Tumor expression of CXCL12 and survival of patients with colorectal cancer: A meta-analysis

SHUQI ZHANG[1] and GUOXIONG LI[2]

[1]Department of Digestive Diseases, The Second Hospital of Jiaxing, Jiaxing, Zhejiang 314000; [2]Department of Digestive Diseases, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, Zhejiang 310000, P.R. China

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Abstract. C-X-C motif chemokine ligand 12 (CXCL12) has been suggested as a possible biomarker of poor prognosis in patients with various malignancies. However, the association between tumor expression of CXCL12 and survival of patients with colorectal cancer (CRC) remains to be comprehensively analyzed. A meta-analysis to systematically evaluate this association was performed in the present study. Relevant cohort studies were retrieved by searching the PubMed, Embase and Web of Science databases from inception to March 22, 2022. A conservative random-effect model incorporating the possible influence of between-study heterogeneity was used to pool the results. A total of 14 cohort studies that included 2,060 patients with CRC contributed to the meta-analysis, and 1,055 (51.2%) of them had higher tumor expression levels of CXCL12. Pooled results showed that a higher tumor expression level of CXCL12 was associated with poor overall survival [hazard ratio (HR), 1.74; 95% confidence interval (CI), 1.29-2.34; P<0.001; I^2, 33%] and progression-free survival (HR, 2.00; 95% CI, 1.47-2.73; P<0.001; I^2, 33%). Subgroup analyses showed that the association between higher cancer expression levels of CXCL12 and poor survival in patients with CRC was not significantly affected by the country of the study, the location of the tumor, the cancer stage or the methods used for measuring tumor CXCL12 levels (all P>0.05). In conclusion, the study found that a higher tumor expression level of CXCL12 was associated with the poor survival of patients with CRC. Studies are warranted to determine if CXCL12-targeted intervention could improve the prognosis of patients with CRC.

Correspondence to: Dr Guoxiong Li, Department of Digestive Diseases, The Affiliated Hospital of Hangzhou Normal University, 126 Wenzhou Road, Gongshu, Hangzhou, Zhejiang 310000, P.R. China
E-mail: ligx56223@163.com

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Introduction

Colorectal cancer (CRC) ranks as the third most prevalent cancer, and ~1.4 million new cases of CRC are diagnosed annually all over the world (1-3). As early diagnosis for patients with CRC is still challenging, a substantial number of patients with CRC are diagnosed at late stages, which is generally associated with a poor prognosis (4). Despite the application of multiple modalities for CRC treatment, such as surgical resection and radio-chemotherapy, the patient prognosis remains poor (5,6). Therefore, the identification of key molecules that are involved in the carcinogenesis and deterioration of CRC is important for the early prevention and treatment of the cancer.

C-X-C motif chemokine ligand 12 (CXCL12), also known as stromal cell-derived factor-1, was initially identified as a key cytokine involved in the metastasis of tumor cells (7,8). Located on the long arm of chromosome 10, the *CXCL12* gene was first cloned from a bone marrow-derived stromal cell line, and was then identified as a pre-B cell growth stimulating factor (9,10). In humans, CXCL12 exists as six different splice variants (CXCL12α to ϕ) (11), which share the first three exons and are encoded by the same *CXCL12* gene (11). The variants differ by the fourth exon, which determines the splice variant length. All CXCL12 isoforms have the first 67 amino acids in common and then exhibit different lengths, with CXCL12α to ϕ being 68, 72, 98, 119, 69 and 79 amino acids long, respectively (11). The amino-terminal domain of CXCL12 binds to the second extracellular loop of C-X-C chemokine receptor type 4 (CXCR4) and activates the signaling pathways downstream (9,10). The third intracellular loop of CXCR4 is necessary for Gαi-dependent signaling, and intracellular loops 2 and 3, as well as the CXCR4 C-terminus, are required for chemotaxis (9,10). Typically, the binding of CXCL12 to CXCR4 triggers multiple signal transduction pathways that control the regulation of intracellular calcium flux, transcription, chemotaxis and cell survival (12,13). In addition, CXCL12 is constitutively expressed in tissues that are vulnerable to metastasis, such as the lung, bone marrow and liver tissues (13). Subsequent preclinical studies showed that expression levels of CXCL12 in certain human tumors were correlated with dedifferentiation and malignant tumor behaviors (14,15). For patients with CRC, accumulating studies have been performed to evaluate the association between tumor expression levels of

CXCL12 and survival outcomes (16,17). However, results of these studies are not always consistent (18-30). Therefore, in the present study, a meta-analysis was performed to comprehensively investigate the possible predictive role of tumor CXCL12 expression for the prognosis of patients with CRC.

Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (31,32) was followed in conceiving, conducting and reporting the study, and the methodology of the meta-analysis was in accordance with the recommendations of the Cochrane's Handbook (33) guidelines.

Literature retrieval. Studies were retrieved by searching the PubMed, Embase and Web of Science electronic databases from the inception of the databases until March 22, 2022. Combined search terms were used, including i) 'CXCL12' OR 'SDF1'; ii) 'colon' OR 'colorectal' OR 'rectal' OR 'anal'; and iii) 'cancer' OR 'carcinoma' OR 'adenoma' OR 'adenocarcinoma' OR 'malignancy' OR 'tumor' OR 'tumour' OR 'neoplasm'. The search was limited to human studies published as full-length articles. No restriction was applied regarding the language of publication. As a supplementation, the citations of the relevant original and review articles were manually checked for possible studies of interest.

Study selection. The PICOS principle was used for study inclusion with the following descriptions: P (patients): Adult patients with a histologically confirmed diagnosis of CRC, regardless of the cancer stage or treatments. I (exposure): Patients with higher tumor expression levels of CXCL12. The methods for measuring tumor CXCL12 expression levels and the cutoff for defining higher tumor CXCL12 expression levels were in accordance with those applied in the original studies. C (control): Patients with lower tumor expression levels of CXCL12. O (outcomes): The primary outcome was overall survival (OS) and the secondary outcome was progression-free survival (PFS), compared with that of patients with CRC and higher vs. lower tumor expression levels of CXCL12. Generally, OS was defined as the time elapsed from treatment and to the date of death from any cause, while PFS was defined as the interval between initiation of the treatment and the first recurrence or progression event. S (study design): Cohort studies, including prospective and retrospective cohorts.

Reviews, preclinical studies, studies including patients that did not have CRC, studies that did not evaluate tumor expression levels of CXCL12 or studies that did not report the survival outcomes were excluded.

Data collection and quality assessing. Two independent assessors conducted the literature search and analysis, data collection and study quality assessments separately. If discrepancies were encountered, they were resolved by discussion to reach a consensus. Data regarding study information, patient demographic factors, cancer stage, methods for measuring the tumor expression levels of CXCL12, cutoffs for defining higher tumor expression levels of CXCL12, number of patients with higher tumor expression levels of CXCL12 and variables adjusted in the regression model for the analysis of the association between CXCL12 and survival outcomes were collected. Study quality assessment was achieved via the Newcastle-Ottawa Scale (NOS) (34), with scoring regarding the criteria for participant selection, comparability of the groups and the validity of the outcomes. The scale ranged between 1-9 stars, with a larger number of stars representing higher study quality.

Statistical analysis. The main objective was to determine the relative risks of OS and PFS of patients with CRC and higher vs. lower tumor expression of CXCL12. These were presented as hazard ratios (HRs) and confidence intervals (CIs). Using the 95% CIs or P-values, HRs and standard errors (SEs) could be calculated, and a subsequent logarithmical transformation was conducted to keep a stabilized variance and normalized distribution. Between-study heterogeneity was estimated with the Cochrane's Q test and the I^2 statistic (35), with I^2>50% reflecting significant heterogeneity. A random-effect model was applied to combine the results by incorporating the influence of heterogeneity (33). The influence of each study on the overall results was observed by performing sensitivity analyses that omitted one study at a time (36). Subgroup analyses were also performed to explore the influences of study characteristics on the outcome. By construction of the funnel plots, the publication bias was estimated based on the visual judgment of the symmetry of the plots, supplemented by the Egger's regression asymmetry test (37). RevMan (version 5.1; Cochrane) and Stata (version 12.0; StataCorp LP) software were applied for these analyses.

Results

Studies obtained. Fig. 1 shows the process of the literature analysis. Briefly, the initial search of the databases retrieved 721 articles, and 588 were left after excluding duplicated records. An additional 549 articles were excluded, as the contents of the titles and abstracts indicated that they were not relevant to the aim of the meta-analysis, which made a total of 39 studies for the full-text review. Finally, after excluding 26 studies through full-text review, 13 studies (18-30) were included. The reasons for the removal of the 26 studies are also presented in Fig. 1. Since 1 report (27) included 2 independent cohort studies, a total of 14 cohort studies were available for the meta-analysis.

Characteristics of the included studies. As shown in Table I, 14 cohort studies involving 2,060 patients with CRC contributed to the meta-analysis. These studies were performed in Japan, the United States, Italy, Tunisia, the Netherlands, Italy, Norway, Switzerland and Korea. All were retrospective cohort studies except for 1 study, which was a prospective cohort study (26). Patients with rectal cancer were included in 3 cohorts (20,23,30), patients with colon cancer were included in 2 cohorts (27), while the remaining 9 cohorts included patients with rectal or colon cancer (18,19,21,22,24-26,28,29). Tumor expression levels of CXCL12 protein were assayed by immunohistochemistry in most of the included studies except 2 studies, in which the reverse transcription-quantitative polymerase chain reaction was applied to measure the tumor CXCL12 mRNA level (20,28). Cutoffs for defining the higher tumor expression levels of CXCL12 varied among

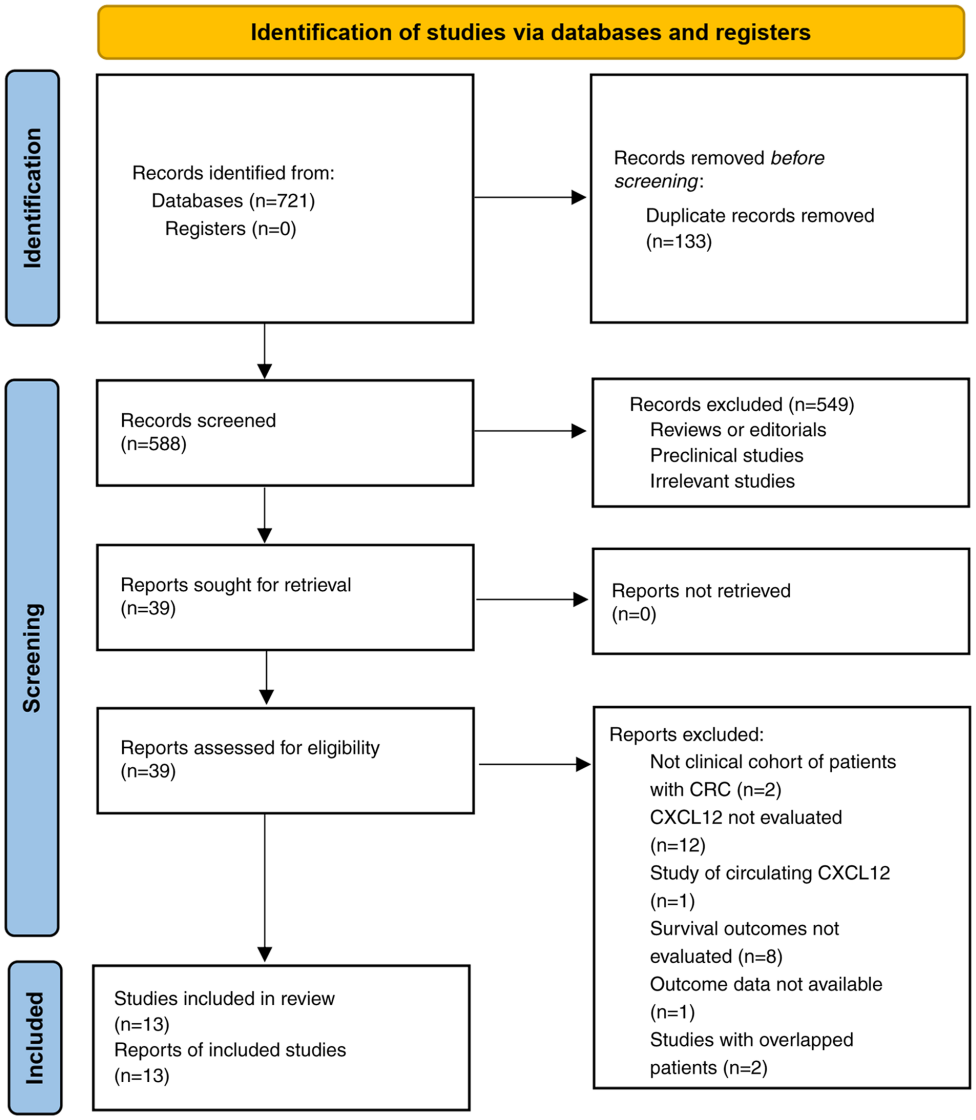

Figure 1. Summarized process of the literature search and study retrieval. CRC, colorectal cancer; CXCL12, C-X-C motif chemokine ligand 12.

the included studies, such as CXCL12 protein expression in ≥50% of the tumor cells, CXCL12 expression in ≥10% of the tumor cells or tumors with detectable CXCL12 mRNA. Overall, 1,055 (51.2%) patients had higher tumor expression levels of CXCL12. The mean expression levels of CXCL12 in CRC varied between 25 and 81% among the included studies. The median follow-up duration of the included studies varied between 23 and 66 months. The outcome of OS was reported in 12 cohorts (18-26,28-30), while the outcome of PFS was reported in 10 cohorts (19-23,26-28,30). In 12 studies, multivariate models were applied to analyze the association between CXCL12 and the survival outcomes, and variables such as age, sex and cancer stage, among others, were adjusted (18-23,25,27-30). In two studies, univariate models were used for the analyses without adjustment of the potential confounding factors (24,26). For one of the included studies, the HRs for the association between tumor CXCL12 expression levels and survival outcomes were separately reported in patients with and without preoperative chemoradiotherapy (PCRT), and these datasets were included into the meta-analysis independently. The NOS of the included studies were 6 to 9 stars, suggesting moderate to good study quality (Table II).

Tumor expression of CXCL12 and the OS of patients with CRC. Pooled results of 12 cohorts (18-26,28-30) showed that a higher tumor expression level of CXCL12 was associated with the poor OS (HR, 1.74; 95% CI, 1.29-2.34; P<0.001; I^2, 33%) of patients with CRC (Fig. 2A). Sensitivity analyses performed by excluding one study at a time showed consistent results (HR, 1.62-1.94; all P<0.05). Subgroup analyses showed that the association between higher cancer expression levels of CXCL12 and poor OS was not significantly affected by study country, tumor location, tumor stage, methods for measuring tumor CXCL12 levels or the models for the analyses of the association (all P>0.05; Table III). Moreover, sensitivity analyses limited to retrospective studies showed similar results (12 studies; HR, 1.79; 95% CI, 1.30-2.47; P=0.004; Table III).

Tumor expression of CXCL12 and the PFS of patients with CRC. Results of the meta-analysis with 10 cohorts (19-23,26-28,30), which were all retrospective studies

Table I. Characteristics of the included studies.

First author, year	Country	Design	Diagnosis	Sample size	Mean age, years	Men, %	Tumor stage	Methods for measuring CXCL12	Definition of higher CXCL12 expression	No. of cases with higher CXCL12	Mean CXCL12 expression level, %	Outcome reported	Median follow-up duration, months	Variables adjusted	(Refs.)
Yoshitake *et al*, 2008	Japan	RC	Patients with CRC who underwent surgery or endoscopic resection	60	63.8	68.3	I-IV	IHC	Greater or equal to the expression level of endothelial 1 cells in the adjacent normal colonic tissues	38	63	OS	35	Age, sex and cancer stage	(18)
Akishima-Fukasawa *et al*, 2009	Japan	RC	Patients with CRC who underwent surgery for curative resection	165	61.8	61.2	II-III	IHC	CXCL12 expression in ≥50% of the tumor cells	120	73	OS and PFS	61	Age, sex, tumor location, size, stage, lymphatic or blood vessel invasion and LN metastasis	(19)
Saigusa *et al*, 2010	Japan	RC	Patients with rectal cancer underwent preoperative CRT	53	62.4	81.1	II-III	qRT-PCR	mRNA of CLCL12 detectable	14	26	OS and PFS	40	Age, sex and cancer stage	(20)
Yopp *et al*, 2012	USA	RC	Patients undergoing partial hepatectomy for metastatic CRC	75	NR	68	IV	IHC	CXCL12 expression in ≥50% of the tumor cells	22	29	OS and PFS	42	Age, sex, clinical risk score and tumor distribution	(22)
Sakai *et al*, 2012	Japan	RC	Patients with liver metastases of CRC	92	NR	63	IV	IHC	CXCL12 expression in ≥10% of the tumor cells	51	55	OS and PFS	38	Age, sex, tumor size and number of metastases	(21)
D'Alterio *et al*, 2014	Italy	RC	Patients with locally advanced rectal cancer undergoing PCRT	68	61	57.4	I-III	IHC	CXCL12 expression in ≥50% of the tumor cells	44	65	OS and PFS	66	Age, sex, tumor histology and stage	(23)
Amara *et al*, 2015	Tunisia	RC	Patients with CRC	124	61	56.5	I-IV	IHC	CXCL12 expression in ≥50% of the tumor cells	89	72	OS	40	None	(24)
de Cuba *et al*, 2016	The Netherlands	PC	Patients with peritoneal metastases of CRC	52	58	43.4	IV	IHC	CXCL12 expression in ≥50% of the tumor cells	28	54	OS	23	None	(26)
D'Alterio *et al*, 2016	Italy	RC	Patients with liver metastases of CRC	33	NR	61	IV	IHC	CXCL12 expression in ≥50% of the tumor cells	17	52	OS and PFS	28	Age, sex, KRAS mutational status, and number and size of metastases	(25)
Stanisavljevic *et al*, 2016 (cohort 1)	Norway	RC	Patients with colon cancer	290	61.9	48	II-III	IHC	CXCL12 expression in ≥10% of the tumor cells	192	66	PFS	30	Age, sex, tumor stage, LN metastasisand adjuvant therapy	(27)

Table I. Continued.

First author, year	Country	Design	Diagnosis	Sample size	Mean age, years	Men, %	Tumor stage	Methods for measuring CXCL12	Definition of higher CXCL12 expression	No. of cases with higher CXCL12	Mean CXCL12 expression level, %	Outcome reported	Median follow-up duration, months	Variables adjusted	(Refs.)
(cohort 2)	Norway	RC	Patients with colon cancer	265	73.5	49	I-III	IHC	CXCL12 expression in ≥10% of the tumor cells	214	81	PFS	30	Age, sex, tumor stage, LN metastasis and adjuvant therapy	
Mitchell *et al*, 2019	USA	RC	Patients with CRC	49	64	51	I-III	RT-qPCR	mRNA of CLCL12 detectable	29	59	OS and PFS	33	Age, sex, tumor stage and lymphatic or blood vessel invasion	(28)
Lalos *et al*, 2021	Switzerland	RC	Patients with CRC	613	70	46.8	I-III	IHC	CXCL12 expression in ≥50% of the tumor cells	156	25	OS	40	Age, sex, tumor grade, stage and lymphatic or blood vessel invasion	(29)
Kim *et al*, 2022	Korea	RC	Patients with locally advanced rectal cancer	121	NR	65.3	II-III	IHC	CXCL12 expression in ≥10% of the tumor cells	41	34	OS and PFS	45	Age, sex, tumor stage, R score and previous chemotherapy	(30)

CXCL12, C-X-C motif chemokine ligand 12; RC, retrospective cohort; PC, prospective cohort; NR, not reported; IHC, immunohistochemistry; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; mRNA, messenger RNA; OS, overall survival; PFS, progression-free survival; KRAS, Kirsten rat sarcoma 2 viral oncogene homolog; CRC, colorectal cancer; LN, lymph node; PCRT, preoperative chemoradiotherapy.

Table II. Detailed quality evaluation of the included studies via the Newcastle-Ottawa Scale.

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Long enough follow-up duration	Adequacy of follow-up of cohorts	Total	(Refs.)
Yoshitake *et al*, 2008	1	1	1	1	1	1	1	1	1	9	(18)
Akishima-Fukasawa *et al*, 2009	0	1	1	1	1	1	1	1	1	8	(19)
Saigusa *et al*, 2010	0	1	1	1	1	1	1	1	1	8	(20)
Yopp *et al*, 2012	0	1	1	1	1	1	1	1	1	8	(22)
Sakai *et al*, 2012	0	1	1	1	1	1	1	1	1	8	(21)
D'Alterio *et al*, 2014	0	1	1	1	1	1	1	1	1	8	(23)
Amara *et al*, 2015	0	1	1	1	0	0	1	1	1	6	(24)
de Cuba *et al*, 2016	0	1	1	1	0	0	1	1	1	6	(26)
D'Alterio *et al*, 2016	0	1	1	1	1	1	1	1	1	8	(25)
Stanisavljevic *et al*, 2016 (cohort 1)	0	1	1	1	1	1	1	1	1	8	(27)
(cohort 2)	0	1	1	1	1	1	1	1	1	8	
Mitchell *et al*, 2019	0	1	1	1	1	1	1	1	1	8	(28)
Lalos *et al*, 2021	0	1	1	1	1	1	1	1	1	8	(29)
Kim *et al*, 2022	0	1	1	1	1	1	1	1	1	8	(30)

Table III. Results of subgroup and sensitivity analyses for the association between CXCL12 and overall survival of patients with colorectal cancer.

Study characteristics	Dataset number	HR (95% CI)	I^2, %	P-value for subgroup effect	P-value for subgroup difference
Country					0.41
Asian	6	1.89 (1.04-3.44)	50	0.04	
Non-Asian	7	1.44 (1.12-1.86)	5	0.005	
Tumor location					0.97
Rectal cancer	4	1.70 (0.61-4.78)	64	0.31	
Rectal or colon cancer	9	1.67 (1.27-2.19)	18	<0.001	
Cancer stage					0.48
I-III	7	1.57 (0.99-2.50)	48	0.05	
IV	4	1.98 (1.27-3.10)	0	0.003	
Methods for measuring CXCL12					0.42
IHC	11	1.64 (1.21-2.24)	31	0.002	
RT-qPCR	2	2.47 (0.96-6.35)	43	0.06	
Method for analysis					0.57
Univariate model	2	2.23 (0.87-5.68)	45	0.09	
Multivariate model	11	1.68 (1.22-2.30)	33	0.001	
Design					
RC only	12	1.79 (1.30-2.47)	39	0.004	

HR, hazard ratio; CI, confidence interval; RC, retrospective cohort; CXCL12, C-X-C motif chemokine ligand 12; IHC, immunohistochemistry; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

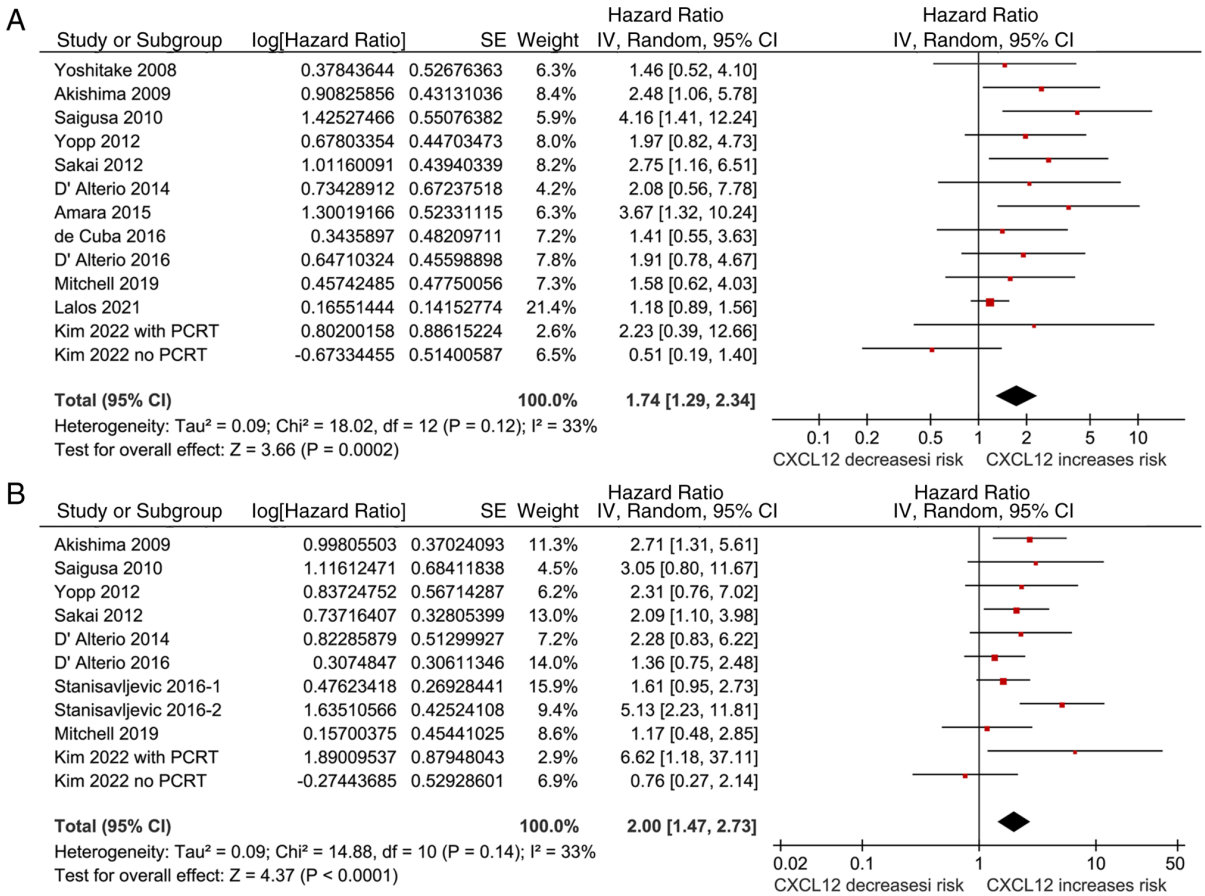

Figure 2. Forest plots for the meta-analyses regarding the association between tumor expression levels of CXCL12 and survival of patients with CRC. (A) Associations between tumor expression of CXCL12 and overall survival, and (B) between tumor expression of CXCL12 and progression-free survival. CXCL12, C-X-C motif chemokine ligand 12; CRC, colorectal cancer; CI, confidence interval; SE, standard error.

with multivariate analyses, showed that a higher tumor expression level of CXCL12 was associated with poor PFS in patients with CRC (HR, 2.00; 95% CI, 1.47-2.73; P<0.001; I^2, 33%; Fig. 2B). Sensitivity analyses performed by excluding

Table IV. Results of subgroup analyses for the association between CXCL12 and progression-free survival of patients with colorectal cancer.

Study characteristics	Datasets number	HR (95% CI)	I^2, %	P-value for subgroup effect	P-value for subgroup difference
Country					0.74
Asian	5	2.16 (1.26-3.70)	35	0.005	
Non-Asian	6	1.92 (1.27-2.90)	40	0.002	
Tumor location					0.76
Rectal cancer	4	2.10 (0.90-4.87)	47	0.09	
Colon cancer	2	2.74 (0.88-8.51)	81	0.08	
Colon or rectal cancer	5	1.80 (1.30-2.51)	0	0.005	
Cancer stage					0.49
I-III	8	2.15 (1.38-3.36)	47	<0.001	
IV	3	1.74 (1.15-2.61)	0	0.008	
Methods for measuring CXCL12					0.64
IHC	9	2.07 (1.46-2.93)	39	<0.001	
RT-qPCR	2	1.65 (0.67-4.06)	27	0.28	

HR, hazard ratio; CI, confidence interval; CXCL12, C-X-C motif chemokine ligand 12; IHC, immunohistochemistry; RT-qPCR, reverse transcription-quantitative polymerase chain reaction.

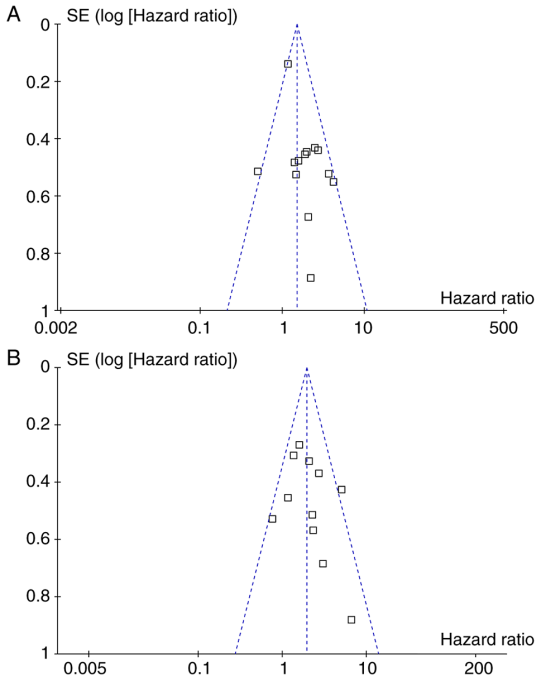

Figure 3. Funnel plots for the publication bias underlying the meta-analyses. Funnel plots for the meta-analysis of (A) overall survival and (B) progression-free survival. SE, standard error.

one study at a time did not significantly affect the results (HR, 1.78-2.13; all P<0.05). Subgroup analyses showed that the association between higher cancer expression levels of CXCL12 and poor PFS was not significantly affected by characteristics such as study country, tumor location, cancer stage or the methods for measuring tumor CXCL12 levels (all P>0.05; Table IV).

Publication bias. Fig. 3A and B display the funnel plots for the outcomes of OS and PFS. Visual inspection revealed symmetry of the plots, reflecting a low risk of publication biases. Egger's regression tests also indicated low risks of publication biases (P=0.18 and P=0.31, respectively).

Discussion

In this meta-analysis, by pooling the results of 14 cohort studies from 13 reports, the results showed that a higher tumor expression level of CXCL12 was associated with the poor OS and PFS of patients with CRC. The results were consistent for sensitivity analyses by excluding one study at a time, and for subgroup analyses according to multiple study characteristics, such as the study country, tumor location, cancer stage and methods for measuring tumor CXCL12. Taken together, these findings suggest that a higher level of CXCL12 expression in tumors may be a predictor of poor prognosis in patients with CRC.

An early meta-analysis in 2017 included 32 studies and showed that high expression levels of CXCL12 were associated with poor OS, but not poor PFS, in patients with various solid malignancies (38). However, significant heterogeneity was observed in this meta-analysis, and further subgroup analyses with 6 studies of patients with CRC failed to show a significant association between the tumor expression level of CXCL12 and the survival outcomes (38). Another meta-analysis, also published in 2017, suggested that a higher tumor expression level of CXCL12 may be associated with poor OS (39). However, only 2 studies before 2011 were included, which made the results less convincing (39). The present meta-analysis has several strengths compared with the previous meta-analyses. First, the focus was on patients with CRC only and updated studies were included, and the results showed that tumor expression levels of CXCL12 may be a predictor of poor OS and PFS in patients with CRC. Second, the robustness of the findings was evidenced by consistent results of sensitivity and subgroup analyses, which indicated that the results were not mainly driven by either of the included cohorts and were not significantly affected by multiple study characteristics. Furthermore, sensitivity analyses limited to studies with multivariate analyses showed a significant association between high CXCL12 expression levels and poor survival in patients with CRC, which implies that the association may not be confounded by factors such age, sex and cancer stage. Taken together, these findings suggest that high expression levels of

CXCL12 may be a predictor of poor survival of patients with CRC.

The potential mechanisms underlying the association between the high tumor expression of CXCL12 and the poor survival of patients with CRC are not yet fully determined. An early preclinical study showed that CXCL12 could activate multiple signals, including extracellular signal-regulated kinase-1/2, stress-activated protein kinase/c-Jun NH2-terminal kinase and matrix metalloproteinase-9 (40), which mediate the reorganization of the actin cytoskeleton, resulting in increased cancer cell migration and invasion in CRC. A subsequent study showed that silencing the CXCL12 gene could significantly inhibit the proliferation, invasion and angiogenesis ability of colon carcinoma cells through downregulation of the mitogen-activated protein kinase-related signaling pathway (41). Moreover, CXCL12 has also been involved in the inflammation-induced progression of CRC. For example, the CXCL12/CXCR4 signaling pathway was shown to play a critical role in promoting the progression of inflammatory colorectal cancer by recruiting immunocytes and enhancing cytoskeletal remodeling (42). In addition, high tumor expression levels of CXCL12 were shown to reduce the sensitivity of CRC to radiotherapy by upregulating the expression of survivin (43). Collectively, the aforementioned results suggest that CXCL12 plays a key role in the progression of CRC. Another important question is whether interventions lowering the expression of CXCL12 in CRC could improve the clinical outcomes of the patients. An ongoing clinical trial evaluating the safety and efficacy of anti-CXCL12 (NOX-A12) in patients with advanced-stage pretreated metastatic CRC and pancreatic cancer (OPERA trial, Keynote-559; ClinicalTrials.gov identifier, NCT03168139) is expected to give an answer.

In the present meta-analysis, the HRs of the included datasets for the association between CXCL12 and survival outcomes were all >1 except for one dataset (Kim *et al* 2022; no PCRT) (30), which showed the HRs for the association were <1. Sensitivity analyses performed by excluding these datasets showed that it did not significantly affect the results (OS: HR, 1.79; 95% CI, 1.38-2.34; P<0.001; I^2, 18%; PFS: HR, 2.12; 95% CI, 1.58-2.84; P<0.001; I^2, 22%). However, between-study heterogeneity was slightly reduced, as evidenced by reduced I^2 for both OS and PFS after removing the datasets, suggesting that this dataset at least partly explains the source of the heterogeneity. The reasons for the discrepancy between this dataset and the other included studies are currently unknown. In the study by Kim *et al* (30), it was shown that a higher expression level of CXCL12 may be associated with poor PFS in patients with CRC who received PCRT, but not in those who did not receive PCRT, suggesting that the association between CXCL12 and the survival of patients with CRC may be modified by the different treatment modalities. However, the present study was unable to determine the influence of anticancer modality on the aforementioned association in this meta-analysis, as most of the included studies did not provide stratified results according to the treatment modalities. Large-scale studies are needed to determine if the association between CXCL12 levels and the survival of patients with CRC is consistent in patients who receive different anticancer treatments.

The present meta-analysis also has certain limitations. Firstly, although the statistical heterogeneity observed in both the outcomes of OS and PFS was not significant (both I^2 values of 33%), there may be clinical heterogeneity among the included studies, which could be a result of differences in patient comorbidities, anticancer treatments and methods for measuring CXCL12. Furthermore, as an outcome of patients with cancer, PFS is highly associated with the cancer stage and treatments. Although the HRs for PFS were pooled with the most adequately adjusted models in individual studies in order to minimize the influence of possible confounding factors on the association, the results may be confounded by differences of study characteristics such as cancer stages and treatment modalities. However, pooling the data of HRs for PFS in prognostic meta-analyses has been well applied in previous studies (44-46). In addition, most of the included studies were retrospective, which may confound the results by possible recall and selection biases. Large-scale prospective cohort studies are needed to confirm the findings of the present study. Finally, a causative association between high tumor expression levels of CXCL12 and poor survival in patients with CRC could not be derived from the present study, as it is a meta-analysis based on observational studies. As aforementioned, clinical trials are warranted to determine the possible influence of anti-CXCL12 on clinical outcomes in patients with CRC.

In conclusion, results of the meta-analysis indicated that a higher tumor expression level of CXCL12 is associated with the poor survival of patients with CRC. Studies are warranted to determine if CXCL12-targeted intervention could improve the prognosis of patients with CRC.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SZ and GL designed the study, searched the literature, evaluated the study quality, extracted the study data, performed statistical analyses and interpreted the results. SZ drafted the manuscript. GL critically revised the manuscript. SZ and GL confirm the authenticity of all the raw data. Both authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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