

## Basic Study

# Clinicopathological significance of overexpression of interleukin-6 in colorectal cancer

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## Abstract

### AIM

To compare the expression levels of interleukin (IL)-6 in colorectal cancer (CRC) tissues and adjacent non-cancerous tissues, and analyse the correlation of IL-6 expression with the clinicopathological parameters of CRC.

### METHODS

Fifty CRC tissue specimens and 50 matched adjacent mucosa specimens were collected. The expression of IL-6 in these clinical samples was examined by immunohistochemical staining. The correlation between IL-6 expression and clinicopathological parameters was assessed by statistical analysis.

### RESULTS

IL-6 expression was significantly elevated in CRC tissues compared with noncancerous tissues ( $P < 0.001$ ). IL-6 expression was positively correlated with tumour TNM stage ( $P < 0.001$ ), but a negative correlation was detected between IL-6 expression and tumor histological differentiation in CRC ( $P < 0.05$ ). Furthermore, IL-6 expression was associated with invasion depth and lymph node metastasis in CRC.

### CONCLUSION

IL-6 might be a useful marker for predicting a poor prognosis in patients with CRC and might be used as a potential therapeutic target in CRC.

**Key words:** Colorectal cancer; Interleukin-6; Invasion

depth; Lymph node metastases

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**Core tip:** Colorectal cancer (CRC) is the fourth leading cause of cancer-related death worldwide. Previous studies have demonstrated that interleukin (IL)-6 is a critical tumor promoter during early CRC tumorigenesis. However, there have been few studies regarding the expression of IL-6 and its prognostic role in CRC. Therefore, we explored the correlation between the expression of IL-6 and the clinicopathological features in CRC. To the best of our knowledge, this is the first analysis of the expression of IL-6 in resected CRC samples using immunohistochemistry combined with biostatistics. The results showed that the expression of IL-6 was correlated with tumour TNM stage and histological differentiation. Furthermore, IL-6 in tumour cells showed stronger immunoreactivity as tumour cells invaded deeply. These data indicated that IL-6 might be used as a potential therapeutic target in patients with CRC.

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## INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies and the fourth leading cause of cancer-related death worldwide<sup>[1-3]</sup>. Over one million new cases of CRC are diagnosed each year, and its incidence is second only to lung cancer<sup>[4,5]</sup>. CRC has been observed to be quite prevalent in Western industrialized countries in the past. In recent decades, a growing number of developing countries have exhibited an acute increase in the incidence of CRC. With the improvement in living conditions, the incidence rate of CRC in China has leapt, and CRC has become the fifth most common cancer. Despite radiotherapeutic and chemotherapeutic regimens and significantly improved surgical outcomes, approximately half of CRC patients will suffer from CRC again within five years of treatment and inevitably surrender to the disease<sup>[6]</sup>. The prognosis evaluation and treatment of CRC currently depend mostly on the pathologic stage of disease when diagnosed and primary surgical therapy. Unfortunately, no specific biomarker that allows for the accurate prediction of outcomes for individual patients currently exists.

Many previous studies have shown that neoplasms arise at sites of chronic inflammation<sup>[7]</sup>. The upregulation of inflammatory cytokines secreted by

inflammatory cells, other mesenchymal cells and tumour cells could facilitate tumour initiation and enhance tumour cell proliferation and invasion<sup>[8-10]</sup>. Among the numerous inflammatory cytokines, interleukin (IL)-6 has continually attracted extensive attention.

IL-6 is a pleiotropic cytokine that is involved in tumour growth, invasion, and metastasis in human malignancies<sup>[11,12]</sup>. There is abundant mechanistic evidence suggesting a significant role of IL-6 in the tumour initiation and progression of a variety of cancers. For instance, Nguyen *et al.*<sup>[13]</sup> demonstrated that IL-6 is a pivotal modulator in the initiation of prostate tumorigenesis, tumour growth, metastasis, and resistance to chemotherapy. Zhang *et al.*<sup>[14]</sup> reported that IL-6 is necessary for pancreatic intra-epithelial neoplasia (PanIN) maintenance and progression. Taniguchi *et al.*<sup>[15]</sup> summarized that serum IL-6 levels correlate with poor prognosis, tumour burden, survival and advanced stages of disease in cancers of the lung, esophagus, mammary gland, ovary, and kidney, among others. In addition, several recent studies have suggested a potential role for IL-6 in colon cancer initiation and progression. It has been shown that serum levels of IL-6 are elevated in CRC patients<sup>[16]</sup>. Furthermore, IL-6 has been shown to promote the growth of colorectal cancer epithelial cells *in vitro*. However, there is relatively little understanding of the correlation between IL-6 expression and clinicopathological features in CRC.

The present study was designed to examine the difference in IL-6 expression between CRC tissues and matched adjacent normal mucosa tissues, and the association between IL-6 expression and clinicopathological features in CRC.

## MATERIALS AND METHODS

### *Surgical specimens*

Fifty primary CRC tissues and 50 matched adjacent normal mucosa tissues were collected from the patients who underwent surgical resection at the Sichuan Provincial People's Hospital (Chengdu, China). The original tumours were staged on the basis of the tumour-node-metastasis (TNM) classification system of the International Union Against Cancer<sup>[17]</sup>. Tumour differentiation was scored according to Edmondson Steiner scoring by senior pathologists. Detailed clinicopathological information was excerpted from the clinical data and a summary of the specific CRC demographics is displayed in Table 1. Informed prior to analysis, all patients consented to the tissue procurement, and the study was approved by the Institutional Ethics Committee of Sichuan Provincial People's Hospital.

### *Immunohistochemical staining*

Human cancer tissue sections were subjected to

**Table 1** Clinicopathological data of colorectal cancer patients in this study

Characteristic	Value
Total number of patients	50
Age (yr)	
Median	61
Range	25-88
Sex, <i>n</i>	
Male	28
Female	22
TNM stage	
I / II	29
III / IV	21
Pathologic grade	
Well	14
Moderate	27
Poor	9

immunohistochemistry analysis using a Dako Envision System (Dako Cytomation GmbH, Hamburg, Germany Denmark) according to the manufacturer's instructions. In brief, tumour blocks were formalin-fixed, paraffin-embedded, and cut into 4- $\mu$ m-thick sections. The sections were deparaffinized in xylene and rehydrated through diminishing concentrations of ethanol (100%, 95%, 85%, and 75%). This was followed by subsequent incubation in 3% H<sub>2</sub>O<sub>2</sub> for 10 min in the dark at room temperature to eliminate endogenous peroxidase activity. Antigen-retrieval was performed by heating the sections for 5 min in citrate buffer (pH 6.0) using the autoclave sterilizer method. The sections were then allowed to cool at room temperature for 60 min, and rinsed twice for 5 min with fresh PBS. Thereafter, the slides were preincubated with healthy bovine or goat serum albumin diluted in PBS (pH 7.4) for 15 min at 37 °C, and then incubated overnight at 4 °C with primary antibody specific for IL-6 (mouse anti-IL-6, dilution 1:100, Proteintech). After three rinses in fresh PBS, the slides were incubated for 40 min at 37 °C with horseradish peroxidase-coupled secondary antibody. Following three additional washes, all specimens were stained with 3,3'-diaminobenzidine (DAB) substrate chromogen system (Dako Cytomation GmbH). Finally, the sections were rinsed in distilled water, and counterstained with Mayer's haematoxylin according to the manufacturer's instructions. Non-immune rabbit IgG at the same dilution as the primary antibody was used as a negative control.

### Evaluation of immunohistochemical staining

Cells with observable brown particles in the cytoplasm were taken as positive. All sections were assessed by two professional pathologists who were blinded to patient outcomes and all clinicopathologic data. The immunohistochemical staining was evaluated according to the intensity (weak = 1, intense = 2) of IL-6 immunostaining and the density (0% = 0, 1%-50% = 1, 51%-75% = 2, > 76% = 3) of positive carcinoma cells<sup>[5]</sup>. The eventual score of each specimen

was calculated by multiplying intensity and density, and the tumours were finally determined as negative expression: score = 0; low expression: score  $\leq$  3; or high expression: score > 3. If the two assessments did not agree for a sample, the sample was re-evaluated and classified based on the evaluations given most frequently by the experts.

### Statistical analysis

The data were analysed with the SPSS 16.0 for Windows (SPSS Inc). Pearson  $\chi^2$  test and Fisher's exact test were used to compare qualitative variables, and quantitative variables were analysed by the *t*-test. The correlation between clinicopathological factors and IL-6 expression was evaluated by the Spearman test for non-parametric variables. *P*-values less than 0.05 were considered statistically significant.

## RESULTS

### IL-6 expression is elevated in CRC

To explore the underlying clinical role of IL-6 in CRC, the expression of IL-6 was examined by immunohistochemical staining in 50 CRC tissue samples and 50 matched adjacent normal mucosa tissue samples. Strong IL-6 staining was mostly located in the cytoplasm of CRC cells (Figure 1A), while partial IL-6 staining was observed in the normal mucosa. Strong IL-6 expression was observed in 8% (4/50) of the normal colorectal mucosa samples and in 46% (23/50) of primary CRC samples. IL-6 expression was significantly increased in the CRC tissues compared with the normal mucosa tissues (*P* < 0.001; Figure 1B).

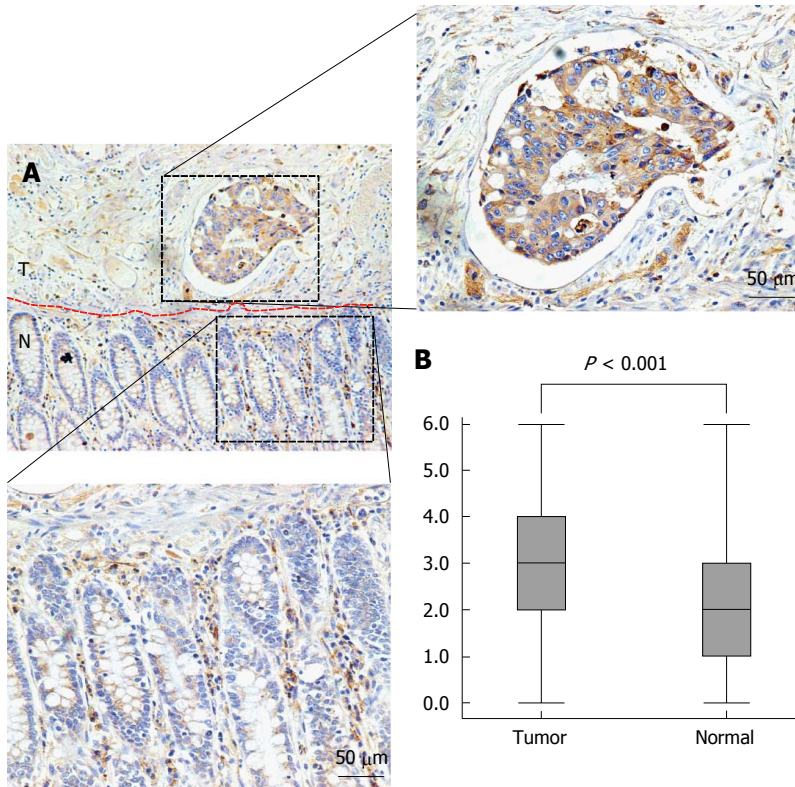
### IL-6 expression is associated with invasion depth and lymph node metastasis in CRC

When analysing the levels of IL-6 expression in colorectal tumour cells by immunohistochemistry, we observed that IL-6 in tumour cells showed stronger immunoreactivity as tumour cells invaded more deeply (Figure 2A). This means that the tumour regions that were closer to the invasion front showed higher IL-6 expression levels. In addition, the majority of tumor cells in lymph node metastases were also IL-6-immunopositive (Figure 2B).

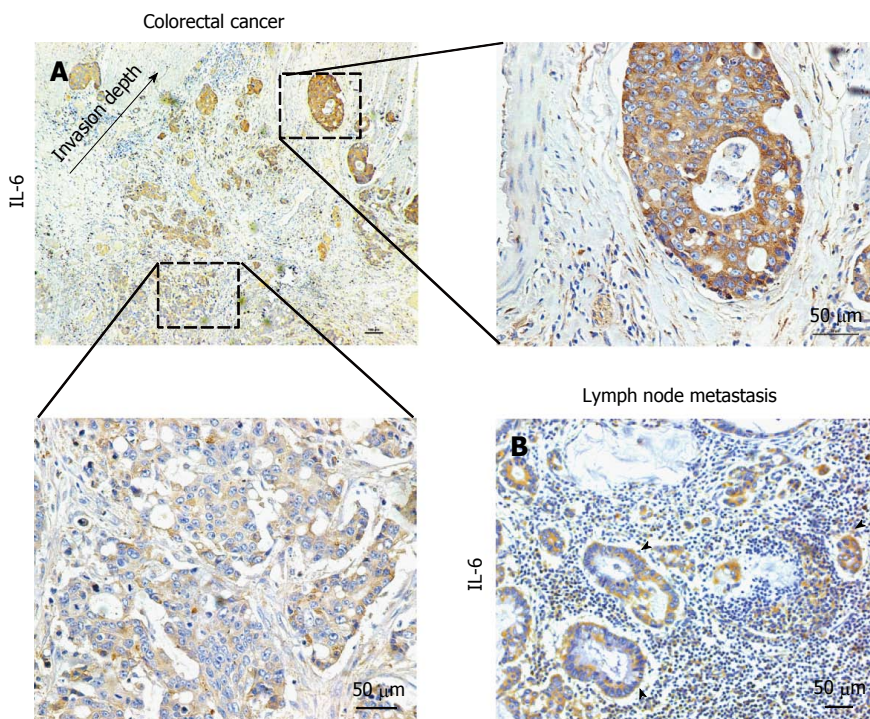
### IL-6 expression correlates with several clinicopathologic factors in CRC

We next analysed the association between the levels of IL-6 expression and clinicopathologic parameters in CRC, including TNM stage (stages I, II, III, and IV) and histological differentiation (well, moderately, and poorly differentiated). The results showed that the levels of IL-6 expression were inversely associated with histological differentiation (*P* < 0.05, Figure 3A and B), but positively correlated with TNM stage (*P* < 0.001, Figure 3C and D). Of the 50 IL-6-positive CRC cases, 14 were well-differentiated, 27 moderately

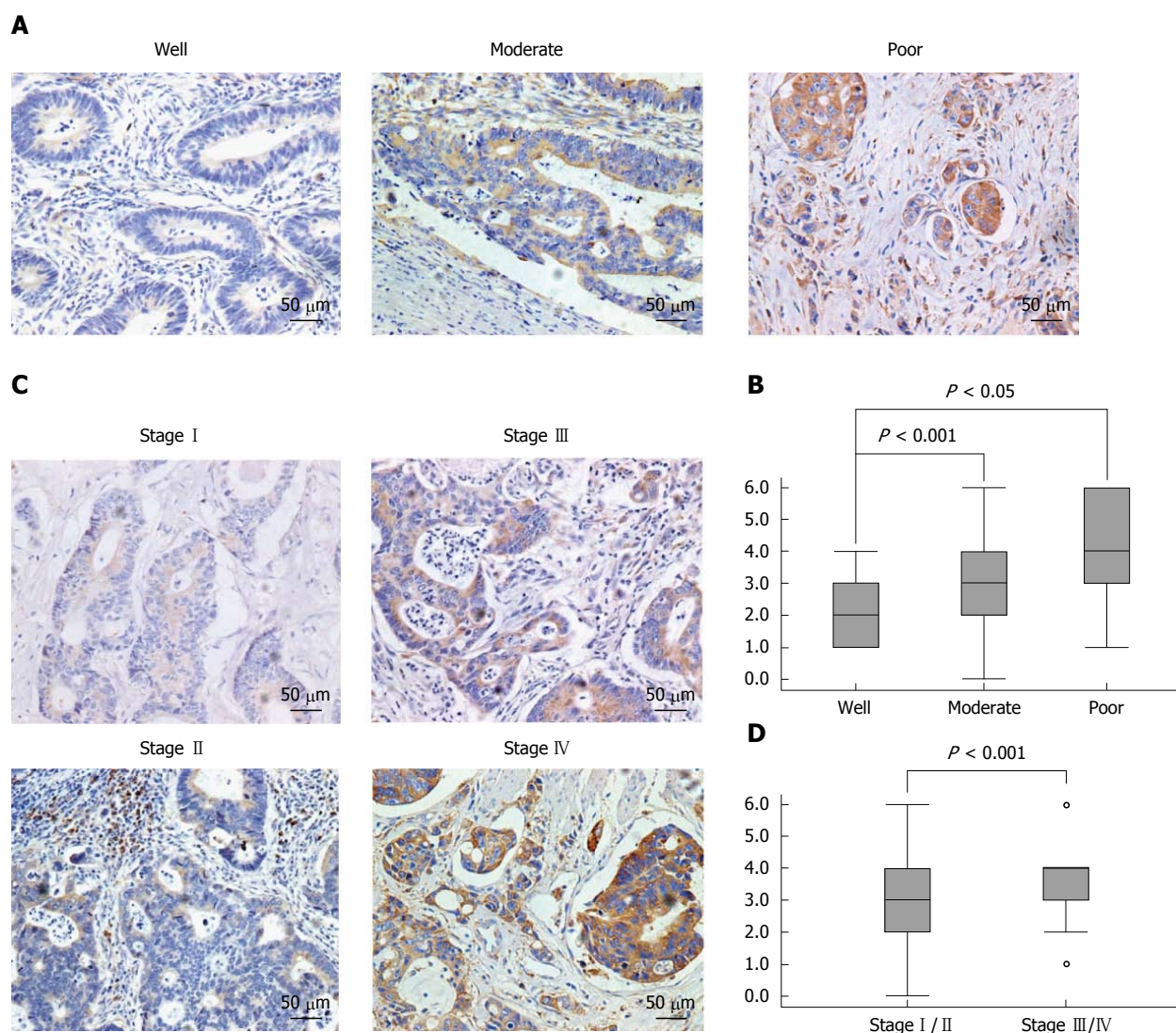




**Figure 1** Interleukin-6 expression is elevated in human colorectal cancer tissue samples. A: Individual FFPE sections demonstrated that colorectal cancer cells had invaded underneath the colorectal mucosa. The IL-6 expression level was elevated in colorectal tumour tissues compared to adjacent non-tumour tissues. "T" refers to tumour tissue, and "N" indicates adjacent non-tumour tissue from the same patient; B: IL-6 expression scores are shown as box plots, with the horizontal lines representing the median, the bottom and top of the boxes representing the 25<sup>th</sup> and 75<sup>th</sup> percentiles, respectively, and the vertical bars representing the range of data.



**Figure 2** Interleukin-6 expression is associated with invasion depth and lymph node metastasis in colorectal cancer. A: Increased expression of IL-6 at the invasive front of human CRC samples compared with tumour centre; B: The tumor cells in lymph node metastases were also IL-6-immunopositive. IL: Interleukin.



**Figure 3** Interleukin-6 expression is significantly correlated with histological differentiation and TNM stage. A: Poorly differentiated colorectal tumours showed higher expression of IL-6 than moderately and well differentiated colorectal tumours; B: Comparison of immunohistochemical scores of IL-6 according to histological differentiation ( $P < 0.05$ ); C: Strong immunoreactivity was more likely to present with advanced-stage (stage III/IV) CRC compared to early-stage (stage I / II); D: Comparison of immunohistochemical scores of IL-6 according to TNM stage ( $P < 0.001$ ).

differentiated and 9 poorly differentiated. In addition, 29 cases were classified as stage I - II, while 21 cases were classified as stage III -IV. Taken together, these analyses indicated that the upregulation of IL-6 in CRC cells correlates with tumour progression.

## DISCUSSION

Chronic inflammation is thought to be the leading cause of many human cancers including CRC<sup>[13]</sup>. In patients with inflammatory bowel disease, the risk of developing CRC is much higher than in the general population<sup>[18]</sup>. However, even in sporadic CRC with no preceding chronic inflammation, inflammatory cells infiltrate the tumour region and secrete inflammatory cytokines, which contribute to cancer development. Such "tumour-elicited inflammation" further emphasizes the importance of chronic inflammation in cancer progression. IL-6 is an NF- $\kappa$ B-regulated inflammatory

cytokine that enforces proliferation and anti-apoptotic effects in tumour cells<sup>[2,13]</sup>. It has been reported that IL-6 expression in serum samples from patients was associated with an increased risk of colorectal adenoma<sup>[19,20]</sup>. Until now, to the best of our knowledge, there have been no relevant studies analysing the levels of IL-6 expression in resected CRC samples by immunohistochemistry combined with biostatistics. In this study, we found that IL-6 expression was elevated in CRC compared with normal mucosa, which is consistent with previous studies<sup>[21,22]</sup>. In addition, we found that the levels of IL-6 expression were inversely associated with histological differentiation, but positively associated with TNM stage. These results imply that IL-6 may be involved in CRC progression. Interestingly, the tumour regions that were closer to the invasion front showed higher IL-6 expression levels. Furthermore, the majority of cancer cells in lymph node metastases were also IL-



6-immunopositive. These results suggested that IL-6 might be associated with CRC invasion and metastasis.

The mechanisms underlying IL-6-mediated CRC initiation and development have been elucidated comprehensively. IL-6 is a critical tumour promoter during early CRC tumourigenesis<sup>[20]</sup>. In mice with colitis-associated cancer, anti-IL-6 receptor antibody treatment reduced the incidence of colitis-associated cancer (CAC) by decreasing the expression of key genes in aerobic glycolysis<sup>[23]</sup>. In an experimental CAC mouse model, researchers found that the expression levels of IL-6 protein were gradually increased after the induction of dysplastic lesions over time. These data suggested that IL-6 might be a therapeutic target in CAC<sup>[24]</sup>. Activation of the IL-6/Stat3 pathway via IL-6 trans-signaling plays an important role not only in CRC initiation but also in CRC development<sup>[25,26]</sup>. According to the growing evidence supporting a critical role for IL-6 signaling in the development of both sporadic and inflammation-associated CRC, therapeutics targeting this pathway could be promising options for CRC patients.

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## COMMENTS

### Background

Colorectal cancer (CRC) is the fourth leading cause of cancer-related death worldwide. Previous studies have demonstrated that IL-6 is a critical tumour promoter during early CRC tumourigenesis. However, there have been few studies regarding the expression of IL-6 and its prognostic role in CRC. The correlation between the expression levels of IL-6 and the clinicopathological features of CRC specimens has not yet been investigated.

### Research frontiers

Previous studies have demonstrated that IL-6 is a critical tumour promoter during early CRC tumourigenesis and that the IL-6/STAT3 signaling pathway plays an important role in the progression of CRC.

### Innovations and breakthroughs

To the best of our knowledge, this is the first analysis of the expression of IL-6 in resected CRC samples and its prognostic role using immunohistochemistry combined with biostatistics.

### Applications

The results showed that the expression levels of IL-6 were correlated with TNM stage and histological differentiation. Furthermore, IL-6 in tumour cells showed stronger immunoreactivity as tumour cells invaded more deeply. These data indicate that IL-6 might be used as a potential target for postoperative adjuvant therapy in patients with CRC.

### Terminology

Invasion depth, also called the depth of tumour invasion, is the most significant histological predictor of lymph node metastasis in colorectal cancer. Increasing evidence indicates that colorectal cancer with submucosal deep invasion correlates with a poor prognosis.

## Peer-review

This is an interesting paper. The method they used to quantify IL-6 in CRC specimens is only a qualitative method.

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