Predictive Role of CC-Chemokine Ligand 2 in Digestive System Cancers: A Meta-Analysis

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Research

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Abstract

Background: CC-chemokine ligand 2 (CCL2) expression as a prognostic factor in digestive system cancers (DSCs) is inconclusive.

Methods: Thus, our aim was to summarize the prognostic role of CCL2 in DSCs. Electronic database was carefully searched. Studies focusing on CCL2 expression as a prognostic marker in DSCs were included for analysis. Pooled data for survival outcomes and clinical features were recorded in terms of the hazard ratio (HR) or odds ratio (OR) and the 95% confidence interval (CI).

Results: In all, 1,458 patients with DSCs from 11 studies were included for analysis. The pooled data revealed that high CCL2 expression group was more easy to occur the presence of distal metastases (OR = 3.83, 95% CI: 1.98–7.38, $P < 0.001$), severer tumor invasion (OR = 2.38, 95% CI: 1.31–4.34, $P = 0.005$), and advanced Tumor Nodal Metastasis stages (OR = 2.47, 95% CI: 1.12–5.45, $P = 0.02$). Moreover, poorer overall survival (HR = 2.09, $P < 0.001$) were observed in the group with high CCL2 expression. High levels of CCL2 also indicated dismay disease-free survival (HR = 1.87, $P = 0.005$).

Conclusions: Our findings indicate that CCL2 can serve as a prognostic indicator in DSCs.

Introduction

Digestive system cancers (DSCs) are highly common malignant neoplasms[1]. DSCs include cancers derived from the digestive tract and accessory organs digestive system[2]. Despite improvements in diagnosis and management, the survival of patients with DSCs is dismay. Generally, the pathological Tumor Nodal Metastasis (pTNM) staging may predict the prognosis of patients with cancer[3]. However, different prognosis may occur in patients with the same pTNM stage. Hence, the development of novel molecular markers are urgently required in clinic.

CC-chemokine ligand 2 (CCL2) was reported and purified in 1989[3–6], its functions in tumor development and progression has been widely investigated[7, 8]. However, the prognostic functions of CCL2 expression in tumor is inconclusive[9] and should be further explored. Moreover, different views were existed for the CCL2 as a prognostic factor in DSCs[10, 11]. Thus, we performed a comprehensively search and pooled data to explore the prognostic role of CCL2 in DSCs.

Methods

Electronic database search

We conducted the meta-analysis using the guidelines as previously described [12]. EMBASE Web of Science, and PubMed databases were applied for searches. Paper that focusing on CCL2 expression as a predictive marker in DSCs were identified. The keywords (cancer, chemokine (C-C motif) ligand 2, prognosis) were applied for information searches. The searches were performed on March 1, 2019. Furthermore, additional searches were required to screen the references of the included studies for meta-analysis. The searching, screening and selecting were done by two independent researches (Z.Z and G.L.).

Criteria for studies included and excluded

A study included for data analysis should meet the following criteria: a, the diagnosis of DSCs were confirmed by pathology; b, the study was reported in English and published as a full paper form; c, CCL2 levels was a prognostic factor for survival outcomes, including disease-free survival (DFS) or overall survival (OS); the exclusion criteria included the following items: a, letters, comments, reviews, basic research studies were excluded; b, studies with survival outcomes but the hazard ratio (HR) could not be measured were excluded.

Data and information extraction

Two independent reviewers (Z.Z and G.L.) extracted the data and recorded in a standard form. The data was provided as follows:

1. authors, the published years, the locations, sample sizes, patients' ages, the methods for CCL2 detection, the cut-off values, and the description of followed-up.

2. Survival outcomes including OS and DFS
3. Any correlations reported between CCL2 and clinical characteristics (tumor status, lymph node status, distal metastasis status, and TNM stages).

Quality assessment

The quality of included studies was detected with the Newcastle–Ottawa scale (NOS), as we previously described[13]. The scores were given ranged from zero to nine, after judgment the studies' quality. The score value ≥ 6 was certified to high quality. Two independent reviewers (M.Y and G.L.) evaluated the quality of each study. Any disagreement was solved by the third investigator(F.Y)[14].

Statistical analysis

The following software were adopted :RevMan (version 5.3; Nordic Cochrane Centre) and STATA (version 12.0). Hazard ratio(HR) and 95% confidence interval (CI) value were used for description of survival outcomes [13]. Odd ratios (ORs) and 95% CIs were applied to record relationships between CCL2 levels and clinicopathologic features. Heterogeneity was measured with I^2 tests,as we previously described[15–17]. In cases where $I^2 < 25\%$, we used a fixed-effects model. Otherwise, a random-effects model was applied[17].A P value less than 0.05 was regard as a significant difference. We also conducted a sensitivity analysis and subgroup analysis [17]. Moreover, we evaluated publication bias with Egger's test [17, 18].

Results

The search and selection flowchart is presented in Fig. 1,according to the PRISMA guideline. After our electronic database search,we retrieved 660, 902, and 1035 studies from PubMed, Web of Science, and EMBASE, respectively. No additional articles were found by screening the references cited in the included studies. NoteExpress software was applied for removing repeated references (n = 1075). After screening titles and abstracts, 48 studies were selected for full text screening.Finally, eleven studies involving 1,458 patients met the inclusion criteria[19–29]. The minimal sample sizes was 50, and the maximal sample sizes was 414. Six studies focused on colorectal cancer[19;20,24,25,27,28],three (all from China) focused on gastric cancer[23, 26, 29], one focused on hepatic cancer[22],one focused on esophageal carcinoma[21],and one focused on pancreatic cancer[24].The years of publication were between 2003 to 2017. The basic characteristic parameters of the included papers and quality scores were outlined in Table 1. OS was reported for 10 studies, and only two studies mentioned of DFS[20, 28].

Table 1
The information of included studies and quality assessment

Study	country	Sample sizes	Ages	Cancer types	Methods of detection	Cut-off values	Outcomes	Follow-up time or description	Quality assessment scores
Chen 2014	china	176	58(21–89)	CRC	Elisa	$\geq 450\text{pg/ml}$	OS	19.6(3–80)	6
DiCaro 2016	Italy	54	NA	CRC	Elisa	ROC values	DFS	56.33 ± 15.74	5
Koide 2004	Japan	56	NA	ECSS	IHC	> 10%	OS	NA	5
Li 2015	China	147	NA	HCC	IHC	NA	OS	NA	4
Liu 2015	China	414	60.28 ± 11.73	GC	IHC	optical density 123.3	OS	42.5	7
Monti 2003	Chile	150	NA	PC	Elisa	> 91ng/ml	OS	15.87 ± 8.53	6
Szczepanik 2015	Poland	45	65.4 ± 9.2	CRC	Elisa	103.21 pg/ml	OS	NA	6
Tao 2014	China	50	49.82(24–59)	GC	IHC	5	OS	1–84	7
Watanabe 2008	Japan	101	65.2	CRC	Elisa	Ca/N Ratio ≥ 1.8	OS	68.4m for surviving patients and 15.9 m for deceased patients	6
Yoshidome 2009	Japan	87	NA	CRC	IHC	> 10%	OS,DFS	30 (8-115)	6
Zhang 2017	China	178	NA	GC	IHC	5	OS	NA	5

CRC, Colorectal cancer; GC, gastric cancer ESCC,esophageal squamous cell carcinoma; NA,not available; OS,overall survival; DFS,disease-free survival; IHC, Immunohistochemical; Ca/N, cancer/Normal; PC, Pancreatic cancer; HCC, hepatic cell carcinoma.

High Ccl2 Expression Predicted A Worse Os In Dscs

CCL2 was a independent predictive factor in patients with colorectal cancer[19:25:27:28]. Furthermore, CCL2 as a prognostic marker was evaluated in gastric cancer, pancreatic cancer,liver cancer and esophageal carcinoma. As outlined in Fig. 2A, an HR of 2.09 (95% CI: 1.77 to 2.48, a P value less than 0.001) indicated that high CCL2 expression predicted a worse OS, based on the pooled data from ten studies[19, 21–29]. Considering the low heterogeneity($I^2 = 12$, $P = 0.33$), a fixed-effect model was adopted for data analysis.

High Ccl2 Expression Predicted A Worse Dfs In Dscs

A study leading by Giuseppe Di Caro group indicated that circulating

CCL2 can predict the disease recurrence[20]. Another study also reported that CCL2 can predict disease metastasis in patients suffered from colorectal cancer[28].Furthermore, high CCL2 expression was found to correlate with an unfavorable DFS, based on

pooled data from two studies[20, 28].The analysis was conducted using a fixed-effect model (HR value was 1.87, 95% CI: 1.21 to 2.88, P = 0.005, Fig. 2B), without heterogeneity ($I^2 = 0$, P = 0.81).As a result, the analysis was conducted using a fixed-effect model.

The Correlation of CCL2 expression and clinicopathological variables in DSCs

Furthermore, the relationship between **clinicopathological features and CCL2 levels was explored**. The group with high CCL2 expression showed a correlation with deeper tumor invasion (a value of OR was 2.38, 95% CI: 1.31 to 4.34, a P value was 0.005; Fig. 3A), based on analysis performed using a random effect model (moderate heterogeneity was detected). CCL2 expression did not significantly correlate with lymph node metastasis (Fig. 3B). Moreover, CCL2 expression was related with distal metastasis (a OR value was 3.83, 95% CI: 1.98 to 7.38, P < 0.001; Fig. 3C) and an advanced TNM stage (a OR value was 2.47, 95% CI: 1.12–5.45, P = 0.02; Fig. 3D). These results are summarized in Table 2.

Table 2
Meta-analysis assessing the relationship between prognostic nutritional index and clinicopathological variables

Characters	Studies	Sample sizes	Pooled OR	P value	Heterogeneity	
					I^2	P
Tumor depth (T3 + T4/T1 + T2)	3	636	2.38 (1.31,4.34)	0.005	46	0.16
Lymph node metastasis (positive/negative)	5	794	1.72 (0.73,4.05)	0.21	81	0.0003
Distal metastasis (M1/M0)	3	648	3.83 (1.98,7.38)	<0.001	0	0.38
TNM stage (III + IV /I + II)	3	660	2.47 (1.12,5.46)	0.02	76	0.02

Sensitivity Analysis And Subgroup Analysis

To confirm the stability of the findings, we conducted sensitivity analyses. The analysis was conducted by detecting the effects of omitting any single study on the OS. The results were reliable, as shown in Fig. 4. Furthermore, we conducted subgroup analyses based on the locations, publication years, sample sizes, detection methods, cancer types, and NOS scores. Meta-regression analysis was also performed to detect the sources of heterogeneity. The results are presented in Table 3.In all of subgroup analyses, the increased of CCL2 level was related with a worse OS, which indicated the reliability of the results.

Table 3

Subgroup and meta-regression assessing high CCL2 expression and overall survival in patients with digestive system cancers

Items	No. of studies	Poor HR and its 95% CI	Z value	P value	Heterogeneity		Meta regression p value
					I ² (%)	P	
country							0.809
East	8	2.21 (1.76, 2.78)	6.77	< 0.001	26	0.22	
West	2	2.02 (1.25, 3.28)	2.85	0.004	0	0.42	
Publish year							0.732
≥ 2015	5	2.20 (1.6, 2.99)	5.01	< 0.001	50	0.09	
< 2015	5	2.28 (1.63, 3.18)	4.82	< 0.001	0	0.77	
Sample sizes							0.386
≥ 100	6	2.12 (1.62, 2.77)	5.48	< 0.001	42	0.13	
< 100	4	2.53 (1.70, 3.77)	4.57	< 0.001	0	0.92	
Primary cancer (CRC v.s. GC and others)							0.866
Colorectal cancer	4	2.15 (1.55, 2.99)	4.58	< 0.00001	2	0.38	
Gastric cancer	3	1.94 (1.54, 2.44)	5.65	< 0.00001	0	0.55	
Other cancer	3	2.57 (1.40, 4.71)	3.06	0.02	58	0.09	
Quality scores							0.150
≥ 6	7	1.92 (1.58, 2.34)	6.47	< 0.001	0	0.66	
< 6	3	2.74 (1.71, 4.38)	4.20	< 0.001	43	0.17	
Detection methods							0.688
Elisa	4	1.91 (1.40, 2.61)	4.10	< 0.001	0	0.55	
IHC	6	2.34 (1.77, 3.09)	5.97	< 0.001	35	0.18	

Publication bias in regard to OS was measured as previously described[18]. The results are shown in Fig. 5 (Begg's test, $P=0.088$; Egger's test, $P=0.035$). Because the P value of 0.035 revealed potential publication bias, the "trim and fill" test was conducted. A symmetrical funnel plot was achieved by imputing data from four studies (Fig. 6). The results also indicated that increased CCL2 level related with a worse OS (HR = 1.881, 95% CI = 1.609–2.199).

Discussion

Our data suggested that high levels of CCL2 were related with poorer OS (HR value was 2.09, $P < 0.001$) and DFS (HR value was 1.87, $P = 0.005$) in patients with DSCs. Furthermore, higher CCL2-expression levels correlated with the presence of distal metastasis (OR = 3.83, $P < 0.001$), deeper tumor invasion (OR = 1.94, $P = 0.005$), and more advanced TNM stages (OR = 2.47, $P = 0.02$).

Our study indicated that increased CCL2 level was correlated with worse OS in patients with DSCs. High CCL2 expression also predicted poorer survival in patients with breast cancer[30], prostate cancer[31], and other cancers[32]. The underlying mechanism whereby high CCL2 levels lower survival is not fully understood. The underlying mechanism might be as follows. In cancer cells, some signaling molecules are involved in regulating constitutive CCL2 production[33], these signaling molecules including nuclear factor of κ B[34], specificity protein 1, and KRAS[35]. Moreover, the level of CCL2 was positive associated with CD68 + macrophages

and inflammatory mediators, which up-regulated the expression of CCL2[36]. Furthermore, stromal cells also contributed to CCL2 production via normal cell–tumor cell interactions[33].In additional, CCL2 plays key roles in cancer progression and metastasis by recruiting tumor-associated macrophages[37–39]. CCL2 was also associated with angiogenesis in cancer[37–39].The results of our study indicated that CCL2 was associated with unfavorable clinical variables (such as advanced TNM stages, the presence of distant metastasis, and deeper tumor invasion).Molecularly targeted therapy is an important antitumor strategy[40].Preclinical cancer models and clinical trials were conducted to assess the effect of CCL2-targeting therapy[41–44].Administering an anti-CCL2 monoclonal antibody reduced 96% of the tumor burden in an animal model of prostate cancer[41].Management with an anti-CCL2 monoclonal antibody also improved survival in animal with glioma[45].Retrospective data from a clinical trial indicated that treatment with effective drugs suppressed CCL2 levels and improved DFS in patients with live metastasis of colorectal cancer[46].

This study had some limitations. First, all papers involved in study were retrospective studies, there were none randomized controlled trials, and selection bias or publication bias may have occurred.Second, the methods for measuring the CCL2 levels varied between the included studies and the cut-off values were not uniform; thus, heterogeneity might have existed. Third, some analyses existed significant heterogeneity. The heterogeneity might have been caused by individual patients with different tumor types, country locations, cut-off values, and follow-up times. Additional analysis were adopted to identify the source of heterogeneity but failed to identify the source. Fourth, as described above, the analysis involved publication bias as determined by performing a bias test, the results indicated that high CCL2 expression was still associated with worse OS. Fifth, the results of this study indicated that the CCL2-expression level was not related to the lymph node status; however, as small number of studies analyzed and the overall sample size, more studies should be performed to evaluate this issue.

In conclusion, CCL2 can serve as a prognostic factor in DSCs. High CCL2 expression was predictive of a worse OS and DFS. Furthermore, CCL2 expression correlated with TNM stages,the presence of distant metastasis, and lymph node metastasis. More randomized controlled trials should be conducted to investigate the predictive role of CCL2 expression in DSCs in the future. Clinical trials focusing on targeted therapy for CCL2 should be conducted to explore the effects of anti-CCL2 treatment.

Abbreviations

CCL2:CC-chemokine ligand 2, CI:confidence interval , DFS: disease-free survival, DSCs: Digestive system cancers , HR :hazard ratio, OR:odds ratio , OS:overall survival.

Declarations

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None.

Disclosure

Availability of data and materials

The data in this manuscript were all provided in the tables and texts.

Authors' contributions

Guixiang Liao ,Zhihong Zhao and Yuxiang Fu provided manuscript writing, data searched and data analysis. All authors corrected and proofed the final text.

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Ethics approval

The study did not need ethics approval.

Competing interests:

The authors declare that they have no competing interests.

Consent for publication

None.

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Figures

Figure 1

The flowchart of study selection.

Figure 3

Forest plot of odds ratio(OR) for the relationship between CCL2 expression and clinicalpathological features: (A) tumor invasion;
(B) lymph node metastasis; (C) distal metastasis; (D) TNM stages.

Figure 4
Sensitivity analysis by omitted every single study.

Figure 5

Publication bias evaluated by Begg's test

Figure 6

Funnel plots with "trim and fill."

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMAChecklist.doc](#)