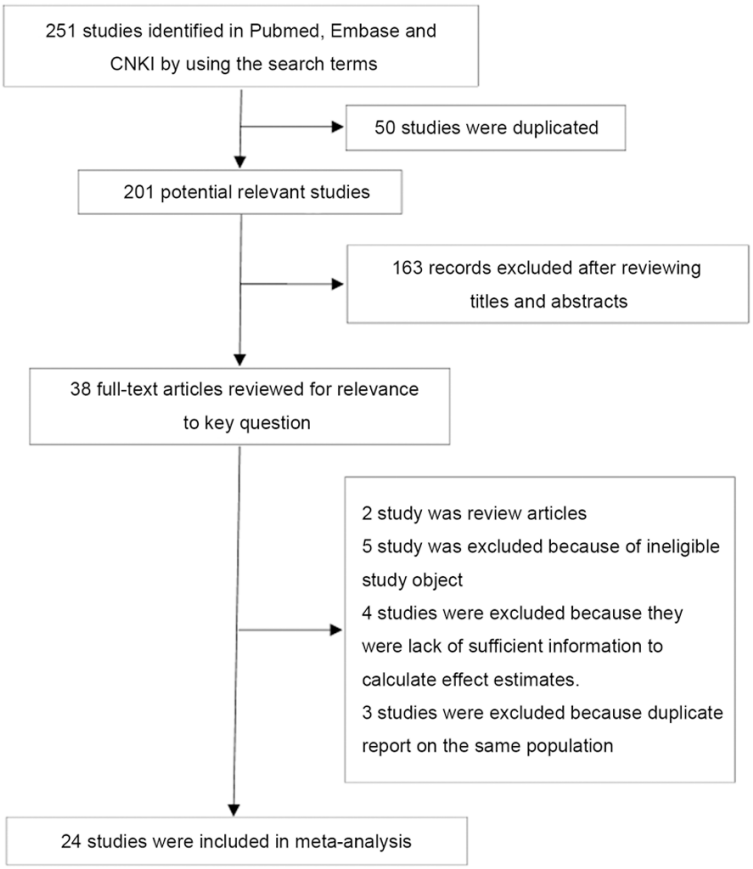

Figure 1. The flow diagram of included/excluded studies.

Materials and methods

Publication search

We searched published studies in the PubMed, Embase and CNKI databases updated to September 2014. The search was limited by using the following search terms: (CXCR4 OR chemokine receptor 4) AND (lung OR pulmonary) AND (cancer OR neoplasms OR carcinoma OR tumor OR adenocarcinoma) AND prognosis. Furthermore, reference lists of main reports and review articles were also reviewed to identify additional relevant publications.

Selection criteria

Two authors reviewed the retrieved titles and abstracts to determine the eligibility of the studies for inclusion in our meta-analysis independently. Published studies were included based on the following criteria: (1) patients with distinctive lung cancer diagnosis by pathology; (2) CXCR4 expression was detected by immunohistochemistry or RT-PCR; (3) CXCR4 expression on human lung cancer tissue; (4) the main outcome of interest focus on prognostic factors and clinicopathological features; (5) full length paper with sufficient data to calculate the odds ratio (OR) or hazard ratio (HR) estimates and their 95% confidence intervals (95% CI). We excluded studies with the following criteria: (1) articles about cell lines or animals; (2) CXCR4 expression on peripheral blood; (3) studies without sufficient data on prognostic factors or clinicopathological features; (4) reviews without original data and studies with duplicated data.

Data extraction

Two investigators performed the data evaluation independently. The following data were extracted from each study: first author, year, country, patients, method, antibody, subcellular localization, No. of patients (CXCR4 high/low), duration of follow-up, prognostic factors (age, gender, tumor size, differentiation, smoking, T stage, N stage, M stage, TNM stage) and survival (overall survival (OS) and disease-free survival (DFS)).

Data synthesis and statistical analysis

All of prognostic factors were analyzed as dichotomous variables; these data were analyzed by random-effect method, and were measured in OR with 95% CI. In survival analysis, the data were measured in HR with 95% CI. If the HR or standard errors (SEs) were not reported in included studies, we calculate or estimate the HR from available data or Kaplan-Meier curves using the methods reported by Tierney *et al.* [35]. Statistical heterogeneity was estimated by means of Cochran's Q test and-squared test. Their-squared test represents the percentage of variation to heterogeneity, which

Table 1. Characteristics of studies included in the meta-analysis

First author [reference]	Year	Country	Patients	Method	Antibody	Subcellular localization	No. of patients (CXCR4 high/low)	Duration of follow-up (months)	Prognostic factors	Survival
Spano [11]	2004	France	Stage I NSCLS	IHC	Abcam	Cytoplasm, nucleus	61 (17/44)	144	A G Sm T M	NA
Zhang [12]	2006	China	NSCLC	IHC	Santa Cruz	Cytoplasm, nucleus	72 (46/26)	60	G T N M St	NA
Cai [13]	2006	China	NSCLC	IHC	Wuhan Boster	Cytoplasm, membrane	40 (18/22)	NA	A G D N	NA
Suzuki [14]	2008	Japan	NSCLC	IHC	Santa Cruz	NA	90 (22/68)	120	NA	OS
Wagner [15]	2009	United States	NSCLC	IHC	R&D	Cytoplasm, nucleus	154 (62/92)	180	G T N M St	DFS
Iwakiri [16]	2009	Japan	NSCLC	RT-PCR	NA	NA	79 (40/39)	60	NA	DFS OS
Reckamp [17]	2009	United States	NSCLC	IHC	R&D	NA	16 (5/11)	34	G Sm St	OS
Xiao [18]	2009	China	Lung cancer	IHC	Wuhan Boster	Cytoplasm, membrane	82 (42/40)	NA	A G Si D N St	NA
Minamiya [19]	2010	Japan	AD of the lung	IHC	Leinco	Cytoplasm, nucleus	79 (37/42)	60	G D Si N St	DFS OS
Yao [20]	2010	China	NSCLC	IHC	Abcam	NA	52 (33/19)	NA	A G D N St	NA
Chen [21]	2011	China	NSCLC	IHC	Abcam	Cytoplasm, membrane	64 (51/13)	NA	M	NA
Otsuka [22]	2011	Canada	Stage IV NSCLC	IHC	UMB2	Cytoplasm	170 (29/141)	50	G Sm M	OS
Wang [23]	2011	China	NSCLC	IHC	R&D	Cytoplasm	208 (117/91)	70	A G Si D Sm T N St	OS
Xi [24]	2011	China	NSCLC	IHC	Wuhan Boster	NA	62 (19/43)	NA	Si D N St	NA
Li [25]	2012	China	SCLC	IHC	Abcam	Cytoplasm	65 (31/34)	87	N M St	DFS
Zhou [26]	2012	China	Stage III NSCLC	IHC	Boao Sen	NA	105 (72/33)	NA	M	NA
Geng [27]	2012	China	NSCLC	IHC	Wuhan Boster	NA	95 (40/55)	NA	A G Si D N St	NA
Hu [28]	2012	China	NSCLC	IHC	ZGBBT	NA	75 (60/15)	60	D T N	NA
Wang [29]	2012	China	Lung cancer	IHC	NA	NA	72 (24/48)	NA	A G N St	NA
Zobair [30]	2013	China	NSCLC	IHC	Abcam	Cytoplasm, nucleus	125 (62/63)	45	G M St	OS
Wang [31]	2013	China	NSCLC	IHC	Abcam	Cytoplasm	86 (53/33)	NA	A G D N St	NA
Li [32]	2014	China	SCLC	IHC	R&D	Cytoplasm, membrane	50 (35/15)	60	A G Si N St	OS
Liu [33]	2014	China	NSCLC	IHC	Abcam	Membrane, nucleus	75 (45/30)	40	A G N M	NA
Ji [34]	2014	China	NSCLC	IHC	Wuhan Boster	Cytoplasm	60 (47/13)	NA	A G D N St	NA

A, age; G, gender; Sm, smoke; Si, tumor size; D, differentiation; T, T stage; N, N stage; M, M stage; St, tumor stage; OS, overall survival; DFS, disease-free survival; NA, not available; AD, adenocarcinoma.

Table 2. Meta-analysis with a random-effect model for the association of CXCR4 expression and prognosis factors

Categories	No. of studies	Comparison	Pooled OR (95% CIs)	I-squared value	p_h*
Age	11	Old vs. young	0.97 (0.71, 1.33)	16.1%	0.291
Gender	17	Male vs. female	1.05 (0.84, 1.32)	0.0%	0.891
Tumor size	6	Large vs. small	0.90 (0.54, 1.48)	40.0%	0.139
Differentiation	10	Poor vs. moderate and high	1.31 (0.75, 2.30)	62.8%	0.004
Smoking	4	Long time vs. short time or never	1.22 (0.55, 2.69)	29.7%	0.234
T stage	5	T3, 4 vs. T1, 2	1.88 (0.76, 4.64)	71.1%	0.008
N stage	16	N1, 2 vs. N0	3.79 (2.15, 6.68)	76.6%	0.000
M stage	9	M1 vs. M0	3.67 (1.84, 7.32)	68.9%	0.001
Tumor stage	15	III, IV vs. I, II	2.78 (1.77, 4.39)	62.0%	0.001

p_h*: *P* value for heterogeneity of each meta-analysis.

is categorized as low (0-40%), moderate (40-60%), high (60-90%), very high (> 90%). Subgroup analyses were carried out based on geographic location, types of cancer or staining location of included studies if a significant heterogeneity was found in overall meta-analysis. Sensitivity analyses were performed by omitting one study at a time to check if the inclusion criteria affected the final results. To identify any potential publication bias, we used Begg's test and Egger's test, and only showed Begg's test in Figures. All statistical analyses were performed with Review Manager 5.2 and STATA 12.0.

Results

Systematic review

We identified 251 studies that fit our search strategy, but only 38 studies matched with inclusion criteria and content (**Figure 1**). After reviewing full text, 2 study was review articles, 5 study was excluded because of ineligible study object, 4 studies were excluded because they were lack of sufficient information to calculate effect estimates, 3 studies were excluded because duplicate report on the same population. Finally, we identified 24 studies to analysis [11-34].

Detailed characteristics of these studies were provided in **Table 1**. The included studies were published between 2004 and 2014, and included 2037 lung cancer patients. 17 studies were performed in China, 3 studies in Japan, 2 studies in United States, each 1 study in France and Canada. In prognostic factors, 11 studies were identified the relationship between age and lung cancer prognosis, 17 studies about gender, 10 studies about differentiation, 6 studies about tumor size, 4 studies about smoking, 5 studies about T stage, 16 studies about N stage, 9 studies about M stage, 15 studies about TNM stage. In survival analysis, 10 studies were demonstrated the association between OS and lung cancer prognosis and 4 studies about DFS.

Association of CXCR4 expression with prognosis factors

CXCR4 expression was not significant related to prognosis factors, such as age (old patients vs. young patients) (pooled OR = 0.97, 95% CI: 0.71-1.33, I^2 = 16.1%), gender (male vs. female) (pooled OR = 1.05, 95% CI: 0.84-1.32, I^2 = 0.0%), tumor size (large vs. small) (pooled OR = 0.90, 95% CI: 0.54-1.48, I^2 = 40%), differentiation (poor vs. moderate and high) (pooled OR = 1.31, 95% CI: 0.75-2.30, I^2 = 62.8%), smoking (long time vs. short time or never) (pooled OR = 1.22, 95% CI: 0.55-2.69, I^2 = 29.7%), T stage (T3, 4 vs. T1, 2) (pooled OR = 1.88, 95% CI: 0.76-4.64, I^2 = 71.1%) (**Table 2**).

However, CXCR4 expression correlated to some prognosis factors, such as N stage (N1, 2 vs. N0) (pooled OR = 3.79, 95% CI: 2.15-6.68, I^2 = 76.6%), M stage (M1 vs. M0) (pooled OR = 3.67, 95% CI: 1.84-7.32, I^2 = 68.9%), tumor stage (III, IV vs. I, II) (pooled OR = 2.78, 95% CI: 1.77-4.39, I^2 = 62.0%) (**Table 2**).

CXCR4 expression on lung cancer survival

Eight studies investigating OS and 4 studies identifying DFS were pooled into the meta-anal-

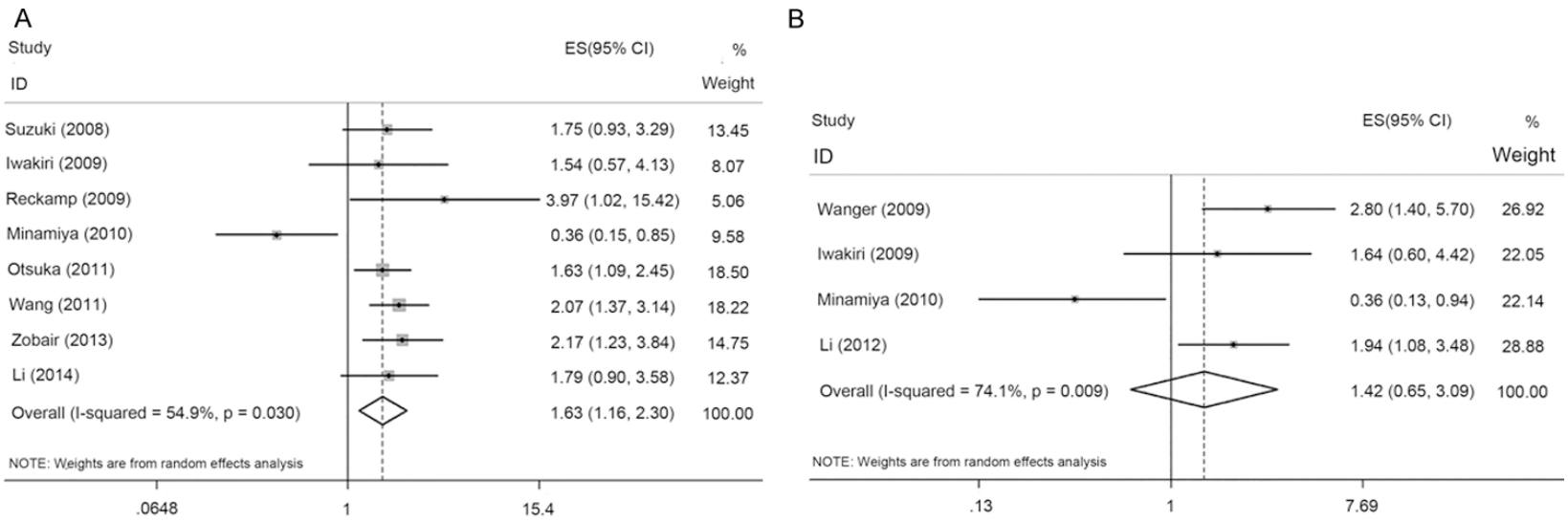

Figure 2. Meta-analysis with a random-effect model for the association of CXCR4 expression and survival factors such as overall survival (A) and disease-free survival (B).

Table 3. Subgroup analyses

	No. of studies	Pooled OR/HR (95% CIs)	I-squared value	p_h*
Differentiation				
Overall	10	1.31 (0.75, 2.30)	62.8%	0.004
Geographic location				
Asia	10	1.31 (0.75, 2.30)	62.8%	0.004
Types of cancer				
NSCLC	8	1.18 (0.58, 2.39)	69.4%	0.002
Lung cancer	2	1.84 (0.91, 3.72)	0.0%	0.780
Staining location				
Cytoplasm & nucleus	2	0.22 (0.02, 1.99)	70.9%	0.064
Cytoplasm & membrane	1	1.71 (0.72, 4.06)	-	-
Cytoplasm	2	1.39 (0.82, 2.38)	0.0%	0.774
T stage				
Overall	5	1.88 (0.76, 4.64)	71.1%	0.008
Geographic location				
Asia	3	3.01 (1.07, 8.45)	55.5%	0.106
Europe	1	1.83 (0.58, 5.83)	-	-
North America	1	0.57 (0.23, 1.40)	-	-
Types of cancer				
NSCLC	5	1.88 (0.76, 4.64)	71.1%	0.008
Staining location				
Cytoplasm & nucleus	3	0.99 (0.49, 1.97)	23.9%	0.269
Cytoplasm	1	3.92 (1.88, 8.19)	-	-
N stage				
Overall	16	3.79 (2.15, 6.68)	76.6%	0.000
Geographic location				
Asia	15	4.26 (2.45, 7.41)	71.5%	0.000
North America	1	0.80 (0.39, 1.64)	-	-
Types of cancer				
NSCLC	12	2.87 (1.66, 4.94)	68.0%	0.000
SCLC	2	2.37 (1.06, 5.30)	0.0%	0.922
Lung cancer	2	31.15 (12.75, 76.10)	0.0%	0.341
Staining location				
Cytoplasm & nucleus	3	1.21 (0.23, 6.21)	88.3%	0.000
Cytoplasm & membrane	3	7.40 (1.52, 35.96)	77.5%	0.012
Nucleus & membrane	1	6.83 (1.94, 24.09)	-	-
Cytoplasm	4	2.64 (1.70, 4.11)	0.0%	0.635
M stage				
Overall	9	3.67 (1.84, 7.32)	68.9%	0.001
Geographic location				
Asia	6	5.67 (3.62, 8.86)	0.0%	0.710
Europe	1	0.59 (0.17, 2.14)	-	-
North America	2	2.75 (0.20, 37.46)	80.3%	0.024
Types of cancer				
NSCLC	8	3.60 (1.64, 7.94)	72.6%	0.001
SCLC	1	4.39 (1.55, 12.43)	-	-
Staining location				
Cytoplasm & nucleus	4	3.44 (0.98, 12.06)	73.6%	0.010

ysis. CXCR4 positive expression significantly correlated with poor OS (pooled HR = 1.63, 95% CI: 1.16-2.30, I^2 = 54.9%). However, CXCR4 expression was not related to DFS (pooled HR = 1.42, 95% CI: 0.65-3.09, I^2 = 74.1%) (**Figure 2**).

Subgroup analyses

We take subgroup analyses in meta-analysis with relative high heterogeneity (I-square > 40%). In subgroup analyses, studies were stratified by geographic location (Asia, Europe and North America), types of cancer (NSCLC, SCLC and Lung cancer) or staining location (cytoplasm & nucleus, cytoplasm & membrane, nucleus & membrane and cytoplasm). In addition, heterogeneity was also showed in the studies which adjusted for these aforementioned risk factors (**Table 3**).

Sensitivity analyses

In sensitivity analyses, we sequentially removed one study at a time and re-analyzed the data to explore the origin of the heterogeneity. This showed that the study by Minamiya et al. [19] substantially impacted the pooled HR in OS and DFS meta-analysis (**Figure 3**). After omitting this study, heterogeneity was no longer observed in OS (pooled HR = 1.89, 95% CI: 1.52-2.34, I^2 = 0.0%) and DFS (pooled HR = 2.14, 95% CI: 1.42-3.22, I^2 = 0.0%). In other sensitivity

Cytoplasm & membrane	1	4.39 (1.08, 17.89)	-	-
Nucleus & membrane	1	7.00 (2.49, 19.70)	-	-
Cytoplasm	2	1.91 (0.40, 9.24)	81.5%	0.020
Tumor stage				
Overall	15	2.78 (1.77, 4.39)	62.0%	0.001
Geographic location				
Asia	13	3.19 (2.12, 4.80)	47.5%	0.029
North America	2	0.78 (0.39, 1.57)	0.0%	0.411
Types of cancer				
NSCLC	11	2.68 (1.44, 4.96)	71.0%	0.000
SCLC	2	2.35 (1.07, 5.20)	0.0%	0.545
Lung cancer	2	3.54 (1.73, 7.21)	9.1%	0.294
Staining location				
Cytoplasm & nucleus	4	1.37 (0.45, 4.19)	82.3%	0.001
Cytoplasm & membrane	4	2.87 (1.73, 4.76)	0.0%	0.717
Cytoplasm	3	6.36 (3.32, 12.19)	1.7%	0.362
OS				
Overall	8	1.63 (1.16, 2.30)	54.9%	0.030
Geographic location				
Asia	6	1.51 (0.97, 2.36)	64.3%	0.016
North America	2	1.99 (0.96, 4.11)	33.8%	0.219
Types of cancer				
NSCLC	8	1.63 (1.16, 2.30)	54.9%	0.030
Staining location				
Cytoplasm & nucleus	2	0.91 (0.16, 5.31)	91.4%	0.001
Cytoplasm	3	1.83 (1.40, 2.39)	0.0%	0.725
DFS				
Overall	4	1.42 (0.65, 3.09)	74.1%	0.009
Geographic location				
Asia	3	1.09 (0.40, 2.99)	76.4%	0.014
North America	1	2.80 (1.39, 5.65)	-	-
Types of cancer				
NSCLC	3	1.22 (0.37, 4.08)	81.9%	0.004
SCLC	1	1.94 (1.08, 3.48)	-	-
Staining location				
Cytoplasm & nucleus	2	1.04 (0.14, 7.72)	90.9%	0.001
Cytoplasm	1	1.94 (1.08, 3.48)	-	-

p_h^*: *P* value for heterogeneity of each meta-analysis.

analyses, we found that no single study altered the original results or heterogeneity significantly.

Publication bias

Begg's and Egger's were created for assessment of possible publication bias. Both of them suggested that the publication bias had little influence on this meta-analysis results (P > 0.05). We only showed Begg's test in **Figures 4** and **5**.

Discussion

Taking statistics from the USA as an example of the evolution of lung cancer [1], it is clear that the prognostic factor for lung cancer which prevents and cures this type of cancer needs to be improved. Exploring new molecular biological prognostic and predictive markers is a hot topic in modern medicine. In recent studies, CXCR4 was considered to be a new prognostic marker in several types of cancer [36-38]. However, results of the relationship between CXCR4 expression and lung cancer prognosis are not conformable in several studies [11-34]. To our knowledge, this meta-analysis is the first study to systematically evaluate the relationship between CXCR4 expression and lung cancer prognosis.

In the present study, a combined analysis of 24 articles which showed the detection of the CXCR4 expression in tumor tissues with poor prognosis outcome in lung cancer patients who were detected with high level of CXCR4 expression. Our meta-analysis results indicated that CXCR4 expression was significantly correlated to lymph node metastasis (N stage), distant metastasis (M stage), tumor stage and overall survival. CXCR4 overexpression also shorten disease-free survival but not notable. On the other hand, high level of CXCR4 expression was also found in patients like elderly, male, smoking, and patients with low differentiate, small

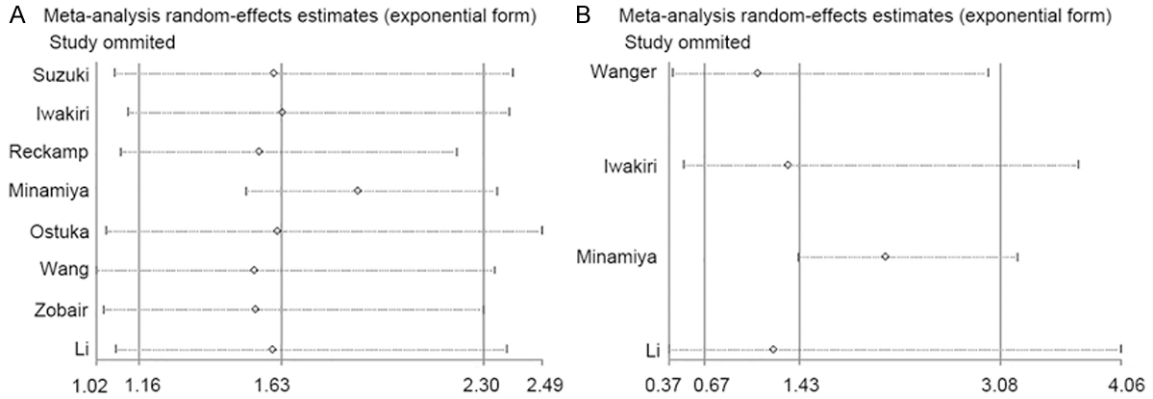

Figure 3. Influence of individual studies on the pooled HR in meta-analysis of overall survival (A) and disease-free survival (B).

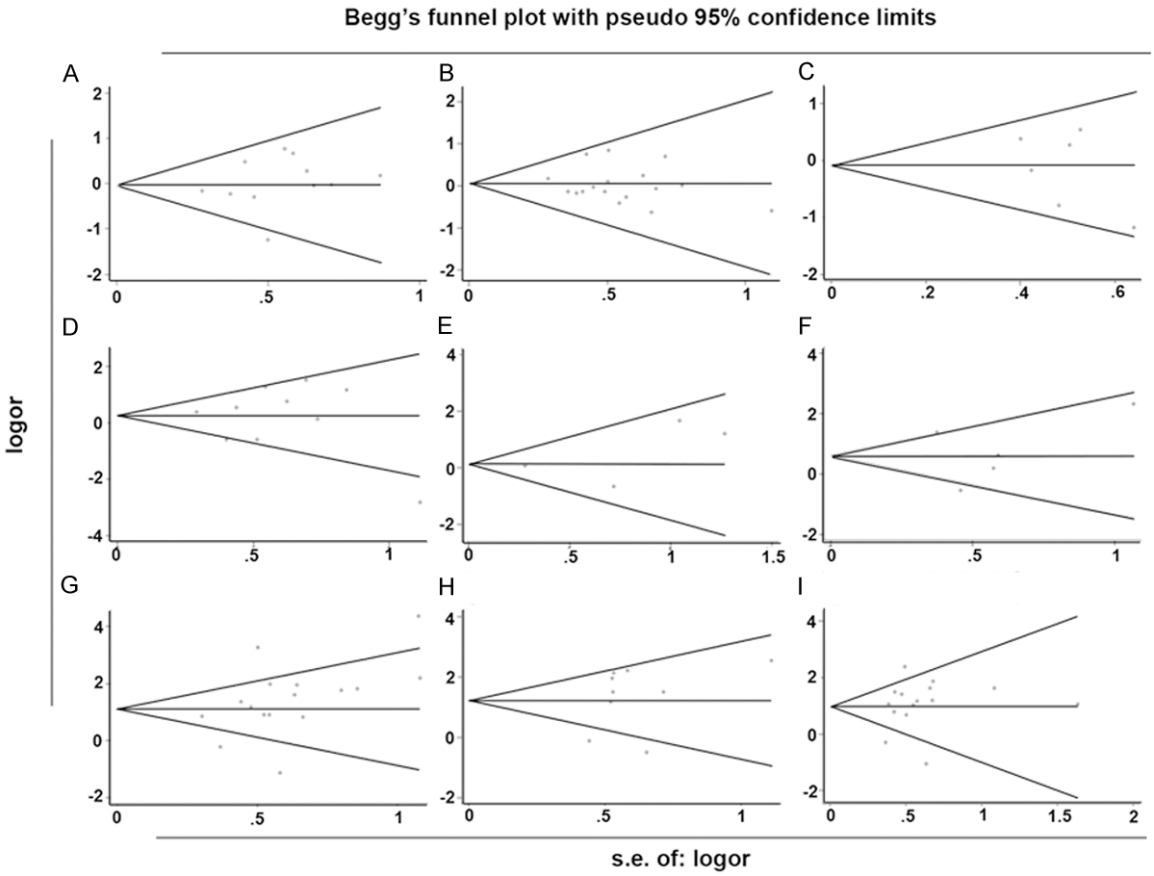

Figure 4. Begg's test results of CXCR4 and prognosis factors such as age (A), gender (B), tumor size (C), differentiation (D), smoking (E), T stage (F), N stage (G), M stage (H), tumor stage (I).

size tumor or deep invasion, but none of these results showed any significance.

What makes CXCR4 relate to the poor prognosis among lung cancer patients? As far as we know, different types of cancers express different chemokines and their receptors, but CXCR4 is the only one that expresses in the majority of cancer types [39, 40]. After Kijima *et al.* first reported the CXCR4 expression in lung cancer [41]; many studies were conducted to investigate the relationship between CXCR4 expres-

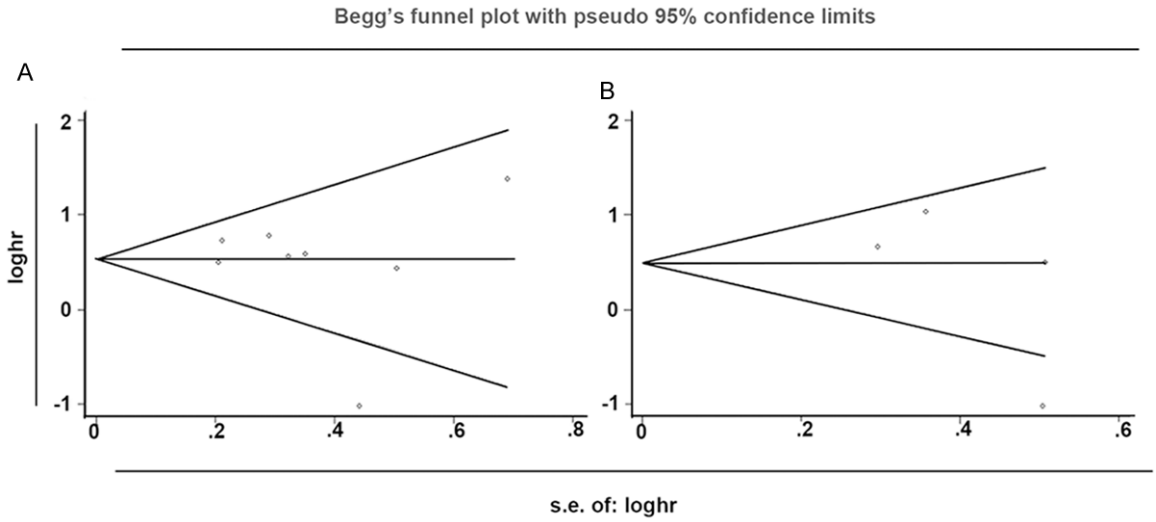

Figure 5. Begg's test results of the overall survival (A) and disease-free survival (B).

sion and lung cancer prognosis. Interestingly, Minamiya *et al.* found that CXCR4 represented low level or negative in normal lung cells while high expression was observed in lung cancer cells [19]. CXCR4 and its chemokine ligand 12 (CXCL12) recruit the endothelial progenitor cells into tumors indirectly, and result in neoangiogenesis [42]. Meantime, reports showed that the EGF receptor HER2 increases CXCR4 expression as well as the invasion and metastasis of HER2-positive breast cancer cells [43]. Lung cancer expressed a substantial percentage of EGFRs on cell surface, and the association between EGFR and CXCR4 may also exist in lung cancer as described in Zobair's study [30]. It is well known that hypoxia is a common phenomenon occurring in the majority of human tumors and has been proved to play an important role in tumor progression. In Liu's study, hypoxia can regulate the CXCR4 mediated metastasis and HIF-dependent invasion, migration and adhesion [44]. From our results, we also found that CXCR4 expression was correlated to lymph node metastasis and distant metastasis, which inferred that CXCR4 was associated with tumor microenvironment and enhanced the cancer cell survival. Bertolini *et al.* Found that CXCR4 was related to lung cancer progenitor cells, and this was the first *in vivo* evidence for a tumorigenic and metastatic subpopulation in lung cancer which characterized by $CD133^+$ expression together with $CXCR4^+$ [45]. CXCR4 was also reported to be associated with cancer stem cells, and *in vivo* study showed its encouraging effect on the chemo resistance [45]. Furthermore, CXCR4 activation augmented the signaling pathways related to cell survival and growth, such as MAPK [46] and PI3K signaling pathways in lung cancer cells [41]. Therefore, the molecular biological mechanisms of how CXCR4 overexpression affects the lung cancer prognosis are complicated and still needs more exploration. For the first time, our meta-analysis study revealed that CXCR4 could be a potential biomarker for poor prognosis of lung cancer.

This meta-analysis had several strengths. It included total 2037 lung cancer patients which should provided sufficient statistical power to detect the association between CXCR4 expression and lung cancer prognosis. A further strength was that we carried out subgroup and sensitivity analyses to explore the potential sources of heterogeneity.

Some limitations of this meta-analysis should be pointed out. First, all published studies and papers written in English or Chinese, Some related published or unpublished studies that meet the inclusion criteria were missed. Most of the studies reported positive results, and studies of negative results were all rejected. Second, the two different types of lung cancer (NSCLC and SCLC) might have different biological behaviors. In this meta-analysis, only two studies demonstrated to SCLC, and only one study could successfully evaluated estimate HR or OR in each prognosis factors except N

stage and tumor stage. Third, most of the included studies had data of the CXCR4 expression which were detected by IHC methods. It might have some bias because of different antibodies and different standards of positive/negative CXCR4 expression. However, it was not available for us to take subgroup analysis to analyze the underlying bias of IHC on the pooled ORs or HRs. Forth, the data of overall survival and disease-free survival was not performed by multivariate analyses in most included studies. We calculated the HR from available data or Kaplan-Meier curves.

In conclusion, this meta-analysis suggested that CXCR4 overexpression was significantly associated to lymph node metastasis, distant metastasis, tumor stage and overall survival in lung cancer. CXCR4 might be a new prognostic biomarker, and it might become a new diagnostic and therapeutic target in lung cancer. Further studies are required to explore the molecular biology mechanism of CXCR4 and factors that result in significant heterogeneity in our meta-analysis.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jinxiao Liang or Xinming Zhou, Department of Thoracic Surgery, Zhejiang Cancer Hospital, 38 Guangji Road, Banshan, Hangzhou 310022, Zhejiang Province, Republic of China. Tel: +86-15857142975; +86-571-88128051; Fax: +86-571-88122508; E-mail: liangjinxiaozch@163.com (JXL); xmzhou58@sina.com (XMZ)

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