

## Review Article

# Clinicopathological and prognostic value of chemokine receptor CCR7 expression in esophageal squamous cell carcinoma: a meta-analysis

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Received October 18, 2017; Accepted May 1, 2018; Epub October 15, 2018; Published October 30, 2018

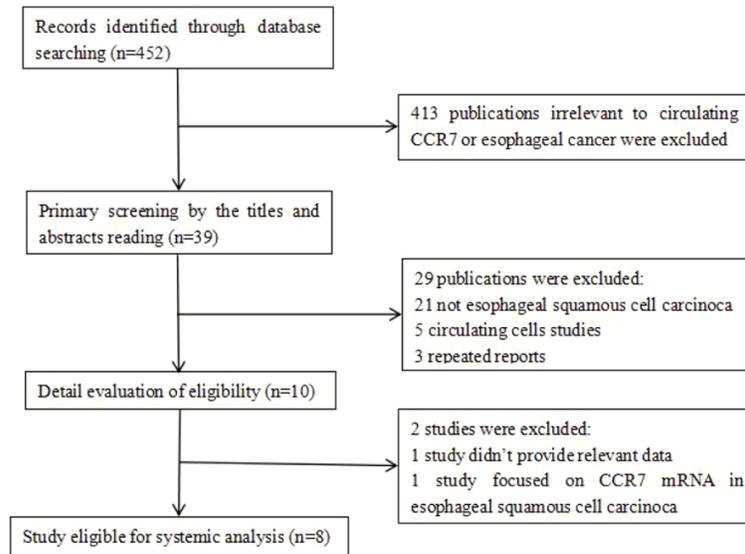
**Abstract:** Background: The prognostic significance of CC chemokine receptor type 7 (CCR7) for the survival of patients with esophageal squamous cell carcinoma (ESCC) remains controversial. Objective: Our aim was to investigate the influence of CCR7 on clinicopathological features and survival outcome in ESCC by performing a meta-analysis. Methods: A comprehensive search in the Embase, Web of Science, PubMed, CNKI, and WanFang databases (up to October 2017) was performed for relevant studies using various search strategies. The odds ratio (OR) and 95% confidence intervals (95% CIs) were used to evaluate the association between CCR7 expression and the clinicopathological features and overall survival rate of ESCC. A sensitivity analysis was carried out to estimate the stability of our results. Results: Eight eligible studies consisting of data for 722 ESCC patients were collected for our meta-analysis. The results reveal that CCR7 expression is associated with depth of invasion (OR: 0.37, 95% CI: 0.19-0.74,  $P=0.005$ ), TNM stage (OR: 0.25, 95% CI: 0.16-0.39,  $P<0.001$ ), and lymph node metastasis (OR: 5.01, 95% CI: 3.47-7.22,  $P<0.001$ ). Four studies (consisting of data for 528 patients) were evaluated for association between CCR7 expression and overall survival (OS), revealing that high CCR7 expression is correlated with poor prognosis in esophageal squamous cell carcinoma patients (HR: 2.06, 95% CI: 1.56-2.71,  $P<0.001$ ). Funnel plots and Begg's test indicated that the publication bias of these eligible studies was insignificant. The sensitivity analysis revealed that no study substantially affected pooled OR/HR. Conclusions: Meta-analysis shows that high CCR7 expression is significantly associated with negative prognosis of ESCC patients in the Asian population.

**Keywords:** Esophageal squamous cell carcinoma (ESCC), clinicopathological features, prognostic, meta-analysis

## Introduction

Esophageal carcinoma is one of the most common malignant digestive solid tumors worldwide. It can be divided into esophageal squamous cell carcinoma and esophageal adenocarcinoma. Esophageal squamous cell carcinoma (ESCC) accounts for more than 90% of esophageal carcinomas in China [1, 2]. Surgical resection remains the primary treatment for ESCC, but the five-year overall survival rate of patients is about 30-50%, and more than half of these patients experience recurrence after two to three years [3, 4]. Therefore, the search for therapeutic molecular targets has attracted much attention for the treatment of esophageal carcinoma.

Chemokine receptors are transmembrane domain receptors that are expressed in the surface of certain cells. They belong to the G protein-coupled receptor (GPCR) superfamily. The family members can be divided into four types (CR, CCR, CX3CR and CXCR) [5, 6]. C-C chemokine receptor type 7 (CCR7) belongs to the CCR type and is expressed by mature T-cells and dendritic cells [7, 8]. CCL19 and CCL21 are 2 high-affinity ligands of CCR7, which can combine with its ligand and induce homing of T-cells and dendritic cells to secondary lymphoid organs for inflammatory and immunological processes [9, 10]. Studies have shown that several chemokines and their receptors-such as CXCL12/CXCR4, CCL5/CCR5 and CCL/CCR8-can facilitate the transfer and dissemination of



**Figure 1.** Flow chart of screened process and include eligible researches.

bases up to June 2017 for Chinese and English language papers. We designed a comprehensive and exhaustive search strategy for the following words in relevant articles: 'esophagus' or 'esophageal'; 'neoplasm', 'cancer' or 'tumor'; and 'CCR7' or 'chemokine receptor 7'. We then performed the function 'related article' in these databases to identify all relevant studies. Studies in the reference lists were retrieved if they were correlated with our topic. Two investigators independently extracted and screened the following data from each publication.

cancer cells [11-13]. CCR7 has also been reported to be expressed in cancer and to promote lymph node metastasis [14]. Recent studies have indicated that CCR7 plays a significant role in transmission and metastasis within the tumor development process and is associated with poor prognosis in some malignancies [15]. For example, Shi et al. [16] and Liu et al. [17] reported that high CCR7 expression was correlated with clinicopathological features and poor prognosis of ESCC.

Although many studies have revealed that CCR7 expression is associated with the clinicopathological features and prognosis of ESCC, some incongruous results have been reported [18]. Whether the diversity of these results is due to limited sample size, different nationalities of study populations or genuine heterogeneity remains unclear. To shed light on this puzzle using the results of relative studies through meta-analysis, we sought to address the value of CCR7 as a factor in the prognosis for ESCC and affirm the association between high CCR7 expression and the clinicopathological features of ESCC.

**Methods**

*Literature search strategy*

We searched and reviewed the PubMed, Embase, Web of Science, CNKI and WanFang data-

*Study selection criteria*

We collected all qualifying studies relevant to a potential correlation between CCR7 expression and the clinicopathological features and clinical outcome of ESCC in this meta-analysis. Two independent investigators filtered eligible articles and followed the same standards and multistep procedures. Patients in the articles fulfilling the following standards were incorporated into this meta-analysis: (1) CCR7 expression was assessed in primary esophageal squamous cell carcinoma tissues; (2) Either randomised controlled studies or observational studies could be collected; (3) The research revealed a connection between CCR7 expression and the clinicopathological features and overall survival (OS) rate for ESCC; (4) Patients with pathologically identified esophageal squamous cell carcinoma underwent detection of CCR7 in neoplastic cells; (5) If similar data appeared, the largest or the most recently conducted study would be selected; and (6) The research must contain a negative control. The exclusion criteria were as follows: (1) Bipartite groups relationship between CCR7 expression and clinicopathological features for esophageal squamous cell carcinoma; (2) CCR7 in circumambient tissues of ESCC and its clinical significance, rather than in ESCC cells; (3) Duplicate or similar studies including the same patients; and (4) All patients had previously accepted chemotherapy or radiotherapy.

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**Table 1.** Major characteristics of the research studies included

Authors	Year	Country	Sample size	Age#	Method	CCR7 expression	Gender		DOV		TNM stage		LNM		HD	
							Male	Female	T1-T2	T3-T4	I-II	III-IV	P	N	WD+MD	PD
Ding [21]	2003	Japan	96	61.18	IHC	H	48	7	20	35	21	34	44	11	37	18
						L	33	8	24	17	29	12	13	28	32	9
Fan [22]	2008	China	56	61	IHC	H	18	16	7	27	8	26	33	1	14	20
						L	12	10	14	8	18	4	7	15	8	14
Tang [23]	2010	China	48	55.2	IHC	H	24	4			18	10	15	23	30	5
						L	19	1			18	2	0	10	6	7
Liu [17]	2013	China	174	57.7	IHC	H	101	26	36	91	79	50	65	62	110	17
						L	36	11	26	21	40	7	9	38	43	4
Zhao [24]	2013	China	40	60.1	IHC	H	19	10			5	25	23	6	16	13
						L	6	5			8	4	5	6	5	6
Irina [18]	2014	Japan	105	NM	IHC	H	26	2	16	12	11	17	21	5	26	2
						L	70	7	41	36	41	36	47	32	69	8
Shi [16]	2015	China	153	50	IHC	H	69	19	55	33			60	29	34	33
						L	47	18	46	19			28	36	54	32
Yang [25]	2015	China	50	61	IHC	H	30	6	10	26			28	3		
						L	11	3	13	1			8	11		

Abbreviations: IHC, immunohistochemistry; H, high; L, low; DOV, depth of invasion; TNM, tumor node metastasis; LNM, lymph node metastasis; P, positive; N, negative; HD, histological differentiation; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; #: Moderate age or Mean.

## Clinicopathology of ESCC

**Table 2.** Main outcomes for meta-analysis of association between CCR7 expression and clinicopathological features, overall survival (OS), and publication bias (Begg's test)

Clinicopathological features and OS	No. of studies	Overall OR/HR (95% CI)	Z, P	Heterogeneity analysis ( $I^2$ , P)	Publication bias (Begg's test) (Z, P)
Gender (Male vs Female)	21, 22, 23, 17, 24, 18, 16, 25	1.23 (0.84, 1.82)	1.06, 0.287	0.0%, 0.951	0.87, 0.386
DOV (T1-T2 vs T3-T4)	21, 22, 17, 18, 16, 25	0.37 (0.19, 0.75)	2.79, 0.005	69.8%, 0.005	1.13, 0.26
TNM stage (I-II vs III-IV)	21, 22, 23, 17, 24, 18	0.25 (0.16, 0.39)	6.32, <0.001	40.5%, 0.135	0.38, 0.707
LNM (P vs N)	21, 22, 23, 17, 24, 18, 16, 25	5.01 (3.47, 7.22)	8.64, <0.001	48.4%, 0.059	1.61, 0.108
HD (WD+MD vs PD)	21, 22, 23, 17, 24, 18, 16	0.90 (0.61, 1.31)	0.56, 0.575	48.5%, 0.07	0.9, 0.368
Overall survival	21, 17, 18, 16	2.07 (1.56, 2.71)	5.13, <0.001	0.0%, 0.705	1.04, 0.296

Abbreviations: DOV, depth of invasion; TNM, tumor node metastasis; LNM, lymph node metastasis; P, positive; N, negative; HD, histological differentiation; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; HR, hazard ratio; OR, odds ratio; CI, confidence interval.

### Data extraction

Two investigators independently screened and extracted data from qualifying studies. When they could not come to a consensus, a third party was consulted. The study was incorporated into this meta-analysis if all three investigators approved. Relevant data were collected from the eligible studies, including first author, country, year of publication, number of patients and detection method of CCR7 expression, in addition to clinicopathological features and relevant survival data. The 95% confidence interval (CI) and hazard ratio (HR) of overall survival (OS) were adopted to count pooled HR.

### Quality assessment

According to the Newcastle-Ottawa scale (NOS) [19], quality assessment mainly concentrated on selection (representative, result of interest, choice of non-exposure, and identification of exposure), level of comparability of design or analysis for studies, and the results (follow up and assessment) of the original studies. Evaluation was executed independently by two investigators, and differences were resolved by consensus with a third reviewer.

### Statistical analysis

Pooled Odds Ratio (OR) and 95% CIs were used to evaluate the relevance between CCR7 expression and clinicopathological features of ESCC, such as gender (male versus female), depth of invasion (T1-T2 versus T3-T4), TNM stage (I-II vs III-IV), lymph node metastasis (positive versus negative), and histological differentiation (well/moderate versus poor differentiation). If the eligible studies offered survival data, HR for overall survival (OS), or 95% CIs, they were included either directly from the stud-

ies or using corresponding calculation methods [20]. Kaplan-Meier (K-M) survival curves were drawn by Engauge Digitizer (version 4.1, <http://digitizer.sourceforge.net/>). The  $I^2$  test and Q test were performed to execute heterogeneity among the studies. A statistically significant heterogeneity was determined when  $p > 0.05$  or  $I^2 < 50\%$ , and a fixed effect model was used, otherwise, a random effects model was selected. The source of heterogeneity was evaluated via sensitivity and subgroup analysis. The probability publication bias was evaluated by the funnel plot and Begg's test. All analyses were performed with STATA version 12.0 (STATA Corporation, TX, USA).

## Results

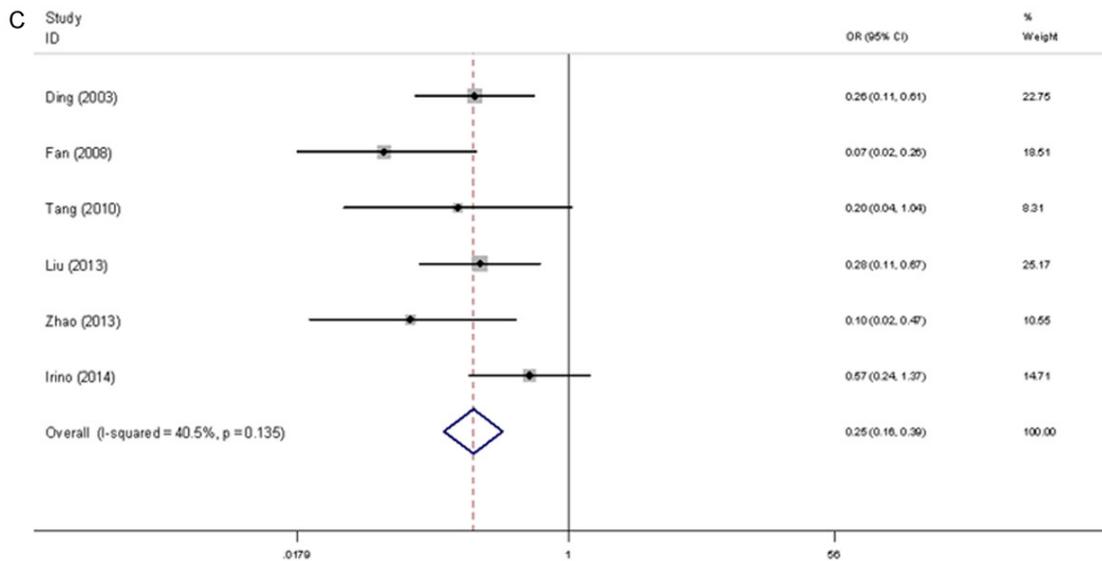
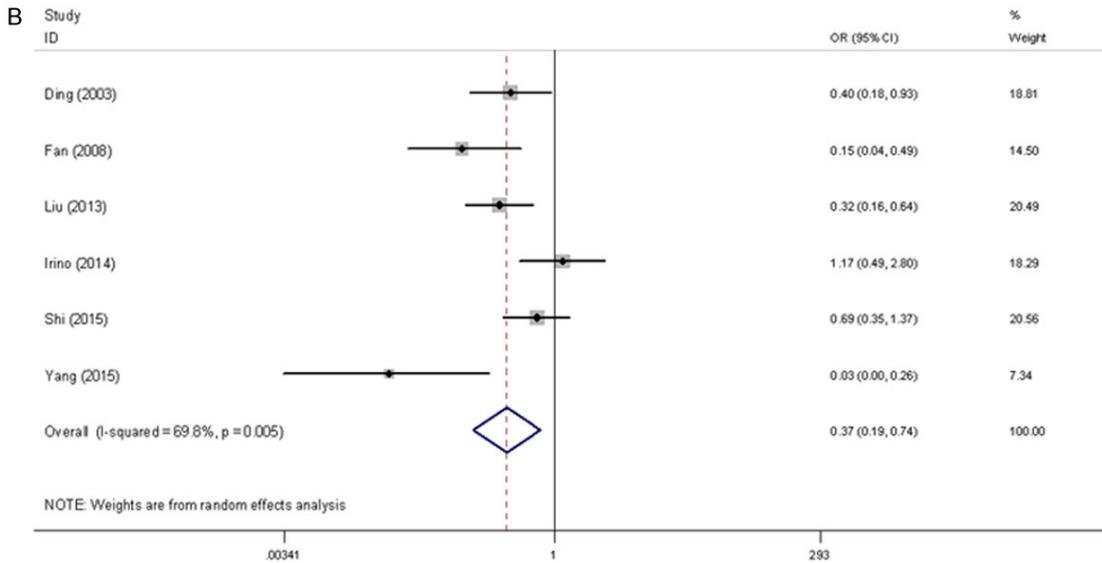
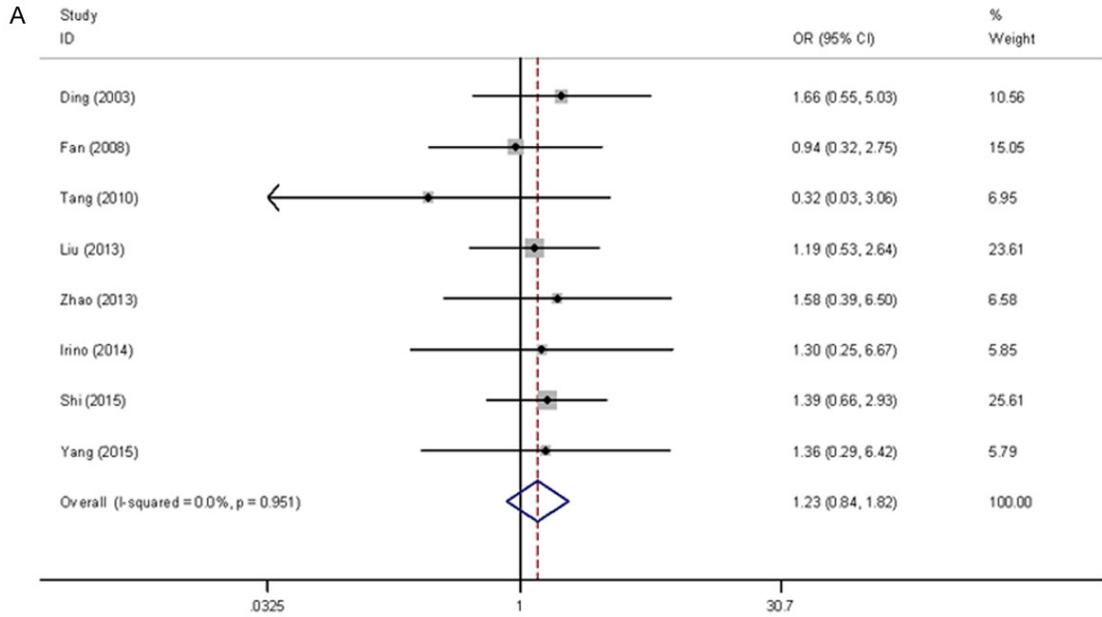
### Study selection

As shown in **Figure 1**, 452 studies were identified by database search. Four hundred and thirteen studies were excluded because of irrelevance to circulating CCR7 or esophageal cancer. Twenty-nine of those were excluded due to not being esophageal squamous cell carcinoma, circulating cells studies, or repeated reports. After all other exclusions, one study did not provide relevant data, and one focused on CCR7 mRNA in esophageal squamous cell carcinoma. Finally, eight eligible studies were included in this meta-analysis [16-18, 21-25]. The detailed option process is shown in a flow chart (**Figure 1**).

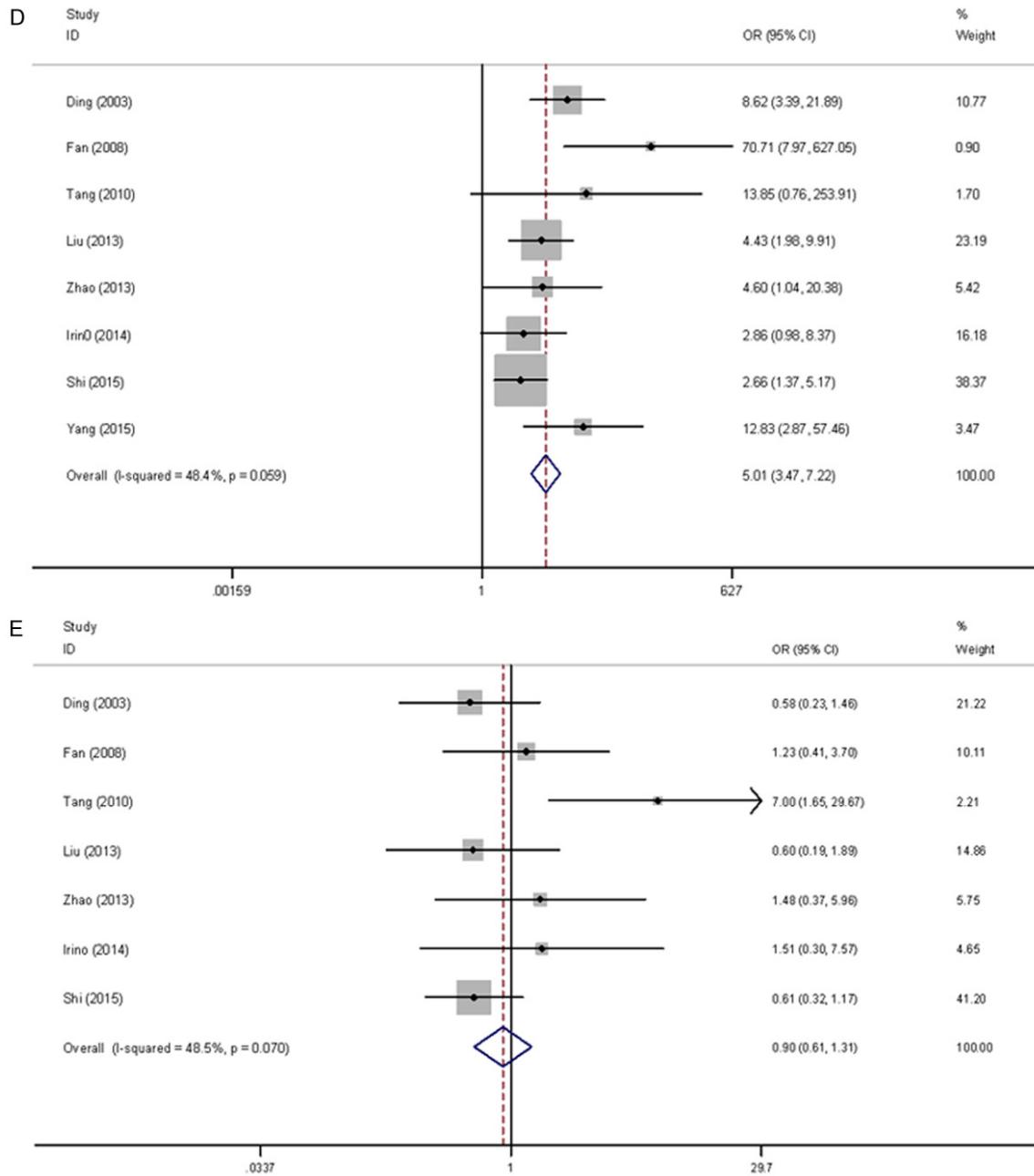
### Study characteristics

As seen in **Figure 1**, eight studies were included in this meta-analysis after cautious selection and screening by the entire search group. The principal and detail characteristics of incorporated studies are summarised in **Table 1**. The

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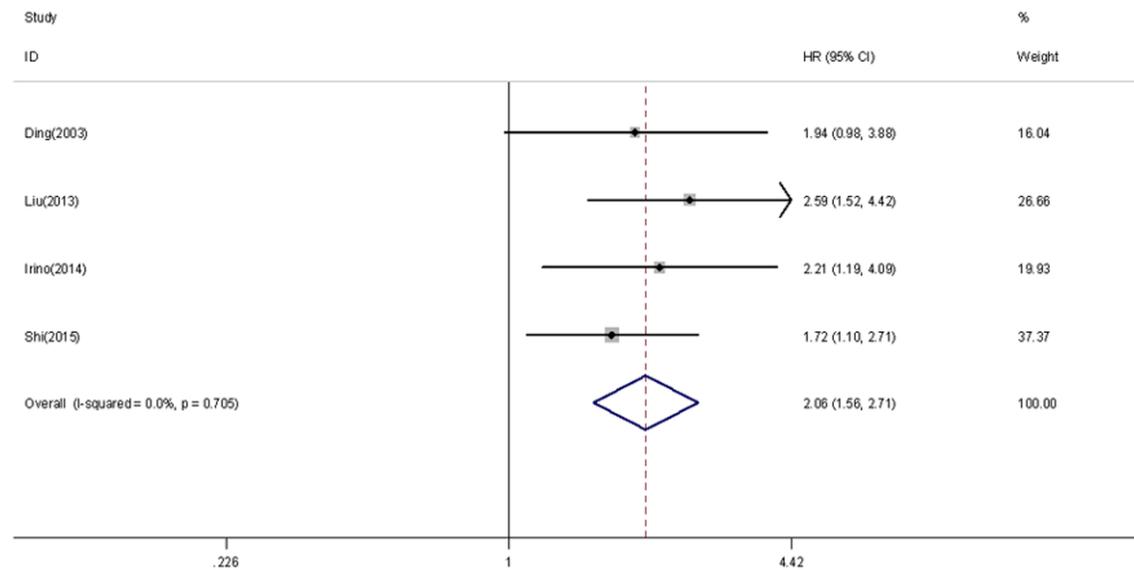


**Figure 2.** Forest plots of CCR7 expression and clinicopathological features of patients with esophageal squamous cell carcinoma. A. Gender, B. Depth of invasion, C. TNM stage, D. Lymph node metastasis, E. Histological differentiation. CI confidence interval, OR odds ratio.

eight eligible studies included data from a total of 722 patients and were published between 2003 and 2015. All the studies included patients from Asian countries or regions (2 from Japan and 6 from China). The percentage of patients with high CCR7 expression ranged from 25% to 75%. All the studies performed immunohistochemistry to observe expression

of CCR7. Clinicopathological features included age, gender, depth of invasion, TNM stage, lymph node metastasis, and histological type. As for depth of invasion, 68.7% of patients were identified as T3 or T4, 71.4% of patients were determined to be in TNM stage III or IV, 56.2% of patients were in a state of lymphatic metastasis, and 57.4% of patients were determined

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**Figure 3.** Forest plot of CCR7 expression associated with hazard ratio for overall survival rate of patients with esophageal squamous cell carcinoma. HR hazard ratio, CI confidence interval.

to be poorly differentiated. Four studies reported the survival data of patients. Among them, only one presented the value of 95% CIs and HRs, and the Kaplan-Meier method was used in three papers. The definition of expressed CCR7 staining varied among the articles. Further detailed characteristics are shown in **Tables 1-2**.

### Quality assessment

According to NOS, the patients in the articles were chosen reasonably. The eventual diagnoses were identified by pathological detection. The same demographic data were used to divide all patients into groups. All studies used fixed criteria for dividing all patients into different groups. All clinical data were gathered in specialised hospitals for all patients. Moreover, all samples used the fixed method of immunohistochemistry to identify expression of CCR7.

### CCR7 expression and clinicopathological features

We assessed the relationship between CCR7 expression and gender, depth of invasion, TNM stage, lymph node metastasis, and histological differentiation. As shown in **Figure 2**, CCR7 expression was insignificantly associated with gender (OR=1.23, 95% CI=0.84-1.82,  $P=0.287$ , fixed effect, **Figure 2A**) and histological differentiation (OR=0.90, 95% CI=0.61-1.31,  $P=$

0.575, fixed effect, **Figure 2E**). However, esophageal squamous cell carcinoma with CCR7 expression was significantly associated with depth of invasion (OR=0.37, 95% CI=0.19-0.74,  $P=0.005$ , random effect, **Figure 2B**), TNM stage (OR=0.25, 95% CI=0.16-0.39,  $P<0.001$ , fixed effect, **Figure 2C**) and lymph node metastasis (OR=5.01, 95% CI=3.47-7.22,  $P<0.001$ , fixed effect, **Figure 2D**).

### CCR7 expression and prognosis

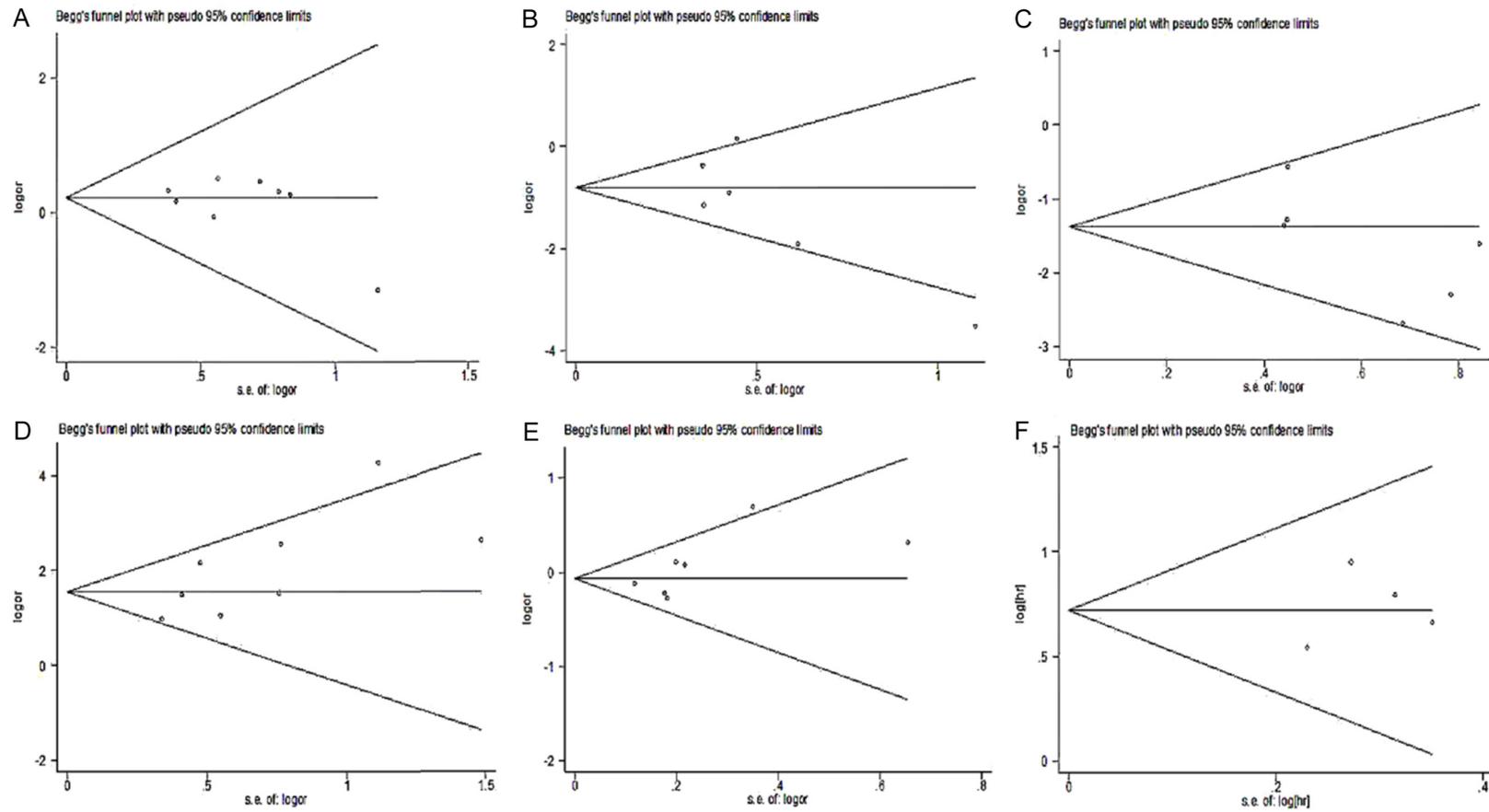
The association between CCR7 expression and OS is evaluated in **Figure 3**. The pooled HR for OS revealed that high expression of CCR7 was associated with poor OS in esophageal squamous cell carcinoma (HR=2.06, 95% CI=1.56-2.71,  $P<0.001$ , fixed effect).

### Publication bias and sensitivity analysis

In our meta-analysis, the values from funnel plots and Begg's test revealed that all included studies showed insignificant publication bias for pooled gender ( $P=0.386$ ), depth of invasion ( $P=0.260$ ), TNM stage ( $P=0.707$ ), lymph node metastasis ( $P=0.108$ ), histological differentiation ( $P=0.368$ ) and overall survival ( $P=0.296$ ). Detailed information is presented in **Figure 4** and **Table 2**.

A sensitivity analysis was conducted to assess whether individual studies affected pooled

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**Figure 4.** Funnel plots of Begg's test outcomes for CCR7 expression and clinicopathological features. A. Gender, B. Depth of invasion, C. TNM stage, D. Lymph node metastasis, E. Histological differentiation, F. Overall survival. OR: odds ratio, SE: standard error.

ORs or HR by removing one study by turns. The sensitivity analysis revealed that no study substantially affected pooled OR/HR. The stability of the meta-analysis was also verified.

### Discussion

CCR7 expression has been reported in many kinds of human carcinoma cells and has been connected with promoted metastasis and invasion of human cancer cells, such as colorectal cancer and gastric cancer cells [26, 27]. An association between CCR7 expression and esophageal squamous cell carcinoma has also been reported by many studies, most of which revealed that high expression of CCR7 is related with some clinicopathological features of ESCC. Nevertheless, some studies have showed incongruous results. In the present study, eight eligible studies including data from 722 patients were summed quantitatively based on our inclusive and quality assessment criteria. Moreover, meta-analysis revealed that high CCR7 expression is correlated with high depth of invasion, lymph node metastasis, high TNM stage and poor differentiation type. This study is a comprehensive meta-analysis that systematically reveals the association between CCR7 expression and clinicopathological features in esophageal squamous cell carcinoma.

Previous studies have suggested that the mechanism of CCL19/CCL21-CCR7 axis could promote invasion and lymph node metastasis of cancer. The CCL19/CCL21-CCR7 axis is better characterised for its important role in the constitution of secondary lymphoid structures responding to physiological situations, mainly through the accumulation of immune cells to these regions [28]. CCL21, as one ligand of CCR7, is fixed in lymphatic endothelial cells (LVs) and becomes a gradient that can gradually induce in the direction of the interstitium [29]. Therefore, spreading of upregulated CCR7 and tumor cells from the primary carcinoma may result from cells sensing the fixed CCL21 gradient and actively migrating toward the lymphatic vessel and the T-cell region of the lymph node. However, CCR7 can promote tumor cell survival through mediated activation of the phosphatidylinositol-3-kinase (PI3K)/Akt pathway [30]. Studies have shown that the CCL21/CCR7 axis can promote expression of E-cadherin, Vimentin, Slug, N-cadherin, and N-cadherin-9, which are regarded as markers of epi-

thelial mesenchymal transition (EMT). In short, CCR7 can irritate tumor cells to obtain an EMT phenotype [31, 32]. Accumulating proofs have indicated that EMT plays a crucial role in occurrence of the tumor development process, especially in cancer metastasis and invasion [33]. Moreover, EMT is associated with poor prognosis of cancer patients [34]. Meanwhile, CCL19 and CCL21 are plentiful in the tumor microenvironment due to expression of CCL19 and CCL21 by lymphatic endothelia, cancer tissue and precancerous lesions, which can induce EMT of cancer cells and further facilitate their metastasis [35].

On the basis of the abovementioned research and of our results indicating an association between CCR7 expression and several exacerbated clinicopathological features, we infer that high CCR7 expression is related to poor OS of ESCC patients. Our results also confirmed this point. Including studies with HRs verified our conjecture that high CCR7 expression is related to poor prognosis of ESCC patients. Nevertheless, there were some insufficiencies in our data collection. Five of the included studies didn't provide enough information about postoperative radiotherapy/chemotherapy, which may have led to some inaccuracies. There were also some limitations within this meta-analysis. First, all the included studies came from Asia. The limited geographical scope makes it difficult to show a relationship between CCR7 expression and the clinicopathological features or prognosis of ESCC among Western patients. Second, the sample size of included studies is small. A small sample size can contribute to clinical heterogeneity and publication bias because small sample experiments are more careful in choosing patients and can also distort the outcomes of a meta-analysis [36]. Third, the heterogeneity of our study sample cannot be overlooked. Most of the CCR7 expression in the included studies was detected by the IHC method. Therefore, different primary antibodies and different antibody concentrations could lead to inconsistent detection of CCR7 expression.

In conclusion, we found an association between aggressive cancer behavior and high CCR7 expression in ESCC patients, and we found data suggesting that CCR7 could be a biomarker for poor prognosis in ESCC. This might be

important for the clinical diagnosis and prognosis of ESCC patients in the Asian population.

### Conclusions

This meta-analysis suggests that high expression of CCR7 in esophageal squamous cell carcinoma is not only strongly associated with depth of invasion, TNM stage and lymph node metastasis but is also a negative prognostic factor for ESCC patients in the Asian population.

### Acknowledgements

This work was funded by the Natural Science Fund Project of Guangdong province, China (No. 2016A030313683), the Social Science and Technology Development Project of Dongguan, Guangdong province, China (No. 2014-108101051; 2016108101039), and the National Natural Science Foundation of China (81200082).

### Disclosure of conflict of interest

None.

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