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## Retrospective Study

## Development of a prognostic model for one-year surgery risk in Crohn's disease patients: A retrospective study

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Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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**Abstract****BACKGROUND**

Accelerated therapeutic treatment should be considered in patients with progressive Crohn's disease (CD) to prevent complications as well as surgery. Therefore, screening for risk factors and predicting the need for early surgery are of great importance in clinical practice.

**AIM**

To establish a model to predict CD-related early surgery.

**METHODS**

This was a retrospective study collecting data from CD patients diagnosed at our inflammatory bowel disease center from January 1, 2012 to December 31, 2016. All data were randomly stratified into a training set and a testing set at a ratio of 8:2. Multivariable logistic regression analysis was conducted with receiver operating characteristic curves constructed and areas under the curve calculated. This model was further validated with calibration and discrimination estimated. A nomogram was finally developed.

**RESULTS**

A total of 1002 eligible patients were enrolled with a mean follow-up period of  $53.54 \pm 13.10$  mo. In total, 24.25% of patients received intestinal surgery within 1 year after diagnosis due to complications or disease relapse. Disease behavior

disclose.

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(B2: OR [odds ratio] = 6.693,  $P < 0.001$ ; B3: OR = 14.405,  $P < 0.001$ ), smoking (OR = 4.135,  $P < 0.001$ ), body mass index (OR = 0.873,  $P < 0.001$ ) and C-reactive protein (OR = 1.022,  $P = 0.001$ ) at diagnosis, previous perianal (OR = 9.483,  $P < 0.001$ ) or intestinal surgery (OR = 8.887,  $P < 0.001$ ), maximum bowel wall thickness (OR = 1.965,  $P < 0.001$ ), use of biologics (OR = 0.264,  $P < 0.001$ ), and exclusive enteral nutrition (OR = 0.089,  $P < 0.001$ ) were identified as independent significant factors associated with early intestinal surgery. A prognostic model was established and further validated. The receiver operating characteristic curves and calculated areas under the curves (94.7%) confirmed an ideal predictive ability of this model with a sensitivity of 75.92% and specificity of 95.81%. A nomogram was developed to simplify the use of the predictive model in clinical practice.

## CONCLUSION

This prognostic model can effectively predict 1-year risk of CD-related intestinal surgery, which will assist in screening progressive CD patients and tailoring therapeutic management.

**Key words:** Crohn's disease; Prognostic model; Nomogram; Early surgery; Inflammatory bowel disease; Retrospective study

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**Core tip:** Predicting the likelihood of Crohn's disease-related early surgery is of great importance in treatment strategy monitoring. Disease behavior, smoking, body mass index and C-reactive protein level at diagnosis, previous perianal or intestinal surgery, maximum bowel wall thickness, use of biologics, and exclusive enteral nutrition were identified as independent significant factors associated with early intestinal surgery. A validated prognostic model and a nomogram were established to aid clinical practice.

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## INTRODUCTION

There has been a sharp rise in the prevalence of Crohn's disease (CD) in Asian countries over the last decade<sup>[1]</sup>. CD patients exhibit heterogenous disease progression. Some patients have quiescent CD<sup>[2,3]</sup>, which remains stable for long periods of time, while others have progressive CD<sup>[4-6]</sup>, and tend to progress to complex complications such as intestinal stenosis or perforation requiring surgery within a year after diagnosis. It is of extreme importance to be able to accurately characterize the differences in disease progression among patients and institute targeted accelerated therapy as necessary.

According to published research, disabling CD is associated with factors such as age less than 40 years old<sup>[7]</sup>, perianal disease<sup>[8,9]</sup>, initial steroid requirement<sup>[10,11]</sup>, and involvement of the upper gastrointestinal tract<sup>[10]</sup>. Population-based cohort studies have reported that 37%-61% of CD patients require surgery within 10 years after diagnosis, 43%-57% of which were identified as having disabling disease<sup>[12-14]</sup>. Progressive CD patients have a higher rate of surgery and shorter interval between diagnosis and surgery<sup>[15,16]</sup>. However, with the emergence of "treat-to-target" theory and widespread application of biologics, factors predicting early CD-related intestinal surgery and progressive CD have varied. Until recently, prognostic models for progressive CD have been lacking. Moreover, region-specific data is necessary, given that disease phenotypes differ among regions and races. Therefore, we conducted a retrospective cohort study aiming to establish a prognostic model to predict the likelihood of intestinal surgery at 1 year after diagnosis, with an aim to guide targeted accelerated therapy for patients at high risk of progressive CD.

## MATERIALS AND METHODS

### Study design and study population

This was a retrospective cohort study collecting data from 1203 CD patients from the inflammatory bowel disease (IBD) center of the Sixth Affiliated Hospital of Sun Yat-Sen University from January 1, 2012 to December 31, 2016. All patients were followed until September 30, 2019 with an average follow-up period of 53 mo and a minimum follow-up period of 32 mo. In total, 201 patients were excluded from the analysis due to incomplete data, loss to follow-up, or death. This study was approved by the ethics committee of Sun Yat-Sen University (2019ZSLYEC-058) and was registered in the Chinese Clinical Trial Registry (ChiCTR1900025751).

### Definition

Diagnosis of CD was made based on a combination of radiographic, endoscopic, and histologic criteria<sup>[17]</sup>. Disease phenotype was classified according to the Montreal classification<sup>[18]</sup>. Serum biomarkers such as C-reactive protein, erythrocyte sedimentation rate, and albumin were collected at the time of diagnosis. Intestinal stenosis was defined by luminal narrowing as well as prestenotic dilation evident on radiologic examinations, or intestinal narrowing which was unable to be passed by endoscope. Penetrating disease was defined as the presence of an abscess or fistula. Perianal disease included perianal fistulas and abscesses. Early abdominal surgery was defined as bowel resection or stoma creation within 1 year after diagnosis due to complications or disease relapse. Therapeutic treatment was categorized as follows: 5-aminosalicylates (oral and/or topical use), corticosteroids (systematic and/or topical use), immunosuppressants (azathioprine, 6-mercaptopurine, methotrexate, cyclophosphamide, or thalidomide), biologics (infliximab or adalimumab), and surgery (abdominal surgery or perianal surgery). Smoking was defined as daily consumption of more than 10 cigarettes for more than 1 year. Alcohol intake was dichotomized around a cut-off of 80 grams of ethanol a day for at least 1 year. Bowel sonography was performed by two experienced gastroenterologists who were blinded to the other procedures. The entire intestinal tract was scanned and bowel wall thickness (BWT) measured in both the longitudinal and transverse slices. A BWT  $\geq 4$  mm was considered abnormal.

### Statistical analysis

Continuous variables are presented as the mean  $\pm$  SD or median  $\pm$  interquartile range, while categorical variables are presented as percentages or proportions. Continuous variables were analyzed using Student's *t*-tests or paired *t*-tests as appropriate, while categorical variables were analyzed using the chi-square or Fisher's exact test. We randomly stratified all the data into a training set and a testing set at a ratio of 8:2 using a random seed of 666. Multivariable logistic regression analysis was conducted to establish a forward stepwise model with receiver operating characteristic curves constructed and areas under the curve (AUC) calculated. The results were then confirmed using a backward elimination procedure. The model was eventually validated with calibration using the Hosmer-Lemeshow goodness-of-fit test, and discrimination was assessed using AUC. A nomogram was established using R software (R Foundation for Statistical Computing, Vienna, Austria). A two-tail *P* value  $< 0.05$  was considered statistically significant. Analyses were performed using IBM SPSS (version 22.0, IBM Corp., Armonk, NY, United States). The statistical methods used in this study were reviewed by Jinxin Zhang from the Department of Medical Statistics, Sun Yat-Sen University.

## RESULTS

### Baseline and follow-up characteristics

A total of 1203 patients with a confirmed diagnosis of CD were enrolled in our study. Of these, 201 (16.7%) patients were excluded for the sake of incomplete data ( $n = 42$ , 20.9%), loss to follow-up ( $n = 156$ , 77.6%), or death ( $n = 3$ , 1.5%). Causes of death included severe infection associated with bone marrow suppression ( $n = 2$ , 66.7%) and cardiac arrest ( $n = 1$ , 33.3%). Of the enrolled patients, 73.65% were male ( $n = 738$ ) (Figure 1), and the mean age at diagnosis was  $28.41 \pm 11.05$  years. The mean follow-up period was  $53.54 \pm 13.10$  mo with a maximum follow-up time of 81 mo.

According to the Montreal classification, the majority of patients were classified as A2 (A1,  $n = 119$ , 11.88%; A2,  $n = 744$ , 74.25%; A3,  $n = 139$ , 13.87%), L3 (L1,  $n = 145$ , 14.47%; L2,  $n = 104$ , 10.38%; L3,  $n = 678$ , 67.66%; L4,  $n = 75$ , 7.49%), and B1 (B1,  $n = 614$ , 61.28%; B2,  $n = 185$ , 18.46%; B3,  $n = 203$ , 20.26%). In this cohort, 40.82% ( $n = 409$ ) of

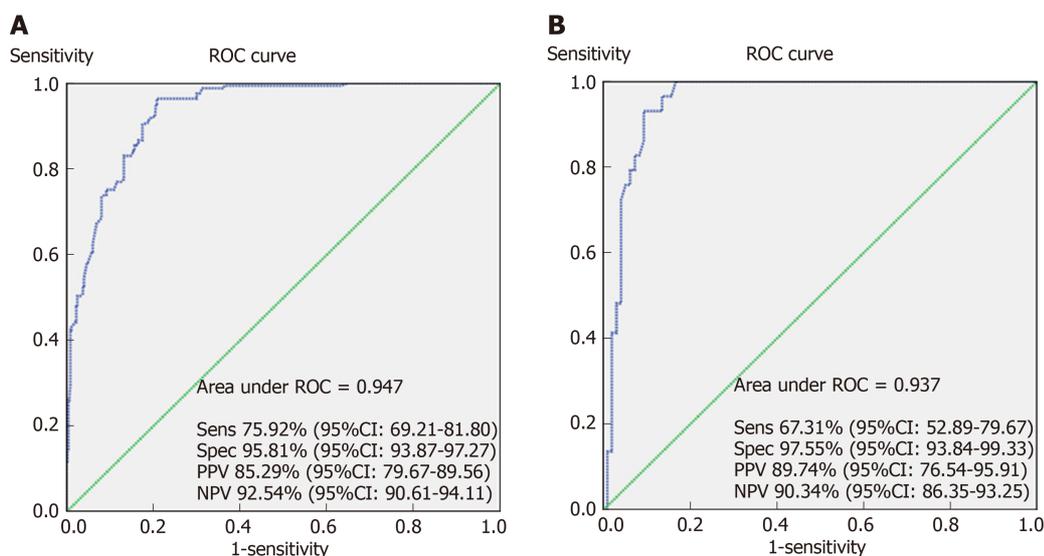


Figure 1 Study flow chart.

patients had previous CD-related intestinal surgery, while 29.84% ( $n = 299$ ) had previous perianal surgery. The main therapies included corticosteroids ( $n = 529$ , 52.79%), immunosuppressants ( $n = 746$ , 74.45%), biologics ( $n = 462$ , 46.11%), and exclusive enteral nutrition ( $n = 230$ , 22.95%), whereas relatively few patients were receiving 5-aminosalicylates ( $n = 202$ , 20.16%). Throughout the study period, 12.87% patients developed complications, including stenosis ( $n = 129$ , 12.87%), perforation ( $n = 139$ , 13.87%), and gastrointestinal bleeding ( $n = 19$ , 1.90%). Nearly a quarter ( $n = 243$ , 24.25%) of patients received intestinal surgery within 1 year. Detailed information regarding patient characteristics is listed in [Table 1](#).

#### **Establishment of a logistic regression model predicting early intestinal surgery**

According to univariate analysis, disease behavior, smoking, body mass index (BMI) and C-reactive protein (CRP) at diagnosis, previous perianal and intestinal surgery, use of biologics, exclusive enteral nutrition, and maximum BWT were significantly associated with early intestinal surgery. The abovementioned factors were evaluated in a multivariable logistic regression analysis, and a prognostic model was established, as shown in [Figure 2](#) [ $X_1$  = Maximum BWT (mm);  $X_2$  = Smoking (0: No, 1: Yes);  $X_3$  = BMI at diagnosis ( $\text{m}/\text{kg}^2$ );  $X_4$  = Previous perianal surgery (0: No, 1: Yes);  $X_5$  = Previous intestinal surgery (0: No, 1: Yes);  $X_6$  = Disease type (stricturing or penetrating disease);  $X_7$  = Use of biologics;  $X_8$  = Use of exclusive enteral nutrition;  $X_9$  = CRP at diagnosis ([Table 2](#))].

#### **Model evaluation and validation and nomogram development**

The receiver operating characteristic curve and calculated AUC (94.7%) confirmed an ideal predictive ability of this model with a sensitivity of 75.92%, specificity of 95.81%, positive predictive value of 85.29%, negative predictive value of 92.54%, positive likelihood ratio of 18.10, and negative likelihood ratio of 0.25 ([Figure 3](#), panel A). The prognostic model was subsequently applied to the validation cohort. Discrimination of the model was acceptable, which confirms a good predictive power and discriminatory ability ([Figure 3B](#)). With respect to calibration, this model showed a good fit using the Hosmer-Lemeshow goodness-of-fit test, with a high level of agreement between calculated risk and the observed outcomes ([Figure 4](#)).

A nomogram was developed to simplify the use of the predictive model in clinical practice ([Figure 5](#)). Probability of early intestinal surgery was easily obtained by calculating the total number of points and matching vertically downward to the risk of surgery at 1 year.

## **DISCUSSION**

In this retrospective study enrolling 1002 CD patients with a mean follow-up period of 53 mo, we identified factors associated with intestinal surgery at 1 year, as follows: Disease behavior, smoking, BMI at diagnosis, previous perianal surgery, previous intestinal surgery, use of biologics, exclusive enteral nutrition, maximum BWT, and

**Table 1 Patient baseline characteristics**

Characteristic	n (%) / mean $\pm$ SD
Male/female	738/264 (73.65/26.35)
Age at diagnosis (yr)	28.41 $\pm$ 11.05
Drinking/not drinking	58/944 (5.79/94.21)
Smoking/not smoking	150/852 (14.97/85.03)
Body mass index at diagnosis (kg/m <sup>2</sup> )	18.58 $\pm$ 2.90
Year of follow-up (mo)	53.54 $\pm$ 13.10
Montreal classification	
Age at diagnosis (%)	
A1	119 (11.88)
A2	744 (74.25)
A3	139 (13.87)
Location at diagnosis	
L1	145 (14.47)
L2	104 (10.38)
L3	678 (67.66)
L4	75 (7.49)
Behavior at diagnosis	
B1	614 (61.28)
B2	185 (18.46)
B3	203 (20.26)
CRP at diagnosis	19.84 $\pm$ 24.25
ESR at diagnosis	34.58 $\pm$ 28.48
Alb at diagnosis	39.14 $\pm$ 25.65
Previous perianal surgery	299 (29.84)
Previous intestinal surgery	409 (40.82)
Complication	287 (28.64)
Stenosis	129 (12.87)
Perforation	139 (13.87)
GI bleeding	19 (1.90)
Treatment	
5-aminosalicylic acid	202 (20.16)
Immunosuppressants	746 (74.45)
Corticosteroids	529 (52.79)
Biologics	462 (46.11)
EEN	230 (22.95)
Surgery within 1 yr after diagnosis	243(24.25)
Surgery within the follow-up period	473 (47.21)

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; Alb: Albumin; GI: Gastrointestinal; EEN: Exclusive enteral nutrition.

CRP level at diagnosis. We combined all associated factors in a prognostic model and established a nomogram to facilitate convenient use in clinical practice so that clinicians can identify patients at risk of early surgery, and implement more aggressive medical management as required. Further, for patients with a high risk of surgery at 1 year, it may be beneficial to consider proactive early surgery, such as to minimize both the duration and expenditure associated with drug therapy.

According to recent cohort studies from Denmark and Canada, 13%, 21%, and 26% of the patients underwent surgical resections after 1, 5, and 10 years, respectively<sup>[19]</sup>. The rate of intestinal surgery at our IBD center was high (24.25%) for the following reasons: Our IBD center was the largest in China for CD patients and a referral center for the entire country; most referred patients had complications and did not respond to medical therapy; our center was particularly famous for gastrointestinal surgery, and thus, a certain part of patients sought surgical treatment here.

Previous research conducted by Zallot *et al*<sup>[20]</sup> suggested that ileal disease and a

**Table 2** Factors associated with possibility of one-year surgery in patients with Crohn's disease

Factor	Univariate analysis			Multivariable logistic regression		
	OR	95%CI	P	OR	95%CI	P
Gender (male <i>vs</i> female)	0.793	0.565-1.113	0.180			
Age (yr)	1.012	0.999-1.025	0.070			
Location (L1 <i>vs</i> L2/L3/L4)						
L2	0.729	0.401-1.324	0.300			
L3	0.853	0.568-1.282	0.445			
L4	0.988	0.526-1.855	0.971			
Behavior (B1 <i>vs</i> B2/B3)						
B2	5.771	3.837-8.680	< 0.001	6.693	3.437-13.032	< 0.001
B3	14.998	10.113-22.242	< 0.001	14.405	7.208-28.790	< 0.001
Maximum BWT	1.391	1.278-1.514	< 0.001	1.965	1.660-2.327	< 0.001
Drinking	1.702	0.970-2.985	0.064			
Smoking	4.359	3.034-6.262	< 0.001	4.135	2.149-7.953	< 0.001
BMI	0.901	0.854-0.950	< 0.001	0.873	0.786-0.968	0.01
Previous perianal surgery	6.776	4.943-9.288	< 0.001	9.483	5.317-16.912	< 0.001
Previous intestinal surgery	5.199	3.794-7.125	< 0.001	8.887	5.045-15.656	< 0.001
5-aminosalicylic acid use	0.709	0.485-1.038	0.077			
Immunosuppressants use	0.974	0.700-1.355	0.877			
Corticosteroid use	0.931	0.697-1.243	0.627			
Biologics use	0.283	0.204-0.392	< 0.001	0.264	0.146-0.476	< 0.001
Exclusive enteral nutrition use	0.359	0.235-0.550	< 0.001	0.089	0.038-0.205	< 0.001
CRP at diagnosis (pathological <i>vs</i> normal)	1.020	1.014-1.026	< 0.001	1.022	1.009-1.036	0.001
ESR at diagnosis (pathological <i>vs</i> normal)	1.005	1.000-1.010	0.058			
Alb at diagnosis (pathological <i>vs</i> normal)	0.981	0.962-1.001	0.058			

CI: Confidence interval; BWT: Bowel wall thickness; BMI: Body mass index; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; Alb: Albumin.

stricturing phenotype significantly increase the risk of resection. Further, changes in disease location as well as progression in behavior were closely linked to a cumulative higher risk of early surgery, as shown in a population-based inception cohort from Denmark<sup>[21]</sup>. According to this prognostic model, disease behavior, including stricturing and penetrating phenotypes, was considered to be a risk factor for early intestinal surgery. However, there was no solid evidence to confirm the link between disease location and surgery risk. In our data, the majority of disease locations at diagnosis were L3 (67.66%), followed by L1 (14.47%) and L2 (10.38%), while L4 accounted for less than 1/10 (7.49%) of all cases. Indeed, disease location distribution differed from the previous report on patients in Denmark<sup>[21]</sup>, which might explain why disease location was not a risk factor in our study.

Smoking is known to increase the risk of surgery in CD patients, with a recent study concluding that it approximately doubled the risk of surgery<sup>[22]</sup>. In our study, we confirmed that smoking exacerbated disease progression and eventually enhanced risk of surgery, as expected based on results from previous studies<sup>[23,24]</sup>. Further, CRP level at diagnosis, indicative of inflammatory processes, was also associated with early surgery, and BMI as a proxy for nutritional status was negatively correlated with the risk of intestinal surgery. Bhattacharya *et al*<sup>[25]</sup> showed that elevated CRP was a predictor of disease relapse as well as exacerbations, based on a clinically quiescent CD cohort, which is comparable to our results. In previous studies, perianal and intestinal surgeries have been associated with a disabling course<sup>[7]</sup>, recurrence<sup>[26]</sup>, and subsequent surgery<sup>[27]</sup>; such factors were found to be independent predictors of early intestinal surgery in this study.

Transabdominal bowel ultrasound can effectively estimate IBD-associated morphological changes in the bowel wall<sup>[28]</sup>. Increased BWT has been observed in active CD patients with intestinal inflammatory infiltration, and patients with intestinal stricture or even obstruction<sup>[29]</sup>. According to our prognostic model, maximum BWT was a significant indicator for early surgery in CD patients, which is consistent with previous research. Since bowel ultrasonography has the advantages of being noninvasive, easily available, patient-friendly, and repeatable, it is widely used

$$P_{1\text{-year surgery}} = \frac{e^{\text{index}}}{1 + e^{\text{index}}}$$

Where prognostic index

$$\begin{aligned} &= -4.276 + 0.676 \times X_1 + 1.419 \times X_2 - 0.136 \times X_3 + 2.249 \\ &\times X_4 + 2.185 \times X_5 + 1.901 \times I[X_6 = \text{stricturing disease}] \\ &+ 2.668 \times I[X_6 = \text{penetrating disease}] - 1.333 \times X_7 - 2.423 \\ &\times X_8 + 0.022 \times X_9 \end{aligned}$$

**Figure 2 Prognostic model.**

in diagnosis, complication screening, and directing treatment.

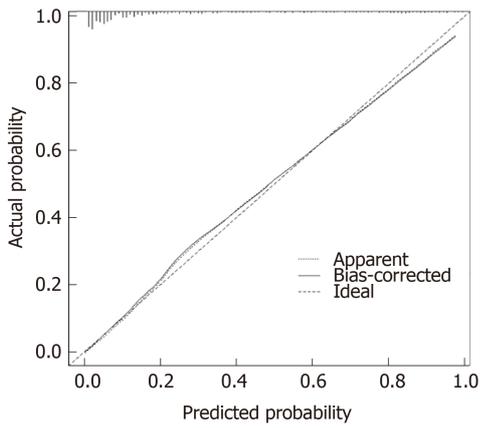
According to the “treat-to-target” approach, mucosal healing<sup>[30]</sup>, histologic remission<sup>[31]</sup>, and even “deep remission” (clinical, endoscopic, and biomarker normalization)<sup>[32]</sup> are the therapeutic goals for gastroenterologists. Therefore, tailored treatments should be considered. Previous research has shown that exclusive enteral nutrition has a similar treatment effect as steroids, especially for remission in pediatric CD<sup>[33]</sup>. Recently, two published studies<sup>[34,35]</sup> from our IBD center have confirmed the therapeutic effect of exclusive enteral nutrition (both through nasogastric tube and orally) in inducing early clinical remission and mucosal healing in adult CD patients with complications. This study showed that 230 (22.95%) patients had received exclusive enteral nutrition treatment during the follow-up period, 76.10% ( $n = 175$ ) of which had complications including intestinal fistula, abdominal abscess, and stricture. Use of exclusive enteral nutrition reduced the risk of surgery, and was found to be an independent protective factor in the prognostic model. To our knowledge, this is the first prognostic model using exclusive enteral nutrition.

In the last decade, CD-related surgery rates have declined. At the same time, use of biologics has become widespread, with biologics becoming a leading therapeutic strategy in CD. As reported by Arieira *et al*<sup>[22]</sup>, biologics prevent phenotype changes and reduce surgery risk in CD patients. In our study, nearly half (45.1%) of the patients had received biologic therapy during the follow-up period, the percentage of which was larger than previous studies. This was because most patients hospitalized in our IBD center had moderate-to-severe active CD with a disabling course, complex complications, or steroid resistance. With treatment goals progressing to deep remission and biologics becoming significantly cheaper to access *via* national medical insurance coverage, it is expected that the use of biologics will increase. In our cohort, we confirmed that use of biologics was a protective factor for early surgery, in keeping with previous studies<sup>[22,36,37]</sup>.

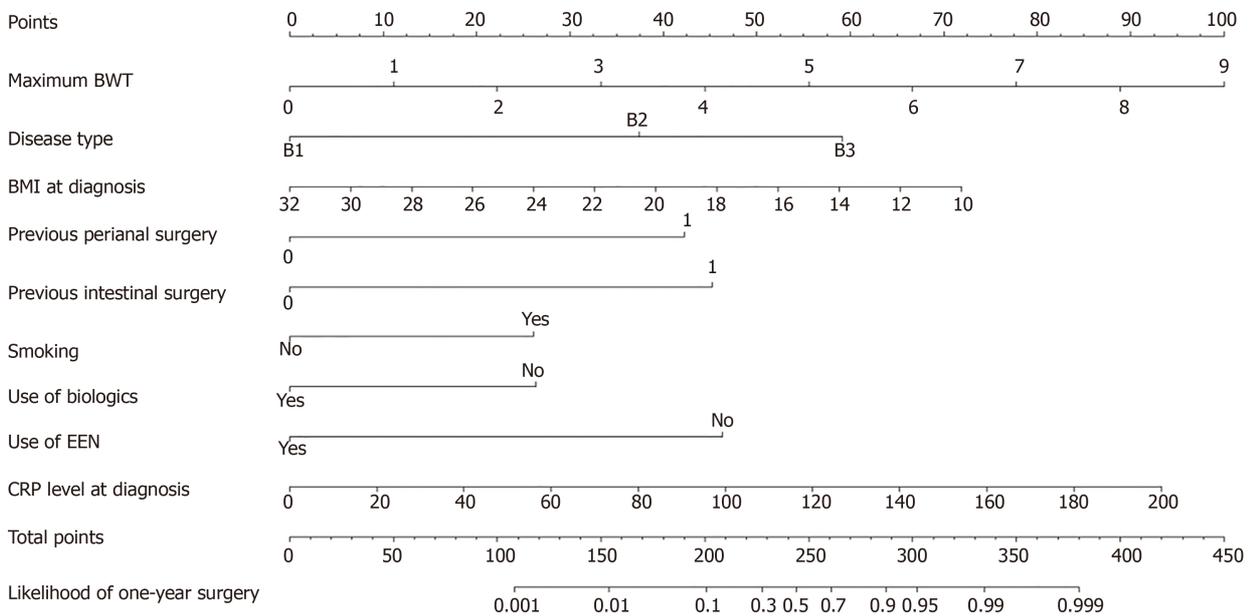
The strength of our study was the relatively large number of CD patients with a confirmed diagnosis and complete follow-up data. Our clinical center is the biggest IBD center in China, with a strong team composed of gastroenterologists, pathologists, radiologists, and gastrointestinal surgeons. Given the size of our cohort and center, it is possible that the cohort presented here somewhat approximates the national cohort. Further, development of the nomogram, a simplified visual tool predicting likelihood of surgery at 1 year, will allow for easy incorporation of our results into clinical practice.

A number of limitations are present in this study. This was a retrospective single-center study, lacking data from different regions of China. Clinical activity scores, endoscopy estimation, and genetic markers were not included in our prognostic model. Future studies with a broader population base and more associated factors are needed to confirm our findings.

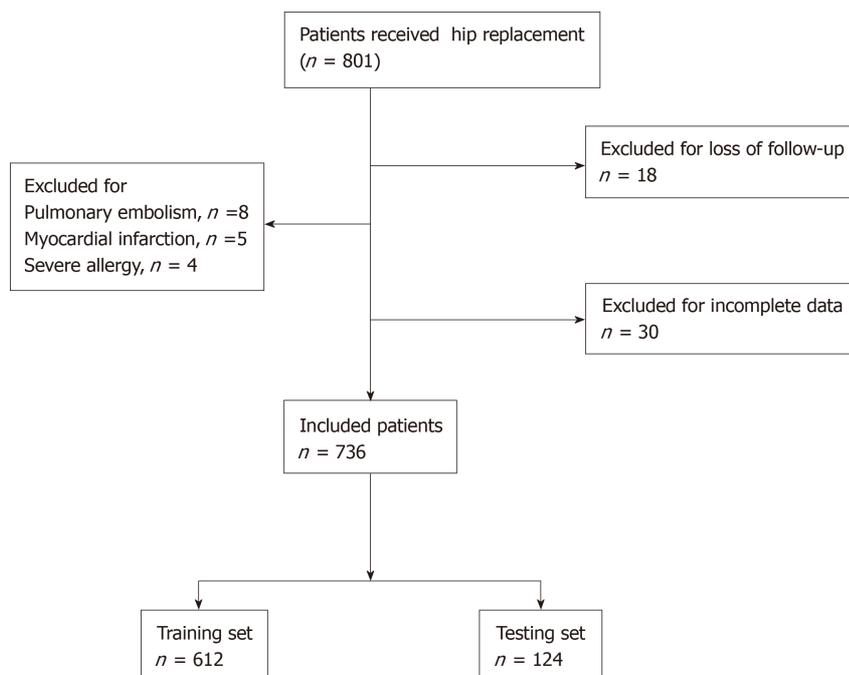
To summarize, we have identified that smoking, CRP at diagnosis, previous perianal and intestinal surgery, disease behavior, and maximum BWT are independent risk factors for intestinal surgery at 1 year, while BMI, use of biologics, and exclusive enteral nutrition are protective factors. A prognostic model and nomogram have been established to facilitate clinical application, serving as the basis for tailored therapy.



**Figure 3 Receiver operating characteristic curves of the training and testing data.** A: Predictive ability of this model was appraised with an area under the curve of 0.947, sensitivity of 75.92%, and specificity of 95.81%; B: Discrimination of the validated model was estimated with an area under the curve of 0.937, sensitivity of 67.31%, and specificity of 97.55%. Sens: Sensitivity; Spec: Specificity; PPV: Positive predictive value; NPV: Negative predictive value.



**Figure 4 Hosmer-Lemeshow goodness-of-fit test demonstrating a good fit of this model.**



**Figure 5** A prognostic nomogram for one-year surgery risk in Crohn’s disease patients. BWT: Bowel wall thickness; BMI: Body mass index; EEN: Exclusive enteral nutrition; CRP: C-reactive protein.

## ARTICLE HIGHLIGHTS

### Research background

Patients with progressive Crohn’s disease (CD) should be given accelerated therapy.

### Research motivation

Predicting CD-related early surgery risk is challenging and important in treatment strategy monitoring.

### Research objectives

This study aimed to establish a model to predict CD-related early surgery.

### Research methods

This was a retrospective study collecting data from CD patients from January 1, 2012 to December 31, 2016. A prognostic model was established and further validated. A nomogram was developed to facilitate clinical practice.

### Research results

A total of 1002 eligible patients were enrolled, and 24.25% received intestinal surgery within 1 year after diagnosis. Disease behavior, smoking, body mass index and C-reactive protein level at diagnosis, previous perianal or intestinal surgery, maximum bowel wall thickness, use of biologics, and exclusive enteral nutrition were identified as independent significant factors associated with early intestinal surgery.

### Research conclusions

This prognostic model can effectively predict CD-related early surgery, serving as the basis for tailored therapy.

### Research perspectives

Future studies with a broader population base and more associated factors including endoscopy estimation and genetic markers are needed to perfect this model.

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