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Original Article

Expression of chemokine receptor CXCR7 in colorectal carcinoma and its prognostic significance

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Abstract: Previous studies have shown that chemokine receptor CXCR7 plays critical roles in tumor development. However, the clinicopathological and prognositic significance of CXCR7 in colorectal carcinoma (CRC) has not been fully understood. The aim of our study is to investigate the expression of CXCR7 and its clinical significance in CRC. First, quantitative RT-PCR and Western blot assays were performed to determine the expression of CXCR7 mRNA and protein in 20 paired of CRC tissues and corresponding adjacent non-tumor tissues. Next, immunohistochemistry was performed to detect the expression of CXCR7 protein in another 96 cases of CRC tissues, and analyze its correlation with clinicopathological factors of patients. Finally, the correlation of CXCR7 with 5-year overall survival (OS) and progression free survival (PFS) was statistically analyzed by the Kaplan-Meier method and Cox proportional hazards model. Results showed that the expression levels of CXCR7 mRNA and protein were significantly higher in CRC tissues than in normal tissues. Positive CXCR7 expression was observed to be significantly correlated with lymph nodal metastasis ($P < 0.001$), distant metastasis ($P = 0.017$), and advanced TNM stage ($P < 0.001$). Patients with positive expression of CXCR7 were demonstrated to be associated with worse OS and PFS ($P < 0.001$, $P < 0.001$, respectively). Moreover, multivariate survival analysis revealed that CXCR7 expression level might be an independent predictive factor for OS and PFS of CRC patients. Collectively, positive CXCR7 expression in CRC was correlated with tumor development and poor prognosis of patients.

Keywords: Colorectal carcinoma, immunohistochemistry, CXCR7, overall survival, progression free survival

Introduction

Colorectal carcinoma (CRC) is one of the most lethal malignancies with the third highest rates of cancer-related morbidity and mortality worldwide, which accounts for 9% of all newly diagnosed cancer cases and 9% of all cancer-related deaths [1]. In China, the incidence of CRC has been increasing and its mortality rate has been the fifth leading cause of cancer-related death [2]. Although great progress has been made in early diagnosis and combined treatment of CRC, the prognosis of patients remains poor owing to the high rate of recurrence and distant metastasis [3-5]. The carcinogenesis of CRC is considered to be a spectrum of sequential steps involving multiple factors and signaling pathways [6]. However, the precise molecular mechanisms underlying CRC development remain incompletely understood. Thus, elucidation of the molecular mechanisms underlying CRC development will contribute to indentifying novel prognostic markers and developing more effective therapeutic strategies for CRC patients.

Chemokine receptor CXCR7 (initially named Receptor Dog cDNA1 or RDC1), belonging to the chemokine receptor family, has been identified as a novel receptor for CXCL12 (also known as stromal-derived factor-1 or SDF-1) [7, 8]. As a membrane-associated receptor, CXCR7 is rarely expressed on normal somatic cells. Whereas, it is highly expressed on activated endothelial cells, fetal liver cells, plancenta and tumor cells [8, 9]. Recently, the roles of CXCR7 in tumorigenesis are increasingly reported. Burns et al reported that MBA-MB 435s cells transfected

with CXCR7 proliferated more rapidly compared with wild-type MBA-MB 435s cells [8]. Miao et al found that CXCR7 promoted growth of tumors formed in a mouse mode of lung cancer and influenced experiment metastasis of lung [10]. Meanwhile, CXCR7 is reported to be highly expressed in aggressive colon carcinoma and associated with tumor growth [11]. The tumor volumes in the mouse mode of CRC treat ed with small hairpin RNA-mediated lentiviral vector were significantly smaller than those of the control group [12]. However, the prognostic value of CXCR7 expression in CRC is not fully understood and remains to be further elucidated.

In the present study, we performed quantitative RT-PCR (qRT-PCR), Western blot and immunohistochemistry assays to investigate the expression of CXCR7 in CRC tissues and corresponding adjacent non-tumor tissues, and then analyze its correlation with clinicopathological factors and prognosis of CRC patients.

Materials and methods

Patients and tissue specimens

A total of 96 cases of CRC tissues and another 20 paired of CRC tissues and corresponding adjacent normal tissues were collected from the Department of Pathology and Department of Surgery of Jinling Hospital between March 2006 and December 2008. None of the patients received any preoperative treatment, including chemotherapy and radiotherapy. All of them were administrated to receive postoperative chemotherapy including XELOX and FOLFOX regimens. Tumor stage was defined based on the criteria proposed by the International Union Against Cancer (UICC). The patient population consisted of 57 male and 39 female individuals. Their clinical data were obtained from medical records and follow-up examinations, which continued from the date of operation to the date of death or the end of the study in September 2014. The data of patients who were lost to follow-up or died from diseases other than CRC were considered censored data in the survival analysis. The tissues used for qRT-PCR and Western blot assays were rapidly frozen in liquid nitrogen and stored at -80°C until use. Written informed consent was obtained from all the patients, and the study was approved by the Ethics Committee of Jinling Hospital prior to initiation.

Quantitative RT-PCR

Total RNAs were isolated from tissues using TRIzol reagent (Invitrogen, CA, USA) and then reverse-transcribed into cDNA in a 20 μL reaction system. The expression of CXCR7 mRNA was detected by qRT-PCR with SYBR Green Mix kit according to the manufacturer's protocol. The primers for CXCR7 were 5'-CTATGACACGCACTGCTACATC-3' and 5'-CTGCACGAGACTGACCACC-3'. The primers for β-actin were 5'-ATGGAGGGGAATACAGCCC-3' and 5'-TTCTTTGCAGCTCCTTCGTT-3'. Data were quantified by densitometric analysis and normalized by the expression of β-actin gene as an endogenous control.

Western blot assay

Total proteins were extracted from tissues, separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to a polyvinylidene fluoride (PVDF) membrane. The membranes were incubated with the primary anti-CXCR7 antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA) at 4°C overnight, and then incubated with horseradish peroxidase-conjugated secondary antibody (Sigma, USA). The detection of protein was performed by enhanced chemiluminescence system.

Immunohistochemistry

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded primary tumor tissues and corresponding adjacent non-neoplastic tissues to investigate the expression of CXCR7. Sections (4 μm) were dried overnight at 69°C, dewaxed with xylene, and rehydrated through graded ethanol. Slides were then heated in a high-pressure cooker containing 10 mmol/L citrate buffer (pH 6.0), boiled, and cooled to room temperature for antigen retrieval. Endogenous peroxidase was blocked with 3% hydrogen peroxide for 20 min at room temperature. The slides were incubated overnight at 4°C with a primary mouse monoclonal anti-CXCR7 antibody (IgG1, Clone# 11G8, MAB-42273, R&D Systems, Inc., Minneapolis, MN 55413 USA) at 8 μg/mL, and then incubated with rabbit EnVision peroxidase-labeled polymer antibody (#K4011; Dako, Produktionsvej 42 DK-2600 Glostrup) for 30 min at room temperature. Finally, the specimens were developed with diaminobenzidine, counterstained with hematoxylin, and mounted. Negative con-

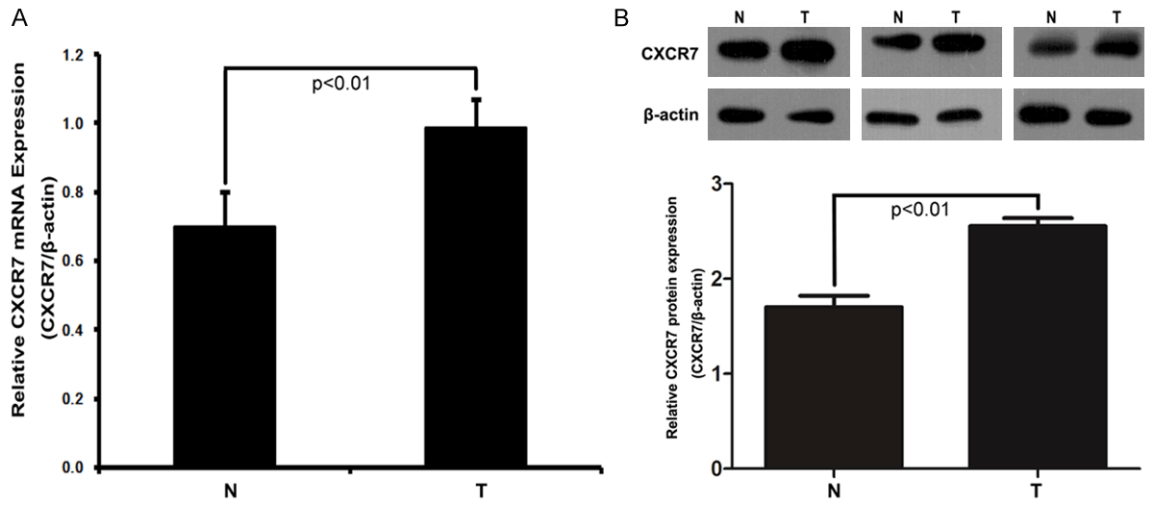

Figure 1. Expression of CXCR7 mRNA and protein in 20 paired of CRC tissues (T) and corresponding adjacent normal tissues (N) by qRT-PCR and Western blot. The relative expression of CXCR7 mRNA (A) and protein (B) was significantly higher in CRC tissues than in normal tissues, $P < 0.01$. β-actin was used as an internal control.

trols were performed by replacing the primary antibody with normal non-specific murine IgG. Immunostaining of CXCR7 was evaluated independently using a semi-quantitative method by two experienced clinical pathologists who were blinded to the clinical data. The immunostaining intensity and the percentage of positive cells were assessed in at least 10 selected fields. The mean percentage of positive cells was categorized into four classes: 0 (< 5%), 1 (5-10%), 2 (10-50%), 3 (50-75%) and 4 (> 50%). The intensity of immunostaining was rated as follows: 0 (no coloring), 1 (slightly yellow), 2 (brown staining), and 3 (tan staining). The final staining score was calculated as the product of these two scores, ranging from 0 to 12. CXCR7 expression was regarded as negative if the score was < 2, and positive if the score ≥ 2 [12].

Statistical analysis

Data for continuous variables were expressed as mean ± standard deviation (SD) and analyzed using one-way ANOVA. The chi-square tests were used to examine the differences between CXCR7 expression and clinicopathological factors. Overall survival (OS) and progression free survival (PFS) curves were constructed using the Kaplan-Meier method and compared by the log-rank test. The univariate and multivariate survival analysis were conducted by the Cox proportional hazards model. All analyses were performed using the SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA) and significance level was set as $P < 0.05$.

Results

Expression of CXCR7 is significantly upregulated in CRC tissues

First, qRT-PCR was performed to detect the expression of CXCR7 mRNA in 20 paired of CRC tissues and corresponding adjacent normal tissues. As shown in **Figure 1A**, the relative expression of CXCR7 mRNA in CRC tissues was significantly higher than that in the corresponding adjacent normal tissues ($P < 0.01$). Then, Western blot was performed to detect the expression of CXCR7 protein in above tissues, and it was observed that the relative expression of CXCR7 protein in CRC tissues was significantly higher than that in the corresponding adjacent normal tissues ($P < 0.01$; **Figure 1B**). Furthermore, immunohistochemistry was performed to detect the expression of CXCR7 protein in another 96 cases of CRC tissues, and showed that CXCR7 was predominantly expressed in the cytoplasm of CRC cells and tumor-associated blood vessel cells (**Figure 2C**, **2D**). This experiment was repeated twice and representative results are shown in **Figure 2**. The expression of CXCR7 was significantly higher in CRC tissues than that in normal tissues ($P < 0.001$), since the rate of CXCR7 positivity in CRC tissues and normal tissues was 64.6% (62/96) and 20.8% (20/96), respectively (**Table 1**). These results indicated that the expression of CXCR7 was significantly upregulated in CRC tissues than in normal tissues.

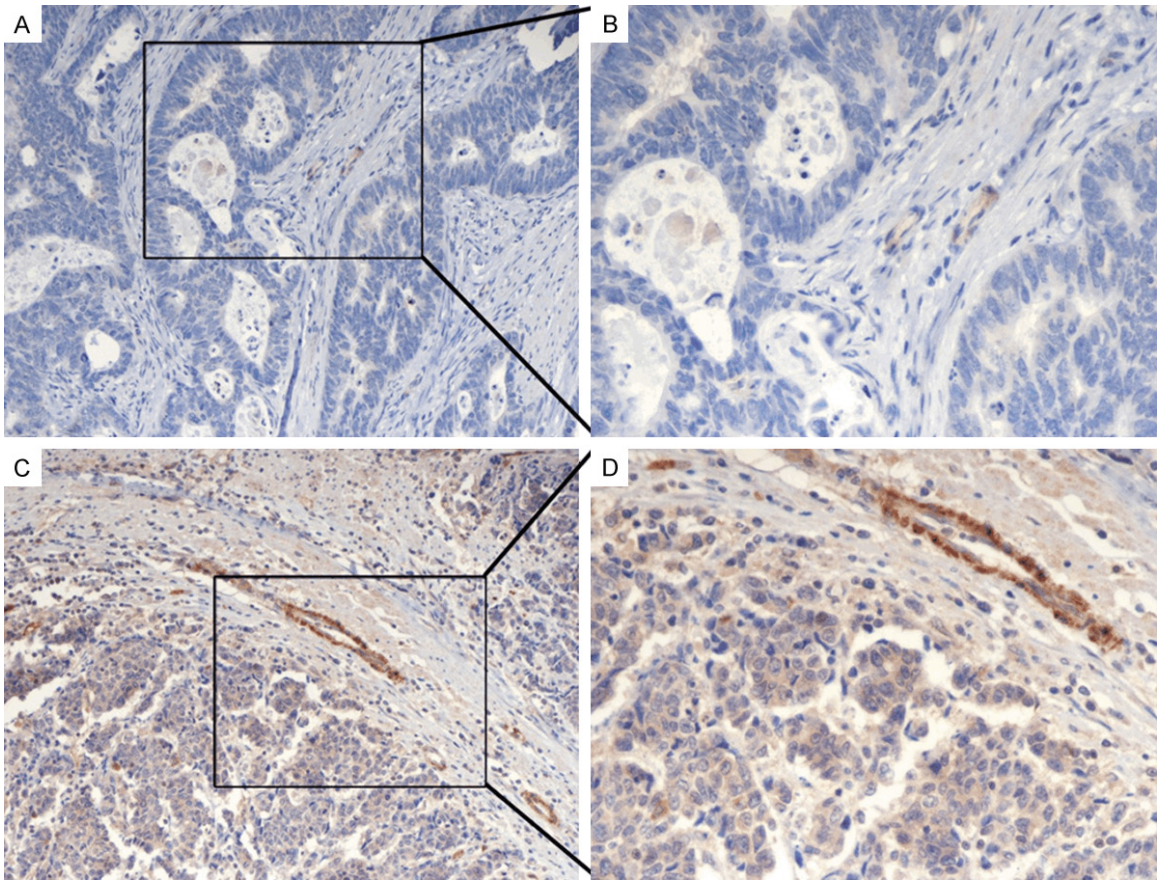

Figure 2. Expression of CXCR7 in 96 cases of CRC tissues by immunohistochemistry. A (200×) and B (400×) showed negative staining for CXCR7 expression. C (200×) and D (400×) showed positive staining for CXCR7 expression.

Table 1. Expression of CXCR7 in CRC and normal tissues

Group	Cases (N)	CXCR7 expression		Positive rate (%)	*P* value
		Negative	Positive		
CRC tissues	96	34	62	64.6	< 0.001
Normal tissues	96	76	20	20.8	

Correlation of CXCR7 expression and clinicopathological factors of CRC patients

Next, the correlation of CXCR7 expression with clinicopathological factors of CRC patients was investigated using the chi-square test. Statistical analyses showed that positive CXCR7 expression was significantly associated with lymph nodal metastasis ($P < 0.001$), distant metastasis ($P = 0.017$), and advanced TNM stage ($P < 0.001$). However, there was no significant correlation between CXCR7 expression and sex, age, tumor site, tumor size, or differentiation ($P = 0.606$, $P = 0.301$, $P = 0.050$, $P = 0.269$, $P = 0.057$, respectively; **Table 2**). Collectively, these results indicated that overexpression of CXCR7 might be associated with the malignant status of CRC.

Correlation of CXCR7 expression with prognosis of CRC patients

The correlation of CXCR7 expression with prognosis of CRC patients was analyzed by the Kaplan-Meier method, and compared by the log-rank test. Kaplan-Meier analysis based on CXCR7 expression is shown in **Figure 3**. It was observed that positive CXCR7 expression was significantly correlated with unfavorable 5-year OS and 5-year PFS ($P < 0.001$, $P < 0.001$, respectively; **Figure 3**). The OS rate of patients with positive CXCR7 expression was significantly lower than that of those with negative CXCR7 expression (30.2% vs. 79.4%; $P < 0.001$; **Figure 3A**). Likewise, the PFS rate of patients with positive CXCR7 expression was significantly lower than that of those with negative CXCR7 expres-

Table 2. Correlation between CXCR7 expression and clinicopathological factors of 96 patients with CRC

Factor	Cases (N)	CXCR7 expression		Positive rate (%)	*P* value
		Negative	Positive		
Sex					0.606
Male	57	19	38	66.7	
Female	39	15	24	61.5	
Age(years)					0.301
< 55	44	18	26	59.1	
≥ 55	52	16	36	69.2	
Tumor site					0.050
Colon	52	23	29	55.8	
Rectum	44	11	33	75.0	
Tumor size (cm)					0.269
< 5	44	13	31	70.5	
≥ 5	52	21	31	59.6	
Differentiation					0.057
Well	11	7	4	36.4	
Moderate	73	25	48	65.8	
Poor	12	2	10	83.3	
Lymph nodal metastasis					< 0.001
No	41	25	16	39.0	
Yes	55	46	46	83.6	
Distant metastasis					0.017
No	82	33	49	59.8	
Yes	14	1	13	92.9	
TNM stage					< 0.001
I/II	36	24	12	33.3	
III/IV	60	10	50	83.3	

sion (21.9% vs. 61.8%; $P < 0.001$; **Figure 3B**). Univariate analysis showed that tumor differentiation, lymph nodal metastasis, distant metastasis, TNM stage and the status of CXCR7 expression were significantly associated with OS ($P = 0.010$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, respectively; **Table 3**) and PFS ($P = 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, respectively; **Table 3**) of CRC patients. Then a multivariate Cox regression model showed that positive expression of CXCR7 was a valid independent predictor of OS ($P = 0.005$), because those patients with positive CXCR7 expression had a 4.426-fold (95% CI: 1.554-12.604) high risk of death (**Table 4**). Likewise, positive CXCR7 expression was also demonstrated to be an independent prognostic predictor of PFS, since those patients with elevated CXCR7 level had high risk of disease progress (HR: 2.700; 95% CI: 1.275-5.717; $P = 0.009$) (**Table 4**). Additionally, distant metastasis also had significantly prognostic influence on OS ($P < 0.001$) and PFS ($P < 0.001$; **Table 4**) of CRC patients.

Discussion

Chemokine receptors are a superfamily of G protein-coupled seven-transmemberane receptors and bind with their ligands with high affinity. At present, at least 20 chemokine receptors have been identified and they are classified into four groups (CCR, CXCR, XCR and CX3CR). The interaction of chemokine receptors and their ligands was initially discovered to mediate the process of infection and inflammation [13]. Recently, it has been increasingly proven to play important roles in tumor progression [14, 15]. For example, CXCR3 participates in the metastasis of several human cancers, such as CRC and breast cancer [16, 17]. CXCR4 is highly expressed in moreover 23 different types of cancer, including CRC, ovarian cancer, malignant melanoma and thyroid carcinoma [16, 18-20]. However, there are only a few studies on CXCR7 and its function. CXCR7 has been reported to be highly expressed in several kinds of human carcinomas and closely correlated with tumor proliferation and migration, and formation of tumor-associated vessels [10, 21-24]. As a scavenge receptor, CXCR7 fails to couple to G-protein receptor to induce intracellular Ca^{2+} mobilization like other chemokine receptors. CXCR7 may signal through β-arrestin and activate the phosphorylation of ERK kinases [25]. Wang et al showed that CXCR7 plays a role in survival, adhesion and invasiveness of tumor cells through the activation of AKT in prostate cancer [26]. Li et al found that knockdown of CXCR7 gene could repress the development of CRC through the ERK and β-arrestin pathways [12]. Systemic CXCR7 antagonists markedly reduced the preestablished metastases to lung from colon cancer [27]. These data indicate that CXCR7 might play a role in controlling progression of

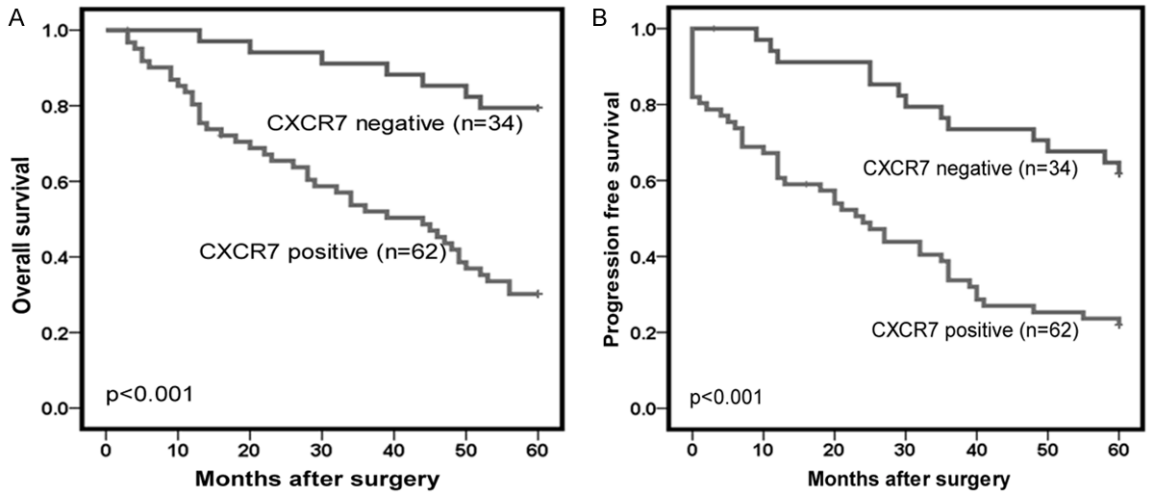

Figure 3. Kaplan-Meier curves for 5-year OS and PFS of CRC patients based on CXCR7 expression. Patients with positive CXCR7 expresssion had worse OS (A) and PFS (B) than those with negative CXCR7 expression, $P < 0.001$.

Table 3. Univariate analysis of clinicopathological factors associated with OS and PFS

Factor	OS			PFS		
	HR	95% CI	*P*	HR	95% CI	P
Sex (male/female)	0.705	0.402-1.236	0.222	0.673	0.404-1.120	0.127
Age (< 55/≥ 55 years)	0.922	0.525-1.619	0.777	0.961	0.578-1.598	0.878
Tumor site (colon/rectum)	0.722	0.411-1.268	0.257	0.743	0.447-1.236	0.253
Tumor size (< 5/≥ 5 cm)	0.877	0.500-1.537	0.646	0.747	0.448-1.246	0.263
Differentiation (poor/well+moderate)	2.598	1.257-5.368	0.010	3.068	1.571-5.992	0.001
Lymph nodal metastasis (Yes/No)	5.797	2.699-12.448	< 0.001	3.410	1.906-6.100	< 0.001
Distant metastasis (Yes/No)	8.816	4.460-17.425	< 0.001	6.851	3.527-13.308	< 0.001
TNM stage (III-IV/I-II)	11.842	4.237-33.100	< 0.001	4.550	2.396-8.641	< 0.001
CXCR7 (positive/negative)	6.144	2.606-14.487	< 0.001	3.722	1.966-7.046	< 0.001

Table 4. Multivariate Cox analysis of clinicopathological factors associated with OS and PFS

Factor	OS			PFS		
	HR	95% CI	*P*	HR	95% CI	*P*
Differentiation (poor/well+moderate)	0.578	0.251-1.331	0.198	0.493	0.226-1.075	0.076
Lymph nodal metastasis (Yes/No)	0.699	0.167-2.933	0.625	0.313	0.073-1.345	0.118
Distant metastasis (M1/M0)	7.020	2.909-16.941	< 0.001	7.492	3.095-18.137	< 0.001
TNM stage (III-IV/I-II)	3.878	0.710-21.179	0.118	0.776	0.166-3.624	0.747
CXCR7 (positive/negative)	4.426	1.554-12.604	0.005	2.700	1.275-5.717	0.009

CRC. However, the clinicopathological and prognostic value of CXCR7 is still unclear in CRC.

In the current study, we first investigated the expression of CXCR7 mRNA and protein in 20 paired of CRC tissues and corresponding adjacent normal tissues by qRT-PCR and Western blot. It was observed that the expression level of CXCR7 mRNA and protein was significantly higher in CRC tissues than that in corresponding normal tissues. Furthermore, we detected the expression of CXCR7 in another 96 cases of CRC tissues by immunohistochemistry and analyzed its association with clinicopathological factors or prognosis of patients. It was observed that CXCR7 expression was significantly associated with higher incidence of lymph nodal metastasis, distant metastasis and advanced TNM stage. These results suggested that CXCR7 might play a critical role in the development of CRC. Meanwhile, patients with positive CXCR7 expression had worse OS

and PFS than those with negative CXCR7 expression. Moreover, multivariate analysis with Cox proportional hazards demonstrated that status of CXCR7 expression was an independent predictive factor for OS and PFS of CRC patients. To the best of our knowledge, this is the first study to explore the prognostic value of CXCR7 in CRC. It was also observed that CXCR7 was mainly expressed in the cytoplasm of CRC cells and tumor-associated blood vessel cells, not in normal vascular cells, suggesting that CXCR7 might be indirectly involved in the formation of neovascularization. This result was consistent with studies in other cancers, such as lung cancer, hepatocellular cancer, prostate cancer and malignant brain cancer [10, 26, 28, 29]. Wang et al showed that CXCR7 upregulates the expression of proangiogenic growth factors such as interleukin-8 and vascular endothelial growth factor, and overexpression of CXCR7 in prostate cancer cells resulted in higher density of neovessels [26]. These results indicate that CXCR7 might play a role in the formation of tumor-associated vasculature and thus promote the development of CRC, but the exact molecular mechanism remains to be further studied.

Taken together, our study demonstrated that positive CXCR7 expression was significantly correlated with certain CRC clinicopathological factors, such as lymph nodal metastasis, distant metastasis and advanced TNM stage. The positive expression of CXCR7 linked to unfavorable OS and PFS of CRC patients. Therefore, CXCR7 may act as a novel predictive indicator for prognosis and even be a potential molecular target for anticancer therapies in CRC. Since the sample size involved in this study is smaller, further investigation is needed to confirm these results in a larger prospective study in future.

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Disclosure of conflict of interest

None.

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