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ABOUT COVER

Editorial board member of *World Journal of Clinical Cases*, Dr. El Ghoch is a Full Professor in the Faculty of Health Sciences, Beirut Arab University, Lebanon. Having received his MD degree from University of Bologna, Italy in 2005, and undertook his postgraduate degree in Clinical Nutrition at the University of Modena and Reggio Emilia, Italy in 2009. In the following 10 year, he had a wide clinical and research activity in Italy in the field of obesity and eating disorders, and gained an international leadership in the study of the body composition in anorexia nervosa. In October 2018 he was appointed as Professor in the Clinical Nutrition, and Chairperson of the Department of Nutrition and Dietetics, Beirut Arab University, Lebanon. His ongoing research interests are body composition, physical activity, weight cycling, etc.

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Retrospective Study

Correlation between age of onset and gastrointestinal stenosis in hospitalized patients with Crohn's disease

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Abstract

BACKGROUND

Patients affected by Crohn's disease (CD) are more likely to develop gastrointestinal stenosis and often undergo surgery during the duration of disease.

AIM

To identify the risk factors for gastrointestinal stenosis in hospitalized CD patients in China.

METHODS

The clinical data of CD patients hospitalized at the Seventh Medical Center, Chinese People's Liberation Army General Hospital from January 2010 to December 2018 were included. Patients with gastrointestinal stenosis were compared to those without gastrointestinal stenosis for clinical variables. The risk factors for gastrointestinal stenosis were identified using univariate and multivariable logistic regression analyses. The treatments for patients with gastrointestinal stenosis were analyzed, and the characteristics of different treatment methods were discussed.

RESULTS

The incidence of gastrointestinal stenosis was 59.02% in the 122 hospitalized CD patients. Age of onset of more than 40 years (odds ratio [OR] = 3.072, 95% confidence interval [CI]: 1.298-7.272, $P = 0.009$) and duration of disease of more than 5 years (OR = 2.101, 95% CI: 1.002-4.406, $P = 0.048$) were associated with the occurrence of gastrointestinal stenosis. Fifteen (20.83%) patients did not undergo surgery and received internal medicine and nutrition treatment. Surgical treatments were performed in 72.22% (52) of cases. The rate of postoperative complications was 15.38% (8 cases), and during a median follow-up period of 46 mo, 11.54% (6 cases) underwent reoperation. A total of 29.17% (21 cases) were

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treated with endoscopic therapy, and during a median follow-up period of 32 mo, 76.19% (16 cases) had no surgical event, 23.81% (5 cases) failed to avoid surgical treatments, and no serious postoperative complications occurred after endoscopic therapy.

CONCLUSION

Age of onset of more than 40 years and duration of disease of more than 5 years may be strongly correlated with a higher risk of gastrointestinal stenosis in hospitalized CD patients. Endoscopic therapy for gastrointestinal stenosis is relatively safe and effective, and may help to prevent or delay surgery.

Key words: Crohn's disease; Gastrointestinal stenosis; Age of onset; Duration of disease; Endoscopy; Surgery

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Core tip: We retrospectively analyzed the clinical information of 122 cases of hospitalized patients with Crohn's disease. Demographics, disease activity, classification, treatment, and complications were compared between patients with and without gastrointestinal stenosis. It was found that age of onset of more than 40 years and duration of disease of more than 5 years were correlated with the occurrence of gastrointestinal stenosis. Endoscopic therapy has gradually become one of the main methods for the treatment of Crohn's disease-related gastrointestinal stenosis due to its safe and effective characteristics.

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INTRODUCTION

Crohn's disease (CD) is a chronic, non-specific inflammatory bowel disease with unknown aetiology, and its incidence and prevalence are increasing year by year. The complication rate of CD can be as high as 50%-70%^[1,2], and gastrointestinal stenosis is the most common serious complication, often leading to a loss of labour capacity and large investment of medical resources. The diagnosis of gastrointestinal stenosis is consistent with a sharp decline in quality of life, with up to 80% of patients having surgery at least once in their lifetime^[3]. In the past 60 years, with advances in treatment, the surgical risk at 1 year, 5 years, and 10 years after CD diagnosis has significantly decreased ($P < 0.05$)^[4]. To reduce the surgical rate and improve the quality of life, exploring the factors related to gastrointestinal stenosis and the characteristics of its treatment is very important.

The aim of this study was to analyse the history of the disease and the medical treatment of patients affected by CD to explore any significant risk factors and the characteristics of treatment for gastrointestinal stenosis.

MATERIALS AND METHODS

Population

The patients affected by inflammatory bowel disease admitted to the Seventh Medical Center, Chinese PLA General Hospital from January 2010 to December 2018 were analyzed, and 122 patients with a clear diagnosis of CD who met the screening criteria were included in the study.

The diagnosis of CD was based on the "Third European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease"^[5]. Gastrointestinal stenosis was defined as CD-associated gastrointestinal stenosis, including inflammatory stenosis,

fibrous stenosis, and mixed stenosis, and can be confirmed by at least one of digestive endoscopy, computed tomography enterography, and magnetic resonance imaging enterography. The age of onset was the age at which the patient first developed symptoms (confirmed by tracing the patient's medical history). Related complications included gastrointestinal perforation, gastrointestinal bleeding, thrombosis, toxic megacolon, gastrointestinal fistula, severe malnutrition, infection, and neoplastic lesions.

The following inclusion criteria were used: (1) During the study period, CD patients treated at our centre were hospitalized; (2) The first diagnosis could clearly confirm the diagnosis of CD; and (3) The first diagnosis was suspected, and the patients' diagnosis of CD was identified during the follow-up period of the study. The exclusion criteria were as follows: (1) Patients with CD who were simply followed in the outpatient clinic; (2) Patients who had not yet been diagnosed with CD during the follow-up period; and (3) Patients lost to follow-up.

Methods

Using a retrospective study method, 122 patients with CD included in the study were divided into a gastrointestinal stenosis group (72 cases) and a non-gastrointestinal stenosis group (50 cases) for comparative analysis. Possible risk factors for gastrointestinal stenosis include gender, age of onset, course of disease, ileal involvement, degree of disease activity, parenteral manifestations, application of biologics and corticosteroids, and related complications. The treatments were also analyzed to explore the characteristics.

The follow-up method was mainly based on the medical records of the inpatients. Patients with no inpatient medical records within 3-6 mo up to December 2018 were followed by telephone or consultations of outpatient data. Due to the characteristics of retrospective studies, the ethics committee of our medical center verified that the ethics review was not necessary, and all study participants' rights to informed consent were waived.

Statistical analysis

The SPSS 20.0 statistical software package was used for statistical analyses and processing. The variables are presented as medians (ranges), the mean $\pm$ SD, or numbers (percentages). The comparison of the categorical variables was performed using the chi-square test or Fisher's exact test as appropriate; the Wilcoxon rank-sum test was used for quantitative and ordinal variables.

The association between variables and gastrointestinal stenosis was assessed using univariate and multivariable logistic regression analyses. Model building was conducted by means of a variable selection based on an initial screening of variables ($P < 0.2$) using univariate analysis, and then multifactor logistic regression analysis was performed. All P values refer to two-tailed tests of significance. $P < 0.05$ was considered significant.

RESULTS

General information

Details regarding demographics, history, activity, and site of involvement of the 122 patients included in the study are reported in Table 1. The majority of the patients were male (69.67%), the mean age of onset was 34.72 ± 15.15 years, and the median duration of the disease was 64 mo (1-492 mo). The incidence of gastrointestinal stenosis was 59.02%.

Factors related to gastrointestinal stenosis

Seventy-two (59.02%) patients were diagnosed with gastrointestinal stenosis, and 50 patients were included in the non-gastrointestinal stenosis group. The comparison between the two groups is shown in Table 2. Age of onset ($P = 0.021$), duration of disease ($P = 0.010$), and ileal involvement ($P = 0.039$) were associated with gastrointestinal stenosis.

In multivariable regression analysis (Table 3), age of onset [odds ratio (OR) = 1.028, $P = 0.046$] and duration of disease (OR = 1.008, $P = 0.013$) were confirmed to be significantly associated with gastrointestinal stenosis. Stratified analysis (Table 4) showed that age of onset of more than 40 years ($P = 0.009$, OR = 3.072, 95% confidence interval [CI]: 1.298-7.272) and duration of disease of more than 5 years ($P = 0.048$, OR =

Table 1 Demographic variables and disease characteristics of Crohn's disease

Variable	No. or median/mean	% or range
Total number of patients	122	
Male gender	85	69.67
Age of onset (yr)	34.72	15.15
Duration of disease (mo)	64	1-492
Gastrointestinal stenosis	72	59.02
L1	33	27.05
L2	27	22.13
L3	59	48.36
L4	2	1.64
L1 + L4	1	0.82
B1 (B1p)	42 (5)	34.43
B2 (B2p)	65 (2)	53.28
B3 (B3p)	8 (1)	6.56
B2 + B3 ¹	7	5.74
Disease activity: Mild	25	20.49
Disease activity: Moderate	84	68.85
Disease activity: Severe	13	10.66

¹As the disease progresses, stricturing and penetrating disease behaviors can coexist. L and B: The phenotype of the Montreal classification of inflammatory bowel disease. p: Combined with perianal disease^[29].

2.101, 95% CI: 1.002-4.406) were correlated with the occurrence of gastrointestinal stenosis.

Treatments for gastrointestinal stenosis

The treatments for gastrointestinal stenosis are shown in [Table 5](#).

Surgical treatments were performed in 52 (72.22%) patients. The incidence of postoperative complications was 15.38% and the rate of reoperation was 11.54% during a median follow-up period of 46 mo (1-204 mo). Postoperative complications included postoperative bleeding in four cases, incision split and infection in two, postoperative anastomotic fistula in one, and abdominal wall fistula in one.

Endoscopic therapy was performed in 21 (29.17%) patients, and 76.19% of the patients had no surgical events during a median follow-up period of 32 mo (2-88 mo), including five patients treated with endoscopic therapy alone and 11 patients with anastomotic stenosis. No serious postoperative complications occurred after endoscopic therapy.

DISCUSSION

Gastrointestinal stenosis is one of the most common serious complications of CD, and its occurrence and development are often related to poor disease control. Approximately 11% of patients have developed gastrointestinal stenosis at the beginning of CD diagnosis^[6], while over 30% would develop gastrointestinal stenosis within 10 years after CD diagnosis^[2,7]. Ileum-type CD patients tend to develop stenosis complications, while colonic- or ileocolic-type CD patients are more likely to have penetration complications^[6]. In this study, the incidence of gastrointestinal stenosis was relatively high (59.02%), which was considered to be related to the following factors. For example, our medical center was a tertiary medical institution, some patients had received non-systematic treatments before visiting our center. In addition, the number of hospitalized CD patients was relatively small, the degree of disease

Table 2 Univariate comparison between gastrointestinal stenosis group and non-gastrointestinal stenosis group

Variable	Gastrointestinal stenosis	Non-gastrointestinal stenosis	P value
Total number of patients	72 (59.02%)	50 (40.98%)	
Male gender	49 (68.06%)	36 (72.00%)	0.761
Age of onset (yr)	37.61 ± 15.14	30.84 ± 14.67	0.021
Duration of disease (mo)	72 (11-492)	45 (3-240)	0.010
Exposure to corticosteroid	23	20	0.360
Exposure to azathioprine	22	13	0.247
Exposure to biologics	35	19	0.585
Disease activity: Severe	11	2	0.065
Disease involved: Ileum	50	44	0.039
Parenteral performance	5	6	0.243
Perforation	4	4	0.594
Gastrointestinal bleeding	5	1	0.243
Thrombosis	1	0	NA
Fistula	7	10	0.114
Severe malnutrition	9	5	0.671
Infection	7	6	0.689
Neoplastic lesions	1	1	0.795

NA: Not available.

Table 3 Multivariable logistic regression analysis between gastrointestinal stenosis group and non-gastrointestinal stenosis group

Variable	β	SE	Odds ratio (95%CI)	P value
Age of onset	0.028	0.014	1.028 (1.000-1.056)	0.046
Duration of disease	0.008	0.003	1.008 (1.002-1.015)	0.013
Fistula	-0.833	0.587	0.435 (0.138-1.373)	0.156
Disease activity: Severe	1.524	0.841	4.593 (0.883-23.896)	0.070
Disease involved: Ileum	-1.003	0.525	0.367 (0.131-1.025)	0.056

CI: Confidence interval.

activity was relatively serious, and the lesion sites of the patients were mostly concentrated in the ileum and ileocecum.

With the extension of the duration of disease, the cumulative incidence of CD-related gastrointestinal stenosis is increasing, which is largely consistent with the results of this study. Previous literature showed that duration and activity of the disease, ileal involvement, need for corticosteroids at diagnosis, perianal diseases, and diagnostic age of less than 40 years were associated with gastrointestinal stenosis and early intestinal complications in CD patients^[8,9], and fistula disease has a high positive predictive value for the occurrence of gastrointestinal stenosis (86.2%)^[10]. In this study, we concluded that age of onset of more than 40 years was significantly correlated with gastrointestinal stenosis ($P < 0.05$). This may be related to the weak physiological function, decreased immune function, and poor repair ability of patients with an age of onset of more than 40 years and the second smaller peak age of the disease around 50-60 years old^[11,12]. It may also be related to the ethnicity and region of the CD population in China. The age of onset is generally younger than the age of diagnosis, which may be helpful to better understand the whole disease process. Therefore, the authors believe that the potential predictive value of age of onset for the occurrence of

Table 4 Correlation between age of onset or duration of disease and Crohn's disease-related gastrointestinal stenosis

Variable	Gastrointestinal stenosis (n = 72)	Non-gastrointestinal stenosis (n = 50)	P value	OR (95%CI)
Age of onset > 40 yr	29	9	0.009	3.072 (1.298-7.272)
Age of onset ≤ 40 yr	43	41		
Duration of disease > 5 yr	39	18	0.048	2.101 (1.002-4.406)
Duration of disease ≤ 5 yr	33	32		

OR: Odds ratio; CI: Confidence interval.

Table 5 Treatments for Crohn's disease-related gastrointestinal stenosis

Variable	n	%
Total number of patients	72	
Internal medicine and nutrition treatment	15	20.83
Surgical treatment	52	72.22
Endoscopic therapy	21	29.17
Surgical treatment		
Reoperation	6	11.54
Postoperative complications	8	15.38
Endoscopic therapy		
No surgery events	16	76.19
Undergo surgery	5	23.81
Postoperative complications	0	0

gastrointestinal stenosis is also worthy of attention, but this also needs further evidence from prospective cohort studies over time.

The pathological types of gastrointestinal stenosis can be divided into inflammatory stenosis and fibrous stenosis, which are essentially the manifestation of the same disease at different stages and often exist at the same time. To date, there has been no reliable treatment to prevent the formation of gastrointestinal fibrosis and stenosis^[13,14], but it has also been reported that azathioprine can delay the occurrence of postoperative complications of fibrous stenosis in CD patients^[15]. Relying on the multidisciplinary team, our medical center formulated "individualized" therapy and highlighted the important role of nutritional treatment. A total of 20.83% of the patients were treated with internal medicine and nutritional therapy to delay the progression of symptoms of gastrointestinal stenosis, and no surgical treatment was performed during the follow-up period. However, due to the relatively short follow-up period, further follow-up studies are needed.

With the development of endoscopy, endoscopic therapy has gradually become one of the most important ways of treating CD-related gastrointestinal stenosis and anastomotic stenosis. Endoscopic therapy mainly includes endoscopic balloon dilatation (EBD), endoscopic stricturectomy (EST), endoscopic stenting, and endoscopic local spray and injection of drugs. EBD has a high immediate success rate, with a symptom remission rate of 42%-90% in a short period of time^[16], and can delay surgery for approximately 6.5 years^[17]. Only 32.8% of patients needed surgery during the follow-up period of 3.3 ± 3.1 years (0-12 years) after EBD^[18], and the postoperative complication rate was 4%-4.6%^[19,20]. In this study, 76.19% of patients did not undergo surgery after a median follow-up of 32 mo (2-88 mo), thus delaying the occurrence of surgery in most patients. There were no serious postoperative complications during the follow-up period. However, endoscopic therapy has some disadvantages, such as stricter indications, increased hospitalization times for dilation, poor long-term efficacy, difficulty in avoiding surgeries in some patients, and high bleeding risk of EST^[21].

To date, surgery is still the main treatment for CD-related gastrointestinal stenosis.

Approximately 80% of CD patients require intestinal resection, and up to 65% undergo a second surgical resection within 10 years^[3]. The surgical methods for gastrointestinal stenosis are divided into two types: Enterectomy and stenoplasty. In this study, the surgical rate was 72.22%, which was roughly the same as that reported above, while the reoperation rate was 11.54% during a median follow-up period of 46 mo. The postoperative complication rate of CD surgery was 21.0%-40.9%^[22-24], and the preoperative use of TNF- α biologics could increase the postoperative complication rate^[22,25]. Appropriate surgical timing, the indications and procedures of surgical intervention, and perioperative nutritional support treatment, including the use of exclusive enteral nutrition, can reduce the risk of postoperative complications in CD patients^[26,27], and the postoperative complication rate of CD patients has been reduced to less than 10% in the literature^[28]. In this study, the postoperative complication rate was 15.38%^[29].

Limitations of the study

As this is a retrospective study, the level of evidence is limited, but due to the large sample size, the results are relatively reliable. Additionally, the age of onset may be biased due to the subjective factors of patients and physicians, but the research data were mainly from the inpatient medical records, which were highly reliable. Next, the patients included in the study were all hospitalized in a single medical center, which failed to account for the characteristics of outpatients and patients in other medical centers and regions. However, the inpatients cover most areas in northern China, and fewer outpatients are only followed at our medical center, so the results of the study are of certain clinical value. Finally, factors and follow-up period were relatively limited, and some patients were followed by telephone or at the outpatient clinic. It was necessary to continue follow-up and conduct a multicenter prospective study.

In conclusion, age of onset of more than 40 years and duration of disease of more than 5 years are correlated with the occurrence of CD-related gastrointestinal stenosis in hospitalized patients, which may be a potential predictor in the future. Endoscopic treatment has a high success rate and is relatively safe, which could delay or prevent the occurrence of surgery. However, due to its stricter indications and higher requirements for surgeons' endoscopic skills and patients' compliance, the wider application of endoscopic treatment is partially limited.

ARTICLE HIGHLIGHTS

Research background

With the development of society, the incidence and prevalence of Crohn's disease (CD) are increasing. CD-related gastrointestinal stenosis is one of the most common serious complications, leading to surgery, loss of labor, increased medical costs, and reduced quality of life. At present, there is a lack of clinical data on CD-related gastrointestinal stenosis in China.

Research motivation

The identification of the factors related to CD-related gastrointestinal stenosis and the analysis of its treatment methods are conducive to improving clinicians' understanding of this disease and reducing or delaying the occurrence of gastrointestinal stenosis.

Research objectives

The primary aim of this study was to investigate the related factors and treatments for CD-related gastrointestinal stenosis.

Research methods

The clinical data of CD patients hospitalized at our medical center from January 2010 to December 2018 were included, and patients with gastrointestinal stenosis were compared to a control group (non-gastrointestinal stenosis) for clinical variables. The risk factors for gastrointestinal stenosis were identified using univariate and multivariable logistic regression analyses. The treatments for patients with gastrointestinal stenosis were analyzed, and the characteristics of different treatment methods were discussed.

Research results

The incidence of gastrointestinal stenosis was 59.02% in the 122 hospitalized CD patients. Age of onset of more than 40 years (odds ratio = 3.072, 95%CI: 1.298-7.272, $P = 0.009$) and duration of disease of more than 5 years (odds ratio = 2.101, 95%CI: 1.002-4.406, $P = 0.048$) were associated with the occurrence of gastrointestinal stenosis. Fifteen (20.83%) patients did not undergo surgery and received internal medicine and nutrition treatment. Surgical treatments were performed in 72.22% (52 cases). The rate of postoperative complications was 15.38% (8 cases), and during a median follow-up of 46 mo, 11.54% (6 cases) underwent surgery again. A total of 29.17% (21 cases) were treated with endoscopic therapy, and during a median follow-up of 32 mo, 76.19% (16 cases) had no surgical event, 23.81% (5 cases) failed to avoid surgical treatments, and no serious postoperative complications occurred after endoscopic therapy.

Research conclusions

In this study, we found for the first time that age of onset of more than 40 years may be a risk factor for CD-related gastrointestinal stenosis, and the correlation between duration of disease of more than 5 years and CD-related gastrointestinal stenosis was also found, but no significant correlation between fistula and gastrointestinal stenosis was found. Endoscopic therapy for gastrointestinal stenosis is relatively safe and effective, and may help to prevent or delay surgery. All these are beneficial to reduce the incidence of gastrointestinal stenosis and improve its therapeutic effect in the future clinical practice.

Research perspectives

Considering the limitations in the selection of participants in this study, further studies are warranted to define the profile of predictors of CD-related gastrointestinal stenosis.

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