

## Original Article

# Prognostic significance of higher CXCR2 expression in digestive system cancers: a systematic review and meta-analysis

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**Abstract:** Although CXCR2 chemokine receptor-2 (CXCR2) expression has been associated with several common cancers, the more important question is whether higher CXCR2 expression influences overall survival (OS) and recurrence-free survival (RFS) rates of digestive system cancers (DSCs). This has not been explicated thoroughly. Therefore, the current meta-analysis was conducted to investigate whether higher CXCR2 expression is associated with DSCs prognosis, including esophageal cancer (EC), gastric cancer (GC) and other cancers. Twelve relevant studies, involving a total of 2,250 cancer cases (333 EC, 970 GC, 711 HC, and 236 other cancer cases), were finally included in this study. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) for OS in higher and lower CXCR2 categories from individual studies were extracted. They were pooled using a random-effects model. Overall HRs of EC, GC, and other DSCs for OS of higher CXCR2 expression were 2.06 (95% CI = 1.31-2.80), 1.95 (95% CI = 1.47-2.43), and 1.58 (95% CI = 1.30-1.86), respectively. Combined cases of all DSCs with higher CXCR2 expression were at increased risk for OS (HR = 1.72, 95% CI = 1.48-1.95) and RFS (HR = 1.31, 95% CI = 1.01-1.61). The current meta-analysis shows decreased OS and RFS rates among all DSC survivors with higher CXCR2 expression. Higher CXCR2 expression may be an important prognostic factor, indicating decreased survival rates in EC and GC.

**Keywords:** CXCR2, digestive system cancers, overall survival, recurrence-free survival

## Introduction

According to recent statistics from the American Cancer Society, cancer is a leading cause of mortality, worldwide. Digestive system cancers (DSCs) are dangerous, accounting for high morbidity and mortality rates [1]. In 2017, 310,440 new DSC cases, including esophageal cancer (EC), gastric cancer (GC), hepatic cancer (HC), and pancreatic cancer (PC), were expected, with 157,700 estimated deaths in the United States every year [2]. CXCR2 chemokine receptor-2 (CXCR2) is a primary receptor of the CXCR superfamily, with a high affinity for chemokines [3]. This chemokine-receptor is expressed on cell membranes of tumor cells, which can promote tumor cell proliferation and invasion, as well as tumor tissue angiogenesis. They regulate the association between tumor cells and extracellular matrix, immune cells, and drug resistance [4-7]. CXCR2 has been associated with the biological behavior of tumors in EC [8],

GC [9], HC [10], PC [11], and CRC [12]. Several studies have researched the relationship between CXCR2 expression and DSCs. However, inconsistent results have been reported by studies concerning the relationship between CXCR2 expression and mortality among DSC survivors [8-10, 13-15]. Moreover, some studies have suggested that significant association was found between higher CXCR2 expression and overall mortality of EC, GC, HC, and other DSC cancers [8, 11, 16]. In contrast, some studies showed no obvious association of CXCR2 with outcomes of EC [13] and GC [9, 14]. Most results were not statistically significant. Recently, Yang et al. conducted a meta-analysis, showing that higher CXCR2 shortened OS rates of solid tumor patients [17]. Furthermore, cancer survivors need evaluation on prognostic factors. Thus, CXCR2 is an important research question influencing survival and recurrence of certain patients. The current systematic review and meta-analysis was conducted to clarify the

relationship between higher CXCR2 and survival among EC, GC, and other DSC patients. Moreover, this study summarized the evidence, analyzing higher category versus the lower category of CXCR2 and OS and RFS for all above mentioned cancers.

## Materials and methods

### *Literature retrieval*

Two authors, systematically, searched PubMed, Embase, the Cochrane Library, and other relevant databases to identify suitable studies from the earliest available date to March 20, 2018. Keywords included “esophageal cancer”, “gastric cancer”, “hepatocellular carcinoma”, “gallbladder cancer”, “pancreatic cancer”, “colon cancer”, “rectal cancer”, “colorectal cancer”, “digestive system cancer”, “digestive system tumor”, “digestive system neoplasm”, “gastroenterological cancer”, “gastroenterological tumor”, “gastroenterological neoplasm”, “gastrointestinal cancer”, “gastrointestinal tumor”, “gastrointestinal neoplasm” combined with “CXC chemokine receptor-2”, “CXC chemokine receptor”, and “CXCR2”. Boolean logic words were jointly used to combine keywords. Present researchers browsed and retrieved potentially eligible studies. Reference lists of retrieved articles and reviews were checked for further relevant studies. Disagreements were resolved by group discussion.

### *Literature inclusion and exclusion criteria*

Inclusion criteria: (1) Compared OS of EC, GC, and other DSCs patients with different CXCR2 ranges; (2) Presented an association estimate with 95% CI or survival curves; and (3) Only articles written in English were included. Full texts of all potentially eligible studies were retrieved. References were carefully browsed to find other studies that met inclusion criteria. When the same patient population was reported in several publications, only the most complete study was included. Eligible studies were searched by two authors, independently, finally reaching a consensus.

### *Quality assessment*

Evaluation analysis was carried out, independently, by two authors after assessment of full texts. A third person was involved to resolve

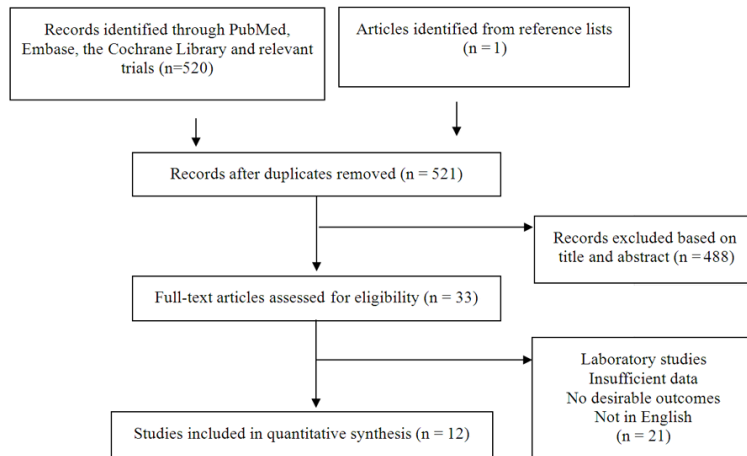
disagreements in the scores, reaching a consensus. The Newcastle Ottawa scale (NOS), recommended by the Cochrane Non-Randomized Studies Methods Working Group, was used in this meta-analysis for quality assessment [18]. Quality evaluation contained eight items, categorized into three dimensions, including selection of exposure and non-exposure cohort participants, comparability, and outcomes and follow-ups of the cohort. Studies with a score of  $\geq 6$  were considered adequately conducted.

### *Data extraction*

Information from included studies was independently extracted by two authors. Disagreements were resolved by consensus. Extracted data from eligible studies included: First author, year, country, study type, duration, sample size, patient age, gender, cancer type, histology, high expression of CXCR2, both univariate HRs (95% CI) and multivariate HRs (95% CI) of OS and RFS from each CXCR2 category, and confounding factors. If the data above was not referred to in original articles, the items were deemed as “NA”. When only Kaplan-Meier survival curves were provided in the original texts, Engauge Digitizer version 2.11 software was used to extract relevant numerical values from survival curves and to calculate HRs (95% CI) [19].

### *Statistical analysis*

This meta-analysis was performed to evaluate reported OS and RFS rates of digestive system cancers with CXCR2 categories. Higher and lower CXCR2 groups were compared to assess survival differences of EC, GC, and other DSCs. A random-effects model was used to perform analysis of pooled HRs with 95% CIs in cases with significant heterogeneity. Univariate HRs were used instead if multivariate HRs were not available during analysis. Multivariate HRs with 95% CIs were commonly adopted to estimate all included studies. Forest plots were formed to visualize study-specific effect sizes and 95% CIs [20]. Subgroup analysis of the higher versus lower CXCR2 category and OS of DSC patients included geographic area (China or Japan), histology [adenocarcinoma (AC) or squamous cell carcinoma (SCC)], number of patients ( $< 150$  or  $\geq 150$ ), cancer stage (stage I-III or I-IV), cut-off



**Figure 1.** Flowchart for inclusion of studies in the meta-analysis.

scores (immunoreactivity score or others), and adjustment for covariates (yes or no). Sensitivity analysis was carried out by excluding one study at a time, assessing whether the summary estimates were robust to inclusion of studies. When the 95% CI of HR did not overlap 1, the result was regarded as statistically significant. Pooled HR < 1 suggests that the higher CXCR2 group had worse prognosis than the lower group for DSC patients. In contrast, pooled HR < 1 suggests the higher CXCR2 group showed a more favorable survival. Heterogeneity was assessed by  $Q$  and  $I^2$  statistics.  $I^2$  values of < 25%, 25%-50%, and  $\geq$  50% indicates low, moderate, and high levels of heterogeneity, respectively [21]. Publication bias was evaluated by Begg's funnel plots and Egger's regression asymmetry test.  $P < 0.05$  indicates statistical significance. All  $P$  values were 2-sides. STATA version 12.0 software (Stata Corporation, College Station, TX) was used to perform all analyses. Ethical approval and patient consent was not required for the current meta-analysis.

## Results

### Identification of relevant studies

The initial literature search retrieved 520 potential eligible studies, based on established search strategies. An additional eleven records were identified from reference lists. The remaining 33 full texts were assessed for eligibility after excluding laboratory studies, duplicates, irrelevant articles, and other unsuitable objects. Because HRs and 95% CRs could not be extracted or calculated, some articles were excluded. In total, 12 articles were included in

this meta-analysis according to inclusion criteria (**Figure 1**). For studies included, four types of tumors were combined and evaluated: esophageal [8, 13, 22], gastric [9, 14-16, 23], hepatic [10, 24], pancreatic [11], and colorectal cancer [12].

### Study characteristics and quality assessment

All included articles were published between 1997-2014. Nine studies were distributed in China. The remaining 3 studies were from Japan. All eligi-

ble studies were retrospective. Tumor histology of the 9 studies was adenocarcinoma. The case number of 5 included studies was more than 150 cases, while the remaining 7 had less than 150 patients. All studies provided OS rates of cancer patients and CXCR2 expression, while 3 studies referred to RFS rates. More than half of the studies provided multivariate HRs and 95% CIs. Multivariate results were adjusted by age, gender, tumor size, lymph node metastasis, TNM stage, tumor differentiation, treatment, and other covariates. According to qualitative assessment criteria, all studies scoring  $\geq 6$  were considered adequately conducted (**Table 1**).

### Higher CXCR2 expression shortens OS of EC, GC, and other DSCs

Association of CXCR2 expression with OS of EC was presented in 3 retrospective studies (**Figure 2**). Pooled HR for higher CXCR2 expression of EC patients was 2.06 (95% CI = 1.31-2.80). This analysis was conducted with a low level of heterogeneity,  $I^2 = 6.6\%$  and Pheterogeneity = 0.343. The studies of Nishi et al., Sui et al., and Wu et al. contributed to 24.0%, 38.45%, and 37.55% of overall HR, respectively. Five retrospective studies involved association of CXCR2 expression and OS of GC (**Figure 3**). Pooled HR for higher CXCR2 expression of GC patients was 1.95 (95% CI = 1.47-2.43). Heterogeneity levels of this analysis were low (Pheterogeneity = 0.833). The study of Xiang et al. and Yang et al. contributed to 8.08% and 1.79% of overall HR, respectively. Additionally, two liver cancer studies, one pancre-

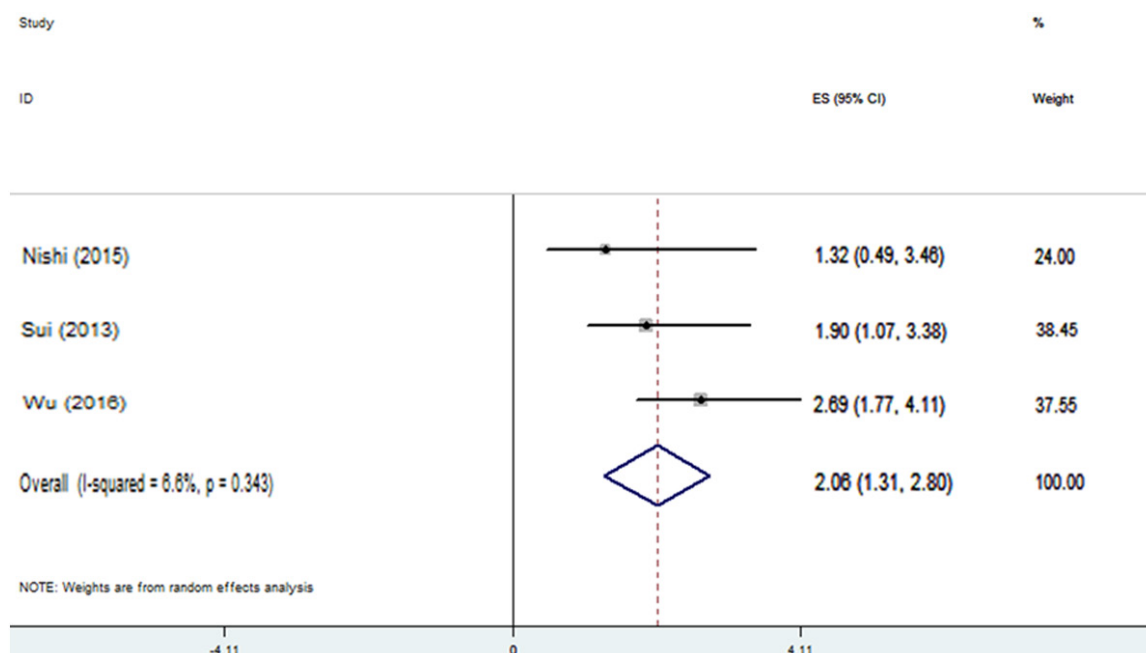
## CXCR2 and digestive system cancers

**Table 1.** Characteristics of relevant studies on higher CXCR2 expression and survival of DSC patients included in the meta-analysis

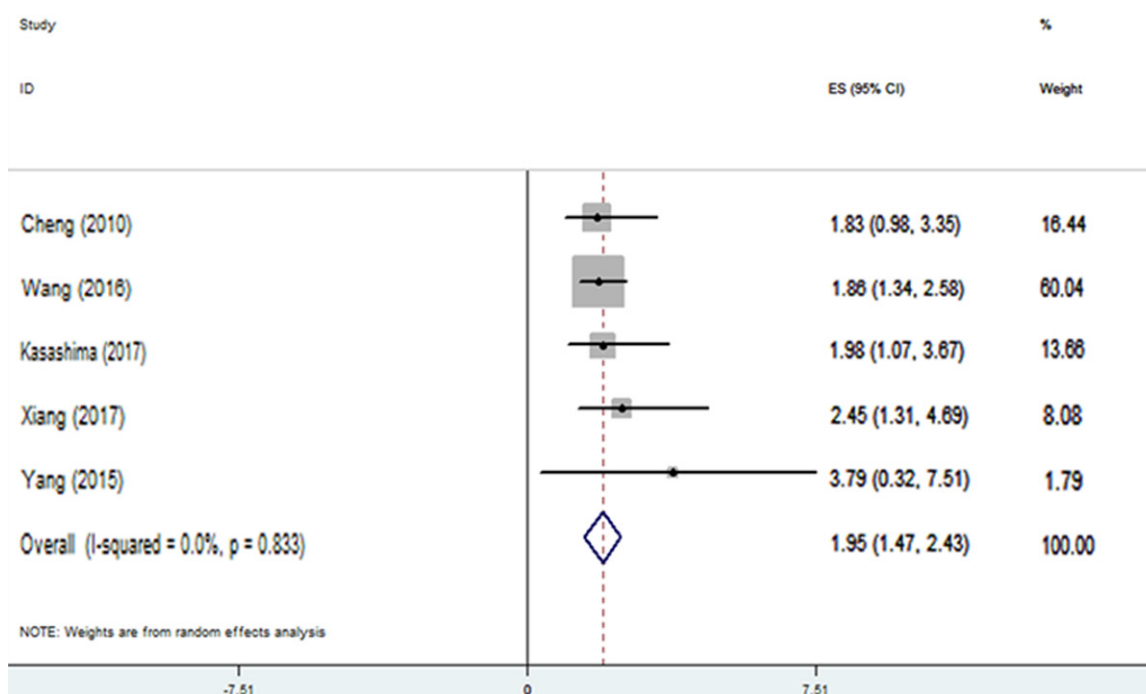
Study	Coun-try	Study Type	Duration	Size	Age* (range)	Gender (M/F)	Cancer Type	Stage	His-tology	High Ep-ression (%)	Cut-off Value	UV HR (95% CI) of OS	MV HR (95% CI) of OS	HR (95% CI) of RFS	Covariates	Quality Score	
Sui, 2013	China	Retrospec-tive study	2008	95	NA	78/17	Esophagus	I-III	SCC	55 (57.9%)	IRS ≥ 8	NA	1.90 (1.07, 3.38)	NA	Age, Gender, Lymph node metastasis, Tumor dimension, TNM stage	6	
Nishi, 2015	Japan	Retrospec-tive study	1997-2002	82	59 (44-81)	73/9	Esophagus	I-III	SCC	33 (40.2%)	+/-	1.32 (0.49, 3.46)	NA	1.62 (0.87, 2.86)	NA		6
Wu, 2016	China	Retrospec-tive study	2008-2014	156	67 (48-86)	91/65	Esophagus	I-III	SCC	74 (47.4%)	> 30% of cell stained	2.69 (1.77, 4.11)	NA	NA	NA		7
Cheng, 2010	China	Retrospec-tive study	2000-2005	116	NA	65/51	Stomach	I-IV	AC	61 (52.6%)	H-score > 90	1.83 (0.98, 3.35)	NA	NA	NA		6
Yang, 2015	China	Retrospec-tive study	2009-2014	112	NA	75/37	Stomach	I-IV	AC	64 (57.14%)	> 30% of cell stained	NA	3.79 (0.32, 7.51)	NA	Age, TNM stage, Depth of invasion, IL-22BP expression, Lymph node metastasis	8	
Wang, 2016	China	Retrospec-tive study	2008	357	59 (27-85)	250/107	Stomach	I-IV	AC	200 (56.0%)	H-score > 200	NA	1.86 (1.34, 2.58)	NA	T stage, Lymph node metastasis, Distant metastasis, Lauren clas-sification	8	
Kasashi-ma, 2017	Japan	Retrospec-tive study	NA	270	NA	116/154	Stomach	I-IV	AC	113 (41.9%)	IRS ≥ 4	NA	1.98 (1.07, 3.67)	NA	Lymphatic invasion, He-patic metastasis, Venous invasion, Peritoneal metastasis and cytology	6	
Xiang, 2017	China	Retrospec-tive study	2007-2009	115	NA	74/41	Stomach	I-IV	AC	67 (58.3%)	IRS > 6.7	2.45 (1.31, 4.69)	NA	NA	NA		7
Li, 2015	China	Retrospec-tive study	2007-2010	259	52 (13-79)	226/33	Liver	I-IV	AC	129 (49.8%)	Median	NA	1.74 (1.17, 2.59)	1.36 (0.99, 1.87)	Age, Gender, HBsAg, Cirrhosis, ALT, AST, AFP, Tumor size, Tumor differ-entiation, Vascular inva-sion, Tumor multiplicity, TNM stage, BCLC stage	7	
Zhou, 2015	China	Retrospec-tive study	2007-2008	452	NA	387/65	Liver	I-IV	AC	226 (50.0%)	Median	NA	1.54 (1.17, 2.03)	NA	AFP, GGT, Liver cirrhosis, Tumor size, Micro-vacular invasion, Tumor encapsulation, Tumor differentiation	6	
Maeda, 2017	Japan	Retrospec-tive study	2006-2011	102	NA	67/35	Pancreas	I-IV	AC	63 (61.8%)	≥ 50% of cell stained	1.54 (1.15, 2.05)	NA	1.20 (0.84, 1.74)	NA		7
Zhao, 2017	China	Retrospec-tive study	2010-2011	134	NA	74/60	Colorec-tum	I-IV	AC	82 (61.2%)	IRS ≥ 6	NA	4.26 (1.47, 12.31)	NA	Dukes stage	8	

SCC = squamous cell carcinoma, AC = adenocarcinoma, M = male, F = female, UV = univariate, MV = multivariate, HR = hazard ratio, 95% CI = 95% confidence interval, ALT = alanine aminotransferase, IRS = immunoreactivity score, AST = aspartate aminotransferase, GGT = glutamyl transpeptidase, AFP = alpha-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, IL-22BP = interleukin-22 receptor 2, NA = not available. \*Median or mean age.

## CXCR2 and digestive system cancers



**Figure 2.** Forest plot shows hazard ratios and 95% CIs for higher CXCR2 expression and overall survival of esophageal cancer.



**Figure 3.** Forest plot shows hazard ratios and 95% CIs for higher CXCR2 expression and overall survival of gastric cancer.

atic cancer study, and one colorectal cancer study were included in the analysis of CXCR2 expression and survival of cancer patients (Figure 4). Pooled HR of the four studies for

higher CXCR2 expression was 1.58 (95% CI = 1.30-1.86). A low level of heterogeneity was found ( $I^2 = 0\%$ , Pheterogeneity = 0.754). The study of Zhao et al. contributed to 0.28% of



overall HR, while the total weight of other three studies was 99.72%.

#### *Higher CXCR2 expression shortens OS of all DSCs with multivariate results*

Seven studies concerning higher versus lower CXCR2 expression and mortality of all DSCs with multivariate results were combined and analyzed (**Figure 5**). EC, GC, HC, and CRC patients with higher CXCR2 expression survived for shorter lengths of time, with a 72% higher risk of death (HR = 1.72, 95% CI = 1.42-2.01) and quite low heterogeneity ( $I^2 = 0\%$ ,  $P_{\text{heterogeneity}} = 0.779$ ), compared with the lower CXCR2 category. Studies of Zhou et al., Wang et al., and Li et al. contributed to 47.25%, 22.73%, and 17.33% of overall HR, respectively.

#### *Higher CXCR2 expression shortens OS of all DSCs*

The current meta-analysis was also performed on overall survival rates of all DSCs from higher and lower CXCR2 groups (**Figure 6**). Compared with the lower CXCR2 category, all DSC patients with higher CXCR2 expression survived for shorter lengths of time, with a 72% higher risk of death (HR = 1.72, 95% CI = 1.48-1.95). Heterogeneity of studies during this analysis was quite low ( $I^2 = 0\%$ ,  $P_{\text{heterogeneity}} = 0.756$ ). Studies of Zhou et al. and Maeda et al. contributed to 29.03% and 26.51% of overall HR, respectively.

#### *Higher CXCR2 expression shortens RFS of all DSCs*

Three included studies provided information concerning the association of CXCR2 expression with RFS of all DSCs (**Table 1**). Pooled HR for higher CXCR2 expression of DSC patients was 1.31 (95% CI = 1.01-1.61). Low heterogeneity was observed in this analysis,  $P_{\text{heterogeneity}} = 0.722$ . Studies of Maeda et al., Li et al., and Nishi et al. contributed to 46.48%, 44.43%, and 9.09% of overall HR, respectively (**Figure 7**).

#### *Subgroup analysis, sensitivity analysis, and publication bias*

Subgroup analysis was conducted for further analysis of included studies. It was found that, compared with the lower CXCR2 category, the higher category showed statistically significant

negative effects on OS of DSC patients in all subgroups (**Table 2**). Regarding the higher versus lower CXCR2 category and OS of DSC patients, there was significant association found for geographic area [China (HR = 1.79; 95% CI = 1.51, 2.07) or Japan (HR = 1.57; 95% CI = 1.16, 1.98)], histology [squamous cell carcinoma (SCC) (HR = 2.06; 95% CI = 1.31, 2.80) or adenocarcinoma (AC) (HR = 1.68; 95% CI = 1.43, 1.92)], number of patients [ $< 150$  (HR = 1.67; 95% CI = 1.30, 2.04) or  $\geq 150$  (HR = 1.75; 95% CI = 1.45, 2.04)], cancer stage [stage I-III (HR = 2.06; 95% CI = 1.31, 2.80) or I-IV (HR = 1.68; 95% CI = 1.43, 1.92)], cut-off scores [immunoreactivity score (HR = 2.09; 95% CI = 1.32, 2.85) or others (HR = 1.68; 95% CI = 1.44, 1.92)], and adjustment for covariates [yes (HR = 1.72; 95% CI = 1.42, 2.01) or no (HR = 1.75; 95% CI = 1.33, 2.17)].

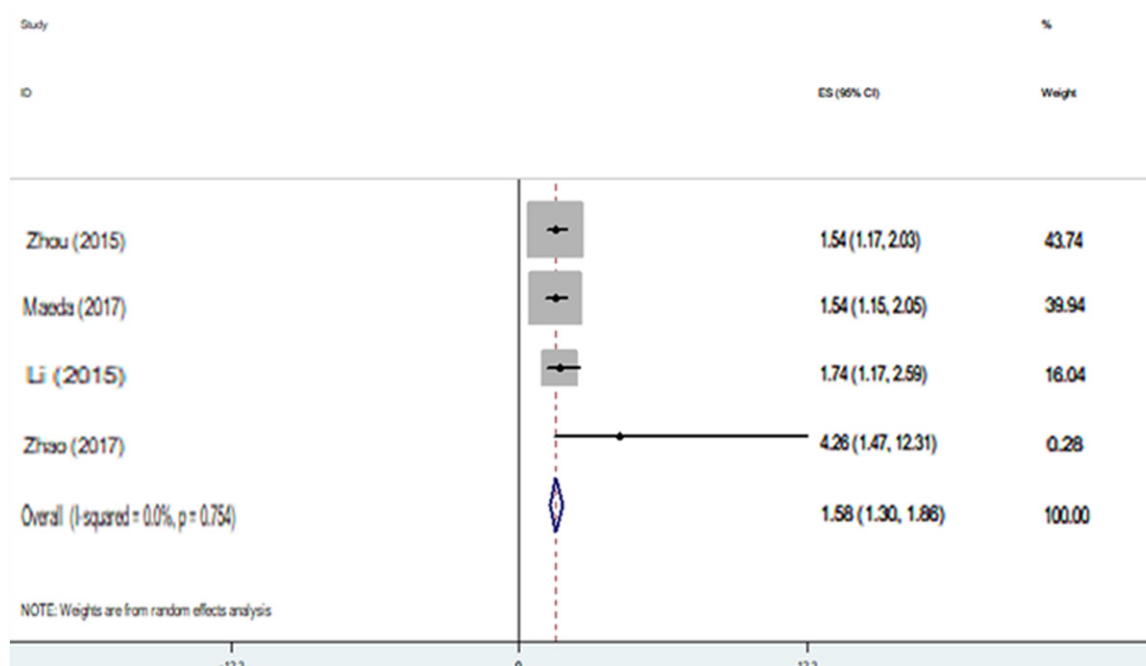
According to sensitivity analysis, excluding a single study per time and analyzing the rest of the articles, there were no significant changes in pooled HRs and 95% CIs. Begg's funnel plot and Egger's regression tests to assess publication bias. The funnel plot for OS and higher CXCR2 category of EC, GC, other cancers, and all DSC patients showed no asymmetry (**Figure 8**). Begg's test for the higher versus lower CXCR2 category and RFS of all DSCs failed to reveal any significant publication bias (**Figure 8**). Moreover, Egger's regression testing for all groups suggested no obvious publication bias.

#### **Discussion**

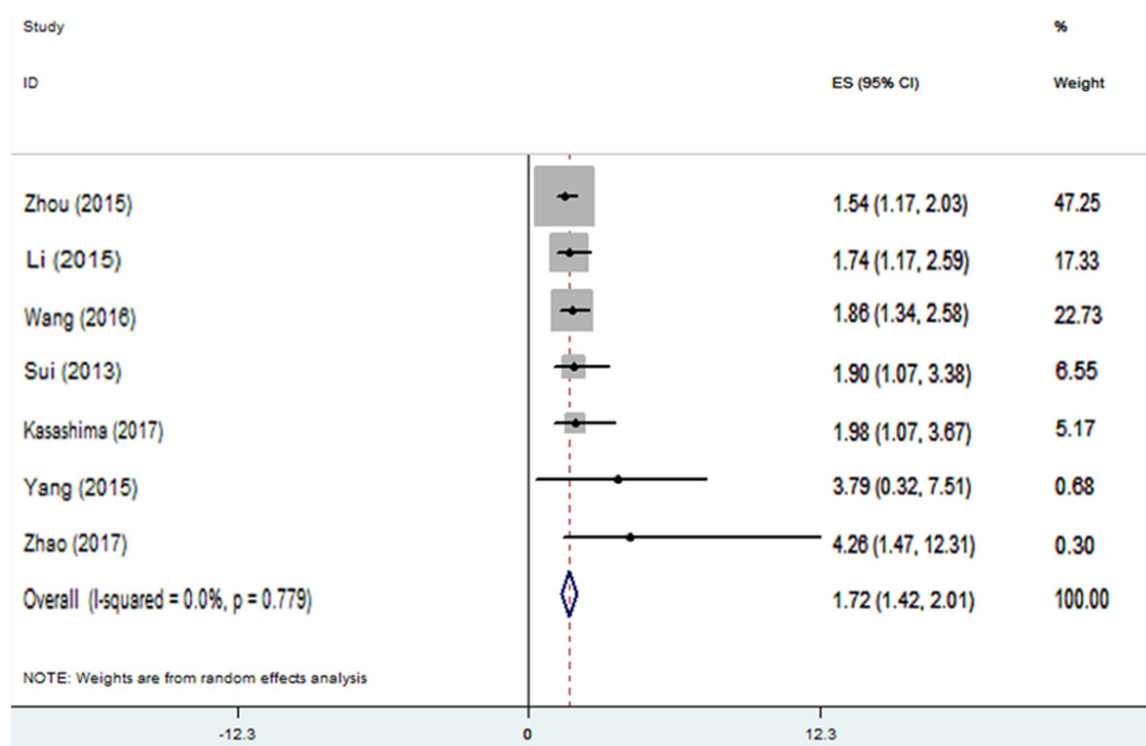
CXC chemokines are secreted by various cells in vivo and primarily induce leukocyte accumulation in lesions and sites of inflammation [25]. As a receptor, CXCR2 might play a critical role in tumor progression. Activating the CXCR2 receptor, most ELR+ CXC chemokines increase the penetration of immunosuppressive cells, reduce apoptosis, and promote angiogenesis, as well as contributing to tumor cell proliferation, migration, and invasion [5-7].

The dispute over the relationship between CXCR2 and survival rates from gastrointestinal cancer has lasted for decades. One recently published meta-analysis evaluated the association of CXCR2 with OS, RFS, and DFS of solid tumors [17]. Yang et al. found that higher CXCR2 could significantly damage the survival of solid tumor survivors, compared with the lower CXCR2 category (HR = 1.82, 95% CI = 1.63-

## CXCR2 and digestive system cancers



**Figure 4.** Forest plot shows hazard ratios and 95% CIs for higher CXCR2 expression and overall survival of other cancers.



**Figure 5.** Forest plot shows hazard ratios and 95% CIs for higher CXCR2 expression and overall survival of digestive system cancers by multivariate analysis.

2.03). However, detailed consideration of higher CXCR2 and mortality of DSC patients was

missed in their study [17]. Studies from Nishi et al., Cheng et al., and Yang et al. suggested that

## CXCR2 and digestive system cancers

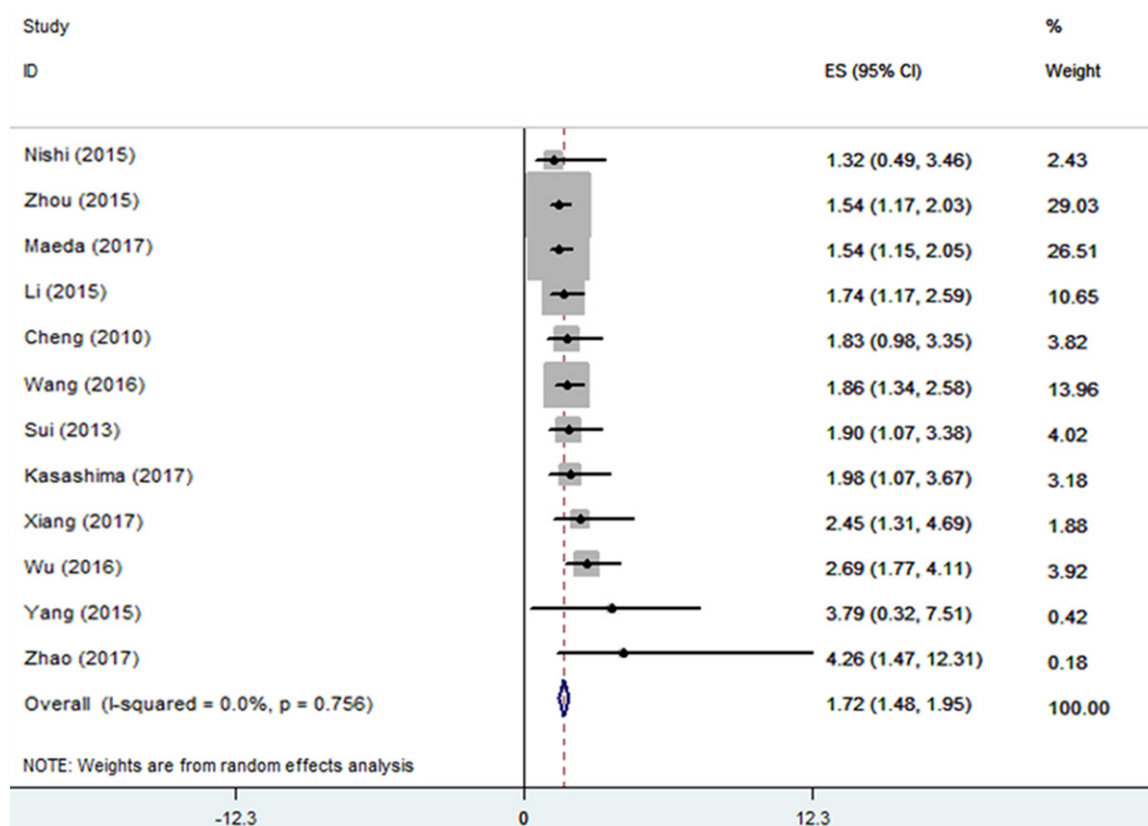


Figure 6. Forest plot shows hazard ratios and 95% CIs for higher CXCR2 expression and overall survival of all digestive system cancers.

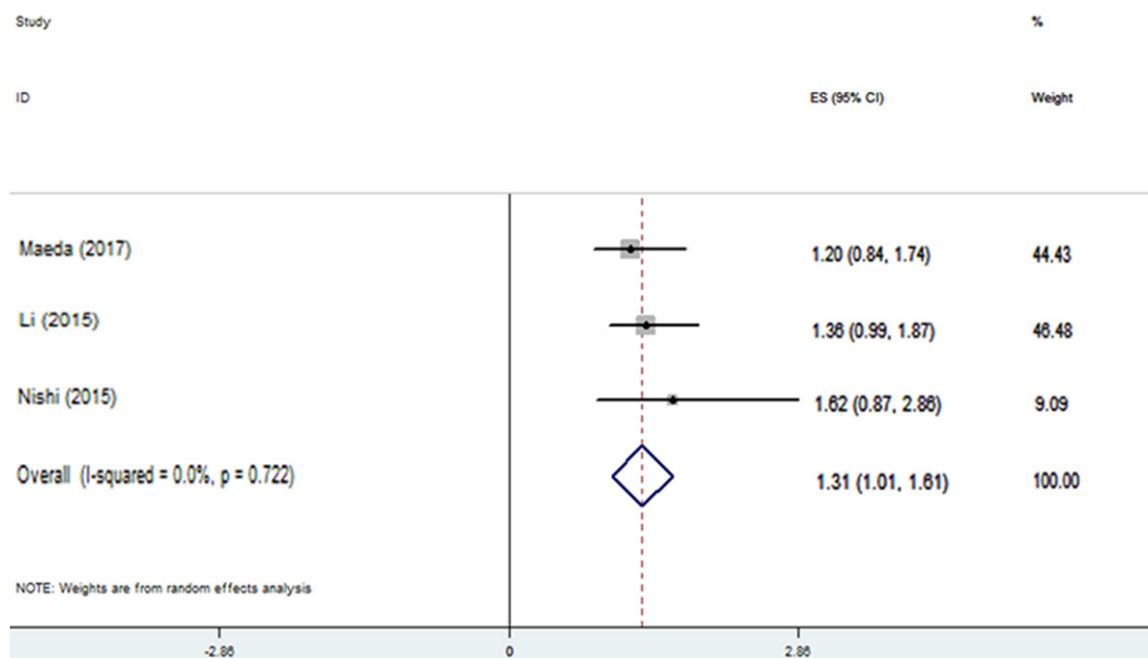


Figure 7. Forest plot shows hazard ratios and 95% CIs for higher CXCR2 expression and recurrence-free survival of all digestive system cancers.



**Table 2.** Random-effects summary estimates of hazard ratios of the association of overall survival of DSC patients with higher CXCR2 expression

	Study	HR (95% CI)	P <sub>heterogeneity</sub>
Region			
China	9	1.79 (1.51, 2.07)	0.619
Japan	3	1.57 (1.16, 1.98)	0.776
Histology			
SCC	3	2.06 (1.31, 2.80)	0.343
AC	9	1.68 (1.43, 1.92)	0.821
Number of patients			
< 150	7	1.67 (1.30, 2.04)	0.705
≥ 150	5	1.75 (1.45, 2.04)	0.457
Cancer stage			
I-III	3	2.06 (1.31, 2.80)	0.343
I-IV	9	1.68 (1.43, 1.92)	0.821
Cut-off			
Immunoreactivity score	4	2.09 (1.32, 2.85)	0.820
Others	8	1.68 (1.44, 1.92)	0.587
Adjusted for covariates			
Yes	7	1.72 (1.42, 2.01)	0.779
No	5	1.75 (1.33, 2.17)	0.369

SCC = squamous cell carcinoma, AC = adenocarcinoma, HR = hazard ratio.

higher CXCR2 is not associated with increased overall morbidity of DSC patients [9, 13, 14]. Therefore, the current meta-analysis was conducted to reveal the prognostic roles of higher CXCR2 on OS and RFS from DSC patients, including EC, GC, HC, PC, and CRC. CXCR2 expression is easily acquired. Clear effects of CXCR2 on survival may aid in the prognosis of cancers. Prognostic effects of higher CXCR2 on EC, GC, and other DSC cancers have been researched. However, the roles of CXCR2 on mortality rates of cancers from the digestive system remain unclear, although some meta-analyses concerning BMI and mortality of solid tumors have been reported.

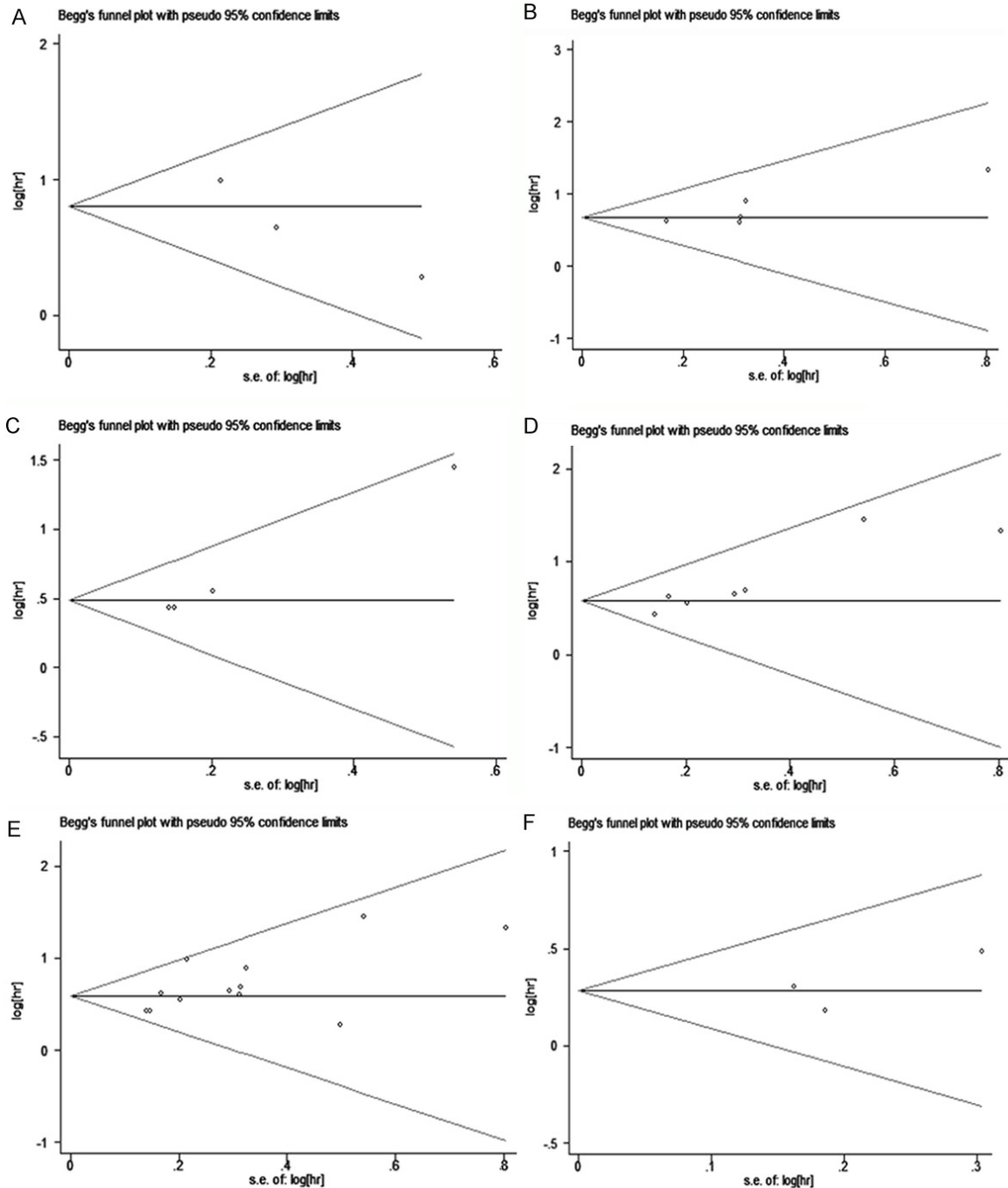
Multivariate results were provided by seven included studies. The remaining five studies only conducted univariate analysis. All articles with multivariate results of OS were combined. The pooled HR was 1.72 (95% CI = 1.42-2.01). Some studies with univariate outcomes were adapted to achieve more credible pooled results. All 12 studies were included, estimating the higher versus lower CXCR2 and overall mortality rates of all DSC survivals. Because of intense research on CXCR2, EC, and GC, sever-

al studies of EC and GC on higher BMI and OS were included, conducting analysis separately. Results of EC (HR = 2.06, 95% CI = 1.31-2.80) and GC (HR = 1.95, 95% CI = 1.47-2.43) were consistent with all DSC patients. Outcomes revealed that patients with higher CXCR2 had higher mortality rates from EC and GC cases.

To further demonstrate the predictive value of higher CXCR2 and OS of DSC patients, subgroup analyses for covariates adjusting were performed. Analysis results of different regions, histology, sample sizes, cancer stages, cut-off values, and adjustments for covariates showed significant association between the higher CXCR2 group and OS of DSC patients, compared with the lower group. Combined analysis of studies from China and Japan revealed consistent results. Pooled HR levels were 1.79 (95% CI = 1.51-2.07) and 1.57 (95% CI = 1.16-1.98), respectively. Analyzing the histology of SCC and AC, the association between higher versus lower CXCR2 and OS of DSC

survivals was statistically significant (HR were 2.06 and 1.68, separately). Additionally, meaningful results were obtained from studies that were both adjusted (HR = 1.72, 95% CI = 1.42-2.01) and unadjusted (HR = 1.75, 95% CI = 1.33-2.17) for covariates. Nine studies included in this meta-analysis referred to tumor grades from I to IV in DSC cases. Combined results revealed that higher CXCR2 may have less influence on stage IV (HR = 1.68, 95% CI = 1.43-1.92), compared to I to III stages (HR = 2.06, 95% CI = 1.31-2.80).

Potential mechanisms of the effects of higher CXCR2 on DSC patients have not been clarified and elucidated thoroughly. Activation of CXCR2 mainly induces PI3K/Akt/GSK-3 $\beta$ /Snail signaling pathways to promote tumor cell invasion and metastasis [24]. Previous reports have demonstrated that the blockade of CXCR2 can significantly retard DSC tumor progression by inhibiting tumor angiogenesis [26]. Additionally, blockade of CXCR2 signaling pathways can significantly enhance the effects of chemotherapy in colon tumor survivals [27]. CXCR2 can also modulate cell cycle regulatory proteins and inhibit cellular apoptosis, promoting tumor cell



**Figure 8.** Begg's funnel plot test for higher CXCR2 expression and survival of digestive system cancers. (A: esophageal cancer, B: gastric cancer, C: other cancers, D: multivariate studies, E: overall survival, F: recurrence-free survival).

proliferation [5]. Moreover, CXCR2 can induce the accumulation of inflammatory cells. This is closely related to the development of DSC tumors. Therefore, CXCR2 overexpression could be associated with poor prognosis of DSC patients. Further thorough studies are necessary to explore the mechanisms behind the

relationship between higher CXCR2 and survival rates of certain cancers.

The current study is the first meta-analysis evaluating the effects of higher CXCR2 on OS and RFS from EC, GC, and other DSCs. Low heterogeneity, analysis of several types of cancer,

adjustments of covariates, and summarized evidence of single studies were the strengths of this study. However, there were several limitations. Different cut-off CXCR2 values from included articles may have significantly influenced pooled results. Although three included studies were from developed countries, techniques, devices, therapies, and other factors may have restricted research. Comprehensive and through analysis requires more research information from developing countries. Except for GC, the number of included articles about EC was limited. Therefore, combined results of GC or EC may be inaccurate.

Treatment strategy and tumor stage may have influenced mortality rates of the general population and overall survival rates of digestive system cancers. However, most included studies did not provide detailed information about these factors. In addition, some usual covariates for survival rates of cancer cases, including lymph node metastasis, tumor grade, and differentiation, were not adjusted for in some studies. Compared with prospective studies, lower clinical evidence levels and more uncontrollable biases found in retrospective studies may have affected current results. Therefore, this analysis was conducted using as many multivariate data factors as possible. The current analysis could not avoid selection bias, however, because inclusion of participants depended on survival times. Additionally, the number of severe cases was less than the actual proportion in cancer patients.

In conclusion, the current research indicates that higher CXCR2 expression decreased overall survival and recurrence-free survival rates of DSC patients. Additionally, higher CXCR2 expression showed negative association with survival rates of EC and GC patients. Therefore, CXCR2 expression may become an important predictor of mortality rates of EC, GC, and other DSCs. In the future, blockade of CXCR2 receptors might contribute to novel cancer treatments.

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### Disclosure of conflict of interest

None.

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