Prognostic and Clinicopathological Significance of CXCL1 Expression in Gastric Cancer: A Meta-Analysis.

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Abstract

Background: Some studies have shown that CXCL1 expression in gastric cancer (GC) is associated with survival and clinicopathological characteristics. However, the evidence remains inconclusive. Thus, we aim to further explore the clinicopathological significance and potential prognostic role of CXCL1 expression in GC.

Methods: Databases of EMBASE, PubMed Web of Science and the Cochrane Library were systematically searched for the eligible studies from their establishment to July 16, 2020, which reported the association between CXCL1 expression and survival in GC. The quantitative meta-analysis was carried out with Stata SE12.0 software.

Results: A total of 1474 patients from 9 eligible studies were included in the present meta-analysis. Our results demonstrated that elevated expression level of CXCL1 was significantly associated with poor overall survival (OS) (HR=1.68; 95%CI: 1.26-2.24, P<0.001). The subgroup analysis revealed that elevated CXCL1 expression was found to be associated with a poor OS in Chinese and Japanese patients. Moreover, the stratification analysis by detection methods showed that elevated CXCL1 expression had a significantly poor OS effect on GC patients by IHC but not by RT-PCR. Besides, high CXCL1 expression was obviously associated with higher depth of tumor invasion, earlier lymph node metastasis and more advanced TNM stage compared with low CXCL1 expression in GC.

Conclusions: CXCL1 may serve as a potential biomarker to predict prognosis and clinicopathological features in GC.

Background

Despite the great improvement of diagnosis and treatment in the past decade, cancer remains a major public health problem worldwide, and is related to high morbidity and high mortality [1]. There were 17.2 million cancer cases worldwide and 8.9 million deaths in 2016[2]. Cancer cases increased by 28% between 2006 and 2016. Among cancers, gastric cancer (GC) has been a common malignant tumor in humans and has become a major health problem. GC ranks sixth for cancer incidence and third for cancer deaths with 834 000 deaths [2]. In view of this situation, numerous investigators are committed to identifying novel applicable prognostic biomarkers, which not only improve poor prognosis but also provide a novel therapeutic target in GC [3–5].

Chemokines are small chemokine proteins (8–10 kDa) with diverse bioactivities that can drive the directed migration of leukocytes to tumor microenvironments [6].There are a number of Chemokines, and researchers have identified approximately 50 chemokines to date [6]. The chemokine (C-X-C motif) ligand 1 (CXCL1), also known as the GRO-1 oncogene, is expressed in macrophages, neutrophils, and epithelial cells. It also has been overexpressed in melanoma tumors and involved in carcinogenesis of melanoma [7, 8]. CXCL1 binds specifically to the CXC chemokine receptor 2 (CXCR2), which is a member of the G protein-coupled receptor superfamily [9]. Previous investigations have demonstrated CXCL1 expression

might play an essential role in the chemoresistance, tumorigenesis, metastasis and angiogenesis of cancer [10–13]. In recent years, previous studies had explored the prognostic effects of CXCL1 in cancers [14–22]. Some studies suggested that high CXCL1 expression correlates with poor survival in GC [21, 22]. However, a study by Junnila et al. reported that over-expression of CXCL1 has better survival in GC [23]. The prognostic value of CXCL1 in GC is controversial.

Therefore, we performed the current meta-analysis to explore the prognostic and clinicopathological significance of CXCL1 expression in GC patients.

Methods

Literature search strategy

We performed a systematic selection of studies published in English from PubMed, EMBASE, Web of Science and Cochrane Library. The studies were published from their establishment to July 16, 2020, which reported the association between CXCL1 and survival in GC patients. The following keywords were searched in combination: " CXCL1 Chemokine" or " Gro alpha Protein " or " MGSA-alpha Chemokine " or " Neutrophil Activating Protein 3 " or " Growth Related Oncogene alpha Protein " and " Neoplasm " or " Neoplasia " or "Tumor" or "Cancer" or “Malignancy” or "Carcinoma". The references and related systematic reviews of the included studies were tracked.

Selection criteria

The studies were selected according to the following inclusion criteria: (1) GC patients were investigated. (2) CXCL1 expression levels were determined in human tissues or plasma samples. (3) According to the expression levels of CXCL1, patients were divided into low and high expression groups; (4) Hazard ratios (HRs) and its 95% confidence intervals (CIs) for OS time should be provided in the original paper or could be calculated through the K-M curves. Exclusion criteria were as follows: (1) studies without available data; (2) Overlapping data; (3) letters, Case reports, reviews, and conference reports; (4) studies not in the English language.

Date extraction and quality assessment

Two reviewers (Yujian Xia and Zhewei Wei) reviewed each eligible study and extracted the data independently, and any disagreements were discussed and judged by the third reviewer (Weibin Huang). The obtained data included the first author, year of publication, country, number of patients, detected method, cut-off value, follow-up time, outcome measures, analysis method, Newcastle-Ottawa Scale (NOS) criteria and clinicopathological characteristics, HRs and their 95% CIs for OS. If the results of OS were provided in the studies, multivariate analysis was considered to be prior to univariate analysis. If only the K-M curve was provided, the survival data was extracted with Engauge Digitizer version 4.1 and calculated the HRs and 95% CIs estimates based on the obtained data [24]. The quality of the studies

was assessed by the NOS criteria [25].The NOS scores ranged from 0 to 9. The studies were considered of high quality when NOS scores were higher or equal to 6.

Statistical Analyses

The meta-analysis was conducted with Stata statistical version 12.0 (Stata Corporation, College Station, TX, USA). The HRs for OS and odd ratios (ORs) for clinicopathological parameter were statistically analyzed. Chi-square-based Q and I^2 tests were used to determine the heterogeneity among the included studies. P_h value < 0.1 indicated significant heterogeneity. The I^2 value ≥ 50% was considered as severe heterogeneity, and then the random-effect model was applied. Otherwise, the Fixed-effect model was applied. Subgroup analysis and sensitivity analysis were used to analyze the sources of heterogeneity. P-value < 0.05 was considered statistically significant.

Results

Search results and study characteristics

According to our search strategy, a total of 927 original articles were initially identified. With 224 duplicated studies removed, 703 articles were left. Then, 623 studies were excluded owing to reviewing titles and abstracts. As a result, 23 studies remained for full-text screening, 14 studies were excluded under the following exclusion criteria: 5 studies for reviews and 9 studies for insufficient data. Finally, 9 studies involving a total of 1474 patients were included [18, 19, 21–23, 26–29]. The flow diagram of literature retrieval was shown in Fig. 1. The main characteristics of the enrolled studies were shown in Table 1. Among these studies, a total of 1474 GC patients were included. The mean sample size of patients was 163 ranged from 34 to 558. The regions represented in the study included Finland (n = 1), Japan (n = 2) and China (n = 6). Moreover, 7 studies used immunohistochemistry (IHC) technique for the detection of CXCL1 expression, while 2 studies chose Real-time polymerase chain reaction (RT-PCR). NOS scores were higher or equal to 6 in all the included studies, indicating that all studies had high quality.

Correlation between CXCL1 expression and prognosis.

The total of 9 eligible studies including 1474 GC patients reported the correlation between CXCL1 and OS. The random-effect model was used to calculate the pooled HR with corresponding 95%CIs, since significant heterogeneity existed among these studies (I^2 = 60.8%, P = 0.009). The result suggested that high CXCL1 expression predicted a poor outcome for OS in GC patients (HR = 1.68; 95%CI: 1.26–2.24, P < 0.001) (Fig. 2). To further explore the source of heterogeneity, we performed subgroup analyses by country (China or Japan or Finland), sample size (< 100 or ≥ 100), detection method (IHC or RT-PCR), analysis method (Multivariate or Univariate) and found that heterogeneity in the subgroup analysis of country disappeared completely (Table 2). The results also showed that high CXCL1 expression was a significant prognostic factor for poor OS in Chinese patients (HR = 1.91; 95%CI: 1.56–2.35, P < 0.001) and Japanese patients (HR = 1.51; 95%CI: 1.12–2.02, P = 0.007), but not in Finnish patients (HR = 0.25; 95%CI: 0.09–0.67, P = 0.006). High CXCL1 expression was associated with poor OS in studies with sample ≥ 100

(HR = 1.69; 95%CI: 1.41–2.02, P < 0.001) but not with sample < 100 (HR = 1.21; 95%CI: 0.32–4.64, P = 0.781). Moreover, the stratification analysis by detection methods showed that elevated CXCL1 expression had a significantly poor OS effect on GC patients by IHC (HR = 1.75; 95%CI: 1.48–2.08, P < 0.001) but not by RT-PCR (HR = 0.81; 95%CI: 0.08–7.81, P = 0.851). CXCL1 overexpression was shown to be a significant prognostic factor for OS in the subgroup stratified by analysis method.

Correlation between CXCL1 expression and clinicopathological features

We analyzed the correlation CXCL1 expression level with clinicopathological features of GC patients (Table 3). The results demonstrated that high CXCL1 expression was associated with higher depth of tumor invasion (OR = 4.20, 95%CI = 2.55–6.91, P < 0.05; I^2 = 2.6%) (Fig. 5C), earlier lymph node metastasis (OR = 2.58, 95%CI = 1.09–6.13, P < 0.05; I^2 = 89.1%) (Fig. 5D) and more advanced TNM stage (OR = 3.88, 95%CI = 2.55–5.90, P < 0.05; I^2 = 45.5%) (Fig. 5F). However, CXCL1 expression was not distinctly associated with gender (P = 0.741) (Fig. 5A), tumor differentiation (p = 0. 060) (Fig. 5B) and distant metastasis (p = 0.194) (Fig. 5E).

Sensitivity analysis and publication bias

The sensitivity analysis for CXCL1 expression and OS was displayed in Fig. 4A. The result indicated that there was no significant effect after removing each of the studies what suggested that the result of the meta-analysis was stability. Begg's funnel plots and Egger's linear regression test were adopted to assess the publication bias of the meta-analysis. The results showed that there was no significant publication bias in the meta-analysis (Begg's p = 0.230, Egger's p = 0.454) (Fig. 4B).

Discussion

Although previous studies have investigated the prognostic effects of CXCL1 expression in GC, there is no consensus in published studies due to controversial results. So we conducted the current meta-analysis to explore the prognostic impact of CXCL1 expression on GC patients. This meta-analysis is the first study to assess the prognostic and clinicopathological value of the CXCL1 in GC patients. This study demonstrated that high CXCL1 expression was significantly related to shorter OS in GC when compared with low CXCL1 expression. Further subgroup analysis revealed that elevated CXCL1 expression was found to be associated with a poor OS in Chinese and Japanese patients, but not in Finnish patients. Moreover, the stratification analysis by detection methods showed that elevated CXCL1 expression had a significantly poor OS effect on GC patients by IHC but not by RT-PCR. The meta-analysis also showed that high CXCL1 expression was related to a higher depth of tumor invasion, earlier lymph node metastasis, more advanced clinical stage and not to other clinicopathological features. Therefore, our study manifested CXCL1 expression could serve as a predictive and prognostic marker for GC patients.

A comprehensive analysis of the molecular mechanism of GC is of considerable significance to improve the early diagnosis rate and individualized treatment. Molecular mechanisms of CXCL1's underlying the

regulatory role in tumorigenesis and tumor progression have been widely researched. Numerous studies have shown that CXCL1 could promote the progression of cancer by activating multiple signaling pathways. Yang et al. revealed that high expression of CXCL1 stimulated breast cancer cell metastasis via the ERK/MMP2/9 pathway[12]. Wang et al. discovered CXCL1 promoted breast cancer metastasis via NF-kB/SOX4 activation [18]. Kuo et al. demonstrated CXCL1 increased cancer cell metastasis by decreasing the level of fibulin-1 expression through NF-kB/HDAC1 epigenetic regulation in prostate cancer [14]. Wei et al. focused on the prognostic effects of CXCL1 expression in GC, and they discovered CXCL1 promoted tumor growth through VEGF pathway activation [22]. In addition, it had been reported that lymphatic endothelial cells could produce CXCL1 and Wang et al. showed CXCL1 secreted by tumor-associated lymphatic endothelial cells could promote the lymph node metastasis of GC via activation integrin β1/FAK/AKT signaling [21]. Determining the underlying mechanism is a prerequisite for determining the prognostic significance of CXCL1 expression. Therefore, more basic researches should be conducted to explore the potential mechanism of CXCL1 in cancer prognosis.

In our study, there were some limitations which should be further discussed in the present study. First, there was no consistent the cutoff value for defining high and low CXCL1 expression, which might lead to the bias of the results. Second, we could not obtain partial HR directly from the original papers. Thus, we had to calculate the HRs from the survival curves, which might not be precise enough. Third, All eligible articles were retrospective research in the meta-analysis, which might lead to a degree of bias.

In conclusion, our study revealed that elevated expression level of CXCL1 was significantly associated with poor OS in GC patients. Moreover, the expression level of CXCL1 was associated with clinicopathological features including TNM stage, lymph node metastasis and depth of tumor invasion.

Abbreviations

GC: gastric cancer; OS: overall survival; CXCL1: chemokine (C-X-C motif) ligand 1; CXCR2: CXC chemokine receptor 2; NOS: Newcastle-Ottawa Scale; ORs: odd ratios; IHC: immunohistochemistry; RT-PCR : Real-time polymerase chain reaction;

Declarations

Acknowledgements

Not applicable

Author contributions

YLH designed the study. YJX and ZWW analyzed the data and wrote the paper, WBH and XJW performed the literature research and confirmed statistical analyses. All authors reviewed the final manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1: The main information of included studies in the meta-analysis

Study	Country	Sample size (high/low)	Method	Cut-off Value	Follow-up (months)	Outcome	Analysis	NOS
Junnila 2010	Finland	11/23	RT-PCR	Fold change	≥60	OS	U	6
Cheng 2011	China	35/81	IHC	Strong staining	≥60	OS	U	6
Xiang 2015	China	79/48	IHC	IS>97.2%	≥60	OS	M	7
Wei 2015	China	41/57	IHC	Strong staining	≥60	OS	U	8
Wang 2016	China	41/59	IHC	IS>3	≥50	OS	U	8
Wang 2017	China	58/47	IHC	NR	≥60	OS	U	7
Kasashima 2017	Japan	144/120	IHC	IS≥3	≥60	OS	M	7
Chen 2018	China	36/36	RT-PCR	Median	≥60	OS	U	6
Yamamoto 2019	Japan	258/300	IHC	IS≥3	≥60	OS	M	8

NR, not reported; IS, immunoreactivity score; U univariate; M multivariate

Table 2: Subgroup analysis of association between CXCL1 and OS for gastric cancer patients

clinicopathological parameters	Studies (n)	HR(95% CI)	P-value	Heterogeneity I^2(%)	P_h
Country					
China	6	1.91(1.56-2.35)	0.000	0.0%	0.534
Japan	2	1.51(1.12-2.02)	0.007	0.0%	0.723
Finland	1	0.25(0.09-0.67)	0.006	—	—
Sample size					
<100	3	1.21(0.32-4.64)	0.781	88.0%	0.000
≥100	6	1.69(1.41-2.02)	0.000	0.0%	0.594
Detection method					
IHC	7	1.75(1.48-2.08)	0.000	0.0%	0.501
RT-PCR	2	0.81(0.08-7.81)	0.851	91.3%	0.001
Analysis method					
Multivariate	3	1.62(1.24-2.10)	0.000	0.0%	0.555
Univariate	6	1.62(1.03-2.54)	0.036	73.8%	0.002

Table 3: Meta-analysis results for the associations of high expression level of CXCL1 with clinicopathological parameters

clinicopathological parameters	Studies (n)	Number of patients	OR(95% CI)	P-value	Heterogeneity I^2(%)	P_h	Model
Gender (male vs female)	6	1252	1.04(0.83-1.31)	0.741	0.0%	0.580	Fixed
Tumor differentiation (poorly/others vs well/moderately)	4	430	2.38(0.96-5.86)	0.060	72.7%	0.012	Random
Depth of tumor invasion (T3-T4 vs T1-T2)	3	332	4.20(2.55-6.91)	0.000	2.6%	0.358	Fixed
Lymph node metastasis (yes vs no)	6	1249	2.58(1.09-6.13)	0.032	89.1%	0.000	Random
Distant metastasis (yes vs no)	4	888	2.08(0.69-6.25)	0.194	75.1%	0.007	Random
TNM stage (III–IV vs I–II)	4	430	3.88(2.55-5.90)	0.000	45.5%	0.139	Fixed

Figures

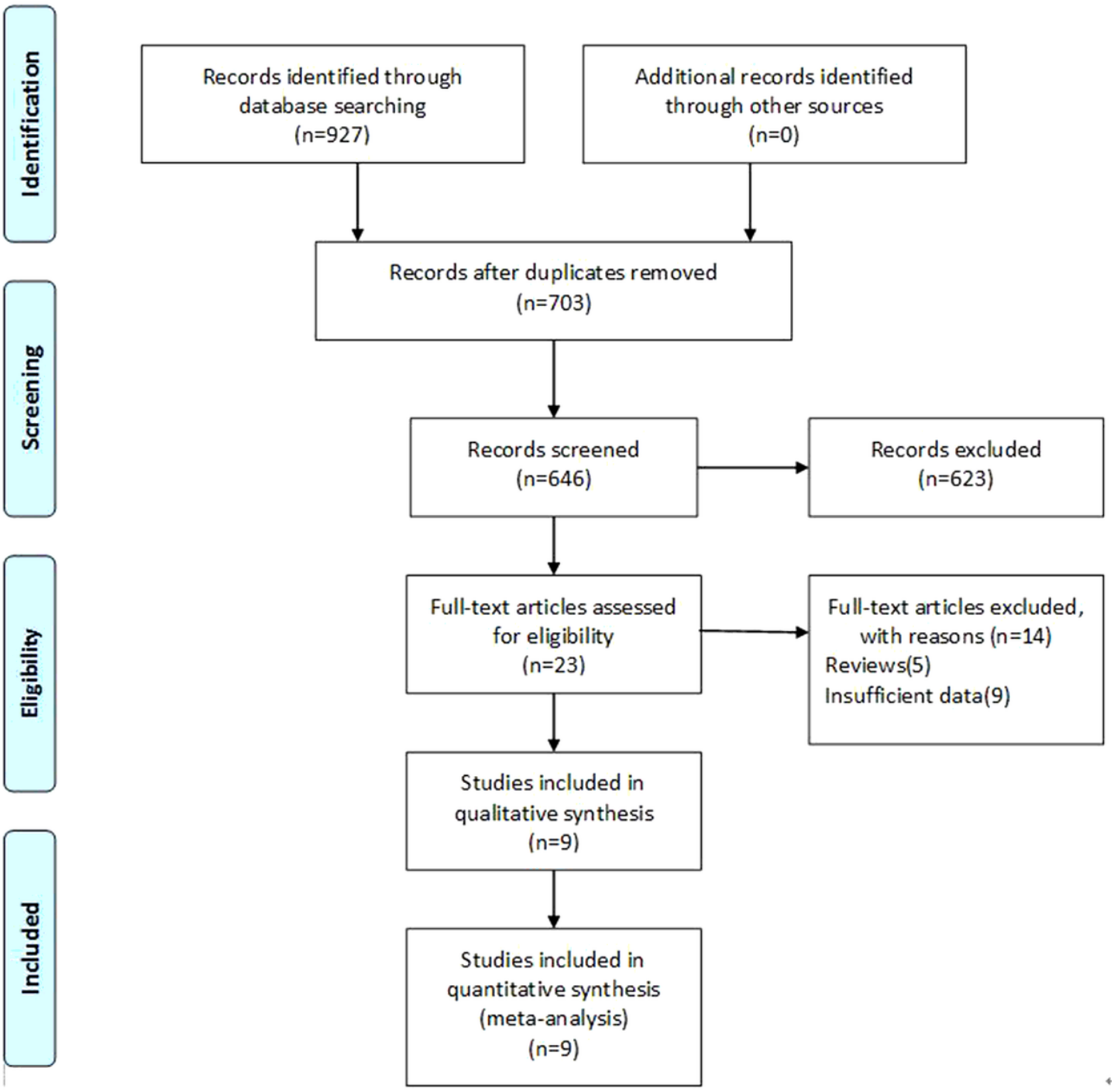

Figure 1

The flow chart of literature search and selection.

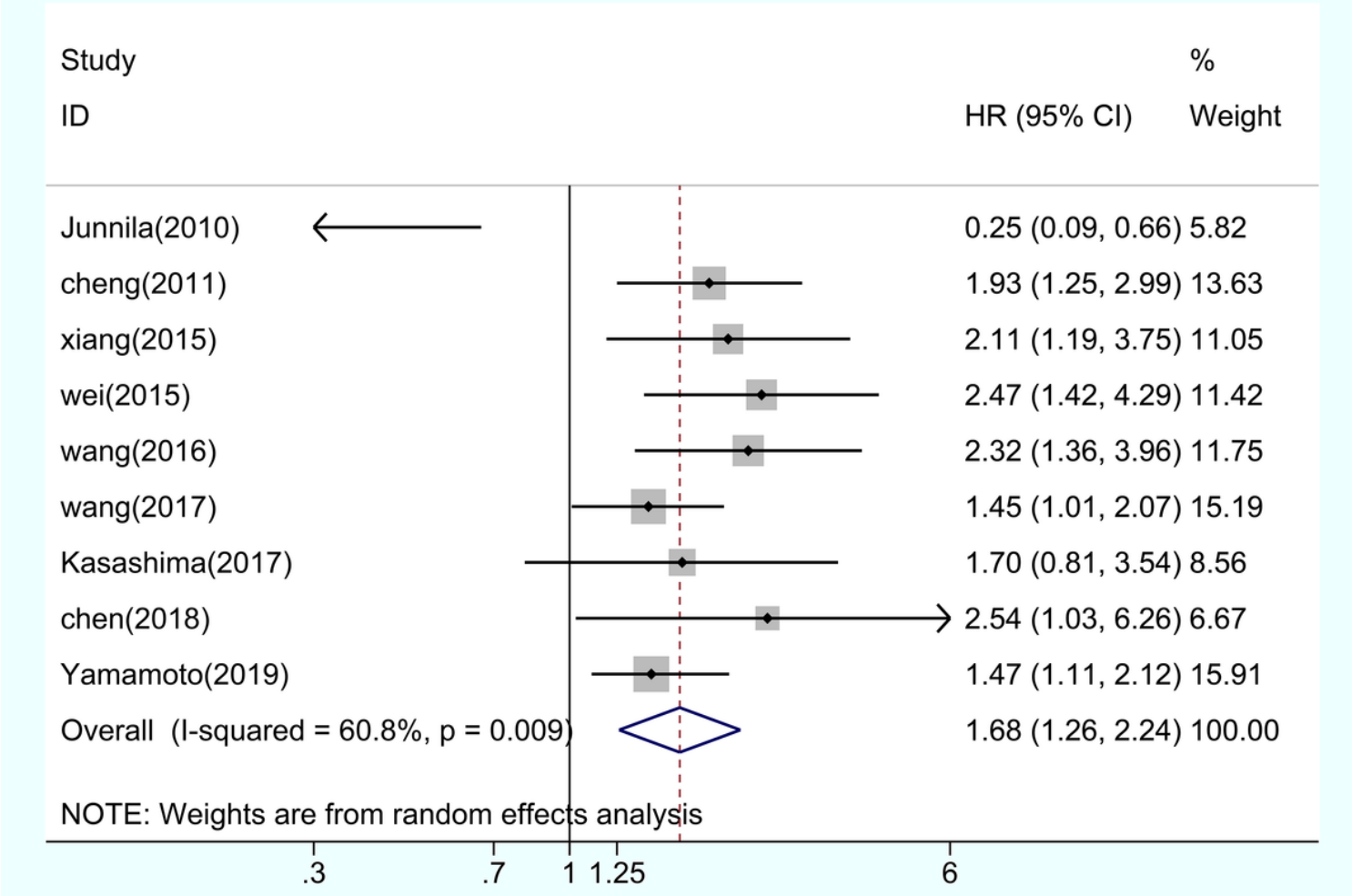

Figure 2

The meta-analysis of the association between CXCL1 expression and OS.

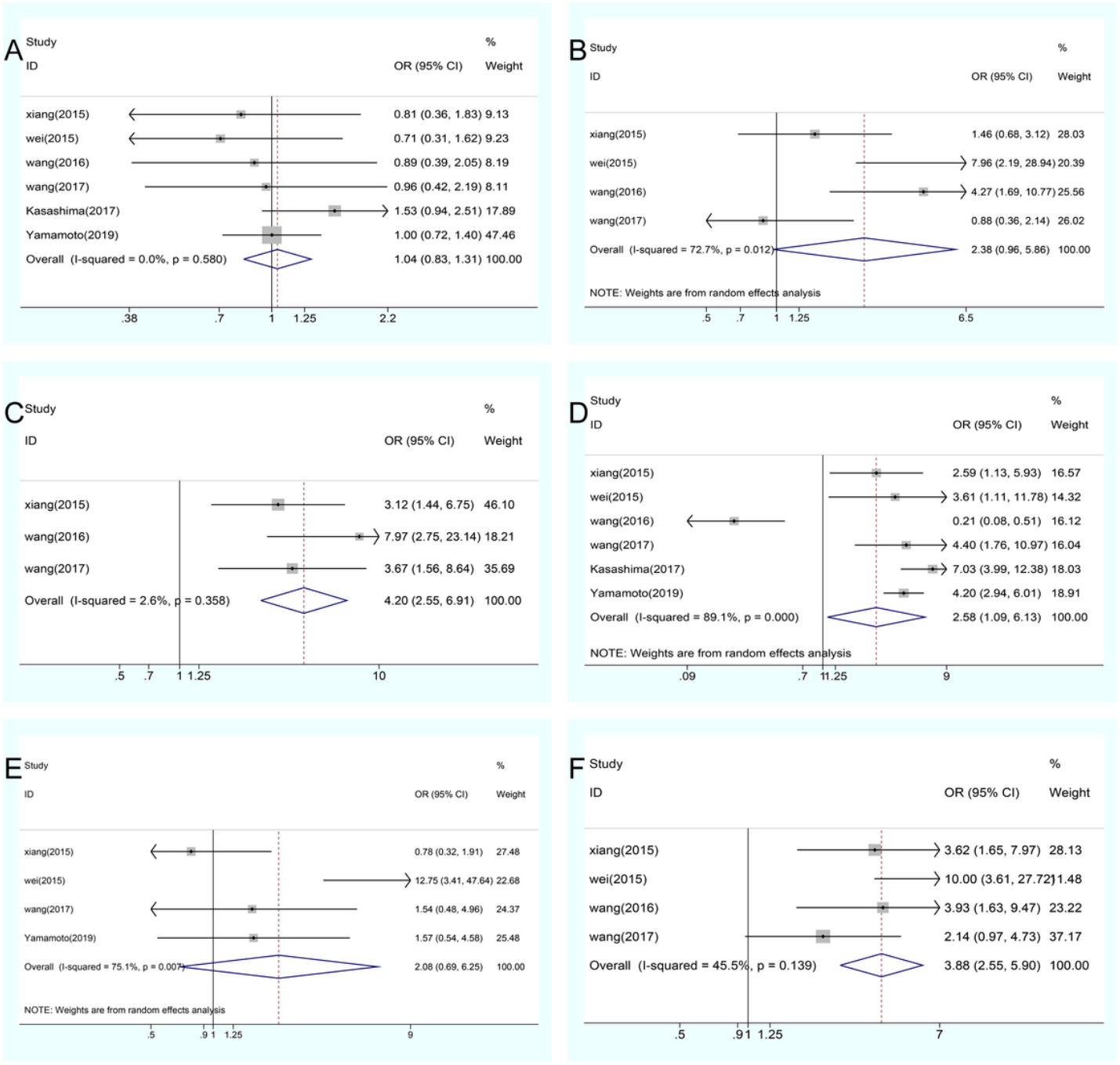

Figure 3

The meta-analysis of the association between CXCL1 expression and (A) gender, (B) tumor differentiation, (C) depth of tumor invasion. (D) lymph node metastasis, (E) distant metastasis, (F) clinical stage.

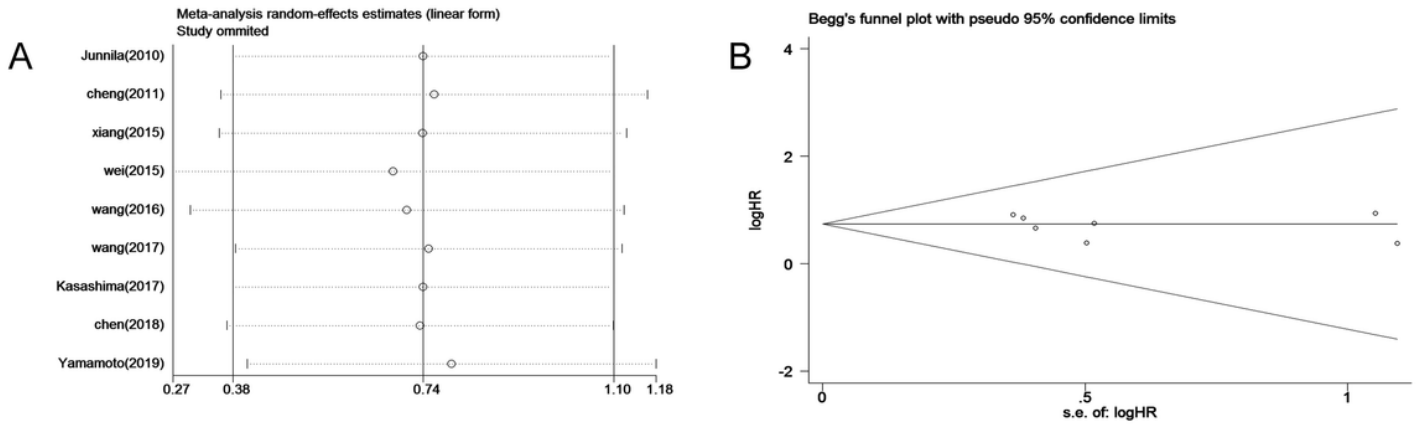

Figure 4

Sensitivity analysis of pooled HR for OS (A) for GC patients abnormally expressed CXCL1.Begg’s test for publication bias (B).