

Case Control Study

Risk factors for recurrence after bowel resection for Crohn's disease

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Abstract**BACKGROUND**

Complications of Crohn's disease such as intestinal obstruction, fistula or perforation often need surgical treatment. Nearly 70%-80% patients with Crohn's disease would receive surgical treatment during the lifetime. However, surgical treatment is incurable for Crohn's disease. The challenge of recurrence postoperatively troubles both doctors and patients. Over 50% patients would suffer recurrence postoperatively. Some certain risk factors are associated with recurrence of Crohn's disease.

AIM

To evaluate the risk factors for endoscopic recurrence and clinical recurrence after bowel resection in Crohn's disease.

METHODS

Patients diagnosed Crohn's disease and received intestinal resection between April 2007 and December 2013 were included in this study. Data on the general demographic information, preoperative clinical characteristics, surgical information, postoperative clinical characteristics were collected. Continuous data are expressed as median (inter quartile range), and categorical data as frequencies and percentages. Kaplan-Meier method was applied to estimate the impact of the clinical variables above on the cumulative rate of postoperative endoscopic recurrence and clinical recurrence, then log-rank test was applied to test the homogeneity of those clinical variables. Multivariate Cox proportional hazard regression analysis was performed to identify the risk factors of postoperative endoscopic recurrence and clinical recurrence.

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RESULTS

A total of 64 patients were included in this study. The median follow-up time for the patients was 17 (9.25-25.75) mo. In this period, 41 patients (64.1%) had endoscopic recurrence or clinical recurrence. Endoscopic recurrence occurred in 34 (59.6%) patients while clinical recurrence occurred in 28 (43.8%) patients, with the interval between the operation and recurrence of 13.0 (8.0-24.5) months and 17.0 (8.0-27.8) mo, respectively. In univariate analysis, diagnosis at younger age ($P < 0.001$), disease behavior of penetrating ($P = 0.044$) and preoperative use of anti-tumor necrosis factor (TNF) ($P = 0.020$) were significantly correlated with endoscopic recurrence, while complication with perianal lesions ($P = 0.032$) and preoperative use of immunomodulatory ($P = 0.031$) were significantly correlated with clinical recurrence. As to multivariate analysis, diagnostic age ($P = 0.004$), disease behavior ($P = 0.041$) and preoperative use of anti-TNF ($P = 0.010$) were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions ($P = 0.023$) was an independent prognostic factor for clinical recurrence.

CONCLUSION

Diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were independent risk factors for postoperative recurrence in Crohn's disease.

Key words: Risk factor; Endoscopic recurrence; Clinical recurrence; Bowel resection; Crohn's disease

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Core tip: Our study aimed at evaluating the risk factors for recurrence after bowel resection in Crohn's disease. This study included 64 patients diagnosed Crohn's disease and received intestinal resection. The result showed that diagnosis at younger age, disease behavior of penetrating and preoperative use of anti-tumor necrosis factor were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions was an independent prognostic factor for clinical recurrence.

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INTRODUCTION

Crohn's disease, one kind of inflammatory bowel disease, is a chronic inflammatory disorder in the digestive tract, with an incidence and prevalence of 6-15 and 50-200 per 100000 persons, respectively^[1]. Although there has been significant improvement in the diagnosis and conservative medical treatment, the risk of surgical resection for Crohn's disease could be as high as 70% to 80% during the lifetime^[2,3]. Unlike the curability of operation for ulcerative colitis, surgical treatment can only help to resolve the complications of Crohn's disease, such as intestinal obstruction, fistula or perforation. In other words, surgical treatment is incurable for Crohn's disease. The challenge of recurrence postoperatively troubles both doctors and patients.

Buisson *et al*^[4] reviewed the rates and risk factors for clinical and endoscopic recurrence in population-based studies, and found that approximately half of patients experienced clinical recurrence at 10 years. And Watanabe *et al*^[5] found that overall 5-year and 10-year cumulative reoperation rates were 31.4% and 61.2% in Japan, respectively. Many factors were found related with postoperative recurrence, such as disease behavior, use of medicine and technique of surgery^[6-8]. Most these studies were about population from Caucasians and Southeast Asia such as Japan and South Korea. Our study aims to evaluate the risk factors for recurrence after bowel resection in patients with Crohn's disease, from a tertiary care center in China.

MATERIALS AND METHODS

Patients selection

Patients diagnosed Crohn's disease and received intestinal resection between April 2007 and December 2013 at the Sixth Affiliated Hospital, Sun Yat-Sen University were enrolled in this study. Data on the general demographic information, preoperative clinical characteristics, surgical information, postoperative clinical characteristics were obtained by careful chart review, including sex, diagnostic age, disease-behavior, anatomical site of disease, perianal lesions, preoperative body mass index, preoperative laboratory examinations, preoperative medication [corticosteroid, immunosuppressant, anti-tumor necrosis factor (TNF)], preoperative duration of disease, indication of operation, postoperative laboratory examinations, postoperative colonoscopy, time of endoscopic recurrence and clinical recurrence. Endoscopic recurrence was defined as the presence of aphthous ulcer, deep and large ulcer, nodular hyperplasia and stenosis at the anastomotic site and in the intestinal wall of the anastomotic site confirmed by postoperative colonoscopy. Clinical recurrence was defined as symptom recurrence including obvious abdominal pain, diarrhea, abdominal mass and extraintestinal manifestations, accompanied with imaging and endoscopic lesions; or complications such as abdominal abscess, fistula formation and intestinal obstruction which may require a second operation.

Statistical analysis

Data analyses were performed with the Statistical Package for Social Science software, version 21.0 (SPSS Inc., Chicago, IL, United States). Continuous data are expressed as median (inter quartile range), and categorical data as frequencies and percentages. Kaplan-Meier method was applied to estimate the impact of the clinical variables above on the cumulative rate of postoperative endoscopic recurrence and clinical recurrence, then log-rank test was applied to test the homogeneity of those clinical variables. Multivariate Cox proportional hazard regression analysis was performed to identify the risk factors of postoperative endoscopic recurrence and clinical recurrence. The differences were considered statistically significant when the two-sided *P* values were < 0.05.

RESULTS

Patient characteristics and surgical variables

A total of 64 patients were included in our study. The average age at diagnosis was 29.23 years old, while the gender ratio was 2.76:1 (male:female 47/17). The distribution of diagnostic age was single-peak curve, with the peak age of 22-36 years old. As to the Montreal classification, 49 (76.6%) patients were A2 subtype; L3 subtype account for 73.4% (47 patients); and most patients manifested B2 subtype (25/39.1%) or B3 subtype (37/57.8%) of disease behavior. 22(34.4%) patients complicated with perianal lesions. Preoperative use of medication was found in 29 patients (45.3%), including 23 cases of steroid, 24 cases of immunomodulator and 4 cases of anti-TNF. The clinicopathological characteristics of the patients are summarized in [Table 1](#).

As to the indications of operation, most patients had to receive operation because of intestinal obstruction (27 cases, 42.3%) and intestinal fistula (34cases, 53.1%). 47 patients who exhibited disease in the ileocolon (L3) mentioned above received ileocolonic resection and 15 patients received intestinal resection. Detail about the surgery was showed in [Table 2](#).

Recurrence

The median follow-up time for the patients was 17 (9.25-25.75) mo. In this period, 41 patients (64.1%) had endoscopic recurrence or clinical recurrence. Endoscopic recurrence occurred in 34 (59.6%) patients while clinical recurrence occurred in 28 (43.8%) patients, with the interval between the operation and recurrence of 13.0 (8.0-24.5) mo and 17.0 (8.0-27.8) mo, respectively. 6 (9.4%) patients needed reoperation because of recurrence. The cumulative rate of endoscopic recurrence was 37.0%, 60.0% and 90.0% at 12, 24 and 36 mo, respectively, after intestinal resection. And the cumulative rate of clinical recurrence was 18.0%, 44.0% and 67.0% at 12, 24 and 36 mo, respectively. The cumulative incidence curve was showed in [Figure 1](#).

The endoscopic recurrence rate for patients with age ≤ 16, between 17-40 and > 40 was 100.0%, 63.0% and 12.5%, respectively; and diagnosis at younger age was significantly correlated with endoscopic recurrence (*P* < 0.001). The endoscopic recurrence rate for patients with B1, B2 and B3 subtype of disease behavior was 0.0%, 50.9%, 73.2%, respectively; and disease behavior of penetrating was significantly

Table 1 Demographic and clinical characteristics of the patients, *n* (%)

Variables	Number of patients
Gender	
Male	47 (73.4)
Female	17 (26.6)
Age at diagnosis	27.5 (8, 78)
Disease period before operation	9.5 (2.0, 48.0)
Montreal classification	
Age, yr	
A1 (≤ 16)	6 (9.4)
A2 (17-40)	49 (76.6)
A3 (> 40)	9 (14.1)
Behavior	
B1 (Inflammatory)	2 (3.1)
B2 (Stricturing)	25 (39.1)
B3 (Penetrating)	37 (57.8)
Location	
L1 (Terminal ileum)	9 (14.1)
L2 (Colon)	1 (1.6)
L3 (Ileocolon)	47 (73.4)
L4 (Upper disease)	7 (10.9)
Perianal disease	22 (34.4)
Preoperative use of medication	29 (45.3)
Steroid	23 (35.9)
Immunomodulator	24 (37.5)
Anti-TNF	4 (6.2)

TNF: Tumor necrosis factor.

correlated with endoscopic recurrence ($P = 0.044$). Moreover, preoperative use of anti-TNF ($P = 0.020$) were significantly correlated with endoscopic recurrence, while complication with perianal lesions ($P = 0.032$) and preoperative use of immunomodulatory ($P = 0.031$) were significantly correlated with clinical recurrence. As to multivariate analysis, diagnostic age [Hazard ratio (HR) 0.323, 95% confidence interval (CI): 0.148-0.703, $P = 0.004$], disease behavior (HR 1.969, 95%CI: 1.028-3.775, $P = 0.041$) and preoperative use of anti-TNF (HR 4.414, 95%CI: 1.424-13.682, $P = 0.010$) were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions (HR 2.956, 95%CI: 1.163-7.513, $P = 0.023$) was an independent prognostic factor for clinical recurrence. Results of univariate and multivariate analyses were showed in [Table 3](#).

DISCUSSION

Crohn's disease is characterized by relapsing episodes of active inflammation alternating with remission of disease^[9]. Recurrence is a common but intractable problem for the patients with Crohn's disease even if they received surgical therapy. It is well known that anastomotic recurrence occurs endoscopically as early as several months after bowel resection and anastomosis, followed by symptomatic recurrence^[10]. The rate of postoperative recurrence varied in different studies. Endoscopic studies have shown that up to 70% patients developed endoscopic recurrence within 1 year and nearly all the patients would have new lesions in the neoterminal ileum at 3 years after resection^[11,12]. Rutgeerts reported that about 20%-30% patients would have a clinical recurrence within the first year after curative resection of the ileum or ileocolon with ileocolonic anastomosis, with a 10% increase after each subsequent year^[13]. In our study, the cumulative rate of endoscopic recurrence was 37.0%, 60.0% and 90.0% at 12, 24 and 36 mo after intestinal resection and the cumulative rate of clinical recurrence was 18.0%, 44.0% and 67.0% respectively. The recurrence rate in our study was similar to the previous reported

Table 2 Surgical details, *n* (%)

Variables	Number of patients
Indication of surgery	
Intestinal obstruction	27 (42.3)
Intestinal fistula	34 (53.1)
Abscess	2 (3.2)
Bleeding	1 (1.6)
Site of resection	
Ileocolon	47 (73.4)
Intestine	15 (23.4)
Colon	1 (1.6)

results.

Many prognostic factors have been investigated to predict postoperative recurrence. The presence of perianal disease has been proved one of the predictors of postoperative recurrence by many previous studies. Bernell *et al*^[14] found perianal fistulas increased the relative risk (RR) of recurrence after resection in Crohn's disease (RR 1.4, 95%CI, 1.2-1.7). Beaugerie *et al*^[15] found the presence of perianal disease significantly associated with subsequent 5-year disease disabling course (overall risk 1.8, 95%CI, 1.2-2.8), which meant more patients with perianal disease required early intensive therapy and suffered from disabling chronic symptoms. Another study from Korea showed patients with perianal Crohn's disease had a higher risk of reoperation^[16]. In our study, we also found preoperative complication with perianal lesions was an independent prognostic factor for clinical recurrence.

Medication is also an important predictor for recurrence of Crohn's disease. Many studies focused on postoperative medication. Yoshida *et al*^[17] conducted a 3-year prospective randomized open trial about the effect of postoperative scheduled infliximab monotherapy on recurrence of Crohn's disease, and the result showed that an early intervention with infliximab monotherapy should prevent clinical, serological, and endoscopic Crohn's disease recurrence following ileocolic resection. Yang *et al*^[8] found postoperative use of anti-TNF agents could reduce the risk of reoperation. Immunomodulators such as 6-MP or azathioprine are also widely used postoperatively and were found independently associated with reduction in surgical rate^[18,19]. In our study, we focused on the preoperative medication and found preoperative use of anti-TNF was significantly associated with endoscopic recurrence and preoperative use of immunomodulatory seemed correlated with clinical recurrence. The opposite effects of postoperative and preoperative medication on postoperative recurrence of Crohn's disease might be due to different severity of disease as in our hospital, preoperative medication especially anti-TNF tended to be used in patients with more aggravated disease.

Other risk factors for postoperative recurrence which have been found in published studies included younger diagnostic age, perforating type of disease, sex, smoking and so on^[7,20]. In our study, we also found diagnosis at younger age and disease behavior of penetrating were associated with an increased risk for endoscopic recurrence.

In conclusion, this retrospective study of Crohn's disease in China revealed that diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were independent risk factors for postoperative recurrence.

Table 3 Univariate and multivariate analysis of factors associated with endoscopic recurrence and clinical recurrence

Variable	Endoscopic recurrence		Clinical recurrence	
	Univariate	Multivariate	Univariate	Multivariate
Gender	0.683		0.939	
Diagnostic age	0.000 ^b	0.004 ^b	0.422	
Disease behavior	0.044 ^a	0.041 ^a	0.686	
Disease location	0.146		0.315	
Perianal disease	0.357		0.032 ^a	0.023 ^a
Preoperative use of steroid	0.739		0.700	
Preoperative use of immunomodulator	0.085		0.031 ^a	0.092
Preoperative use of anti-TNF	0.020 ^a	0.010 ^a	0.438	
Preoperative body mass index level	0.230		0.705	
Preoperative leukocytosis	0.760		0.627	
Preoperative C-reactive protein level	0.290		0.917	
Preoperative erythrocyte sedimentation rate level	0.078		0.247	
Preoperative albumin level	0.368		0.271	

^a*P* < 0.05,

^b*P* < 0.01. TNF: Tumor necrosis factor.

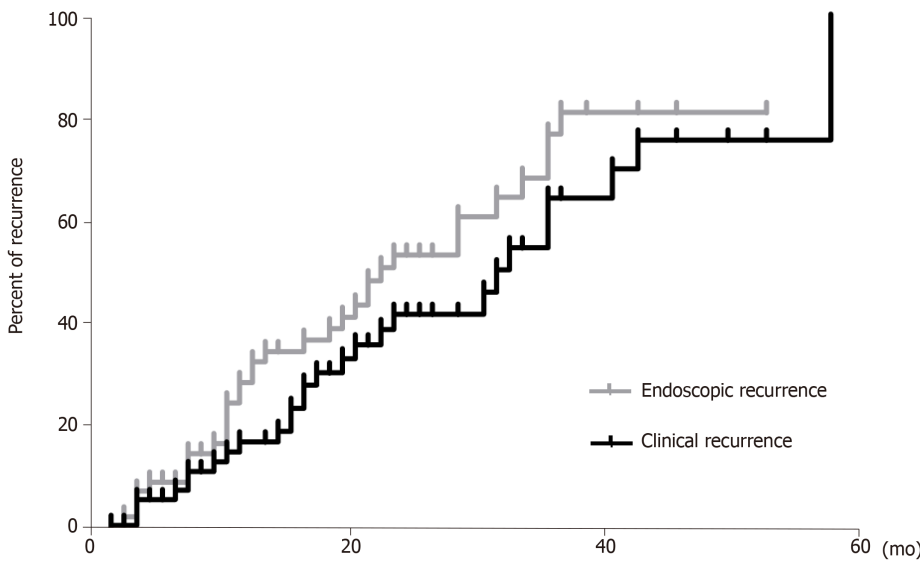


Figure 1 Kaplan–Meier curves for endoscopic recurrence and clinical recurrence.

ARTICLE HIGHLIGHTS

Research background

Nearly 70%-80% patients with Crohn's disease would receive surgical treatment during the lifetime. However, surgical treatment is incurable for Crohn's disease. The challenge of recurrence postoperatively troubles both doctors and patients. Over 50% patients would suffer recurrence postoperatively.

Research motivation

A great amount of patients with Crohn's disease would receive surgical treatment but over one half patients would suffer recurrence postoperatively. It is important to recognize the risk factor for postoperative recurrence. Further clinical research base on certain risk factor would favor the prognosis.

Research objectives

This study aims to evaluate the risk factor of endoscopic recurrence and clinical recurrence after bowel resection for Crohn's disease. Further relative clinical research could focus on the risk factor found in this study and help to improve the prognosis for certain patients.

Research methods

Patients diagnosed Crohn's disease and received intestinal resection were included in this study. Data on the general demographic information, preoperative clinical characteristics, surgical information, postoperative clinical characteristics were collected. Continuous data are expressed as median (inter quartile range), and categorical data as frequencies and percentages. Kaplan-Meier method was applied to estimate the impact of the clinical variables above on the cumulative rate of postoperative endoscopic recurrence and clinical recurrence, then log-rank test was applied to test the homogeneity of those clinical variables. Multivariate Cox proportional hazard regression analysis was performed to identify the risk factors of postoperative endoscopic recurrence and clinical recurrence.

Research results

Diagnosis at younger age, disease behavior of penetrating and preoperative use of anti-tumor necrosis factor (TNF) were significantly correlated with endoscopic recurrence, while complication with perianal lesions and preoperative use of immunomodulatory were significantly correlated with clinical recurrence. As to multivariate analysis, diagnostic age, disease behavior and preoperative use of anti-TNF were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions was an independent prognostic factor for clinical recurrence. The result of this study discovered some risk factors for recurrence in patients with Crohn's disease after bowel resection. Prospective clinical study with more patients remains to be performed to confirm the result.

Research conclusions

Diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were independent risk factors for postoperative recurrence in Crohn's disease. Patients with younger diagnostic age, disease behavior of penetrating and preoperative use of anti-TNF tended to have endoscopic recurrence, while patients with perianal lesions tended to suffer from clinical recurrence. Some certain factors are associated with postoperative recurrence of Crohn's disease. In this study, diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were proved as independent prognostic factors. The recurrence rate of Crohn's disease after bowel resection is high and some certain clinical factors have been proved associated with postoperative recurrence. In this study, we found diagnostic age, disease behavior and preoperative use of anti-TNF were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions was an independent prognostic factor for clinical recurrence. Diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were related with postoperative recurrence in Crohn's disease. This study adopts the classical methods. Endoscopic recurrence occurred in 34 (59.6%) patients while clinical recurrence occurred in 28 (43.8%) patients, with the interval between the operation and recurrence of 13.0 (8.0-24.5) mo and 17.0 (8.0-27.8) mo, respectively. Diagnostic age, disease behavior and preoperative use of anti-TNF were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions was an independent prognostic factor for clinical recurrence. Diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were related with postoperative recurrence in Crohn's disease. Patients with such risk factors should be strictly followed up and receive appropriate medical therapy if necessary.

Research perspectives

Diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were independent risk factors for postoperative recurrence in Crohn's disease. Prospective clinical study with more patients remains to be performed to confirm the results. Prospective clinical trial with multi centers and more patients would be the best method for future research.

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