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ORIGINAL SCIENTIFIC REPORT

The Presence of Postoperative Infectious Complications is Associated with the Risk of Early Postoperative Clinical Recurrence of Crohn's Disease

Zhen Guo[1] · Lei Cao[1] · Feilong Guo[1] · Jianfeng Gong[1] · Yi Li[1] · Lili Gu[1] · Weiming Zhu[1] · Jieshou Li[1]

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Abstract

Background The purpose of the study was to identify risk factors for early clinical and surgical recurrence in Crohn's disease (CD) patients who underwent intestinal resection.

Method This was a retrospective study. Consecutive patients who underwent intestinal resection with a primary anastomosis from January 2011–December 2014 were enrolled. Gender, age at surgery, clinical phenotypes of CD, serum albumin and C-reactive protein level the day before surgery, smoking status at surgery, anastomosis technique, number of anastomoses, details of postoperative complications, the postoperative prophylactic treatment were assessed to figure out risk factors for postoperative clinical and surgical recurrence within 1 year after the initial resection by univariate and then multivariate analysis.

Results Two hundred and thirty-seven patients were analyzed. The risk of early postoperative clinical recurrence was 2.99 times higher in patients suffered postoperative infectious complications [odds ratio (OR) 2.99; 95% CIs, 1.42–6.32; $p = 0.004$], while never-smoking was found to be a protective factor for early clinical recurrence (OR 0.326; 95% CIs, 0.18–0.59; $p < 0.0001$). For surgical recurrence within 1 year after resection, the presence of postoperative intra-abdominal septic complications might be a risk factor (OR 6.77; 95% CIs, 1.61–28.5; $p = 0.009$). Smoker at surgery was also a risk factor for early surgical recurrence (OR 5.41; 95% CIs, 1.36–21.5; $p = 0.017$).

Conclusion The presence of postoperative infectious complications was identified as a possible risk factor for early postoperative clinical recurrence after resection in CD patients.

Introduction

Over 80% of patients with Crohn's disease (CD) require at least one major surgery during the course of disease for stricture or fistula [1]. However, surgery is not curative as CD frequently recurs, especially in patients with resection and primary anastomosis. Within 1 year of surgery, 20–38% of patients suffer clinical recurrence, and more than 5% of them require further surgery due to CD recurrence [2–4].

Previous studies have revealed numerous risk factors of postoperative clinical recurrence and re-operations in the long term, such as young age at diagnosis [5], penetrating disease behavior [6], short disease duration from the diagnosis to the first surgery [6, 7], colonic disease [8], family history [6, 9], presence of postoperative complications [10], and smoking [11, 12]. However, few studies have evaluated the risk factors for earlier postoperative clinical and surgical recurrence.

Zhen Guo and Lei Cao have contributed equally to this work.

✉ Weiming Zhu
juwiming@nju.edu.cn

[1] Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, No. 305 East Zhongshan Road, Nanjing 210002, People's Republic of China

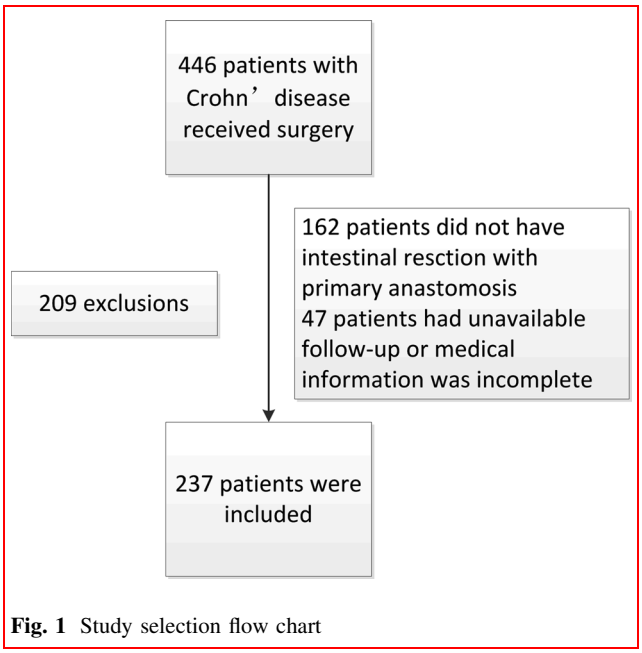

Fig. 1 Study selection flow chart

Increasing evidences indicate early intensive therapy, like anti-TNF drugs may be the most effective strategy for CD postoperative recurrence, but widespread use of such therapy may lead to overtreatment [13, 14]. Balancing costs and risks against efficacy of early intensive therapy has been challenging [15]. Identification of risk factors for early postoperative clinical recurrence may be helpful to optimize strategy for management of postoperative CD. Therefore, we conducted this study to search for possible risk factors of early postoperative clinical recurrence and surgical recurrence after the initial resection.

Materials and methods

Patients

The data for CD patients who had surgery from January 2011–December 2014 were extracted from our prospectively maintained computerized database. Patients undergoing intestinal resection with primary anastomosis were included in this study, and those who lost to follow-up were excluded. The present study was approved by our institutional ethics committee. Informed consent was obtained from all individual participants included in the study.

For each patient, the following data were collected: gender, age at surgery, clinical phenotypes of CD, level of serum albumin and C-reactive protein (CRP) the day before surgery, smoking status at surgery, laparotomy or laparoscopy, anastomotic methods, number of anastomoses, history of previous intestinal resections, details of postoperative complications, clinical recurrence and surgical recurrence within 1 year after resection, and the postoperative prophylactic treatment. The diagnosis of CD was confirmed by histological findings of resected specimen. Clinical phenotypes were classified according to the Montreal Classification. A former smoker was a person who had given up smoking at least 3 months prior to surgery. Postoperative intra-abdominal septic complications (IASCs) were any anastomotic leak, enterocutaneous fistula, or intra-abdominal abscess occurring within 1 month after resection. Postoperatively used immune-modulators were azathioprine or *Tripterygium wilfordii* Hook. F. (a Chinese herbal drug with immunosuppressive effect). Immune-modulators were taken from 2 to 4 weeks after surgery, with a dose of 1.5–2.5 mg/kg/d for azathioprine, and 1–2 mg/kg/d for *Tripterygium wilfordii* Hook. F.

Definition of recurrence

Early clinical recurrence was defined as a Crohn's Disease Activity Index (CDAI) score > 150 and C-reactive protein (CRP) > 10 mg/L within 1 year after surgery, and early surgical recurrence was defined as a repeat resection due to new complications of CD (not for IASCs in postoperative period), or recurrent symptoms refractory to medical treatment within 1 year after surgery.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD), and categorical data were expressed as frequencies and percentages. We used a Pearson Chi-square test or the Fisher's exact test (when strata comprised a sample size less than 6) for the categorical variables. Only univariate significant factors were included in a multivariate logistic regression model to identify risk factors for clinical and surgical recurrence within 1 year after the initial resection. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated. All P values were two-sided, and a p value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL).

Results

Patients' characteristics

A total of 237 CD patients (166 males) underwent intestinal resection with primary anastomosis were included in the final analysis (Fig. 1). The mean age at the time of surgery was 35.0 $\pm$ 12.6 years. According to the Montreal Classification, 47 (19.8%) patients were diagnosed as A1 (age $\leq$ 16), 175 (73.8%) patients were diagnosed as A2 (age

Table 1 Postoperative complications

Anastomotic leakage	12 (21.4)
Intra-abdominal abscess	8 (14.3)
Enterocutaneous fistula	0
Wound infection	17 (30.4)
Bowel paralysis	7 (12.5)
Diarrhea	8 (14.3)
Fever of unknown origin	4 (7.1)
Total	56

between 17 and 40), and 15 (6.3%) patients were diagnosed as CD after the age of 40. Disease behavior at the time of surgery was non-stricturing/non-penetrating (B1) in 25 (10.5%) patients, structuring (B2) in 125 (52.7%) patients, and penetrating (B3) in 87 (36.7%) patients. In terms of disease location, the majority (44.3%) of patients were diagnosed as L1 (Ileal), 19.4% of the patients were L2 (Colonic), 35.9% of the patients were L3 (Ileocolonic), and only one patient was diagnosed as L4 (Upper gastrointestinal). A total of 40 (16.9%) patients received previous resections. In terms of albumin and CRP levels the day before surgery, majority of the patients (79.7 and 72.6%) were normal. The smoking status at the time of surgery was never in 126 (53.2%) patients, former in 92 (38.8%) patients, and current in 19 (8.0%) patients. Eighty-five (35.9%) surgeries were conducted laparoscopically. Most patients (84.0%) had a side-to-side anastomosis, and only 16 (6.8%) patients had more than one anastomosis. Fifty-six (23.6%) patients developed postoperative complications, and 20 (8.4%) of them suffered IASCs. The details of complications are shown in Table 1. More than half of the patients (133) received azathioprine or *Tripterygium wilfordii* Hook. F. postoperatively, while only 19 (8.0%) patients used anti-TNF drugs. Within 1 year after the initial resection, 78 (32.9%) patients had clinical recurrence, and 17 (7.2%) patients had surgical recurrence.

Univariate analysis

Univariate analysis for the risk factors of early postoperative clinical recurrence was performed, and the results indicated that presence of postoperative infectious complications ($p = 0.010$) was a possible risk factor for early postoperative clinical recurrence, while never-smoking ($p = 0.027$) and postoperative immune-modulators ($p = 0.043$) reduced the risk of clinical recurrence within 1 year after resection. However, the presence of IASCs ($p = 0.34$) was not associated with increased risk of early clinical recurrence (Table 2). On another univariate analysis for risk factors of early surgical recurrence, the current

Table 2 Patients' characteristics and univariate analysis of variables associated with early clinical recurrence

Characteristics	No recurrence (159)	Recurrence (78)	OR	*p* value
Gender, male/female	111/48	55/23	1.03	0.91
Age at diagnosis				
≤16	29 (18.2)	18 (23.1)	1.35	0.48
17–40	118 (74.2)	57 (73.1)	0.94	0.98
>40	12 (7.5)	3 (3.8)	0.49	0.4
Age at surgery				
≤16	4 (2.5)	0	0.22	0.31
17–40	103 (64.8)	45 (57.7)	0.74	0.36
>40	52 (32.7)	33 (42.3)	1.51	0.19
Disease location				
Ileal	71 (44.7)	34 (43.6)	0.96	0.99
Colonic	27 (17.0)	19 (24.3)	1.57	0.24
Ileocolonic	60 (37.7)	25 (32.1)	0.78	0.48
Upper GI	1 (0.6)	0	0.67	1
Disease behavior				
Non-stricturing, non-penetrating	21 (13.2)	4 (5.1)	0.36	0.07
Stricturing	79 (49.7)	46 (59.0)	1.46	0.23
Penetrating	59 (37.1)	28 (35.9)	0.95	0.97
Albumin ≤30 g/L the day before surgery	27 (17.0)	21 (26.9)	1.80	0.106
CRP ≤10 g/L the day before surgery	122 (76.7)	50 (64.1)	0.54	0.058
Smoke status at surgery				
Never	93 (58.5)	33 (42.3)	0.52	**0.027**
Former	55 (34.6)	37 (47.4)	1.71	0.078
Current	11 (6.9)	8 (10.3)	1.54	0.53
Previous resections	22 (13.8)	18 (23.1)	1.86	0.11
Laparoscopic resection	51 (32.1)	34 (43.6)	1.64	0.11
Anastomosis type			0.62	0.26
Side-to-side anastomosis	137 (86.2)	62 (79.5)		
End-to-end anastomosis	22 (13.8)	16 (20.5)		
Number of anastomoses >1	13 (8.2)	3 (3.8)	0.45	0.28
Presence of infectious complications	20 (12.6)	21 (26.9)	2.56	**0.010**
Presence of non-infectious complications	11 (6.9)	4 (5.1)	0.73	0.78
Presence of IASC	11 (6.9)	9 (11.5)	1.76	0.34
Immunomodulator postoperatively	97 (61.0)	36 (46.2)	0.55	**0.043**
Anti-TNF drugs postoperatively	16 (10.1)	3 (3.8)	0.36	0.13

Bold values indicate statistical significance ($p < 0.05$)

Table 3 Patients' characteristics and univariate analysis of variables associated with early surgical recurrence

Characteristics	IR = 1 (220)	IR > 1 (17)	OR	*p* value
Gender, male/female	151/69	12/5	1.10	1.0
Age at diagnosis				
≤16	41 (18.6)	6 (35.3)	2.38	0.18
17–40	164 (74.5)	11 (64.7)	0.63	0.55
>40	15 (6.8)	0	0.38	0.61
Age at surgery				
≤16	4 (1.8)	0	1.38	1.0
17–40	137 (62.3)	11 (64.7)	1.11	0.84
>40	79 (35.9)	6 (35.3)	0.97	0.96
Disease location				
Ileal	99 (45)	5 (29.4)	0.51	0.31
Colonic	44 (20)	2 (11.8)	0.53	0.54
Ileocolonic	76 (34.5)	10 (58.8)	2.71	0.081
Upper GI	1 (0.5)	0	4.18	1.0
Disease behavior				
Non-stricturing, non-penetrating	24 (10.9)	1 (5.9)	0.51	1
Stricturing	114 (51.8)	11 (64.7)	1.71	0.44
Penetrating	82 (37.3)	5 (29.4)	0.70	0.61
Albumin ≤30 g/L the day before surgery	45 (20.5)	3 (17.6)	1.20	0.781
CRP ≤10 g/L the day before surgery	158 (71.8)	14 (82.4)	0.43	0.512
Previous resections	36 (16.4)	4 (23.5)	1.57	0.50
Smoker at Surgery				
Never	121 (55)	5 (29.4)	0.34	**0.047**
Former	84 (38.2)	8 (47.1)	1.44	0.64
Current	15 (6.8)	4 (23.5)	4.21	**0.036**
Laparoscopic resection	82 (37.3)	3 (17.6)	0.36	0.17
Anastomosis type				
Side-to-side anastomosis	187 (85)	12 (70.6)	0.42	0.16
End-to-end anastomosis	33 (15)	5 (29.4)		
Number of anastomoses >1	16 (7.3)	0	0.35	0.61
Presence of infectious complications	37 (16.8)	4 (23.5)	1.52	0.51
Presence of non-infectious complications	12 (5.5)	3 (17.6)	3.71	0.081
Presence of IASC	16 (7.3)	4 (23.5)	3.92	**0.043**
Immunomodulator postoperatively	127	6	0.40	0.12
Anti-TNF drugs postoperatively	19 (8.6)	0	0.3	0.37

Bold values indicate statistical significance ($p < 0.05$)

IR intestinal resection

smoker ($p = 0.036$) and presence of IASCs ($p = 0.043$) were risk factors for repeat resections within 1 year after the initial resection, while never-smoking ($p = 0.047$) was a protective factor for early re-operations (Table 3).

Multivariate analysis

We then used multivariate logistic regression to confirm the impact of univariate significant factors on CD clinical recurrence within 1 year after resections. Presence of infectious complications (OR 2.99; 95% CIs, 1.42–6.32; $p = 0.004$) remained a significant risk factor, and never-smoking (OR 0.326; 95% CIs, 0.18–0.59; $p < 0.0001$) was still a protective factor. But the postoperative use of immune-modulator (OR 0.64; 95% CIs, 0.36–1.14; $p = 0.129$) lost its protective effect. In the multivariate logistic regression for risk factors of early surgical recurrence, the current smoker (OR 5.41; 95% CIs, 1.36–21.5; $p = 0.017$) and presence of IASCs (OR 6.77; 95% CIs, 1.61–28.5; $p = 0.009$) remained the risk factors, while never-smoking (OR 0.16; 95% CIs, 0.045–0.58; $p = 0.005$) was still found to be a protector (Table 4).

Table 4 Multivariate analysis of the risk factors associated with the early postoperative recurrence

Factors	OR	95% CI	*p* value
Clinical recurrence			
Never-smoking	0.326	0.18–0.59	<0.0001
Presence of infectious complications	2.99	1.42–6.32	0.004
Surgical recurrence			
Never-smoking	0.16	0.045–0.58	0.005
Smoker at surgery	5.41	1.36–21.5	0.017
Presence of IASC	6.77	1.61–28.5	0.009

Discussion

Postoperative recurrence is an emerging central problem in the management of CD. Previous studies indicated an intensive strategy, such as earlier use of anti-TNF therapy after surgery could reduce clinical recurrence [16, 17], but the optimal use of such therapy has not been established. Revealing risk factors for early clinical recurrence is helpful in CD postoperative management.

Endoscopic recurrence can predict clinical recurrence and other long-term outcomes and has been used to tailor postoperative therapy. However, in the POCER study, the rate of clinical recurrence was still high at 18 months after surgery even the authors stepped up the therapy according to the endoscopic finds at 6 months [17]. Earlier use of an intensive therapy according to the predictors of early clinical recurrence may help decrease the risk of recurrence further.

In the present study, we aimed to identify risk factors for early postoperative clinical and surgical recurrence, and results showed the presence of postoperative infectious complications was associated with an increased risk of early clinical recurrence after intestinal resection, while never-smoking may reduce this risk. In addition, the presence of IASCs and smoker at the time of surgery were possible independent risk factors for surgical recurrence within 1 year after the initial surgery.

The negative effects of smoke on CD recurrence both in the short and in the long term have been reported by numerous studies [11, 12]. Our study confirmed that CD patients who never smoked were at a lower risk of early clinical recurrence and surgical recurrence. Besides, smoking at the time of surgery was associated with a higher risk for re-operation due to disease recurrence within 1 year after surgery. Therefore, the cessation of smoking is essential in the preoperative management of CD.

The incidence of postoperative complications in CD is high, range from 4.5 to 30% [18–20]. The impact of complications on economic cost, duration of hospital stay, and patients' quality of life has been established, and risk factors for postoperative complications were also evaluated by previous studies [21, 22]. To our knowledge, this is the first study identifying presence of infectious complications as one risk factor for early clinical recurrence after resections in CD. The influence of postoperative complications on CD long-term outcomes has been reported by several studies. Holzheimer et al. [23] detected the development of postoperative complications was an independent predictor for CD recurrence in 4.5 years follow-up. Besides, Riss et al. found a significant correlation between postoperative complications and surgical recurrence of CD in 8.4 (±2.4) years follow-up, and Abdelaal et al. confirmed this correlation in pediatric CD recently [8, 10]. In addition, another study analyzed 311 patients with resection for CD, and the presence of IASCs could also lead to increased number of repeat resections [24]. In summary, the presence of postoperative infectious complications seems to play a role in CD clinical and surgical recurrence both in the short term and in the following years. But these data did not prove causal relations between postoperative complications and CD recurrence. It can be assumed that patients with a more severe course of disease are at an increased risk to develop postoperative IASCs, but at the same time they are at an increased risk for postoperative recurrence, especially surgical recurrence, which means the development of postoperative infectious complications itself reflects a severe disease phenotype, which need a greater attention after surgery. At the same time, the severe inflammatory response caused by postoperative complications, no matter IASCs or wound infections, may trigger the early clinical recurrence of CD.

Although the serum albumin ≤30 g/L and abnormal CRP levels have been identified as risk factors for the postoperative complications (22), our study failed to find any association between abnormal albumin/CRP level and early postoperative recurrence. This indicated that the influence of postoperative infectious complications on CD early clinical recurrence after surgery may result from the complications themselves rather than the poor nutritional and inflammatory status before surgery.

Anastomotic technique may also affect the outcomes of CD surgery. Our previous meta-analysis indicated that compared with end-to-end or end-to-side anastomosis, side-to-side anastomosis may lead to fewer surgical recurrence because of its wide lumen configuration [25]. In 2003, a new anastomotic technic (Kono-S anastomosis) for CD was developed, and recent study reported this kind of anastomosis was safe and effective in reducing the risk of surgical recurrence in CD. The 5 and 10 years surgical recurrence-free survival rate was up to 98.6% in Japan group, and no surgical recurrence was observed in US group with a median follow-up of 32 months. In the present study, only end-to-end and side-to-side

anastomoses, mainly side-to-side, were performed, and no influence of anastomotic technique on the early clinical and surgical recurrence was observed [26]. More studies are needed to confirm the effect of Kono-S anastomosis in reducing postoperative clinical and surgical recurrence in CD. Immunosuppressive medications are routinely used postoperatively in CD patients with clinical risk factors. Although the postoperative use of immune-modulator was associated with a lower rate of postoperative clinical recurrence within 1 year after surgery in our univariate analysis, its protective effect was not detected by the multivariate analysis. At the same time, some previous studies have demonstrated that azathioprine may decrease the likelihood of clinical recurrence and re-operation in CD [27, 28]. Patients with risk factors for postoperative recurrence should receive immune-modulators, but a more active therapy should be considered in patients at high risk of early clinical and surgical recurrence.

Anti-TNF therapy is most effective for prevention of CD postoperative endoscopic and clinical recurrence. However, our results failed to found the association between postoperative use of anti-TNFs and early CD clinical recurrence. This may partly because the small number of patients (19 patients) who received anti-TNF therapy after surgery was not enough to test the difference. Limited data are available for the effect of anti-TNF drugs on surgical recurrence. In a case–control study, use of a TNF inhibitor was found to be a protector for surgical recurrence by univariate analysis but not multivariate regression [29].

There are several limitations of our study. First, this was a single center retrospective study; thus, our study could be biased in some way. Besides, the sample size may be not large enough to analyze all potential risk factors. In addition, the small number of patients suffered surgical recurrence may impact the applicability of findings about risk factors for early re-operation.

In conclusion, our study indicated in CD patients undergoing resection with primary anastomosis, the presence of postoperative infectious complications was associated with a higher risk of clinical recurrence within 1 year after surgery. An early intensive postoperative therapy like anti-TNF drugs in these patients should be considered.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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