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Meta-analysis of CXCR7 Expression Related to Clinical Prognosis in Cancers

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Abstract

Purpose: Recently, higher expression of chemokine receptors in patients with various cancer types has been observed and indicated to have prognostic significance in the clinical progression of cancers. Former research has determined that CXCR7, as a member of chemokine receptor C-X-C family, empowers greater affinity with chemokine CXCL12 than CXCR4. The present study investigated the correlation of clinical characteristics and CXCR7 expression in cancers using meta-analysis.

Methods: A comprehensive search on Pubmed and Web of Science identified CXCR7-related clinical studies. Methodological quality of these studies was evaluated and all the data were extracted, calculated and analyzed. This meta-analysis was carried out with Stata 12.0.

Results: Fifteen eligible studies consisting of 1780 participants were included. The results showed that CXCR7 significantly relates to tumor occurrence (pooled RR=3.12, 95% CI: 1.71-5.70, P=0.000), tumor grades (pooled RR=1.41, 95% CI: 1.14-1.75, P=0.002), tumor stages (pooled RR=1.51, 95% CI: 1.26-1.82, P=0.000) and lymph node metastasis (pooled RR=1.49, 95% CI: 1.14-1.94, P=0.000), respectively.

Conclusion: Highly expressed chemokine receptor CXCR7 potentially increases tumor occurrence risk. Higher CXCR7 expression is associated with poorer prognosis, advanced stages, differentiation grades and poor lymph node metastasis in patients with various cancers. Thus, highly expressed CXCR7 could be a potential biomarker in the prognosis of cancers.

Keywords: CXCR7; Cancer; Tumor grade; Tumor stage; Lymph node metastasis; Meta-analysis

Introduction

Chemokines are a group of small molecular peptides that play predominant roles in inflammation and cancer biology. CXCL12 (or SDF-1, stromal-derived growth factor) is one of the member of the chemokines, which are low-molecular-weight signaling peptides involved in cell homing and mobilization. The CXCL12-CXCR4/CXCR7 axis is believed to be a significant signal axis that contributes to tumor progression [1].

The chemokine receptor CXCR4, as a member of the four groups (CXC, CX3C, CC, and C), is a 352-amino acid heptahelical transmembrane receptor. CXCR4 potentiates growth, angiogenesis/angiostasis, invasion/metastasis and prognosis of various cancers, including esophageal cancer, renal cancer, breast cancer, colorectal carcinoma, glioma, gastric cancer and ovarian cancer [1-8]. CXCR4 is significantly associated with tumor stage, lymph node status, distant metastasis and poor survival [1,3-6,8,9].

CXCR7 is a novel receptor of CXCL12, and is involved in the progression and metastasis in various cancers. There are literatures indicating that CXCR7 binds to CXCL12 with greater affinity than CXCR4 to CXCL12 (Kd = 0.4 nM versus 3.6 nM) [10,11]. Furthermore, the roles of CXCR7 in neovascularization, tumor invasion and proliferation have been verified [12-14]. On the other hand, the clinical pattern of CXCR7 in various cancers has not been thoroughly summarized, and controversy still exists in different researches. Zhen Liu et al. found no relationship between CXCR7 expression and histological grade, whereas Gebauer et al. found that CXCR7 expression had an association with grading in cancers [15,16].

Meta-analysis has great advantages in confirming clinical confounding outcome of disparate studies by using data and results of published articles. In this study, the meta-analysis aims to review and systematically assess the potential correlations of CXCR7 expression with the clinicopathological indicators in various cancers.

Materials and Methods

Search strategy

We carried out a comprehensive literature review on PubMed, Web of Science and Embase up to December 2014. We used the following terms: "CXCR7 or RDC1 or C-X-C chemokine receptor type 7", and "carcinoma or cancer or tumor or neoplasm". All references from retrieved articles were scanned to identify other potentially available reports.

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Selection criteria

All eligible articles that indicated any associations between CXCR7 and clinicopathological indicators in various tumors were collected in this meta-analysis by two reviewers independently. The inclusion criteria that eligible studies had to meet were as follows: (1) CXCR7 expression evaluated in the primary tumor tissues, (2) researches revealed the association between CXCR7 expression and tumor clinicopathological indicators and prognosis, (3) CXCR7 expression examined by immunohistochemistry (IHC), reverse transcription PCR (RT-PCR), (4) articles published as a full paper in English, (5) for duplicate articles, only the most complete and/or recently published one was included. The exclusion criteria were as follows: (1) reviews, comments, case reports, conference abstracts, editorials, letters, and non-English language papers, (2) articles with insufficient or unavailable information of CXCR7 expression with clinicopathological parameters and prognosis.

Data extraction and quality assessment

The following information was retrieved independently by two authors (Qian Cheng and Zhirong Sun) from each publication: first author, publication year, country, number of patients enrolled, histology and disease stage.

Disagreements in data extraction were resolved by consensus and by referring back to the original article.

Quality assessment

Quality assessment was carried out by two independent investigators through reading and scoring each publication according to the quality scale for the biological prognostic factors.

Data analysis

Statistical analysis was conducted using Stata 12.0 (Stata Corporation, USA). To assess heterogeneity of studies, we used the I^2 test and Fixed-effects models (Mantel-Haenszel, $I^2 < 50\%$). In the case when there was heterogeneity (Mantel-Haenszel, $I^2 \geq 50\%$) among studies, we performed a random effect model to pool the RRs; otherwise, a fixed effect model was selected.

Results

Identification of eligible studies

Initially, 407 articles were retrieved using the search strategy described above. 356 of which were excluded due to having irrelevant titles or abstracts, non-original articles or non-English language articles. Through further scrutinizing the entire paper, 36 articles were excluded for insufficient data. Finally, a total of 15 articles were applicable, and 1780 patients of various cancers were enrolled in the meta-analysis (Figure 1).

All the features of the 15 eligible studies with a total of 1780 patients were summarized in Table 1. Among them, two articles were from Germany, two from Italy, one from France, one from USA, and nine from China. The expression of CXCR7 was detected using immunohistochemistry in 12 studies, and the other three studies applied immunohistochemistry on a tissue microarray. Tumor tissues in this meta-analysis were taken from cancers in thyroid, cervical, colorectal, cutaneous, hepatocellular, esophageal, pancreatic, renal, gallbladder, mesothelioma and oral. The years of the studies range from 2010 to 2014, and antibodies used for CXCR7 detection were mainly from R&D and Abcam.

Correlation of CXCR7 expression with clinicopathological parameters

There were eight studies, with a total of 635 patients, included in the correlation analysis between CXCR7 expression and tumor occurrence. The results are shown in Figure 2A (RR=3.12, 95% CI: 1.71-5.70, P<0.001, I^2=84.2%), which indicate that CXCR7 expression was significantly higher in tumor tissue than in its relevant normal tissue.

There were eight studies, with a total of 348 patients, enrolled in the correlation analysis between CXCR7 expression and tumor grade. The results are shown in Figure 2B (RR=1.41, 95% CI: 1.14-1.75, P<0.01, I^2=41.6%), which indicate that CXCR7 expression was higher in tumor grade III and IV compared to grade I and II. We can interpret as CXCR7 expression correlates with worse tumor grade and prognosis potential.

There were nine studies, with a total of 1238 patients, involved in the correlation analysis between CXCR7 expression and tumor stage. The results are showed in Figure 2C (RR=1.51, 95% CI: 1.26-1.82, P<0.001, I^2=49.4%), which demonstrate that CXCR7 expression was

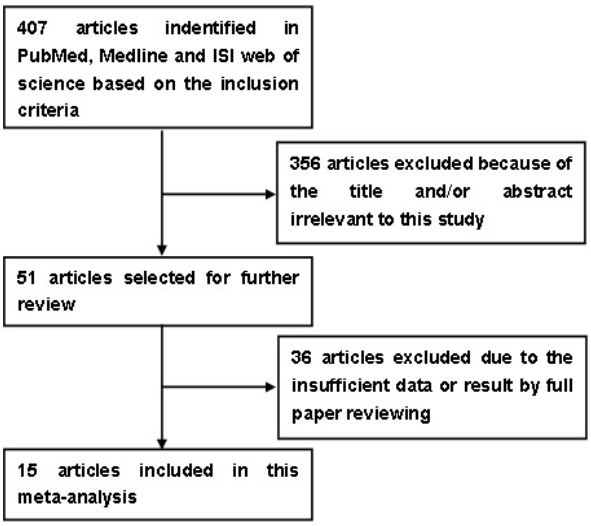

Figure 1: Flow chart for the selection of eligible papers.

First author	Year	Country	Histology	Cases	Method	Antibody
Liu [17]	2012	China	Thyroid	112	IHC	R&D
Kurban [18]	2014	China	Cervical	152	IHC	Santa Cruz
Xu [19]	2011	China	Colorectal	86	IHC	R&D
Guillemot [20]	2012	France	Colorectal	43	IHC	R&D
Hu [21]	2014	China	Cutaneous	60	IHC	R&D
Neve Polimeno [22]	2014	Italy	Hepatocellular	86	IHC	R&D
Zheng [23]	2010	China	Hepatocellular	35	IHC	Abcam
Tachezy [24]	2013	Germany	Esophageal	299	TMA	R&D
Liu [16]	2014	China	Pancreatic	88	IHC	R&D
Gebauer [15]	2011	Germany	Pancreatic	249	TMA	R&D
D'Alterio [25]	2010	Italy	Renal	272	IHC	R&D
Wang [26]	2012	China	Renal	97	TMA	R&D
Yao [27]	2011	China	Gallbladder	72	IHC	Abcam
Li [28]	2011	USA	Mesothelioma	61	IHC	Abcam
Xia [29]	2011	China	Oral	68	IHC	Abcam

Table 1: Characteristics of the collected studies.

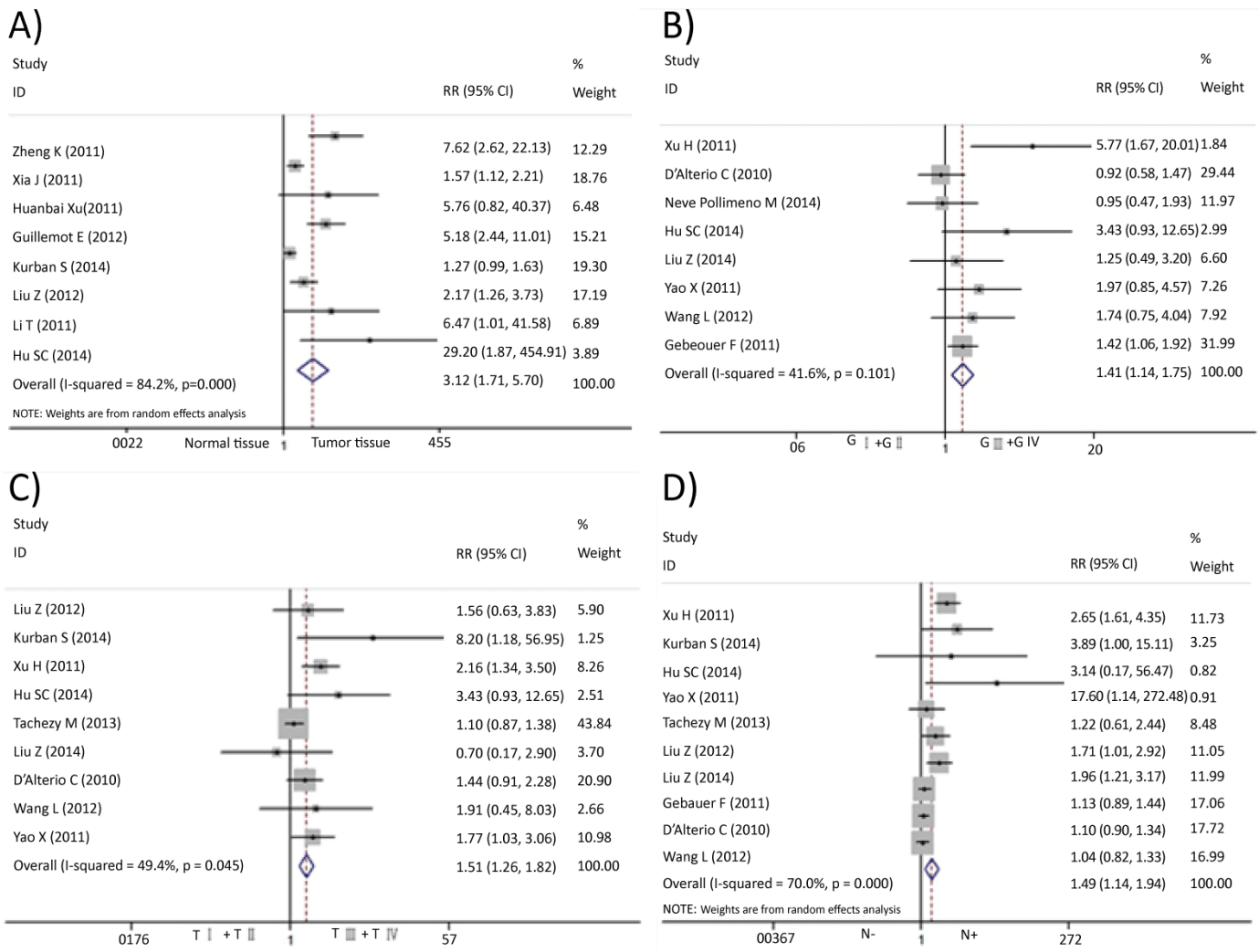

Figure 2: The forest plot of RRs was assessed for the association between CXCR7 and clinicopathological features such as tumor occurrence (A), grading (B), stage (C), lymph node metastasis (D).

significantly higher in tumor stage III and IV than in stage I and II. It is shown that CXCR7 expression correlates with worse tumor stage and prognosis potential.

There were ten studies, with a total of 995 patients, included in the correlation analysis between CXCR7 expression and lymph node metastasis. The results are revealed in Figure 2D (RR=1.49, 95% CI: 1.14-1.94, P<0.001, I^2=70.0%), which indicate that CXCR7 expression was significantly higher in metastatic lymph node compared to normal lymph node. We can state that CXCR7 expression predicts lymph node metastasis potential and poorer prognosis.

Publication bias

Neither Begg's nor Egger's tests indicated evidence of significant publication bias. In addition, no publication bias was observed in the funnel plot of enrolled studies (Figure 3).

Discussion

Chemokines play an important role in oncogenesis and tumor progression. CXCR7, as a recently discovered chemokine receptor, has demonstrated its characteristics in six aspects out of the ten top hallmarks of tumors, including resisting cell death, inducing angiogenesis, sustaining proliferative signaling, activating invasion and metastasis, tumor-promoting inflammation, and cancer-related genes [14,17-22]. Both CXCR4 and CXCR7 are receptors of chemokine CXCL12 and have been reported in multiple tumor types. However, the functions of highly expressed CXCR7 in tumor tissues are unclear. Past report has implied that CXCR7 may play a more critical role in pancreatic cancer progression and prognosis. Shen et al. regarded CXCR4 as a key receptor involved in tumor invasion and prognosis, while Liu et al. [9] considered CXCR7 to be more important for long term survival in pancreatic cancer patients [9,23,24]. Implications of CXCR7 have been revealed in various tumors, including nervous system, digestive system, endocrine system, genital system, blood system, respiratory system, and urinary system, respectively [9,15,25-29]. However, systemic study of the correlation of CXCR7 with clinicopathogy and prognosis in various tumors is still vacant. This study was initiated from the aspect of CXCR7 expression, and its correlation with tumor grade, tumor stage, and lymph node metastasis. In cervical cancer research [30], colorectal cancer research by Xu et al. [19] cutaneous squamous cell

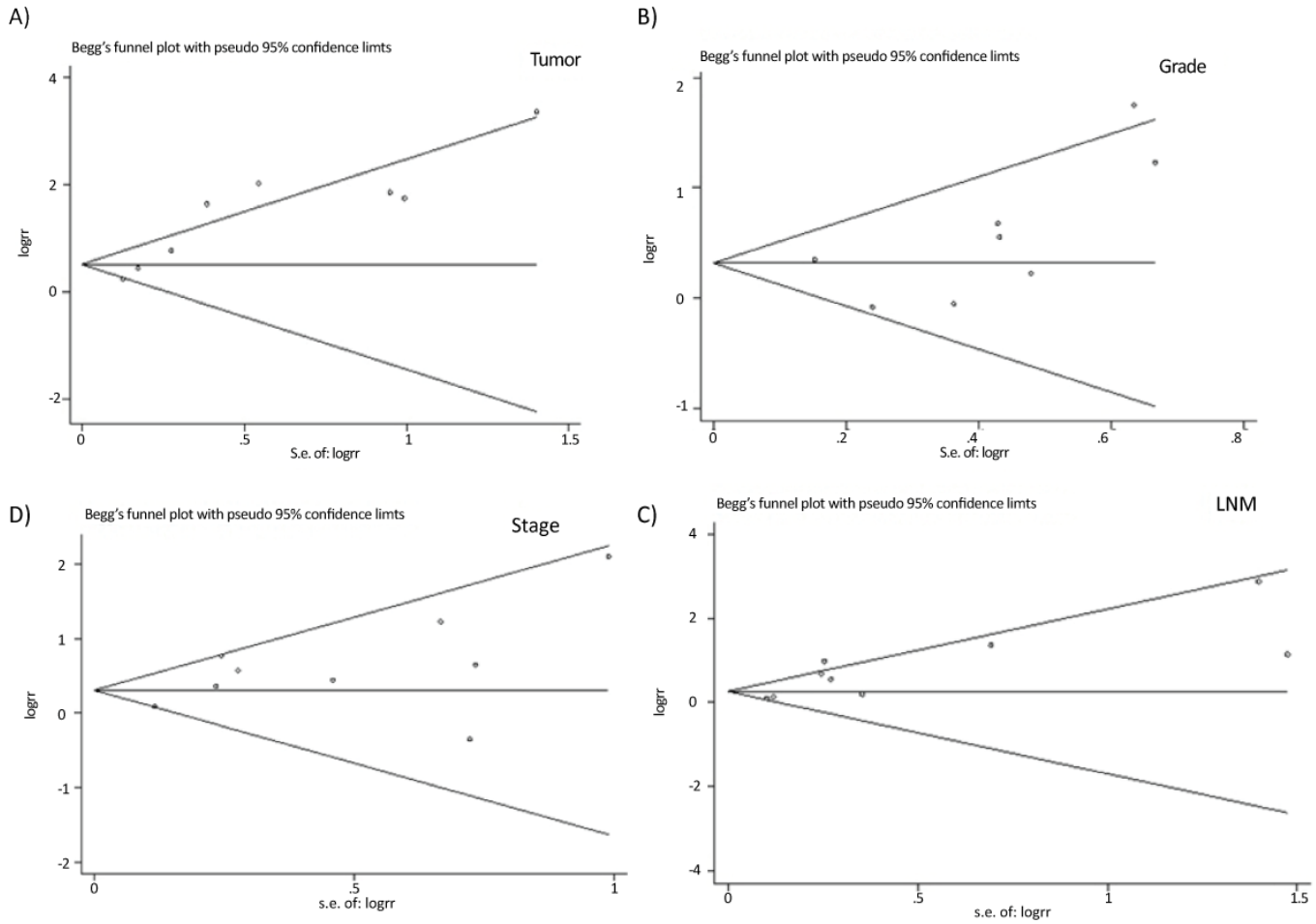

Figure 3: Begg's test result of publication bias for the association between CXCR7 and clinicopathological features such as tumor occurrence (A), grading (B), stage (C), lymph node metastasis (D).

carcinoma research by Hu et al. [21] renal cancer research by Wang et al. [26] and gallbladder cancer research by Yao et al. [27] all of these studies have consistent results for tumor grade, stage and lymph node metastasis [30-34]. These significant clinicopathological relative factors revealed their roles in tumor development [35-40]. This meta-analysis has drawn the distance between CXCR7 and the clinicopathological indicators closer. Furthermore, CXCR7 may become a valuable biomarker for tumor grade and stage discrimination, and prognosis evaluation through tissue biopsy for diagnosis and prognosis [41].

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Conflict of Interest

We declare that we have no conflict of interest.

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