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ORIGINAL ARTICLE

Positive expression of chemokine (C-C Motif) ligand 18 and prognosis in cancer: A meta-analysis

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Summary

Purpose: *Chemokine (C-C Motif) Ligand 18 (CCL18) is a chemotactic cytokine involved in the pathogenesis and progression of various cancers by activating downstream signaling pathways and affecting cellular behaviors. We conducted a meta-analysis to evaluate the CCL18 as a prognostic marker for cancer and determine the relationship between CCL18 and clinicopathological features of cancer.*

Methods: *We searched the PubMed, Cochrane, Embase, Web of Science and SinoMed databases for publications to investigate the association between CCL18 expression and survival outcome in cancer. Hazard ratios (HRs) and 95% confidence intervals (CI) of overall survival (OS) were pooled. Odds ratios (ORs) of clinicopathological features were computed. Meta-analysis was performed using STATA 12.0 software.*

Results: *Our meta-analysis identified a total of 17 studies including 2829 cases. Meta-analysis revealed that the expression of CCL18 in various cancer tissues was significantly higher than that in the normal group (OR=16.694, 95% CI=14.117–27.476, p<0.01, random effects). The abnormal expression of CCL18 was associated with lymph node metastasis (OR=4.409, 95% CI=2.129–9.128, p<0.01, random effects) and TNM stage (breast cancer subgroup: III+IV vs I+II OR=13.187, 95% CI=8.417-20.660, p<0.01; gastric cancer subgroup: III+IV vs I+II OR=0.034, 95% CI=0.008-0.137, p<0.01) but is was not related to gender (male vs. female: OR=0.88, 95% CI=0.667-1.162, p=0.368) and age (>60 vs. ≤60 years: OR=1.118, 95% CI=0.795-1.571, p=0.522). CCL18 overexpression was associated with poor overall prognosis of breast cancer (Hazard Ratio/HR=2.969, 95% CI=1.361-6.478, p<0.01, random effects).*

Conclusions: *CCL18 is highly expressed in cancer tissues and is closely related to tumor metastasis and prognosis, and its role in tumor development is worth of further study.*

Key words: *cancer, CCL18, immunohistochemistry, meta-analysis, prognosis*

Introduction

Cancer is becoming the leading cause of death in the developed world and the second leading cause in the developing world; this accounts for approximately 13% of deaths worldwide [1]. With the in-depth study of cancer, studies have shown that tumor microenvironment plays a key role in tumor growth and proliferation by providing the biomarkers for the occurrence, development, invasion and metastasis of cancer [2,3], including growth factors, cytokines and chemokines secreted by both tumor and stromal cells [4].

The Chemokine (C-C motif) ligand 18 (CCL18) belonging to the CC chemokine family is predominantly produced by monocyte-derived cells

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with M2 phenotype and is located at chromosome 17q11.2 with a molecular weight of about 8-10×10^3 kDa [5]. Numerous studies have demonstrated that CCL18 is expressed constitutively in ovarian cancer, gastric cancer, glioma and non-small cell lung cancer [6-9], and could promote cancer cell growth and invasion [10-13], suggesting CCL18 may contribute largely to cancer development and progression. However, the role of CCL18 in cancer progression is controversial. For example, CCL18 participates in immunosuppression of antitumor response in ovarian cancer [14], while it correlates positively with prolonged survival in gastric cancer patients [15]. Therefore, we conducted this meta-analysis of the association of CCL18 expression with the survival and clinicopathological features in cancer to examine the exact relationship between CCL18 expression and cancers.

Methods

Search strategy

We searched PubMed, Cochrane Embase, Web of Science and SinoMed databases from inception up to March 20, 2017. The following search strategies were used for search: PubMed: Search ("CCL18 protein, human" [MeSH]) OR (AMAC-1 protein, human) OR (CC chemokine PARC, human) OR (DC-CK1 protein, human) OR (MIP-4 protein, human) OR (PARC chemokine, human) OR (pulmonary AND activation-regulated chemokine, human) OR (SCYA18 protein, human) OR (small inducible cytokine subfamily A, member 18 protein, human) OR (alternative macrophage activation-associated CC-chemokine 1, human) OR (DCCK1 protein, human) AND ("Neoplasms"[Mesh]) OR (Neoplasias) OR (Neoplasm) OR (Tumors) OR (Benign Neoplasms) OR (Neoplasms, Benign) OR (Malignancies) OR (Cancers).

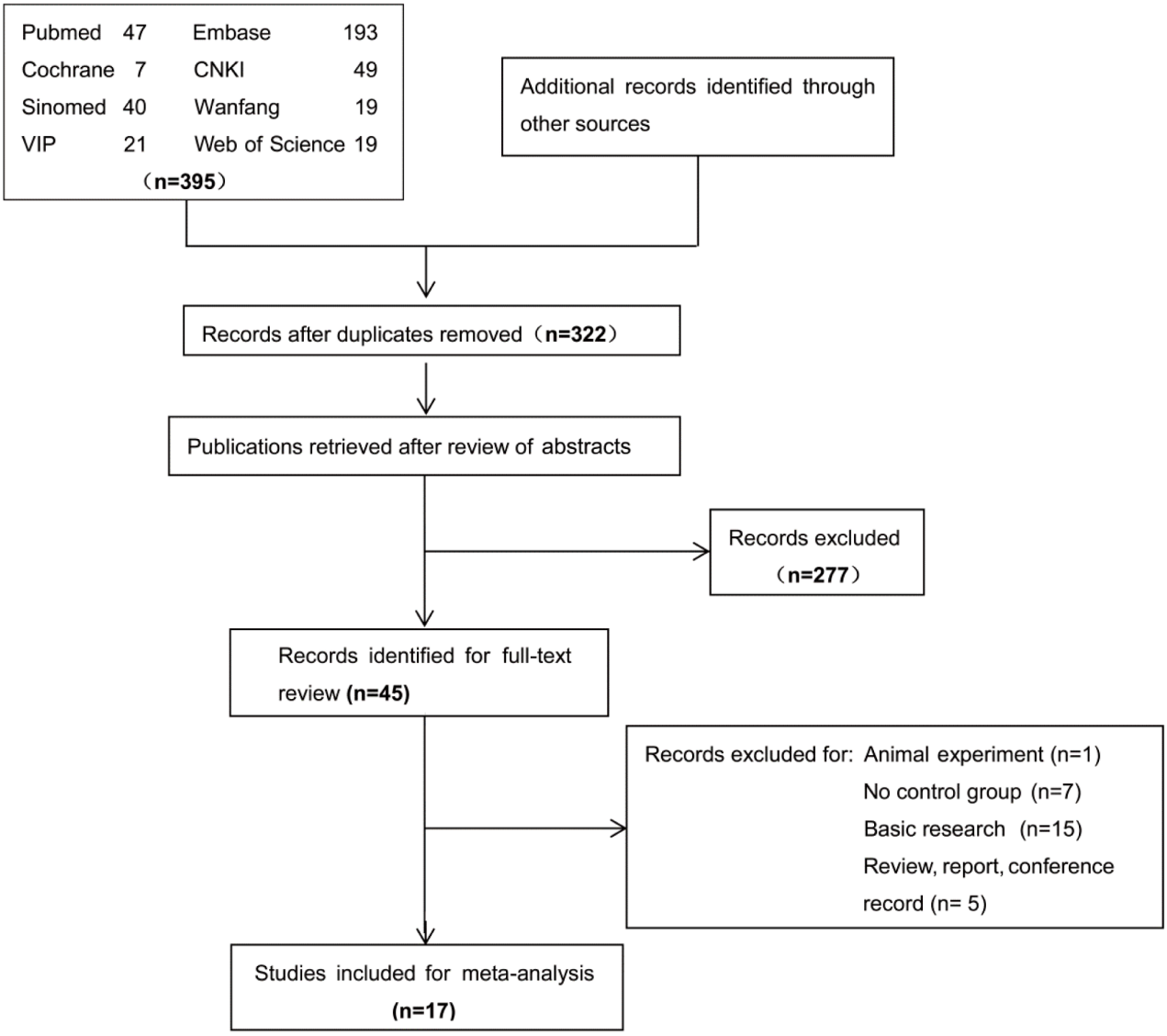

Figure 1. The flowchart of retrieval and selection of studies.

Selection criteria

The selected literature should meet the following inclusion criteria: (1) retrospective or prospective cohort studies, (2) publication focused on the relationship between CCL18 and cancer, (3) the determination of CCL18 protein in cancer tissue using immunohistochemistry (including ELIVISION method, SP method and SABC method), (4) articles containing sufficient published data to estimate the ORs value and 95% CI or HR, (5) the Chinese literature should have been published in official scientific Journals.

Data extraction

Two reviewers independently extracted information from the retrieved papers to reduce the bias and enhance the credibility with a predesigned Excel sheet. The following information was extracted: name of the first author, publication time, country, total number of patients, recruitment time, follow-up duration, tumor type, clinicopathological features, antibody epitope, method and score for its evaluation, cutoff for considering CCL18 overexpression, positive rate, HR, and 95% CI. If HR and their 95% CI were not reported, we extracted data from Kaplan-Meier curves to estimate the HR according to the proposed method as described previously [16]. The Kaplan-Meier survival curves were read by Engauge Digitizer version 8.1.

Quality assessment

Quality assessment was performed in each eligible study using the Newcastle-Ottawa Scale (NOS) [17]. This tool has been developed to assess the quality of non-randomized studies and relied on three aspects: 1) subject selection: 0-4; 2) comparability of subject:0-2; 3) clinical outcome:0-3. A study with a score of at least 5 was considered of high quality.

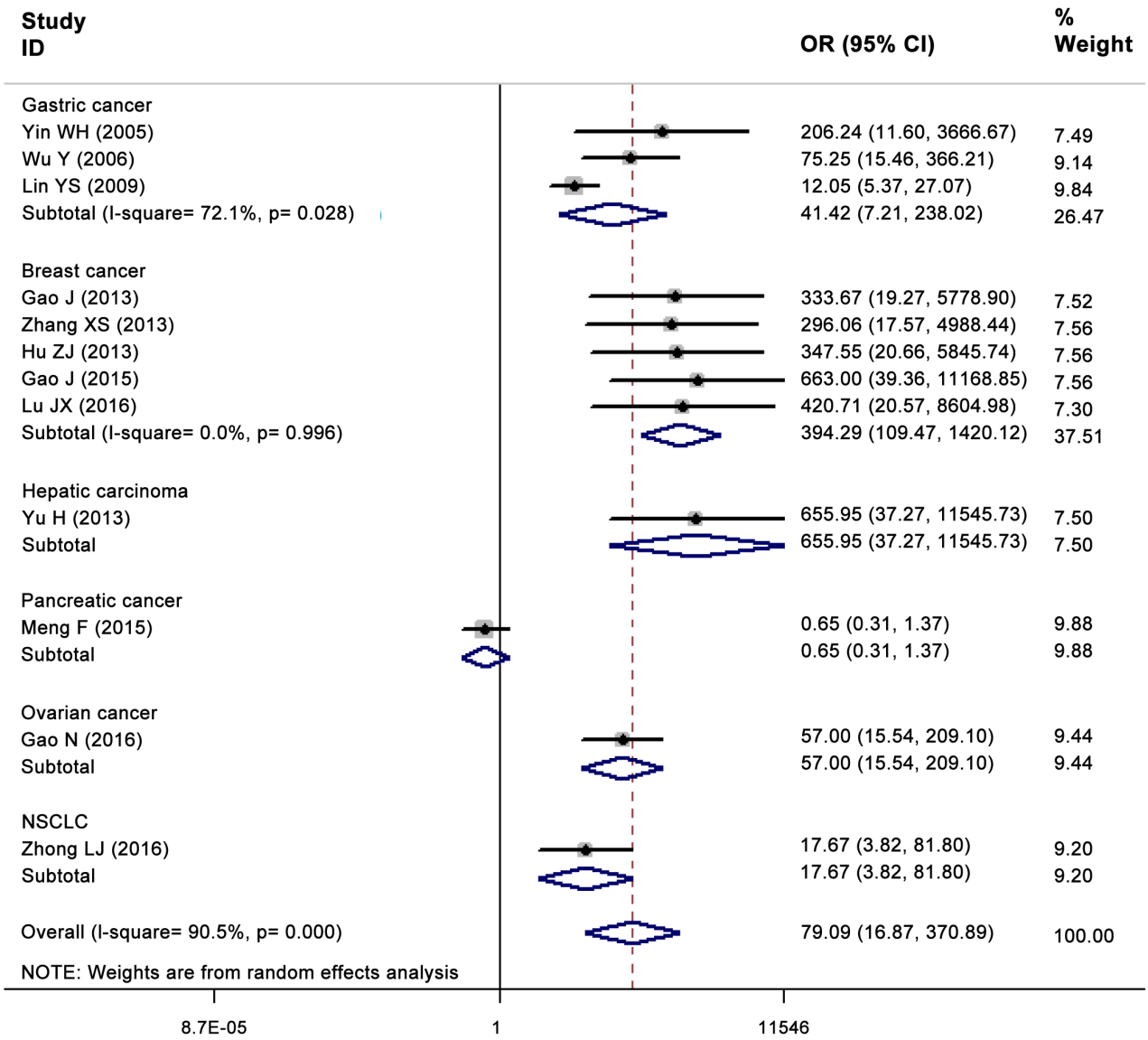

Figure 2. Forest plot showing the OR of CCL18 overexpression vs. normal CCL18 expression in different types of cancer subgroups.

Statistics

The meta-analysis was performed using STATA version 12.0 (StataCorp, College Station, Texas, USA). Combined ORs and their 95% CIs were used to evaluate the association between CCL18 and clinicopathological features (age, gender, tumor size, lymph node metastasis and tumor stage). The prognostic Pooled HRs of OS and their 95%CI were calculated to assess the prognostic value of CCL18 in the patients with cancer. Heterogeneity assumption was tested using the chi-square test based on the Q statistic. $P_H<0.10$ revealed significant heterogeneity. The pooled HR or OR were obtained by using a random-effect model. Otherwise, a fixed-effect model was used. What is more, we quantified the heterogeneity by I^2 metric ($I^2<25\%$, $25\%\leq I^2\leq 50\%$, $I^2>50\%$, represented low, moderate, and extreme heterogeneity, respectively). In addition, sensitivity analysis was tested by using the "metaninf" STATA command to evaluate the influence of a single study on overall estimate after sequential exclusion of each individual study. Furthermore, the Begg's test was used to judge the publication bias in the literature, and used the fill and trim method to further analyze the impact of publication bias on the effect. It was considered statistically significant with a p value less than 0.05.

Results

Search results and characteristics of included studies

The flowchart of retrieval and selection of studies is shown in Figure 1. Identified were 395 articles in total after the primary computerized literature search. After analyzing all of articles with the inclusion and exclusion criteria, 17 studies were finally included in this meta-analysis to assess the prognostic value of CCL18 expression in cancer [18-34]. The characteristics of these studies are shown in Table 1. Among the selected studies, 14 showed the specific antibodies for the detection of CCL18 expression with immunohistochemistry, but the remaining 3 didn't report what kind of antibodies they used [21,22,26]. In addition, the cutoff value of CCL18 was different due to various criteria. Six studies [19,21,22,25,29,32] defined positive cutoff value higher than 10%, another 5 studies [20,23,24,26,28] identified more than 5^+ cells as positive at high magnification, and the other 5 studies [27,30,31,33,34] used the multiplication of the staining intensity to the number of stained cells as criterion. All selected articles were retrospective cohort studies and were of high quality as per the NOS quality criteria.

Expression of CCL18 in cancer tissues

To explore the relationship between CCL18 protein expression and cancer, 12 studies were subjected to pooled analysis. As shown in Figure 2, CCL18 overexpression was correlated with cancer tissue but not with adjacent non-tumor tissue (OR=19.694, 95% CI=14.117-27.476, p=0.000) with significant heterogeneity (I^2=90.5%, p=0.000). Further subgroup meta-analyses demonstrated that these inconsistent findings of CCL18 expression might be due to the heterogeneity by cancer types. Positive correlation of CCL18 and cancer was observed in both breast cancer tissues (OR=357.537, 95% CI=98.147-1302.459, p<0.01) and gastric cancer (OR=95.093, 95% CI=23.765-380.496, p=0.000). There was no heterogeneity in breast cancer (I^2=0.0%, p=0.996), while a significant heterogeneity in gastric cancer was observed (I^2=72.1%, p=0.028).

Association of CCL18 with clinicopathological parameters

To further understand the role of CCL18 as a prognostic biomarker, we investigated the association between CCL18 expression and clinicopathological parameters of cancer by using a random effects model. As shown in Table 2 and Figure 3, CCL18 overexpression across 4 types of tumors (breast, [19,24-26,28,29,31] pancreatic [18], ovarian [30], and non-small cell lung cancer [32,33]) was significantly associated with lymph node metastasis (OR=4.409, 95% CI=2.129-9.128, p<0.01), but not significantly associated with age (OR=1.118, 95% CI=0.795-1.571, p=0.522), sex (OR=0.88, 95% CI=0.667-1.162, p=0.368) and tumor size (OR=0.518, 95% CI=0.202-1.329, p=0.171). Even though heterogeneity in TNM stage between these studies (I^2=93.2%, p=0.000) was observed, CCL18 overexpression was associated with advanced TNM stage in breast cancer (III+IV vs I+II: OR=13.187, 95% CI= 8.417-20.660, p<0.01), while high CCL18 expression tended to be inversely associated with advanced TNM stage in gastric cancer (III+IV vs I+II: OR=0.034, 95% CI= 0.008-0.137, p<0.01).

Correlation between CCL18 expression and survival outcome

To investigate the correlation of CCL18 expression with OS in cancer patients, 5 studies including 2 with breast cancer [19,20], one with colorectal [20], pancreatic [18] and ovarian cancer [30], were assessed by pooled analysis. Our results demonstrated that CCL18 overexpression was not associated with OS (p=0.099) but there was obvious heterogeneity (I^2=82.9%, p=0.006) among these studies. However, CCL18 overexpression was associated with poor prognosis of breast cancer (HR=2.969, 95% CI=1.361-6.478, p=0.006), and there was moderate heterogeneity between

Table 1. Main characteristics of the selected studies in the meta-analysis

Reference	*Country*	*Type of cancer*	*Measurement method*	*No of patients*	*Antibody (company)*	*HR (95% CI)*	*Cut-off*	*NOS*
Yin WH (2005)	China	Gastric cancer	IHC	75	No (R&D, USA)	N	≥10%	6
Wu Y (2006)	China	Gastric cancer	IHC	90	No (R&D, USA)	N	≥10%	6
Lin YS (2009)	China	Gastric cancer	IHC	138	Rabbit anti-human CCL18 polyclonal (Peprotech, USA)	N	≥5% stained cells	5
Chen J (2011)	China	Breast cancer	IHC	623	Mouse anti-human monoclonal CCL18 antibody (R&D, USA)	2.44 (1.54-3.87)	≥10%	6
Gao J (2013)	China	Breast cancer	IHC	109	Rabbit anti-human CCL18 polyclonal (Abcam, UK)	N	≥5% stained cells	5
Zhang XS (2013)	China	Breast cancer	IHC	140	Rabbit anti-human CCL18 polyclonal (Abcam, UK)	N	≥10%	6
Hu ZJ (2013)	China	Breast cancer	IHC	150	No (DAKO Denmark)	N	≥5% stained cells	5
Yu H (2013)	China	Hepatic carcinoma	IHC	120	Goat polyclonal IgG to MIP-4	N	≥3 scores	6
Yuan R (2013)	China	Colorectal cancer	IHC	371	Rabbit anti-human CCL18 polyclonal (Peprotech, USA)	0.419 (0.256-0.685)	≥5% stained cells	7
Gao J (2015)	China	Breast cancer	IHC	179	Primary antibody against CCL18 (Abcam, UK)	N	≥5% stained cells	7
Meng F (2015)	China	Pancreatic cancer	IHC	124	Rabbit anti-CCL18 (Abcam, UK)	1.52 (0.75-3.08)	19.5 cells/40× magnification	7
Ye XG (2015)	China	Breast cancer	IHC	94	Rabbit anti-human CCL18 polyclonal (Abcam, UK)	6.66 (1.34-33.13)	≥10%	5
Gao NN (2016)	China	Ovarian cancer	IHC	120	Rabbit anti-human CCL18 polyclonal (R&D, USA)	3.1 (1.51-5.61)	≥6 scores	7
Lu JX (2016)	China	Breast cancer	IHC	65	Rabbit anti-human CCL18 polyclonal (Abcam, UK)	N	≥6 scores	5
Zhong LJ (2016)	China	Non-small-cell lung cancer	IHC	100	Rabbit anti-human CCL18 polyclonal (R&D, USA)	N	≥10%	7
Shi L (2016)	China	Non-small-cell lung cancer	IHC	241	Anti-macrophage inflammatoty protein (Abcam, UK)	N	≥5 scores	7
Xiao J (2016)	China	OSCC	IHC	90	Antobodies against CCL18 (Abcam, UK)	N	≥1 scores	7

Note: [a]the percentage of stained cells were calculated; positive: ≥10%; [b]the microscopic fields (400x) from the greatest accumulation of positive signals (hotspots) were selected. The values of stained cells were calculated; positive: ≥5 stained cells; [c]final scores were the product of the score for staining intensity (range 0 to 3) and staining cell numbers [range 0 to 4:0 (0%);1 (1-25%); 2 (26-50%); 3 (51-75%); 4 (>75%)]. Positive: ≥3 scores; [d]the microscopic fields (40x) were selected. The values of stained cells were calculated; positive: ≥19.5 stained cells. [e]final scores were the product of the score for staining intensity (range 0 to 3) and staining cell numbers [range 0 to 4:0 (0-5%);1 (6-25%); 2 (26-50%); 3 (51-75%); 4 (>75%)]. Positive : ≥6 scores; [f]final scores were the sum of the score for staining intensity (range 0 to 2) and staining cell numbers [range 1 to 3:1 (1-10%; 2 (11-49%); 3(51-100%)]. Positive: ≥2 scores; [g]final scores were the product of the score for staining intensity (range 0 to 3) and staining cell numbers [range 0 to 4:0 (0%);1(1–10%); 2 (11-50%); 3 (51-80%); 4 (81-100%)]. Positive: ≥5 scores; [h]five microscopic fields (400x) were selected and the final scores were the product of the score for staining intensity (range 0 to 3) and staining cell numbers [range 0 to 3:0 (1-5%);1 (5–30%); 2 (31-70%); 3 (71-100%)]; Positive : ≥3 scores.

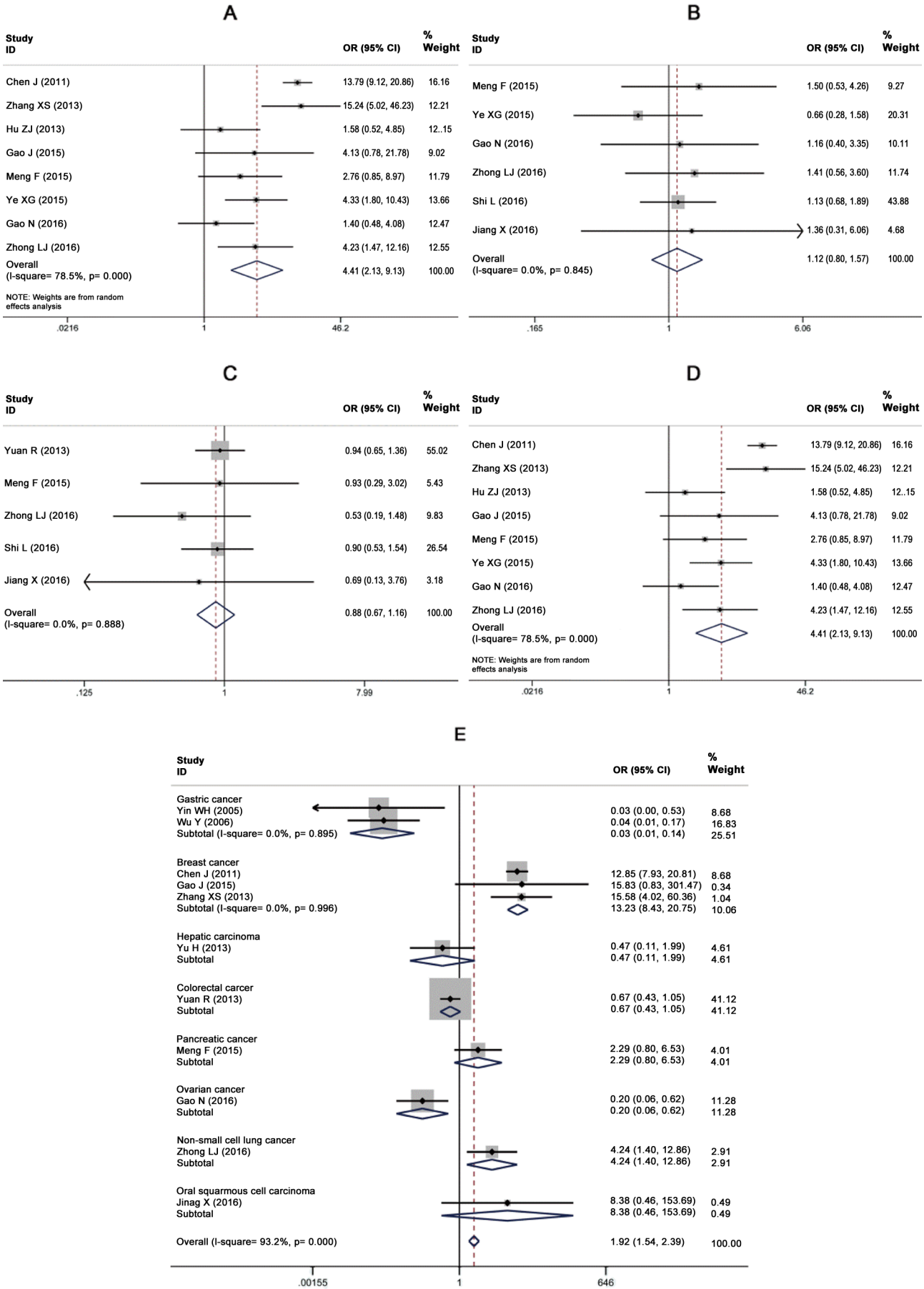

Figure 3. Forest plots showing the OR of CCL18 overexpression vs. normal CCL18 expression for clinicopathological features. **(A)** Lymph node metastasis; **(B)** age; **(C)** Sex; **(D)** Tumor size; **(E)** TNM stage.

these 2 studies [19,29] (I^2=28.1% p=0.238) when only breast cancer studies were included in the analysis.

Sensitivity analysis and publication bias

Based on the results of computed OR in Figure 4, the estimated pooled mean and the corresponding 95% CI of the combined effects with one exclusion study was similar with the overall pooled OR and its corresponding 95% CI. This indicated that no individual study was dominant over the results. The publication bias of the included studies was evaluated through funnel plots and Egger's tests. No publication bias affecting the HRs for OS was registered in the included studies (p=0.496, Figure 5A). However, the funnel was asymmetric and the publication bias was obvious when CCL18 expression was analyzed in cancer tissues, but further sensitivity analyses of Trim and Fill Method indicated the result was reliable (Figure 5B). Finally, we also analyzed the pooled HRs by using two ways of HR extraction, and we found no major deviations.

Discussion

Cancer, particularly tumor metastasis, is the main cause of malignancy-related mortality worldwide, thereby, it is important to establish effective targeted therapies by identifying biomarkers/molecular targets involved in tumor metastasis or prognosis of cancer. Among these biomarkers, CCL18, an important chemokine, may play a critical role on the prediction of cancer prognosis [35]. As demonstrated previously, CCL18 contributes to cancer progression and migration through regulating tumor microenvironment, including tumor growth, metastasis and invasion of several solid

Table 2. Meta-analysis of CCL18 overexpression and clinicopathological features in cancer

Clinicopathological parameters	*OR*	*CI*	*p*	*Heterogeneity*		*Effect model*
Lymph node metastases	4.409	2.129-9.128	<0.01	I^2=78.5%	p<0.01	Random effect
Age	1.118	0.795-1.571	0.522	I^2=0%	p=0.845	Fixed effect
Gender	0.88	0.667-1.162	0.368	I^2=0%	p=0.888	Fixed effect
Tumor size	0.518	0.202-1.329	0.171	I^2=69.4%	p=0.020	Random effect
TNM stage						
Breast cancer	13.187	8.417-20.660	<0.01	I^2=0.0%	p=0.959	Random effect
Gastric cancer	0.034	0.008-0.137	<0.01	I^2=0.0%	p=0.895	Random effect

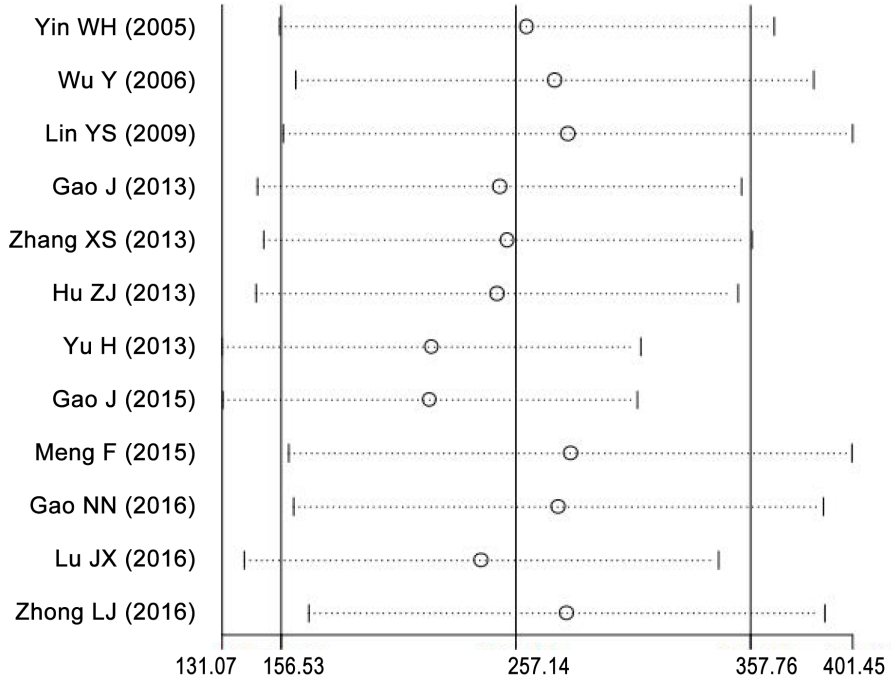

Figure 4. Effect of individual studies on pooled OR for CCL18 overexpression vs. normal CCL18 expression cancer.

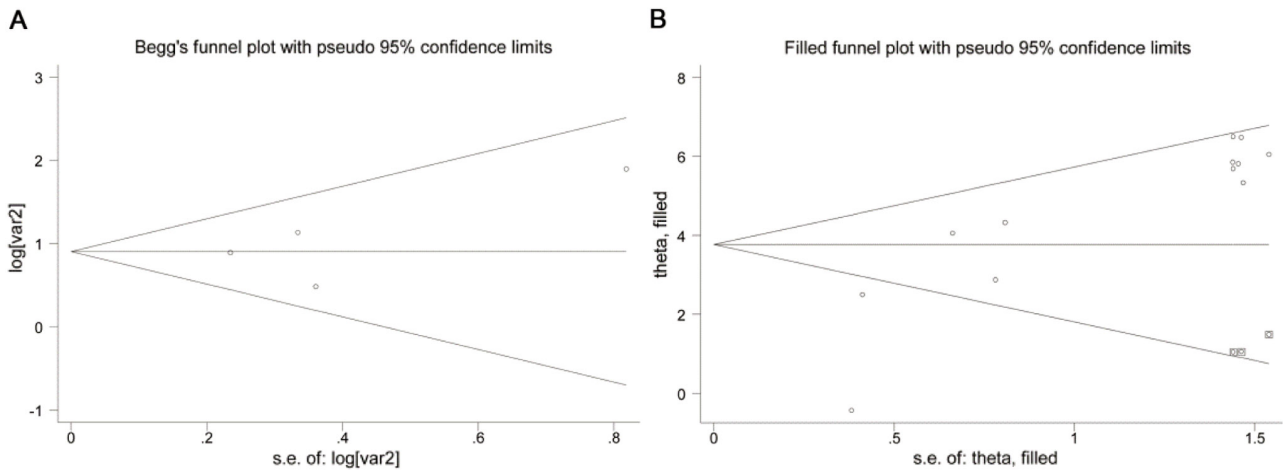

Figure 5. (A) Funnel plots in the analysis of correlation between CCL18 expression and survival outcome. **(B)** Funnel plot of Trim and Fill Method in the analysis of expression of CCL18 in cancer tissues.

human cancers [36,37]. This suggests that the expression of CCL18 on cancer cells may work as a key biomarker to indicate the metastatic propensity of cancer cells. Our meta-analysis revealed that CCL18 was highly expressed in cancer tissues and was statistically significant compared with the control groups. In concordance with our findings, Wang et al. reported that both serum levels and tissue levels of CCL18 expression in ovarian cancer patients are elevated [38,39], while Rajy et al. reported that CCL18 expression is higher in gastric cancer tissues than in normal tissue by immunohistochemistry and Tissue Microarrays (TMA) [40], suggesting that CCL18 may be a critical factor influencing cancer progression. In addition, we also found that the association between CCL18 overexpression and cancer had an obvious heterogeneity (I^2=90.5%, p=0.000). Further subgroup meta-analysis has shown that there is no heterogeneity in breast cancer (I^2=0.0%, p=0.996) but an obvious heterogeneity in gastric cancer (I^2=72.1%, p=0.028), indicating the expression of CCL18 in cancer may be tissue-specific. Our results are not consistent with Weidenbusch et al. study, who reported that CCL18 expression in Osteosarcoma is significantly lower than healthy people by protein expression profile [41]. In general, the expression of CCL18 is associated with the occurrence of cancer, and more studies are needed to fully confirm this correlation.

Meanwhile, we also assessed the associations between CCL18 expression and clinicopathological characteristics in human cancer. The results showed that increased CCL18 expression was significantly associated only with tumor lymph node metastasis, but not with age, sex and tumor size; this suggested that CCL18 may play an important role in tumor metastasis. Our meta-analytical results were supported by research evidence-based molecular mechanism. Wang et al. found that CCL18 levels are positively correlated with the metastases of ovarian cancer patients and overexpression of CCL18 results in enhanced migration and invasion of the Skov3 ovarian cancer cells [39]. Lin et al. found CCL18/PITPNM3 enhances the migration, invasion and EMT through NF-κB signaling pathway in hepatocellular carcinoma [42]. Additionally, Song et al. demonstrated that CCL18 promotes invasion and metastasis by inducing EMT and activating the NF-kB pathway in tumor cells; more interestingly, they also revealed granulocyte-macrophage colony stimulating factor (GMCSF), a cytokine induced by CCL18, triggers a feedback loop to enhance CCL18 production from tumor-associated macrophages [43].

Since obvious heterogeneity was detected when we compared the expression of CCL18 with tumor TNM stage, we further performed subgroup analyses to explore whether the significant heterogeneity is due to cancer type. Our results showed that elevated CCL18 expression is positively associated with advanced TNM stage in breast cancer, while is negatively associated with advanced TNM stage in gastric cancer. Besides, we found that CCL18 overexpression in breast cancer patients is also associated with a poor OS, which is consistent with previous studies [39,43]. However, for the obvious heterogeneity among different cancers, one possible explanation is CCL18 acts differentially through multiple regulatory machinery depending on cancer type. Therefore, further large-scale research in different tumors should be needed to define reliably the prognostic significance of CCL18 in cancer.

There are some limitations in the present meta-analysis. Firstly, the expression of CCL18

in all included studies was detected by different methods such as immunohistochemistry, various CCL18 antibodies or their epitopes and this has led to inconsistent results due to technical variations. Secondly, CCL18 expression was evaluated without acceptable, standardized method, and cut-off definition; these factors are possible sources of heterogeneity. Thirdly, the low number of studies was not enough to clarify the correlation between cancer and CCL18, especially the lack of high-quality publications. Also, the sampling bias might be considered because most of the subjects in these included studies were Asians, mainly from China. These factors might cause a potential publication bias. Finally, since the HRs and their corresponding 95% CI were reported in few studies, we extracted them from the survival curves, which was the only feasible method [18]; even this, it seems to be less reliable than directly extracted from literature.

In conclusion, the present meta-analysis identified for the first time that the increased CCL18 expression may not only predict poor prognosis, but also be associated with positive lymph node metastasis in cancer patients. In addition, despite the contrary relationships, CCL18 is closely related to advanced TNM stage in both breast cancer and gastric cancer. Therefore, CCL18 may play an important role in tumor metastasis and prognosis, and it probably is a poor prognostic factor and a therapeutic target for cancer patients. Nevertheless, eligible studies with large sample sizes are necessary to clarify the exact role of CCL18 in the prediction of prognosis in cancer.

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Conflict of interests

The authors declare no conflict of interests.

References

1. World Cancer Report 2014. World Health Organization 2014, p 22. ISBN 9283204298.
2. Wang M, Zhao J, Zhang L et al. Role of tumor microenvironment in tumorigenesis. J Cancer 2017;8:761-73.
3. Chung HH, Or YZ, Shrestha S et al. Estrogen reprograms the activity of neutrophils to foster protumoral microenvironment during mammary involution. Sci Rep 2017;7:46485-98.
4. Xie HY, Shao ZM, Li DQ. Tumor microenvironment: driving forces and potential therapeutic targets for breast cancer metastasis. Chin J Cancer 2017;36:36-45.
5. Kodelja V, Müller C, Politz O, Hakij N, Orfanos CE, Goerdt S. Alternative macrophage activation-associated CC-chemokine-1, a novel structural homologue of macrophage inflammatory protein-1 alpha with a Th2-associated expression pattern. J Immunol 1998;160:1411-8.
6. Schutyser E, Struyf S, Proost P et al. Identification of biologically active chemokine isoforms from ascitic fluid and elevated levels of CCL18/pulmonary and activation-regulated chemokine in ovarian carcinoma. J Biol Chem 2002;277: 24584-93.
7. Wu J, Liu X, Wang Y. Predictive value of preoperative serum CCL2, CCL18, and VEGF for the patients with gastric cancer. BMC Clin Pathol 2013;13:15-9.
8. Cheng W, Ren X, Zhang C et al. Bioinformatic profiling identifies an immune-related risk signature for glioblastoma. Neurology 2016;86:2226-34.
9. Zhong L, Hong W, Luo HQ, Xu M. Expression and clinical significance of bFGF and CCL18 in non-small cell lung cancer. Int J Clin Exp Med 2016;90:8490-7.
10. Meng F, Li W, Li C, Gao Z, Guo K, Song S. CCL18 promotes epithelial-mesenchymal transition, invasion and migration of pancreatic cancer cells in pancreatic ductal adenocarcinoma. Int J Oncol 2015;46:1109-20.
11. Zhang B, Yin C, Li H et al. Nir1 promotes invasion of breast cancer cells by binding to chemokine (C-C motif) ligand 18 through the PI3K/Akt/GSK3β/Snail signalling pathway. Eur J Cancer 2013;49:3900-13.
12. Shi L, Zhang B, Sun X et al. CC chemokine ligand 18(CCL18) promotes migration and invasion of lung cancer cells by binding to Nir1 through Nir1-ELMO1/DOC180 signaling pathway. Mol Carcinog 2016;55:2051-62.
13. Jiang X, Wang J, Chen X et al. Elevated autocrine chemokine ligand 18 expression promotes oral cancer cell growth and invasion via Akt activation. Oncotarget 2016;7:16262-72.
14. Zohny SF, Fayed ST. Clinical utility of circulating matrix metalloproteinase-7 (MMP-7), CC chemokine ligand 18 (CCL18) and CC chemokine ligand 11 (CCL11) as markers for diagnosis of epithelial ovarian cancer. Med Oncol 2010;27:1246-53.

15. Leung SY, Yuen ST, Chu KM et al. Expression profiling identifies chemokine (C-C motif) ligand 18 as an independent prognostic indicator in gastric cancer. Gastroenterology 2004;127:457-69.
16. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:1-16.
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
18. Meng F, Li W, Li C, Gao Z, Guo K, Song S. CCL18 promotes epithelial-mesenchymal transition, invasion and migration of pancreatic cancer cells in pancreatic ductal adenocarcinoma. Int J Oncol 2015;46:1109-20.
19. Chen J, Yao Y, Gong C et al. CCL18 from Tumor-Associated Macrophages Promotes Breast Cancer Metastasis via PITPNM3. Cancer Cell 2011;19:541-55.
20. Yuan R, Chen Y, He X et al. CCL18 as an independent favorable prognostic biomarker in patients with colorectal cancer. J Surg Res 2013;183:163-9.
21. Yin WH, Wu Y, Ma Y, Cai GL, Yu GY. The role of chemokine ligand 18 (CCL18) in the metastasis of gastric cancer. J Mathemat Med 2005;4:315-7.
22. Wu Y, Zhao SY, Yin WH, Wang JP, Ye HJ, Ma Y. Expression of Chemokine CC-motif Ligand 18(CCL18) in gastric cancer. Acta Med Sinica 2006;19:6-8.
23. Lin YS, Wu Y, Yin WH, Yu GY, Ma Y. The diagnostic value of chemokine CC-motif ligand18 (CCL18) for gastric cancer. Chin J Gastroenterol Hepatol 2009;18:527-9.
24. Gao J, Tang W, Ye XG et al. The expression and significance of CCL18 and microvessel density in breast cancer. Chin J Clinicians (Electronic Edition) 2013;7: 566-9.
25. Zhang XS, Gao J, Zhen WB et al. Expression and significance of CCL18 in breast cancer. Hainan Med J 2013;19:2815-7.
26. Hu ZJ, Xu HB, Ren XC et al. The expression of CCL18 and MVD in breast cancer and the relationship between their expression levels and patients' prognosis China Mod Doctor 2013;51:20-2.
27. Yu H, Jia XM, Zhang C, Cheng WD. The expression of PLK1 and CCL18 in primary liver cancer and their relationship with clinical pathology. China J Mod Med 2013;23:48-52.
28. Gao J, Li ZH, Tang W, Wu QN, Liu GH, Zheng WB. Chemokine C-C motif ligand 18 expression correlates with tumor malignancy in breast cancer. Pathol Biol (Paris), 2015;63:199-203.
29. Ye XG, Pan LX, Chen L, Zhen WB. The expression of CCL18 in breast cancer and its relationship with patient prognosis. Acad J Guangzhou Med University 2015;43:72-5.
30. Gao NN. Expression of CCL18 in ovarian cancer and its relation to prognosis. J Pract Oncol 2016;31:446-9.
31. Lu JX, Xu Y, Jiang X, Chen XP. Expression and significance of phosphatase and tensin homologue deleted on chromosome 10 and chemokine ligand 18 in elderly patients with triple-negative and non-triple negative breast cancer. Chin J Gerontol 2016;36:2354-6.
32. Zhong LJ, Hong W, Luo HQ, Xu M. Expression and clinical significance of bFGF and CCL18 in non-small cell lung cancer. Int J Clin Experim Med 2016;9:8490-7.
33. Shi L, Zhang B, Sun X et al. CC chemokine ligand 18(CCL18) promotes migration and invasion of lung cancer cells by binding to Nir1 through Nir1-ELMO1/DOC180 signaling pathway. Molec Carcinogenesis 2016;55:2051-62.
34. Xiao J, Wang J, Chen XJ et al. Elevated autocrine chemokine ligand 18 expression promotes oral cancer cell growth and invasion via Akt activation. Oncotarget 2016;7:16262-72.
35. Sun JH, Fan N, Zhang Y. Correlation between serum level of chemokine (C-C motif) ligand 18 and poor prognosis in breast cancer. Genet Mol Res 2016;15:1-6.
36. Ploenes T, Scholtes B, Krohn A et al. CC-chemokine ligand 18 induces epithelial to mesenchymal transition in lung cancer A549 cells and elevates the invasive potential. PLoS One 2013;8:e53068.
37. Lane D, Matte I, Laplante C et al. CCL18 from ascites promotes ovarian cancer cell migration through proline-rich tyrosine kinase 2 signaling. Mol Cancer 2016;15:58-69.
38. Wang Q, Li D, Zhang W, Tang B, Li QQ, Li L. Evaluation of proteomics-identified CCL18 and CXCL1 as circulating tumor markers for differential diagnosis between ovarian carcinomas and benign pelvic masses. Int J Biol Markers 2011;26:262-73.
39. Wang Q, Tang Y, Yu H et al.CCL18 from tumor-cells promotes epithelial ovarian cancer metastasis via mTOR signaling pathway. Molec Carcinogenesis 2016;55:1688-99.
40. Raja UM, Gopal G, Shirley S, Ramakrishnan AS, Rajkumar T. Immunohistochemical expression and localization of cytokines/chemokines/growth factors in gastric cancer. Cytokine 2017;89:82-90.
41. Weidenbusch B, Weidenbusch MJ, Burdach S. Immunologic signatures of osteosarcoma: Implications for prognosis and therapy. J Clin Oncol 2016;34:e14564.
42. Lin Z, Li W, Zhang H et al. CCL18/PITPNM3 enhances migration, invasion, and EMT through the NF-κB signaling pathway in hepatocellular carcinoma. Tumor Biol 2016;37:3461-8.
43. Song E. The role of CCL18 signaling in breast tumor associated macrophages promoting cancer progression. Cancer Res 2016;76 (Suppl 7; abstr no.IA24).