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REVIEW

Prognostic and clinicopathological significance of CXCL1 in cancers: a systematic review and meta-analysis

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ABSTRACT

Background The prognostic value of Chemokine (C-X-C motif) ligand 1 (CXCL1) in various types of cancer remains controversial. Here we aimed to evaluate the prognostic role of CXCL1 for cancer.

Methods A comprehensively search of the PubMed, Embase, Web of Science, Wanfang and China National Knowledge Internet databases was conducted to retrieve eligible studies meeting the inclusion criteria. Overall survival (OS), progression-free survival (PFS) and various clinicopathological parameters were defined as endpoints. Stata SE12.0 software was used for quantitative meta-analysis.

Results A total of 17 studies encompassing 2265 cancer patients were included. Our meta-analysis showed that patients with higher CXCL1 expression had significantly shorter OS, according to both multivariate (HR 1.51, 95% CI 1.19–1.83, P < .01) and univariate analysis (HR 2.08, 95% CI 1.62–2.54, P < .01). Furthermore, higher CXCL1 expression was significantly correlated with advanced TNM stage and lymph node metastasis (both P < .05).

Conclusions High CXCL1 expression is a risk factor for cancer prognosis indicating a poor OS, and advanced TNM stage and lymph node metastasis, demonstrating that it may be a promising prognostic biomarker for different cancers.

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CXCL1; GRO alpha; cancer; prognosis

Introduction

Cancer is a global disease with increasing morbidity and lethality, which significantly increases the economic burden to society and families of patients with cancer.[1] The National Cancer Center released the latest issue of national cancer statistics in February 2018. The data showed that about 10,000 people were diagnosed with cancer every day in China and the cumulative risk for a person to develop cancer is 36% by the age of 85. Cancer has become the second-ranking cause of death in the USA, and is therefore a major public health problem.[2] The chemokine (C-X-C motif) ligand 1 (CXCL1), also named GRO-1 oncogene as a small cytokine that belongs to the family of CXC chemokines originally characterized by Richmond et al.[3] This cytokine, secreted by melanoma cells, is involved in the pathogenesis of melanoma partially due to its mitogenic properties. In humans, this protein, encoded by the CXCL1 gene, plays a major role in inflammation, angiogenesis, tumorigenesis, and wound healing.[4–6] In recent years, many lines of evidence have indicated that aberrant expression of CXCL1 is closely correlated with tumorigenesis and metastasis in various malignancies, such as primary human cancers of the breast, gastric, bladder, colorectal, lung, liver, and pancreas.[7–10] Moreover, several studies have demonstrated that the overexpression of CXCL1 was correlated with poor prognosis of patients with cancer.[11,12] However, there has been no meta-analysis assessing the usefulness of CXCL1 expression for the prognosis of tumors. Hence, it was necessary to conduct a systematic review and meta-analysis to elucidate if CXCL1 has prognostic potential for cancer. Here we aimed to evaluate the prognostic and clinicopathological significance of CXCL1 expression from tissue and serum samples of patients with cancer.

Materials and methods

Literature retrieval strategy

Studies included in the meta-analysis were obtained by conducting a systematic computerized literature search of the PubMed, Embase, Web of Science, Wanfang and China National Knowledge Internet databases. The following combinations of keywords were used in the search: ("CXCL1, Chemokine" OR "CXCL1 Chemokine" OR "Gro-alpha Protein C" OR "GRO alpha Protein") AND ("neoplasm" OR "cancer" OR "tumor"). Additional studies were obtained by manually screening the reference lists. The studies included were published from 1996 to June 2018.

Inclusion criteria and exclusion criteria

Eligible studies were included in the meta-analysis if they fulfilled the following criteria: 1) containing comparisons of

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different levels of CXCL1 expression; 2) focusing on the prognostic role of CXCL1 for cancer; 3) reporting OS, PFS, or other clinicopathological parameters; and 4) having sufficient data. Exclusion criteria were: 1) insufficient data or animal research data; 2) overlapping data; and 3) expert opinions, case reports, reviews or letters.

Data extraction and quality assessment

The information and data we obtained were extracted from the included studies by Zulei Zhang and Yaofei Jiang, and a third investigator (Yan Luo) was called upon to resolve any disagreements. For each study, we recorded the information and encompassing the first author's family name, publication year, country, cancer type, total sample size, sample type, analysis method, cut-off value, follow-up times (years), outcome measures, prognostic parameters (e.g., OS, or PFS) and some other clinicopathological parameters such as gender, age, TNM stage, lymph node metastasis, tumor size, distant metastasis, depth of invasion, vascular invasion and neural invasion. Multivariate analysis results of OS were preferentially extracted from the included studies. For those studies that only provided an overall-survival curve, we extracted the corresponding survival data using Engauge Digitizer version 4.1.

Statistical analysis

The statistical analysis of HRs for OS and risk ratios (RRs) for clinicopathological parameters was conducted using Stata SE12.0. We used the random-effects model to pool data with statistical heterogeneity determined by the inconsistency index ($I^2 \geq 50\%$) and the chi-squared test ($P \leq 0.10$). The robustness of the results was investigated using sensitivity analysis. Begg's rank correlation test was used to assess the publication bias, determined as positive if $Pr > |z| \leq 0.1$.[13]

Results

Literature search

After searching for the indicated keywords in PubMed, Web of Science, Embase, Wanfang and China National Knowledge Internet databases, 386 relevant studies were identified. Three additional records were identified by manually searching the references of these studies. Among them, 267 articles were retained after excluding duplicates. However, 250 studies were excluded after screening the titles, abstracts and data. Finally, we included 17 studies in this meta-analysis[7–10,12,14–25] (Figure 1), encompassing 12 prospective studies[7–9,12,15,17–19,21–23,25] and 5 retrospective studies.[10,14,16,20,24]

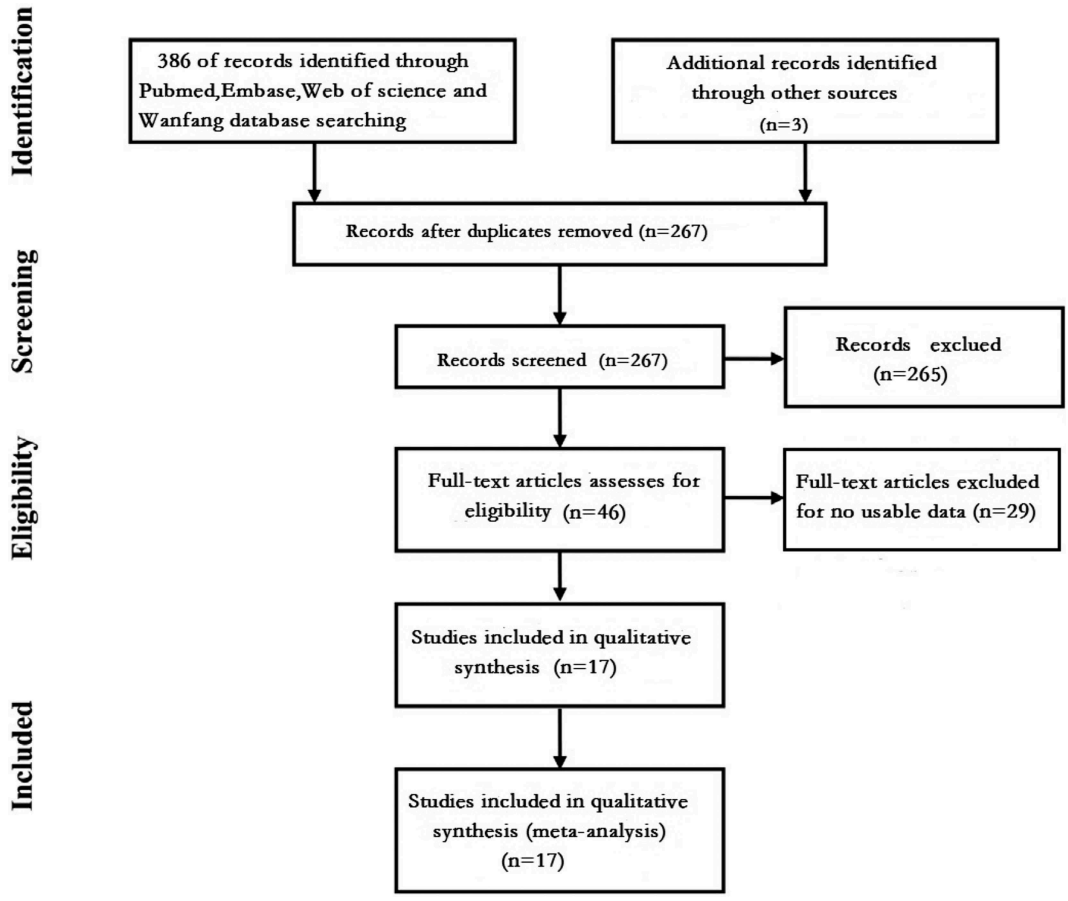

Figure 1. Flow chart showing the steps of document retrieval and selection.

Characteristics of the included studies

As shown in Table 1, 17 studies encompassing 2265 cancer patients were included for analysis, with sample sizes ranging from 48 to 292.[7–10,12,14–25] Regarding the sample types, 14 studies[7–10,12,14–18,20,22,24,25] were based on tissue samples, 2 used serum samples,[21,23] and one investigated the patients' urine.[19] With respect to the level of CXCL1 expression and cut-off values, 12 studies used immunohistochemical methods (IHC) for detection, and immunoreactivity scores for the cut-off value determination,[9,10,12,14–18,20,22,24,25] while several other studies used different detection methods and cut-off values,[8,19,21] and 4 studies failed to report the details of how they arrived at the cut-off values.[7,8,16,23] Among the 17 studies, 12 were from China,[8,9,12,14–16,18,20–23,25] 2 were from Japan,[17,19] 2 from the United States,[10,24] and 1 from France.[7] Among the predefined endpoints, 13 studies reported OS,[9,12,14–22,24,25] 3 studies reported PFS[8,10,21] and 10 studies reported clinicopathological parameters.[10,12,14–18,20,22,25] Moreover, 10 different types of carcinoma were analyzed, including esophageal squamous cell carcinoma (ESCC),[15] hepatocellular carcinoma (HCC),[22,23] bladder cancer,[19,24] breast cancer,[7] gastric cancer,[9,12,16–18,20] cervical squamous cell carcinoma (CSCC),[21] colorectal cancer (CRC),[14] non-small cell lung cancer (NSCLC),[8] pancreatic cancer and urothelial cancer of the bladder (UCB).[10] Regarding the types of treatment, fourteen studies used surgical resection,[7–10,12,14,16–20,22,23,25] one study used radio-chemotherapy,[15] and two other studies did not report the treatment modalities.[21,24] Multivariate analysis was employed in 11 studies,[9,12,14,15,17–19,21,22,24,25] while univariate analysis was used in 8 studies[12,14–16,19,20,24,25] as the analysis model for OS. In addition, the Newcastle-Ottawa scale (NOS) score was 2 (6–9 stars) in all of the included studies.

Meta-analysis of the association between CXCL1 expression levels and OS

Thirteen articles reporting OS were included in the meta-analysis.[9,12,14–22,24,25] According to different methods, it was divided into multivariate analysis[9,12,14,15,17–19,21,22,24,25] and univariate analysis.[12,14–16,19,20,24,25] The fixed effects model was used because of no significant heterogeneity (I^2 = 13.8%, P = .279). The results indicated that cancer patients with higher CXCL1 expression had significantly shorter OS, in both multivariate analysis (HR 1.51, 95% CI 1.19–1.83, P < .01) and univariate analysis (HR 2.08, 95% CI 1.62–2.54, P < .01), as shown in Figure 2. The robustness of both the results was confirmed by sensitivity analysis (Figure 3). However, the Begg's rank correlation test indicated the presence of significant publication bias ($Pr > |z|$ = 0.075) (Figure 4). Moreover, we performed subgroup analyses based on the types of treatment, and we found that higher levels of CXCL1 expression were significantly correlated with poorer OS in the patients that underwent surgical resection (HR 2.01, 95% CI 1.67–2.36, P < .01) or radio-chemotherapy (HR 3.78, 95% CI 1.89–5.67, P < .01), as shown in Fig. S1.

Association between CXCL1 expression levels and PFS

Three studies reported PFS. Among them, two studies demonstrated significantly shorter PFS in cancer patients with higher

Table 1. Basic information of the included studies.

Study	Year	Country	Diseases	Total (M/F)	Treatment types	Sample	Assay	Cut-off value	Follow-up (year)	Outcome measures	Analysis type
Bieche[7]	2007	France	Breast cancer	48	Surgery	Tissue	RT-PCR	NR	10	RFS	U
Cao[8]	2017	China	NSCLC	50 (14/36)	Surgery	Tissue	CBA kit	NR	≥2	PFS	U
Cheng[9]	2011	China	GC	116 (65/51)	Surgery	Tissue	IHC	Strong staining	5	OS	M
Miyake[10]	2016	USA	UCB	142	Surgery	Tissue	IHC	IS	10	PFS	U
Xiang[12]	2015	China	GC	127 (92/35)	Surgery	Tissue	IHC	IS>97.2%	7	OS	M and U
Zhuo[14]	2018	China	CRC	276 (166/100)	Surgery	Tissue	IHC	IS≧4	5	OS	M and U
Zhang[15]	2017	China	ESCC	141 (75/66)	Radio-chemotherapy	Tissue	IHC	Strong staining	3	OS	M and U
Wang[16]	2017	China	GC	105 (71/34)	Surgery	Tissue	IHC	NR	≥8	OS	U
Kasashima[17]	2017	Japan	GC	264 (114/150)	Surgery	Tissue	IHC	IS>3	5	OS	M
Wang[18]	2016	China	GC	100 (65/35)	Surgery	Tissue	IHC	IS≧3	5	OS	M
Nakashima[19]	2015	Japan	Bladder cancer	175 (132/43)	Surgery	Urine	ELISA	35 pg/mg	4.5	OS	M and U
Wei[20]	2015	China	GC	98 (62/36)	Surgery	Tissue	IHC	Strong staining	5	OS	U
Zhang[21]	2014	China	CSCC	292 (F)	NR	Serum	Luminex technology	<748.43 pg/ml	3	OS, DFS	M
Cao[22]	2014	China	HCC	48 (41/7)	Surgery	Tissue	IHC	Strong staining	>6	OS	M
Chen[23]	2013	China	HCC	179 (160/19)	Surgery	Serum	Luminex technology	NR	8	DFS	U
Miyake[24]	2013	USA	Bladder cancer	142	NR	Tissue	IHC	IS≧3	4	OS, DFS	M and U
Lian[25]	2016	China	Pancreatic cancer	160	Surgery	Tissue	IHC	IS≧3	5	OS	M and U

CRC: colorectal cancer; IHC: immunohistochemical method; IS: immunoreactivity score; OS: overall survival; M: multivariate analysis; U: univariate analysis; ESCC: esophageal squamous cell carcinoma; CRC: colorectal Cancer; ELISA: enzyme-linked immunoassay; NSCLC: non-small cell lung cancer; GC: gastric cancer; CBA kit: human proinflammatory chemokine panel (13-plex) (BioLegend, San Diego, CA); UCB: urothelial cancer of the bladder; CSCC: cervical squamous cell carcinoma; HCC: hepatocellular carcinoma; NR, not reported.

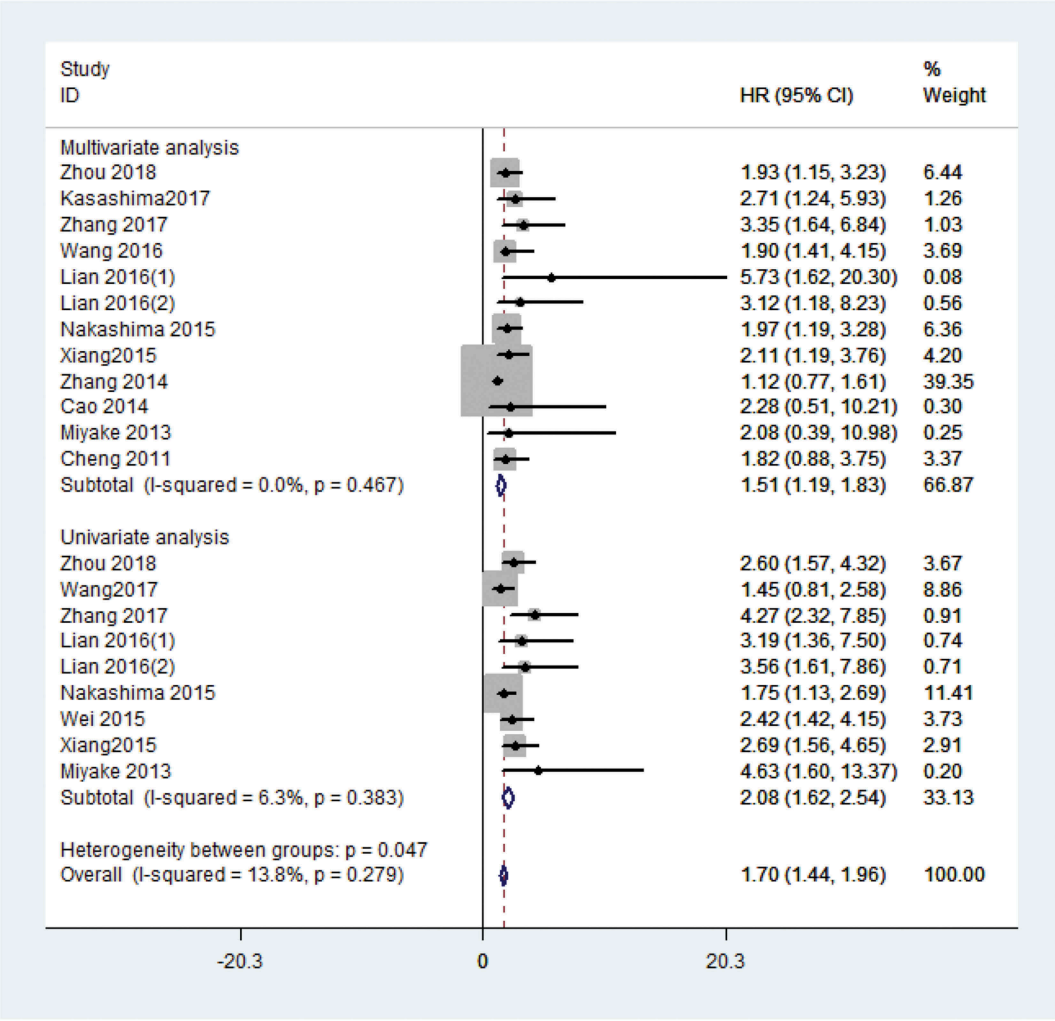

Figure 2. Forest plot for the meta-analysis of OS by multivariate analysis and univariate analysis.

CXCL1 expression compared to those with low CXCL1 expression by univariate analysis,[8,10] while one demonstrated comparable outcomes by multivariate analysis.[21]

Meta-analyses of the association between CXCL1 levels and clinicopathological parameters

Ten articles were included for meta-analyses of clinicopathological parameters.[10,12,14–18,20,22,25] As shown in Table 2, there was no significant correlation between CXCL1 expression and gender (RR 1.00, 95% CI 0.92–1.08; P = .967) (Figure 5a). Similar results were observed for age (RR 1.08, 95% CI 0.97–1.19; P = .145) (Figure 5b), tumor size (RR 1.40, 95% CI 0.92–2.14; P = .116) (Figure 5c), distant metastasis (RR 2.18, 95% CI 0.70–6.81; P = .181) (Figure 5d), degree of tumor differentiation (RR 0.98, 95% CI 0.67–1.43; P = .910) (Figure 6a), and neural invasion (RR 1.30, 95% CI 0.87–1.95; P = .199) (Figure 6b). However, higher CXCL1 expression was significantly correlated with a more advanced TNM stage (RR 1.73, 95% CI 1.47–2.04; P < .001) (Figure 6c) and lymph node metastasis (RR 1.77, 95% CI 1.07–2.92; P = .026) (Figure 6d).

Discussion

Chemokines are a class of single-subunit chemotactic cytokines ranging in size from 8 to 15 kDa. Their division into the four subfamilies CXC, CC, CX3L and C (where X stands for any amino acid) was determined by the position of conserved cysteines at the amino terminus.[26] The CXC subfamily was further subdivided into ELR+ and ELR- chemokines according to whether the CXC domain has a tripeptide Glu-Leu-Arg (ELR motif) before, wherein the "ELR" motif is neutral. The interaction of granulocyte ligands/receptors is critical.[27,28] As a member of the ELR+ subpopulation, CXCL1 (also known as GRO-α) was originally isolated from the culture supernatants of melanoma cells and is specific for its receptor CXCR2, a G protein-coupled receptor belonging to the seven-transmembrane family. Chemokine-ligand interactions play different roles in a variety of biological functions, such as angiogenesis, inflammation, wound healing and tumor development.[29] In recent years, it has been found that CXCL1 plays an important role in tumor formation, since it is upregulated in melanoma, colorectal cancer, breast cancer, bladder cancer, ovarian epithelial cancer (epithelial ovarian cancer, EOC) and gastric cancer.[30]

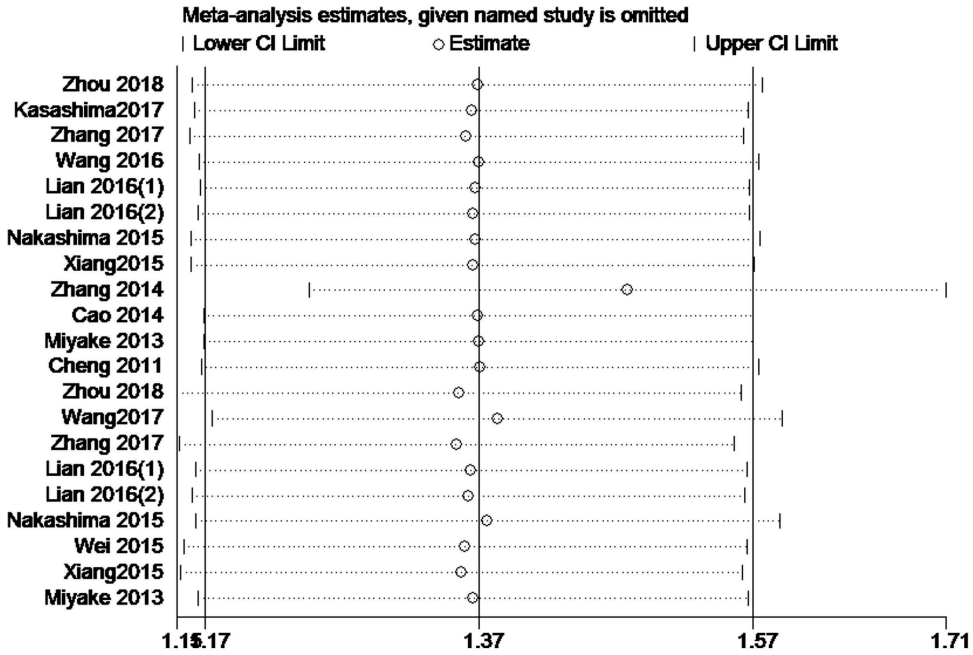

Figure 3. Sensitivity analyses for the meta-analysis of OS.

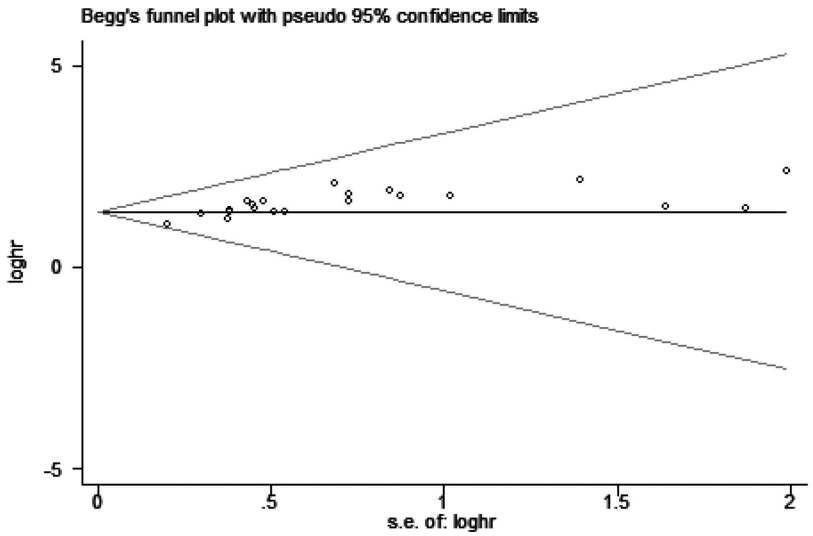

Figure 4. Assessment of publication bias for the meta-analysis of the association between CXCL1 level and OS using Begg's rank correlation test.

Table 2. The meta-analyses of clinical parameters.

Variables	Included studies	Patients (n)	RR 95%CI	*P*	I^2	Mode
Gender (male versus female)	10	1474	1.0 [0.92, 1.08]	0.967	0.00%	Fixed
Age (old versus young)	9	1319	1.08 [0.97, 1.19]	0.145	16.60%	Fixed
TNM stage (III/IV versus I/II)	5	478	1.73 [1.47, 2.04]	<0.001	38.20%	Fixed
LNM (yes versus no)	3	681	1.77 [1.07, 2.92]	0.026	89.20%	Random
Tumor size (large versus small)	9	1210	1.40 [0.92, 2.14]	0.116	84.40%	Random
Distant metastasis (yes versus no)	3	451	2.18 [0.70,6.81]	0.181	78.00%	Random
Differentiation (poor versus good)	4	452	0.98 [0.67, 1.43]	0.910	80.00%	Random
Neural invasion (yes versus no)	2	346	1.30 [0.87, 1.95]	0.199	0.00%	Fixed

LNM: lymph node metastasis; OR: odds ratio; CI: confidence interval.

To our best knowledge, this is the first comprehensive and systematical meta-analysis of the value of CXCL1 for cancer prognosis. In this study, we found that the cancer patients with higher CXCL1 expression had significantly worse OS compared to those with low CXCL1 expression. Thus, the findings of this meta-analysis indicate that high CXCL1

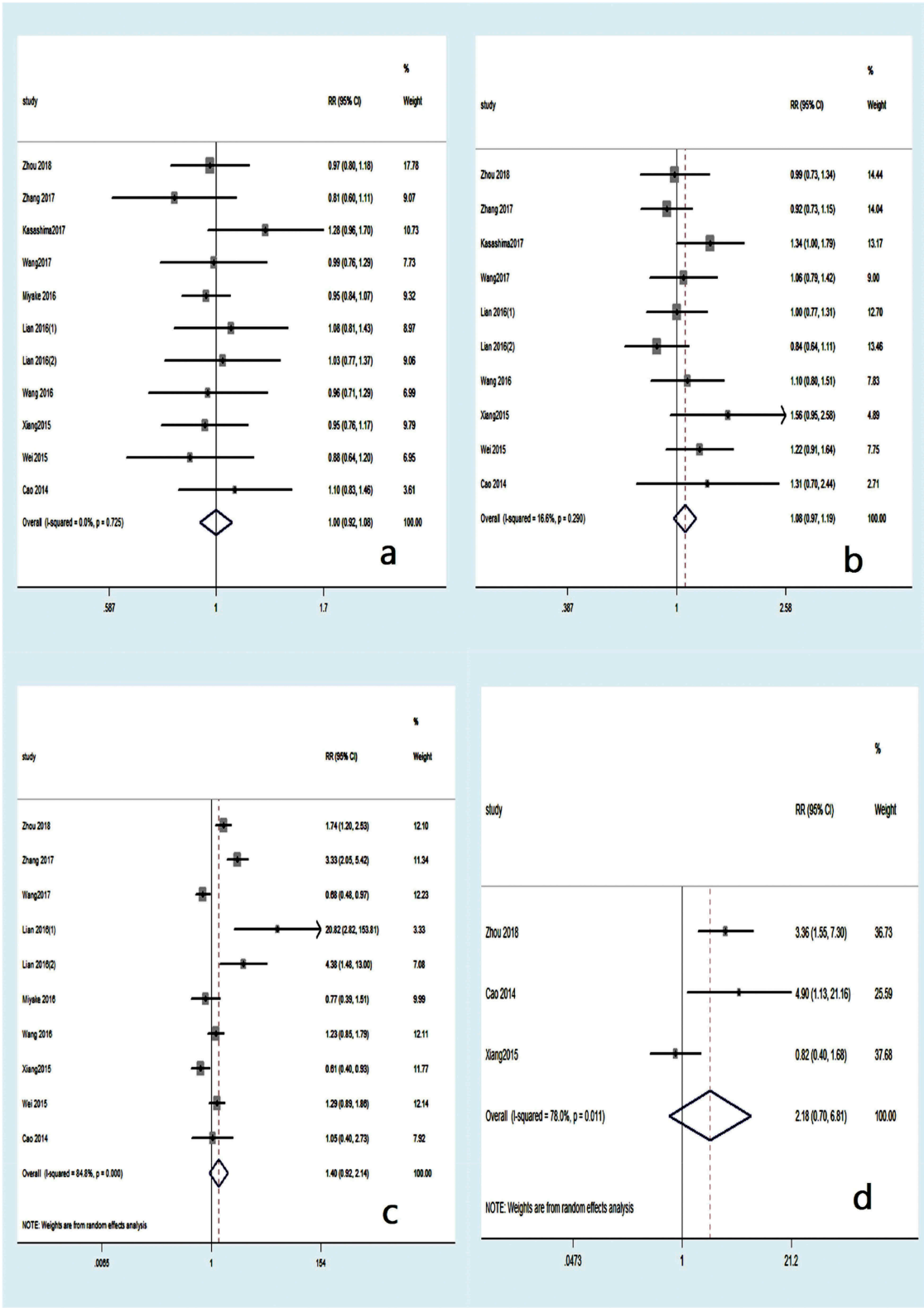

Figure 5. Forest plot for the meta-analysis according to gender (a), age (b), tumor size (c), and distant metastasis (d).

expression might serve as a risk factor for unfavorable prognosis of cancer. Furthermore, we also found that high CXCL1 expression was significantly correlated with a more advanced TNM stage and lymph node metastasis. All of these findings demonstrated that high CXCL1 expression might be used for predicting a worse prognosis in various kinds of carcinoma.

Some studies explained the underlying mechanisms of the relationship between CXCL1 dysregulation and cancer. Zhou

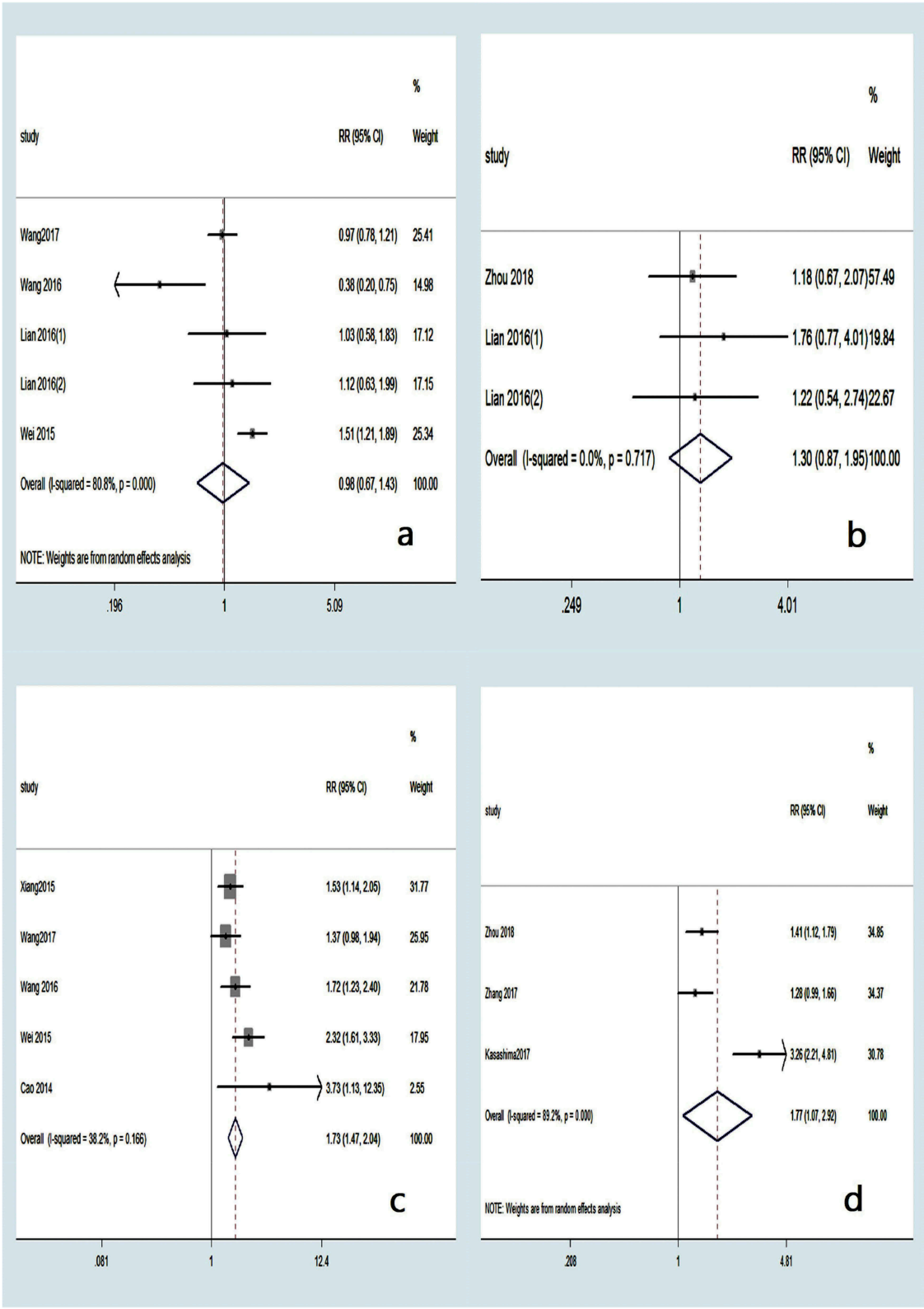

Figure 6. Forest plot for the meta-analysis according to degree of tumor differentiation (a), neural invasion (b), TNM stage (c), and lymph node metastasis (d).

et al. found that CXCL1 plays an important role in both cancer progression and metastasis in colorectal cancer patients by inducing glycolysis.[14] Zhang et al. found that cancer-associated fibroblasts (CAF) secrete CXCL1, which inhibits the expression of the reactive oxygen species (ROS)-scavenging enzyme superoxide dismutase 1, leading to increased ROS accumulation following irradiation, which enhanced DNA damage repair and thereby mediated radio-

resistance. CAF-secreted CXCL1 was found to mediate radioresistance via the activation of the Mek/Erk pathway.[15] Xu et al. found high expression of CXCR2 in gastric cancer tissues, which was positively correlated with disease stage and Ki67 proliferation index, as well as lymphatic vessel density (LVD), suggesting that CXCL1 and its receptor CXCR 2 play a crucial role in lymphatic metastasis of gastric cancer.[31] In addition, Nakashima et al. found that patients with higher urine CXCL1 were statistically more likely to develop intravesical recurrence after transurethral resection (TUR), and multivariate analysis identified urine CXCL1 as an independent predictor of post-TUR intravesical recurrence.[19] Li et al. established a homologous tumor cell clone library from an in situ mouse model of pancreatic cancer and found that tumor cell-derived CXCL1 directly inhibits T cell infiltration and reduces responsiveness to immunotherapy, while ablation of CXCL1 promoted T cell infiltration and sensitivity to a combination immunotherapy regimen.[32] Understanding the role of CXCL1 in tumor progression may help to design strategies to inhibit tumor cell growth by selectively perturbing its function, which would make CXCL1 into an invaluable new biomarker for tumor therapy and potential therapeutic targets.[14,16,20,24,25] However, only a few studies have investigated the mechanisms underlying the prognostic role of CXCL1 in cancer to date. Thus, more fundamental research is needed to decipher the prognostic value of CXCL1 for cancer.

Finally, the constraints of the prognostic role of CXCL1 for human cancer found in this meta-analysis should be discussed. Firstly, potential risk bias might have been a factor. Because positive outcomes were more likely to be published than negative ones, we tried to identify all relevant information. However, some missing data was still unavoidable. Secondly, there was statistical heterogeneity in this analysis, which might be partially explained by different cut-off values for CXCL1 expression and different study protocols. Thirdly, in the selected studies, most of the patients were from Asia. Therefore, the results we obtained may be more representative of Asians. Fourthly, for those studies that only provided overall-survival curves, we extracted the survival data using Engauge Digitizer version 4.1, which compromises the precision of the data. Finally, only 17 studies with a total of 2265 patients were included in this meta-analysis, and even less studies were included in the subgroup analyses of OS and clinicopathological parameters, which led to relatively inadequate data. Since there are limitations in the recognized investigations and the current meta-analysis, our outcomes should be interpreted with caution, and the conclusions of this meta-analysis require detailed consideration.

In summary, high CXCL1 expression was found to be a risk factor for cancer prognosis indicating a poor OS, advanced TNM stage and lymph node metastasis, demonstrating that it may be a promising prognostic biomarker for cancer.

Disclosures

The authors have no conflicts of interest or financial ties to disclose.

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