

Original Research

Clinicopathological and prognostic significance of CXCR4 high expression in renal cell carcinoma: A meta-analysis and literature review

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ABSTRACT

Introduction: Previous results have indicated that CXCR4 is an oncogene in several types of human tumors including renal cell carcinoma (RCC). However, the correlation between CXCR4 expression and clinicopathological characteristics of RCC remains unclear.

Materials and methods: We conducted a meta-analysis to quantitatively evaluate the association of CXCR4 expression with the incidence of RCC and clinicopathological characteristics. Final analysis of 1203 patients with RCC from 14 eligible studies was performed.

Results: We observed that CXCR4 expression is significantly higher in RCC than in normal renal tissue, and the pooled OR from 7 studies including 435 RCC and 297 normal renal tissues was OR = 46.23, 95% CI = 7.18–297.69, $p < 0.0001$. CXCR4 expression is not associated with gender status and clinical stages. However, CXCR4 expression was significantly associated with pathological grades, metastatic status, and overall survival in patients with RCC.

Discussion: These results indicate that CXCR4 expression is associated with increased risk, progression, and prognosis for patients with RCC. The determination of CXCR4 expression may provide a biomarker for tumor risk evaluation, progression, and prognosis of patients with RCC.

1. Introduction

Recently, the α -chemokine receptor C-X-C chemokine receptor type 4 (CXCR4) has been found to be the most widely expressed receptor in tumors and identified as a potential drug target for human tumor owing to its crucial role in cell proliferation, migration, and tumor metastasis, as well as its critical roles in promoting and maintaining cancer stem cells (CSCs) [2,3]. A number of studies have also demonstrated that CXCR4 is highly expressed in RCC [4–7]. Recent studies made significant progress in understanding CXCR4 nuclear function and metastasis in RCC [8]. Overexpression of notch1-upregulated CXCR4 in RCC CSCs indicates that CXCR4 could be a potential therapeutic target in human RCC [9]. Treatment with CXCR4 antagonist in combination with conventional therapy and/or immunotherapy could improve the anticancer immune response in patients with RCC [10]. However, controversies continue to exist about the roles of CXCR4 expression in progression, metastasis, and prognosis owing to the limited number of patients in individual studies. In addition, the roles of CXCR4 in RCC have not been thoroughly studied. Meta-analysis has great advantages in confirming pathological and prognostic factors in patients with

cancer by avoiding disadvantages of small sample size. In this meta-analysis study, we analyze the effect of CXCR4 expression in patients with RCC.

2. Material and methods

2.1. Search strategy and selection criteria

We searched Embase, PubMed, ISI Web of Knowledge, EBSCO, Cochrane Library database, Google Scholar, Chinese Wanfang Database, CNKI, and CBM to identify studies published from January 1, 2000, to January 5, 2019, using the following search terms: "renal," "kidney," "carcinoma, tumor or cancer or neoplasm or," "CXCR4, or C-X-C chemokine receptor type 4," and "expression."

An eligible study had to meet the following criteria: (1) research revealing the relationship between CXCR4 expression and RCC clinicopathological parameters, (2) high CXCR4 expression detected in primary RCC tissues, and (3) studies providing sufficient information to estimate hazards ratio (HR) about overall survival (OS) and 95% confidence interval (CI). We used the following exclusion criteria: (1)

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studies using the same population or overlapping database, (2) studies analyzing the correlation between *CXCR4* mRNA expression and clinicopathological parameters, (3) studies utilizing cell lines or animals.

2.2. Data extraction

Primary data were extracted using a customized form, which included first author, year of publication, geography location, number of cases, cancer stage, clinicopathological parameters, immunohistochemical staining method, percentage rate of expression, and follow-ups. Two reviewers extracted the data independently, and disagreements were discussed until a consensus was reached.

2.3. Statistical analysis

The pooled ORs with its 95% CIs were calculated. The heterogeneity among studies was determined using the Cochran's Q statistic and *I* [2] tests. When the *I* [2] value was below 50%, the fixed effects model was used; when the *I* [2] value was 50% or greater, a random effects model was used. Publication bias was assessed using a method reported by Egger et al. [11]. The meta-analysis was performed using Review Manager 5.3 (Cochrane Collaboration, Software Update, Oxford, UK). The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines. A P-value less than 0.05 is considered statistically significant.

3. Results

3.1. Identification of relevant studies and quality assessment

A total of fourteen studies were included in the meta-analysis [7,12–24] (Fig. 1), and 1203 participants from five countries were involved. The characteristics of the included studies are provided in Table 1. Based on the quality evaluation with the Newcastle-Ottawa Quality Assessment Scale (NOQAS), the overall quality of fourteen studies was scored ranging from six to eight, which indicates good quality (data not shown).

3.2. Increased *CXCR4* expression in RCC

We first determined whether *CXCR4* expression was significantly higher in RCC than in normal renal tissue. The pooled OR from 7 studies, including 435 RCC and 297 normal renal tissue, is shown in Fig. 2 (OR = 46.23, 95% CI = 7.18–297.69, $p < 0.0001$), which indicates that *CXCR4* expression is significantly higher in RCC than in normal renal tissue.

3.3. Relationship between the frequency of *CXCR4* expression and gender status

We then determined whether the *CXCR4* expression rate in patients with RCC was associated with gender status. The pooled OR from 5 studies, including 469 males and 276 females, is shown in Fig. 3 (OR = 0.79, 95% CI = 0.49–1.41, $p = 1.28$), indicating that *CXCR4* expression is not significantly associated with gender status in patients with RCC.

3.4. Association between the frequency of *CXCR4* expression and RCC grades as well as stages

The pooled OR from 6 studies, including 561 grades I and II, 346 grades III and IV, is shown in Fig. 4 (OR = 2.45, 95% CI = 1.24–4.82, $p = 0.01$), which demonstrates that *CXCR4* expression is significantly higher in patients with RCC in high Fuhrman grades than in those with low Fuhrman grades. However, *CXCR4* expression is not significantly higher in advanced 335 RCC (grades III and IV) than in early-stage 642 RCC (grades I and II), OR = 1.53, 95% CI = 0.82–2.85, $p = 0.18$, as shown in Fig. 5.

3.5. Association between the frequency of *CXCR4* expression and RCC metastatic status and prognosis

We then determined whether *CXCR4* expression rate in patients with RCC is associated with metastatic status. The pooled OR from 5 studies, including 97 metastatic RCC and 446 without metastatic RCC, is shown in Fig. 6 (OR = 1.83, 95% CI = 1.04–3.23, $p = 0.04$), which

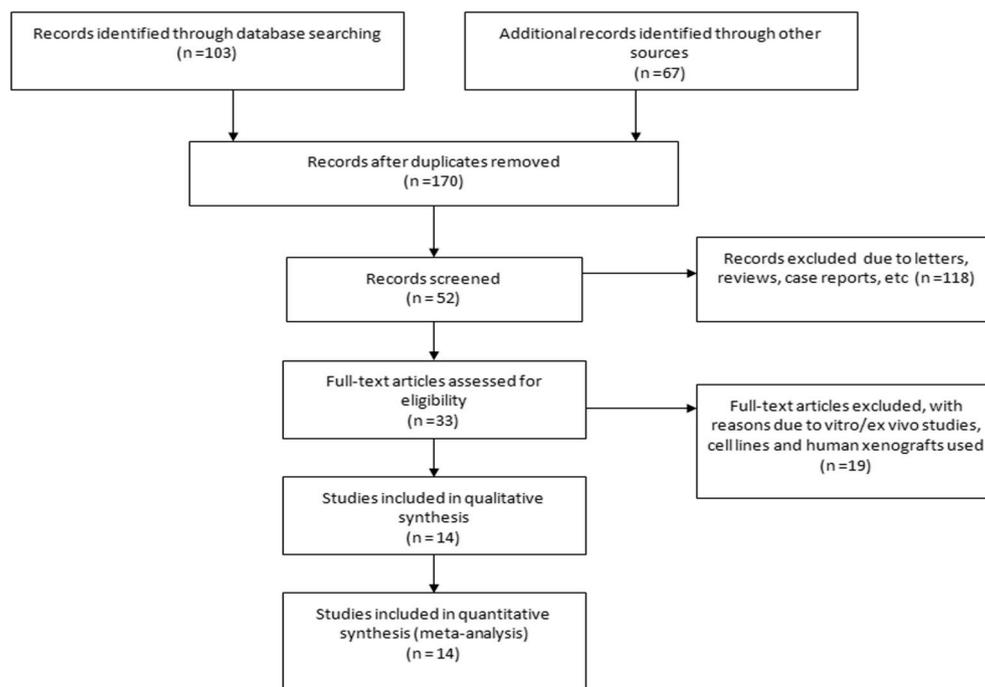


Fig. 1. Flowchart of study selection.

Table 1
Basic characteristics of the included studies.

| Study | Country | Patients | Histology (cases) | Methods | Antibody source | CXCR4 distribution | Definition of CXCR4 positive |
|-----------------------------|-------------|----------|--------------------------------|---------|------------------------|----------------------------------|----------------------------------|
| An et al., 2014 [22] | China | 110 | Clear cell | IHC | R&D | Predominantly nucleolus | Staining score |
| Huang et al., 2013 [12] | China | 45 | Not known | IHC | R&D | Cytoplasm | Staining score |
| Wang et al. 2012 [13] | China | 97 | Clear cell (81) Others (16) | IHC | R&D | Predominantly nucleolus | ≥ 30% |
| Li 2011 [14] | China | 117 | Clear cell | IHC | R&D | Nuclear and membrane | Semi-quantitative scoring system |
| D'Alterio et al., 2010 [15] | Italy | 182 | Clear cell (150) | IHC | R&D | Cytoplasm and membrane | > 20% |
| Shi et al. [23] | China | 56 | Others (32) Clear cell | IHC | R&D | Nuclear and membrane | Semi-quantitative scoring system |
| Zhao et al., 2011 [16] | China | 40 | Not known | IHC | Santa Cruz | Cytoplasm and membrane | ≥ 10% |
| Wang et al., 2011 [24] | China | 43 | Clear cell | IHC | R&D | Nuclear and cytoplasm | Semi-quantitative scoring system |
| Wang et al., 2009 [17] | China | 43 | Clear cell | IHC | Chemicon International | Membrane, cytoplasm, and nucleus | Semi-quantitative scoring system |
| Schrader et al., 2002 [18] | Germany | 10 | Clear cell | IHC | Santa Cruz | Cytoplasm | Semi-quantitative scoring system |
| Li al 2013 [19] | France | 104 | Clear cell | IHC | Abcam | Nucleus, cytoplasm, and membrane | ≥ 25% |
| Wehler et al., 2008 [20] | Germany | 113 | Clear cell | IHC | Capralogics Inc. | Cytoplasm | > 50% |
| Staller al 2003 [7] | Switzerland | 195 | Clear cell | IHC | R&D | Cytoplasm | Semi-quantitative scoring system |
| Hao et al., 2010 [21] | China | 48 | Clear cell | IHC | R&D | Cytoplasm and/or nucleus | Semi-quantitative scoring system |

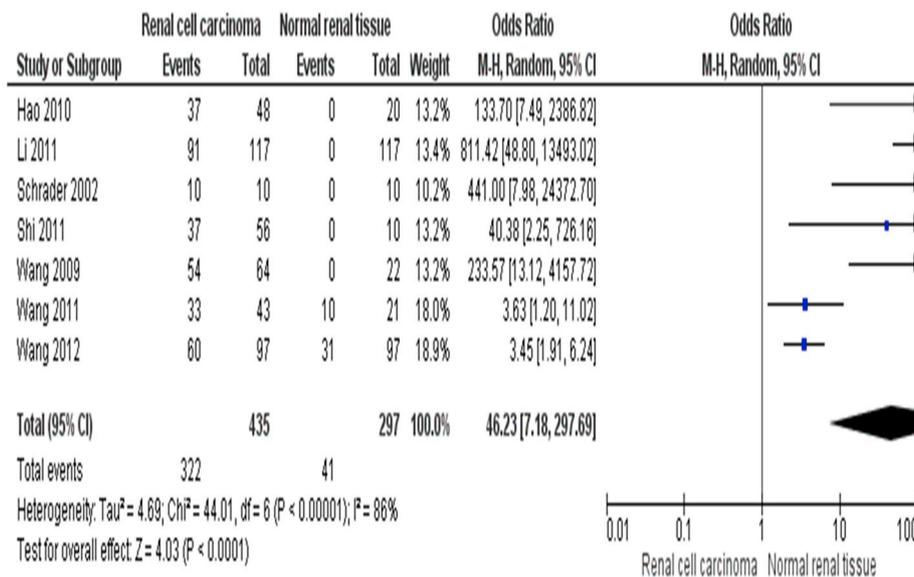


Fig. 2. Pooled OR from 7 studies including 336 RCC and 266 normal renal tissue.

indicates that CXCR4 expression is significantly higher in patients with metastatic RCC than in patients with nonmetastatic RCC. Finally, the pooled HR for OS showed that CXCR4 expression was significantly associated with worse survival in patients with RCC as shown in Fig. 7 (HR = 5.19, 95% CI = 3.79–52.53, $p < 0.00001$).

3.6. Sensitivity analysis and publication bias

Sensitivity analysis was performed by removing one study at a time, and we found that the ORs or HRs did not significantly change, indicating the stability of the present meta-analysis. In the case of comparison between normal renal tissue and RCC, the range of ORs was 7.95–46.23. In the case of comparison between male and female RCC, the range of ORs was 0.73–0.95. In the case of comparison between two grades of RCC, the range of ORs was 1.87–2.89. The funnel plots were

largely symmetric (Fig. 8), suggesting that no publication bias exists in the meta-analysis of the relationship between CXCR4 expression status and clinicopathological characteristics.

4. Discussion

Recently, a number of studies have demonstrated that the presence of CXCR4 in tumor cells is able to activate chemotaxis and signify proliferation, invasion, metastasis, and angiogenesis in several tumors, including RCC [25–29]. Although there have been some studies that determined the precise expression and prognostic impact of CXCR4 in RCC, the conclusions regarding the roles of CXCR4 expression in RCC and its clinical significances are still controversial [30,31]. We searched all articles, including those published until recently, and conducted the meta-analysis to determine the correlation between CXCR4 expression

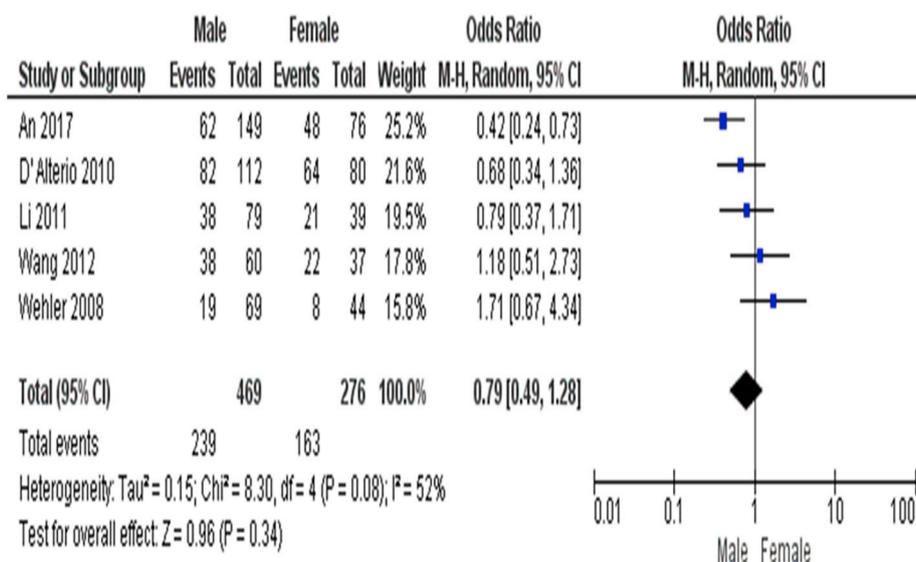


Fig. 3. A total of 754 patients with RCC of either gender pooled from 5 studies.

and clinicopathological characteristics in patients with RCC.

Analyses of the pooled data showed that RCC has a higher CXCR4 expression than normal renal tissue. CXCR4 overexpression in RCC indicates localization of more CXCR4 proteins in the nucleus of cancer cells. Recent studies have shown that CXCR4 nuclear localization requires its nuclear localization sequence (NLS, residues 146-RPRK-149) and nuclear localization of CXCR4 promoted RCC tumorigenicity both *in vitro* and *in vivo* [32]. Aberrant CXCR4 expression was significantly higher in high Fuhrman grades (III and IV) than in low Fuhrman grades (I and II), OR = 2.45, 95% CI = 1.24–4.82, *p* = 0.01. The pooled OR from 5 studies indicates that CXCR4 expression is significantly higher in patients with metastatic RCC than in patients with nonmetastatic RCC, OR = 1.83, 95% CI = 1.04–3.23, *p* = 0.04. These results indicate that CXCR4 overexpression in RCC may promote cancer cell progression and metastasis. CXCR4 nuclear localization promoted nuclear accumulation of hypoxia-inducible factor-1α (HIF-1α), thereby promoting the expression of genes downstream of HIF-1α [32]. Reciprocally, nuclear HIF-1α promoted CXCR4 transcription, thus forming a feed-forward loop [32]. Therefore, CXCR4 and hypoxiaHIF-1α, colocalized in RCC cells and interacting with each other, may promote cell proliferation, migration, and metastasis. Importantly, the pooled HR for OS shows that CXCR4 expression is significantly associated with poor prognosis,

HR = 5.19, 95% CI = 3.79–52.53, *p* < 0.00001. However, the pooled OR from 5 studies indicates that CXCR4 expression is not significantly associated with gender in patients with RCC, OR = 0.79, 95% CI = 0.49–1.41, *p* = 1.28. CXCR4 expression is also not significantly associated the clinical stages, OR = 1.53, 95% CI = 0.82–2.85, *p* = 0.18. The results from our study demonstrate that the expression rate of CXCR4 in RCC is significantly higher than that in the normal renal tissues, indicating that CXCR4 expression is common in RCC and is a risk factor in RCC initiation.

CXCR4 expression may not associate with tumor's clinical stage status but may play an important role in RCC progression and development. In addition, CXCR4 expression is strongly correlated with metastatic status and prognostic outcome in patients with RCC. The nonclear cell renal cell carcinomas (nccRCCs) including chromophobe RCC (ChRCC) and papillary renal cell carcinomas (pRCCs) are a diverse group of rare-variant renal carcinomas and exhibit a distinct clinical behavior, as well as response to therapy [33]. A recent study [34] showed a significant difference when comparing the expression levels of CXCR4 in the ccRCC samples with those in the ChRCC and pRCC samples, indicating increased CXCR4 expression is associated with more aggressive tumor behavior in patients with RCC, especially in pRCC and ccRCC subtypes owing to their more metastatic behavior.

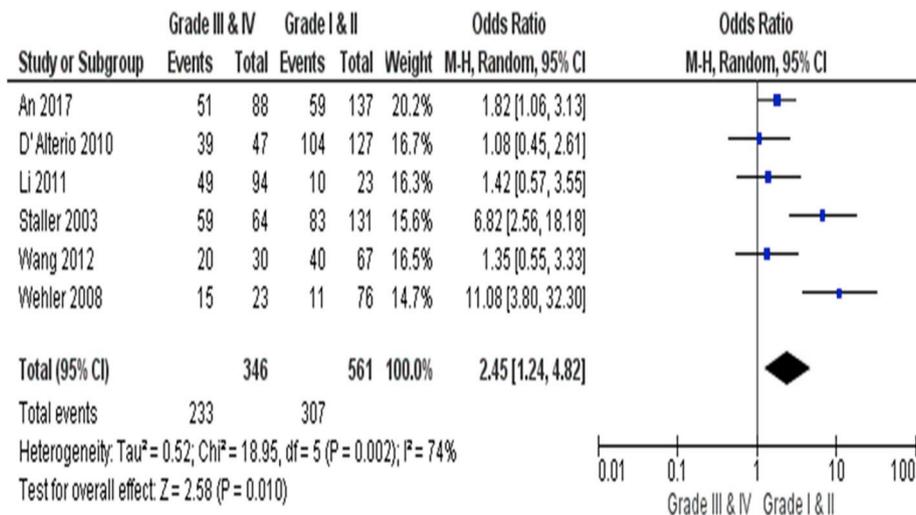


Fig. 4. Pooled OR from 6 studies including 346 grades III and IV, 561 grades I and II.

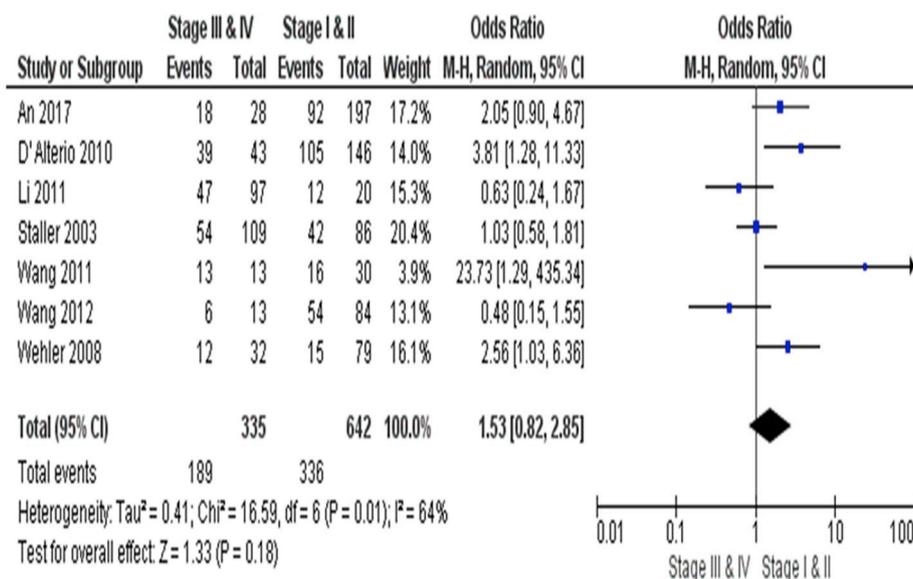


Fig. 5. 977 patients with RCC pooled from 7 studies including 335 stages III and IV, 642 stages I and II.

The limitations of this meta-analysis include the following: first, publication bias may exist, as positive results were more likely published. Second, the present study results were based on individual unadjusted ORs, and further confirmation needs to be done with other potential risk factors. Third, there is some statistical heterogeneity between the included studies. In addition, the definition of a CXCR4-positive standard was different in almost each study, and different antibodies were obtained from a number of sources. Further, different CXCR4 antibodies may have different immunohistochemical staining and/or different functions on tumor cells [35]. CXCR4 immunohistochemical staining may also have a different staining pattern, as CXCR4 nuclear staining or its nuclear localization may be responsible for certain metastatic changes in cancer cells and can be used to distinguish metastatic RCC cells [36]. Of all the fourteen studies, nine (64.3%) were from Asia (China), which may introduce bias in the study.

In conclusion, CXCR4 expression is correlated with the risk of RCC development. CXCR4 expression could be a potential biomarker of prognosis and a drug target for personalizing treatments for patients with RCC. Further large-scale studies are still needed and will provide more insight into the role of CXCR4 in the clinical implementation for patients with RCC.

Ethical approval

There is no any ethical approval needed in this study.

Sources of funding

The authors have no any financial disclosures.

Author contribution

XS, JM and HY participated in the design of the study, identify related studies.

XS, HZ, HH and YS reviewed and extracted data from eligible studies.

XS drafted the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

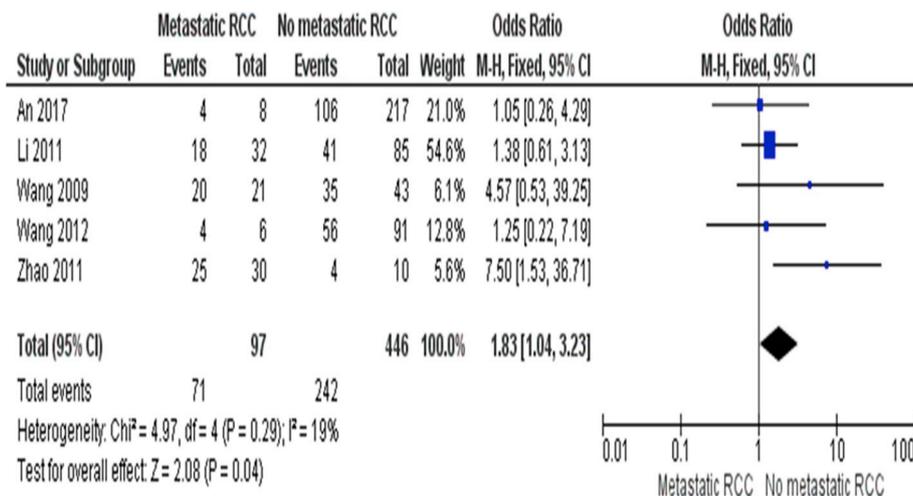


Fig. 6. 545 patients with RCC pooled from 5 studies including 97 metastatic RCC and 446 non-metastatic RCC.

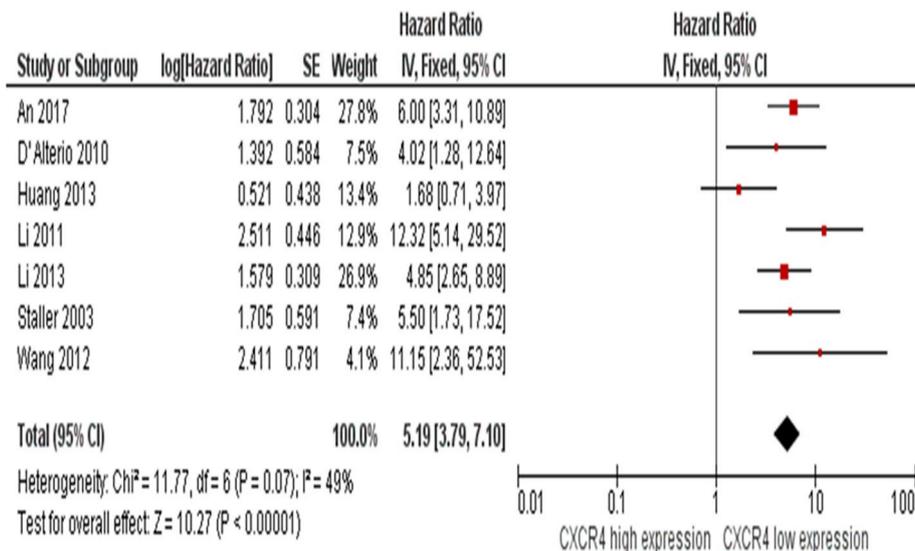


Fig. 7. Seven studies included investigated the prognostic difference between overall survival (OS) and CXCR4 expression.

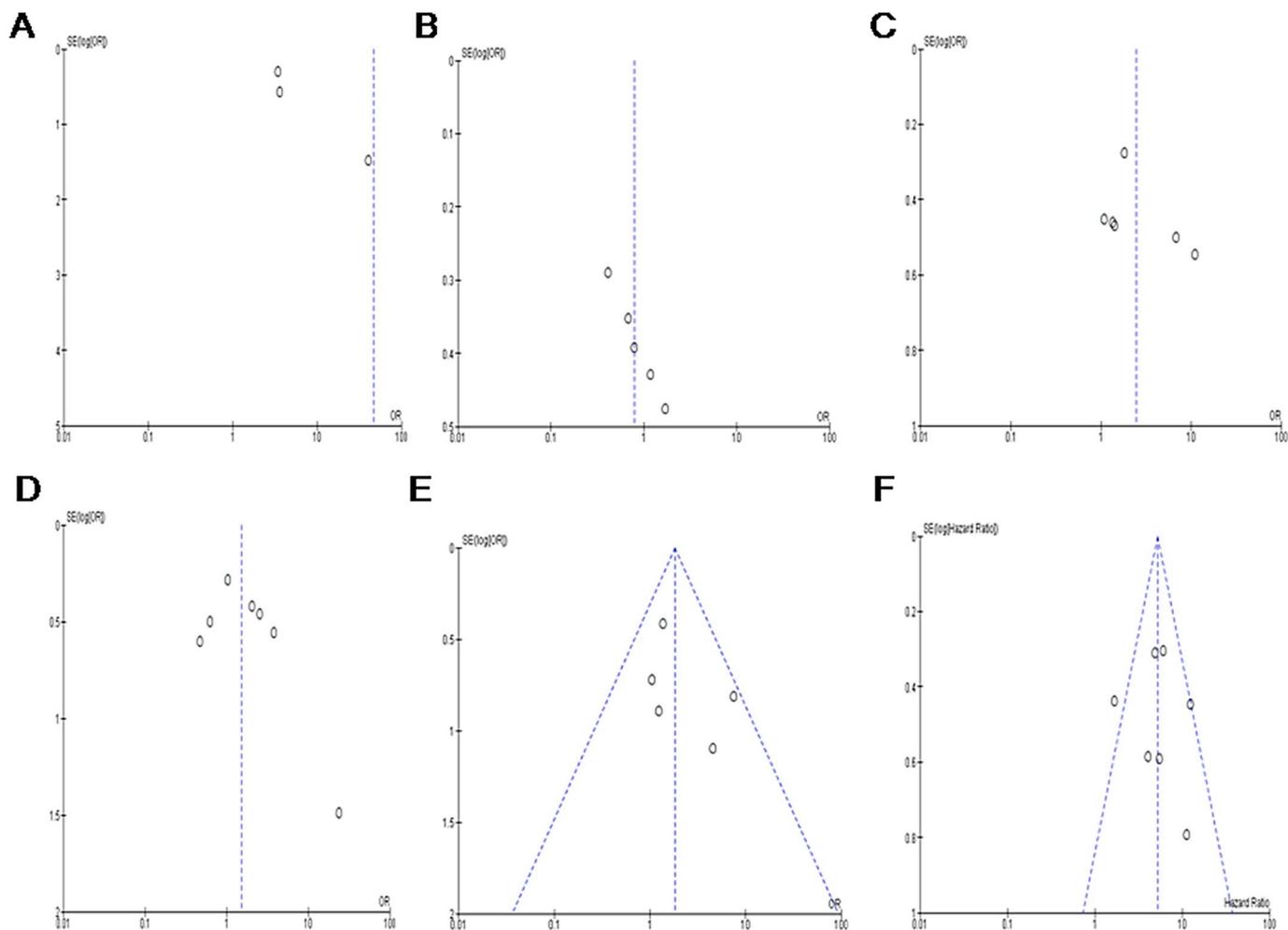


Fig. 8. Funnel plot from 7 studies comparing RCC and normal renal tissue (A). The funnel plot from 5 studies was used to determine CXCR4 expression and the gender status in patients with RCC (B). The funnel plot from 6 studies compared CXCR4 expression between low Fuhrman grades (III and IV) and high Fuhrman grades (I and II) (C). The funnel plot from 6 studies was used to determine CXCR4 expression in different clinical-staged RCC (D). The funnel plot from 5 studies was used to determine the relationship between CXCR4 expression and metastatic status in RCC (E). The funnel plot from 7 studies was used to determine the relationship between CXCR4 expression and overall survival (OS) in RCC (F). X-axis: value of odds ratio (OR) (A–E) or hazards ratio (F); Y-axis: Standard error (SE) multiplied log scale of OR, or hazards ratio.

Trial registry number

<https://www.crd.york.ac.uk/prospero/#myprospero>.

Registration number: CRD42019136205.

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Research data for this article

Data is available if request.

Competing interest

The authors have no financial involvement with any organization or entity with a financial interest in the subject matter or materials discussed in the manuscript.

Provenance and peer review

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijso.2019.08.021>.

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