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ORIGINAL CONTRIBUTION

A Validated Prognostic Model and Nomogram to Predict Early-Onset Complications Leading to Surgery in Patients With Crohn's Disease

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BACKGROUND: Predicting aggressive Crohn's disease is crucial for determining therapeutic strategies.

OBJECTIVE: We aimed to develop a prognostic model to predict complications leading to surgery within 1 year after diagnosis of Crohn's disease and to create a nomogram to facilitate clinical decision making.

DESIGN: This is a retrospective study.

SETTING: This study was conducted from January 2012 to December 2016 in a single tertiary IBD center.

PATIENTS: Patients diagnosed with Crohn's disease showing B1 behavior according to the Montreal classification were included.

MAIN OUTCOME MEASURES: We measured the occurrence of complications that would ultimately lead to surgery, including severe GI bleeding (Glasgow-Blatchford score ≥6), stenosis, and perforations, confirmed by endoscopy, CT scan, and/or interventional radiology.

RESULTS: The mean follow-up period was 54 months (SD 13 months). Of the 614 eligible patients, 13.5% developed complications leading to surgery. Multivariable logistic regression revealed the independent predictors of early-onset complications to be age (adjusted odds ratio per 10-year increase in age = 0.4; 95% CI, 0.2–0.8; $p = 0.004$), disease duration (adjusted odds ratio = 2.7, 95% CI, 1.9–3.8; $p < 0.001$), perianal disease (adjusted odds ratio = 16.0; 95% CI, 4.3–59.9; $p < 0.001$), previous surgery (adjusted odds ratio = 3.7; 95% CI, 1.6–8.6; $p = 0.003$), and extraintestinal manifestations (adjusted odds ratio = 7.6; 95% CI, 2.3–24.9; $p = 0.001$). The specificity and sensitivity of the prognostic model were 88.3% (95% CI, 84.8%–91.2%) and 96.6% (95% CI, 88.1%–99.6%), and the area under the curve was 0.97 (95% CI, 0.95–0.98). This model was validated with good discrimination and excellent calibration using the Hosmer-Lemeshow goodness-of-fit test. A nomogram was created to facilitate clinical bedside practice.

LIMITATIONS: This was a retrospective design and included a small sample size from 1 center.

CONCLUSIONS: Our validated prognostic model effectively predicted early-onset complications leading to surgery and screened aggressive Crohn's disease, which will enable physicians to customize therapeutic strategies

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Registered at Chinese Clinical Trial Registry (ChiCTR1900025751).

UN MODELO DE PRONÓSTICO VALIDADO Y UN NOMOGRAMA PARA PREDECIR COMPLICACIONES PRECOCES QUE REQUIRAN CIRUGÍA EN PACIENTES CON ENFERMEDAD DE CROHN

ANTECEDENTES: Predecir una enfermedad de Crohn muy agresiva es fundamental para determinar la estrategia terapéutica.

OBJETIVO: Desarrollar un modelo de pronóstico para predecir las complicaciones que requieran cirugía dentro el primer año al diagnóstico de enfermedad de Crohn y crear un nomograma para facilitar la toma de decisiones clínicas.

DISEÑO: El presente etudio es retrospectivo.

AJUSTE: Estudio realizado entre Enero 2012 y Diciembre 2016, en un único centro terciario de tratamiento de enfermedad inflamatoria intestinal.

PACIENTES: Se incluyeron todos aquellos pacientes diagnosticados de enfermedad de Crohn que mostraban manifestaciones tipo B1 según la clasificación de Montreal.

PRINCIPALES MEDIDAS DE RESULTADO: Medimos la aparición de complicaciones que finalmente conducirían a una cirugía, incluida la hemorragia digestiva grave (puntuación de Glasgow-Blatchford ≥ 6), estenosis y perforaciones, confirmadas por endoscopía, tomografía computarizada y / o radiología intervencionista.

RESULTADOS: El período medio de seguimiento fue de 54 meses (desviación estándar 13 meses). De los 614 pacientes elegibles, el 13,5% desarrolló complicaciones que llevaron a cirugía. La regresión logística multivariable reveló que los predictores independientes de complicaciones de inicio temprano eran la edad (razón de probabilidades ajustada [ORa] por aumento de 10 años en la edad = 0,4; intervalos de confianza del 95% [IC del 95%]: 0,2-0,8, p = 0,004), duración de la enfermedad (ORa = 2,7, IC del 95%: 1,9-3,8, p <0,001), enfermedad perianal (ORa = 16,0, IC del 95%: 4,3-59,9, p <0,001), cirugía previa (ORa = 3,7, 95% IC: 1,6-8,6, p = 0,003) y manifestaciones extraintestinales (ORa = 7,6, IC del 95%: 2,3-24,9, p = 0,001). La especificidad y sensibilidad del modelo pronóstico fueron 88,3% (IC 95%: 84,8% -91,2%) y 96,6% (IC 95%: 88,1% -99,6%), respectivamente, y el área bajo la curva fue 0,97 (95% % CI: 0,95-0,98). Este modelo fue validado con buena discriminación y excelente calibración utilizando la prueba de bondad de ajuste de Hosmer-Lemeshow. Se creó un nomograma para facilitar la práctica clínica al pié de la cama.

LIMITACIONES: Diseño retrospectivo que incluyó un tamaño de muestra pequeña en un solo centro.

CONCLUSIONES: Nuestro modelo de pronóstico validado predijo eficazmente las complicaciones precoces que conllevaron a cirugía y la detección de enfermedad de Crohn agresiva, lo que permitió a los médicos personalizar las estrategias terapéuticas y controlar la enfermedad. Consulte **Video Resumen** en http://links.lww.com/DCR/B442. *(Traducción—Dr. Xavier Delgadillo)*

Registrado en el Registro de Ensayos Clínicos de China (ChiCTR1900025751).

KEY WORDS: Crohn's disease; Prognostic model; Nomogram; Complication; Retrospective study

Crohn's disease (CD) is a type of chronic transmural inflammatory condition affecting any segment of the GI tract.[1] It has a wide range of intestinal symptoms and extraintestinal manifestations, with varying phenotypes of disease behavior, making the application of "treat to target" even more challenging.[2] Most patients have experienced progression to complications, including stenosis, perforation, and severe GI bleeding, ultimately leading to surgery. According to the analysis by Thia et al[3] of a population-based cohort, 19% to 36% of patients newly diagnosed with CD developed complications. This percentage increased along with the progression of inflammation. Approximately 50% of patients with CD developed complications within 5 years and nearly 70% developed complications within 10 years after diagnosis.[4,5] Even during the periods when patients with aggressive CD are asymptomatic, subclinical inflammation may progress and lead to irreversible bowel damage and complications.[6] Therefore, the diagnosis of aggressive CD and identification of the risk of early-onset complications are crucial because the initiation of intensive therapeutic strategies can effectively reduce the rate of complications and surgery.

The commonly used classification systems, in particular, the Montreal classification,[7] identify stricturing and penetrating complications after they have manifested or become clinically apparent. Thus, such classification systems have limitations in the early evaluation of the course and behavior of CD. It is essential to evaluate patients and predict complication risks in newly diagnosed patients with nonstricturing and nonpenetrating disease to guide treatment. Thus, in this study, we aimed to develop a prognostic model to aid in predicting the risks of complications leading to surgery within 1 year after diagnosis of

CD. Furthermore, we created a nomogram to facilitate clinical decision making.

MATERIALS AND METHODS

Patient Population

This retrospective study collected data from patients in the IBD center of Sun Yat-Sun University Sixth Affiliated Hospital from January 1, 2012, to December 31, 2016. Patients were included if they had an unequivocal diagnosis of CD; B1 disease behavior (nonstricturing, nonpenetrating) according to the Montreal classification; no complications at diagnosis; and at least 1 year of follow-up. The exclusion criteria were as follows: potential diagnosis other than CD, B2 (stricturing) or B3 (penetrating) disease behavior, and loss of follow-up or incomplete data. Data of consecutive patients with CD admitted to our IBD center were identified by an experienced gastroenterologist (J.Y.Y.) and were collected from the hospital's electronic database, with discrepancies being resolved after discussion by 2 specialists (Y.J. and J.K.). Eligible patients were followed up to at least 1 year for screening complications that could lead to surgery by endoscopy and imaging. All patients with complications were fully evaluated by a professional surgeon (J.K.) for surgical indication and specific procedures. This study was approved by the Ethics Committee of Sun Yat-Sen University (2019ZSLYEC-058), permitted by the Chinese Clinical Trial Registry (ChiCTR1900025751), and, therefore, has been conducted in accordance with the ethical standards stated in the Declaration of Helsinki. The requirement for written informed consent was waived by our Institutional Review Board because it was a retrospective study that used anonymous data.

Outcomes and Definitions

The main outcome of this study was the occurrence of complications that could lead to surgery, including severe GI bleeding, stenosis, and perforations. Severe GI bleeding was defined as hemorrhage in any part of the digestive tract with a Glasgow-Blatchford score ≥6[8,9] confirmed by endoscopy, CT scan, and/or interventional radiology. We considered the cause for bleeding to be exclusively associated with CD. Stenosis was defined as prestenotic dilation (often defined as >3 cm[10]) confirmed by radiological examinations with or without obstructive symptoms.[10,11] Perforation was defined as external fistulas (enterocutaneous and perianal fistulas) and/or internal fistulas (enteroenteric, enterovesical, or enterovaginal fistulas) confirmed by cross-sectional imaging[10] or surgery.[12,13] Crohn's disease-related surgeries consist of bowel segment resection (ileocolic resection with primary anastomosis or end ileostomy, subtotal colectomy with ileorectal anastomosis or end ileostomy, segmental colon resection, segmental small-bowel resection, and total proctocolectomy), stricturoplasty, and fistula repair (incision and drainage of abscess, seton placement, fistulotomy, and fistulectomy). Intra-abdominal surgical procedures, including bowel segment resection and stricturoplasty, were defined as major surgeries, whereas fistula repair was defined as a minor surgery.

Selection of Predictors

Candidate predictive factors were selected from demographic and disease-related variables that were previously reported in the literature as potential factors. All factors mentioned above were identified before the diagnosis of complications leading to surgery by a professional gastroenterologist (J.Y.Y.).

We collected patients' clinical information, including age, sex, smoking and drinking habits, previous history of surgery (perianal surgery and/or appendectomy with indication of anal fistula, perianal abscess and/or appendicitis), laboratory parameters at diagnosis (C-reactive protein, erythrocyte sedimentation rate, and albumin), duration of disease before diagnosis, extraintestinal manifestations (arthropathies and dermatological, ocular, and hepatobiliary disease),[2] and therapeutic strategies. A diagnosis of CD was made according to the internationally accepted criteria[14] based on a combination of radiographic, endoscopic, and histological presentations, and disease phenotype was classified according to the Montreal classification.[7] In this study, L4 disease location referred specifically to isolated L4 including esophagogastroduodenal, jejunal, and proximal ileal disease. Patients were stratified according to therapeutic strategies during the initial 1 year after diagnosis into either a glucocorticoid + immunosuppression group, biologics (combine immunosuppression or not) group, or 5-aminosalicylic acid group (5-ASA).

Statistical Analyses

Continuous variables are presented as either mean and SD or median and interquartile range and were analyzed using Student *t* tests. Categorical variables are presented as percentages or proportions and were analyzed using the χ^2 or Fisher exact test. All cases were allocated a random number ranging from 0 to 100 generated by IBM SPSS (version 22.0, IBM Corp, Armonk, NY) with random seed as 2020, to ensure that the entire statistical analyses could be easily repeated. Cases with numbers ranging from 0 to 80 were assigned to the training set, and those with numbers ranging from 80.0001 to 100 were assigned to the testing set. Thus, data were randomly stratified into a training set and a testing set at a ratio of 8:2. The actual sample size for the training and testing sets were 484 and 130. Risk factors with a p value <0.20 in the univariable analysis were included in the multivariable analyses. Logistic regression with a backward stepwise selection was used to select risk factors for the multivariable model. A significance level of

0.20 was required to allow a risk factor into the model, and a significance level of 0.20 was required for a risk factor to stay in the model. Receiver operating characteristic curves were constructed while areas under the curve (AUC) were calculated both in the training and testing sets. The optimal cutoff point was identified using the Youden J statistic.[15] Our model calibration was evaluated using the Hosmer-Lemeshow goodness-of-fit test, and discrimination was assessed using AUC. The model development and validation processes were in accordance with the recommended guidelines.[16,17] The application of this prognostic model could be visualized by means of a nomogram conducted using R software (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed p value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Clinical information of 614 patients newly diagnosed with CD with B1 behavior were analyzed in our IBD unit, the biggest IBD center in China. A total of 73.78% (n = 453) of cases were men with a mean age of 26.8 (SD 10.9) years, mean disease duration of 1.3 (SD 1.6) years, and mean follow-up period of 53.5 (SD 12.8) months. Most of the patients were classified as A2 (A1, n = 79, 12.9%; A2, n = 466, 75.9%; A3, n = 69, 11.2%), and L3 (L1, n = 82, 13.4%; L2, n = 70, 11.4%; L3, n = 413, 67.3%; L4, n = 49, 8.0%). Biologics therapy was administered to 54.2% of patients (n = 333, 5-ASA, n = 132, 21.5%; glucocorticoid + immunosuppression, n = 328, 53.4%), whereas 50.2% of patients received more than 1 form of medical therapy (n = 308). A total of 83 patients (13.5%) developed complications leading to surgery within 1 year after diagnosis. The most common complications were stenosis (n = 48, 57.8%), followed by perforation (n = 26, 31.3%) and severe GI bleeding (n = 9, 10.8%). Consequently, 70 patients (84.3%) underwent a bowel segment resection, 8 patients (9.6%) underwent stricturoplasty, and 5 patients (6.0%) underwent a fistula repair. Table 1 displays the details of patient characteristics in all cases and in each subgroup divided according to the different types of complications. No data were missing for any of the investigated risk factors.

Prognostic Model Development and Validation

According to the univariate analysis, variables, including age at diagnosis, disease duration, previous surgery, perianal disease, and extraintestinal manifestations, were significant factors related to early-onset complications. Based on all the related variables considered in the multivariable logistic regression analysis, a prognostic model was developed as follows (Table 2):

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

where prognostic index

$$= -3.892 + 0.984 \times x_1 - 0.904 \times x_2 + 2.773 \times x_3 + 1.295 \times x_4 + 2.031 \times x_5$$

(x_1 = disease duration (year); x_2 = age (year, adjusted for age as per 10-year increase in age); x_3 = perianal disease (0: no, 1: yes); x_4 = previous surgery (0: no, 1: yes); x_5 = extraintestinal manifestations (0: no, 1: yes)).

This model showed an ideal receiver operating characteristic curve, and the calculated AUC was 0.97. A relatively high specificity (88.3%) and sensitivity (96.6%) confirmed the efficiency of the predictive and distinguishable ability of the model. The variance inflation factor of each risk factor in our model ranged from 1 to 3, which verified that there were no high correlations among the groups. This prognostic model was then applied to our testing cohort. Table 2 and Figure 1 showed the comparison of parameters in both the training and testing cohort. Calibration analysis showed that the predicted risks of complications of this model closely agreed with the actual risks (Fig. 2).

Nomogram Establishment

Nomogram is a user-friendly prognostic device widely used as a tool to aid clinical decision making.[11,18] In our study, a prognostic nomogram integrating all significant independent factors from our multivariable logistic regression analysis was created (Fig. 3). The points for each of the parameters were summed and vertically matched with the risk of complications leading to surgery within 1 year after diagnosis.

DISCUSSION

In our research, we identified age, perianal disease at diagnosis, disease duration, previous surgery, and extraintestinal manifestations as significant independent factors associated with complications leading to surgery 1 year after a diagnosis of nonstricturing and nonpenetrating CD. A validated prognostic model can precisely predict negative outcomes and is the cornerstone in preventive and tailored therapeutics, especially for CD because of its complexity. This model was based solely on clinical and demographic variables, making it easily and broadly applicable to the real-world setting.

Stenosis and perforation are common complications of CD associated with surgical intervention. Approximately 5% of patients with CD experience GI bleeding in their lifetimes.[19] More than 80% of bleeding episodes resolve spontaneously or after medical therapies, whereas a small proportion become life-threatening hemorrhages manifested by hemodynamic instability and hemorrhagic shock, and ultimately require salvage surgery.[20] According

TABLE 1. Patient baseline characteristics

Characteristic	*Total*	*Complications*		
		GI bleeding	*Perforation*	*Stenosis*
n	614	9	26	48
Male, n (%)	453 (73.8)	7 (77. 8)	21 (80.8)	29 (60.4)
Age at diagnosis, y, mean ± SD	26.8 ± 10.9	20.3 ± 10.2	25.12 ± 8.4	25.6 ± 11.7
Drinking, n (%)	34 (5.5)	1 (11.1)	0 (0.0)	3 (6.3)
Smoking, n (%)	72 (11.7)	1 (11.1)	2 (7.7)	7 (14.6)
Disease duration, y, mean ± SD	1.3 ± 1.6		2.8 ± 2.7	2.7 ± 2.8
BMI, kg/m^2, mean ± SD	18.8 ± 2.9	17.8 ± 3.1	17.7 ± 2.4	18.6 ± 2.7
Follow-up, mo, mean ± SD	53.5 ± 12.8	54.9 ± 10.8	59.4 ± 10.1	53.2 ± 14.9
Montreal classification, n (%)				
Age at diagnosis				
A1	79 (12.9)	5 (55.6)	2 (7.7)	8 (16.7)
A2	466 (75.9)	3 (33.3)	22 (84.6)	35 (72.9)
A3	69 (11.2)	1 (11.1)	2 (7.7)	5 (10.4)
Location at diagnosis				
L1	82 (13.4)	2 (22.2)	2 (7.7)	5 (10.4)
L2	70 (11.4)	1 (11.1)	3 (11.5)	9 (18.8)
L3	413 (67.3)	5 (55.6)	19 (73.1)	32 (66.7)
L4	49 (8.0)	1 (11.1)	2 (7.7)	2 (4.2)
CRP at diagnosis, mg/L, mean ± SD	17.9 ± 18.1	18.5 ± 16.4	22.07 ± 20.63	16.7 ± 21.6
ESR at diagnosis, mm/h, mean ± SD	34.5 ± 28.8	34.9 ± 32.4	44.7 ± 30.8	29.3 ± 19.9
Alb at diagnosis, g/L mean ± SD	40.0 ± 32.1	40.2 ± 7.5	37.0 ± 6.6	38.5 ± 6.7
Previous surgery, n (%)	217 (35.3)	6 (66.7)	13 (50.0)	38 (79.2)
Perianal disease, n (%)	87 (14.2)	8 (88.9)	13 (50.0)	33 (68.8)
EIM, n (%)	95 (15.5)	7 (77.8)	21 (80.8)	35 (72.9)
Treatment, n (%)				
5-ASA	132 (21.5)	1 (11.1)	3 (11.5)	13 (27.1)
Biologics (+IM)	333 (54.2)	5 (55.6)	12 (46.2)	23 (47.9)
Corticosteroids + IM	328 (53.4)	7 (77.8)	14 (53.9)	23 (47.9)

Alb = albumin; 5-ASA = 5-aminosalicylic acid; CRP = C-reactive protein; EIM = extraintestinal manifestations; ESR = erythrocyte sedimentation rate; IM = immunosuppressant.

to a Mayo Clinic series,[21] as many as 39% of patients with GI bleeding required surgery because of the difficulties in localization and poor response to medical treatments. Severe GI bleeding is an indication for surgery and should not be ignored, despite its rarity. Therefore, we included severe GI bleeding with a Glasgow-Blatchford score of >6 as a complication leading to surgery in our study design to predict aggressive CD comprehensively.

Pediatric-onset CD shows more aggressive disease behavior than does adult-onset CD.[22] Older patients with CD have significantly less perianal and penetrating diseases and a lower necessity for surgery due to its milder disease phenotype than do younger patients with CD.[23] In this study, we found that age was negatively correlated with aggressive CD, consistent with the results from previous studies.[22,23]

Gastrointestinal inflammation continues to progress before obvious clinical manifestations emerge in CD,[24] which contributes to the more severe bowel damage in disease of longer duration. According to the "treat to target" strategy,[25] physicians achieve not only clinical remission, but also mucosal,[26] radiological,[27,28] and histological healing,[29,30] to block the progression of inflammation. The landmark SONIC trial,[31] stratified by disease duration, associated a shorter disease duration with higher efficacy in achieving therapeutic goals. Similar findings have been obtained with vedolizumab treatment in patients with CD.[32] We found that longer disease duration was associated with a higher risk of complications leading to surgery, which can be attributed to the exacerbation of inflammation as duration prolongs.

Perianal diseases, including perianal fistulas and abscesses, are present in up to 25% of patients with CD worldwide, and are increasing in incidence and disease duration.[33,34] Peyrin-Biroulet et al[35] developed an IBD disability index in 2012 without taking perianal disease into account; hence, this index is limited in its applications for guiding clinical decision making. In our prognostic model, perianal disease at initial diagnosis was considered a risk factor, which predicted a worse disease course and early occurrence of complications.

Disease severity is suspected to closely correlate with the development of extraintestinal manifestations at initial diagnosis, especially in pediatric patients with CD.[36] Data from the PediIBD Consortium Registry showed that the cumulative incidence of extraintestinal manifestations was 9% at 1 year, 19% at 5 years, and 29% at 15 years after diagnosis.[37] With only 12.9% patients aged <16 years in

TABLE 2. Factors associated with surgery-relative complications in Crohn's disease

	Univariate analysis (n = 484)			*Multivariable logistic regression (n = 484)*			
Factor	*OR*	*95% CI*	*p value*	*OR*	*95% CI*	*p value*	*β ± SE*
Sex (male vs female)	1.3	0.7–2.4	0.377				
Age. y[a]	0.7	0.6–1.0	0.062	0.4	0.2–0.8	0.004	−0.90±0.31
Location (L1 vs L2/L3/L4)							
L2	1.2	0.4–3.3	0.738				
L3	0.8	0.4–1.8	0.647				
L4	0.8	0.2–2.9	0.756				
Disease duration	1.6	1.4–1.9	<0.001	2.7	1.9–3.8	<0.001	0.98±0.18
Drinking	1.0	0.3–3.5	0.998				
Smoking	1.2	0.5–2.7	0.729				
BMI	0.9	0.8–1.0	0.147				
Previous surgery	5.2	2.9–9.3	<0.001	3.7	1.6–8.6	0.003	1.30±0.44
Perianal disease	27.0	13.9–52.4	<0.001	16.0	4.3–59.9	<0.001	2.77±0.67
EIM	44.7	21.9–91.2	<0.001	7.6	2.3–24.9	0.001	2.03±0.60
Treatment							
5-ASA	0.9	0.4–1.8	0.734				
Corticosteroid + IM	1.0	0.6–1.8	0.945				
Biologics (+IM)	0.9	0.5–1.6	0.832				
CRP at diagnosis (pathological vs normal)	1.0	0.9–1.0	0.610				
ESR at diagnosis (pathological vs normal)	1.0	0.9–1.0	0.783				
Alb at diagnosis (pathological vs normal)	1.0	0.9–1.0	0.703				

Alb = Albumin; 5-ASA = 5-aminosalicylic acid; β = estimated regression coefficient; CRP = C-reactive protein; EIM = extraintestinal manifestations; ESR = erythrocyte sedimentation rate; IM = immunosuppressants; SE = standard error.
[a]Adjusted data for age as per 10-year increase in age.

our study cohort, 15.5% patients had extraintestinal manifestations at diagnosis with an average disease course of 1.28 years, illustrating that the relationship of extraintestinal manifestations with the course of CD must not be ignored. As for young age[38,39] and previous surgery,[40,41] the reported independent factors that predicted disabling CD were integrated in our prognostic model to improve its predictive ability.

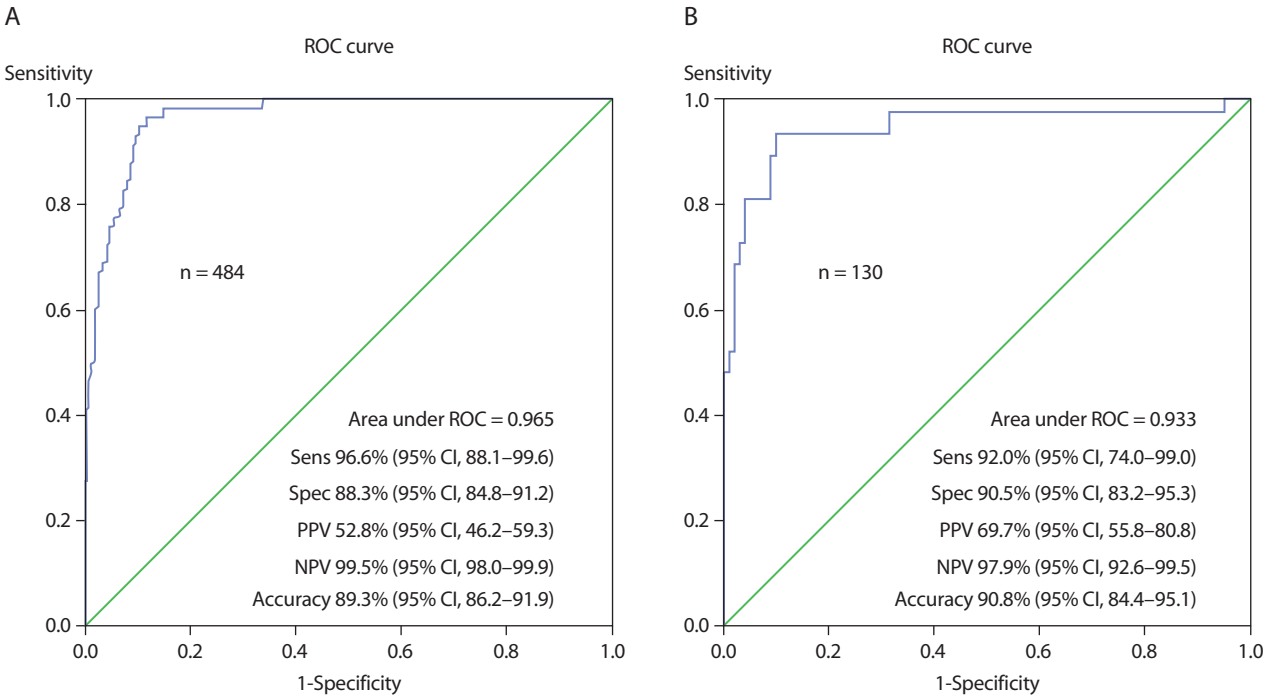

FIGURE 1. Receiver operating characteristic curves in training and testing cohort. A, Predictive ability of this model was appraised with an area under the curve of 0.965, sensitivity of 96.6%, and specificity of 88.3%. B, Discrimination of the validated model was estimated with an area under the curve of 0.933, sensitivity of 92.0%, and specificity of 90.5%. NPV = negative predictive value; PPV = positive predictive value; ROC = receiver operating characteristic.

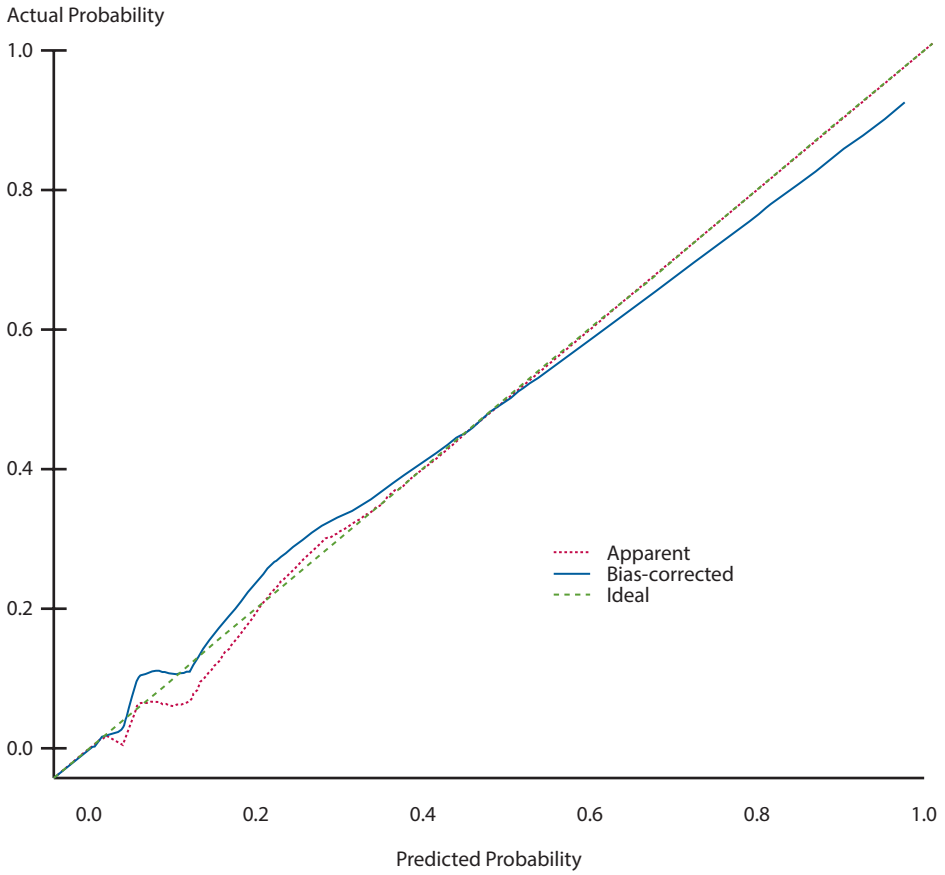

FIGURE 2. The Hosmer-Lemeshow goodness-of-fit test ($p = 1$) demonstrated a good fit for the final multivariable logistic regression model.

We found that treatments exerted little influence on disease progression. Likely explanations are as follows: the treatments we observed in this study included 5-ASA, glucocorticoids, immunosuppressants, and biologics. As therapeutic strategies evolve, new agents have emerged that provide better clinical responses. Treatments administrated in our study focused on achieving symptomatic remission, which is insufficient for ameliorating underlying inflammation, preventing disease progression to complications, or lowering surgery risk. Moreover, we could not exclude potential selection bias by the gastroenterologists involved in this retrospective study. These reasons likely explain why we found no associations between treatments and disease progression, especially without the effective prediction of the aggressive phenotype of CD. The model we established can help distinguish aggressive CD at high risk of developing complications leading to surgery. We expect this to aid physicians in treatment adjustment and disease monitoring in a prophylactic fashion. More importantly, intensive therapeutic strategies for patients at a high risk of early-onset complications might enhance their quality of life, lower surgery rates, or even influence the natural course of CD. Further prospective clinical trials are warranted to verify the effects of therapeutics on early-onset complications.

Our study's limitations included its retrospective design and relatively small participant size from a single tertiary referral center. Nevertheless, we have limited these drawbacks and strengthened our study by including a relatively long follow-up period and precise definitions of each parameter before initiating the study. The patients were followed up by regular physicians with complete data collection, and the nomogram facilitated clinical practice. To our knowledge, this was the first prognostic model to integrate several factors, including extraintestinal manifestations and disease duration, to predict complications leading to surgery in patients with CD. Undoubtedly, prospective studies with a broader population base are needed to validate our findings.

CONCLUSION

In this study, we identified age, extraintestinal manifestations, previous surgery, perianal disease, and disease duration as independent factors associated with complications leading to surgery in patients with CD. We have developed a prognostic model and a nomogram to aid in personalized clinical decision making.

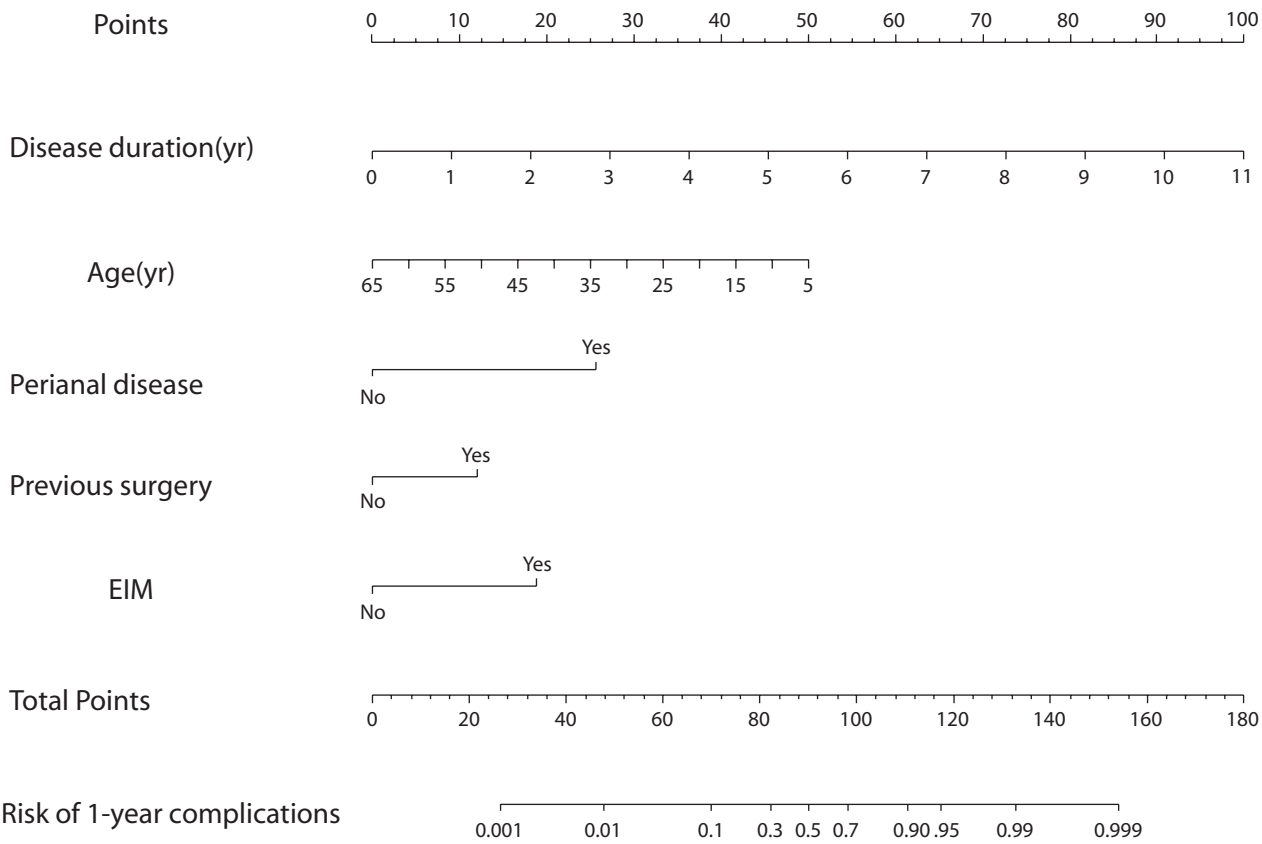

FIGURE 3. A prognostic nomogram for risk of complications leading to surgery within 1 year after diagnosis in patients with Crohn's disease. The nomogram consisted of 6 significant risk factors. Each factor was associated with the number of points. After summing up the points from each factor, we came up to a total point score, which corresponds to the risk of 1-year complications leading to surgery. EIM = extraintestinal manifestations.

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REFERENCES

1. Banerjee S, Peppercorn MA. Inflammatory bowel disease. Medical therapy of specific clinical presentations. *Gastroenterol Clin North Am.* 2002;31:185–202.
2. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol.* 2018;113:481–517.
3. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology.* 2010;139:1147–1155.
4. Louis E, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut.* 2001;49:777–782.
5. Rieder F, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: a systematic review. *Gut.* 2013;62:1072–1084.
6. Koliani-Pace JL, Siegel CA. Prognosticating the course of inflammatory bowel disease. *Gastrointest Endosc Clin N Am.* 2019;29:395–404.
7. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut.* 2006;55:749–753.
8. Deutsch D, Romegoux P, Boustière C, Sabaté JM, Benamouzig R, Albaladejo P. Clinical and endoscopic features of severe acute gastrointestinal bleeding in elderly patients treated with direct oral anticoagulants: a multicentre study. *Therap Adv Gastroenterol.* 2019;12:1756284819851677.
9. Oakland K, Chadwick G, East JE, et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. *Gut.* 2019;68:776–789.
10. Bruining DH, Zimmermann EM, Loftus EV Jr, Sandborn WJ, Sauer CG, Strong SA; Society of Abdominal Radiology Crohn's Disease-Focused Panel. Consensus recommendations for evaluation, interpretation, and utilization of computed tomography and magnetic resonance enterography in patients with small bowel Crohn's disease. *Radiology.* 2018;286:776–799.
11. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. *Lancet Oncol.* 2015;16:e173–e180.

12. de Groof EJ, Carbonnel F, Buskens CJ, Bemelman WA. Abdominal abscess in Crohn's disease: multidisciplinary management. *Dig Dis.* 2014;32(suppl 1):103–109.
13. Patil SA, Cross RK. Medical versus surgical management of penetrating Crohn's disease: the current situation and future perspectives. *Expert Rev Gastroenterol Hepatol.* 2017;11:843–848.
14. Gomollón F, Dignass A, Annese V, et al; ECCO. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *J Crohns Colitis.* 2017;11:3–25.
15. Youden WJ. Index for rating diagnostic tests. *Cancer.* 1950;3:32–35.
16. Núñez E, Steyerberg EW, Núñez J. [Regression modeling strategies]. *Rev Esp Cardiol.* 2011;64:501–507.
17. Fenlon C, O'Grady L, Doherty ML, Dunnion J. A discussion of calibration techniques for evaluating binary and categorical predictive models. *Prev Vet Med.* 2018;149:107–114.
18. Park SY. Nomogram: an analogue tool to deliver digital knowledge. *J Thorac Cardiovasc Surg.* 2018;155:1793.
19. Daperno M, Sostegni R, Rocca R. Lower gastrointestinal bleeding in Crohn's disease: how (un-)common is it and how to tackle it? *Dig Liver Dis.* 2012;44:721–722.
20. Toh JW, Stewart P, Rickard MJ, Leong R, Wang N, Young CJ. Indications and surgical options for small bowel, large bowel and perianal Crohn's disease. *World J Gastroenterol.* 2016;22:8892–8904.
21. Pardi DS, Loftus EV Jr, Tremaine WJ, et al. Acute major gastrointestinal hemorrhage in inflammatory bowel disease. *Gastrointest Endosc.* 1999;49:153–157.
22. Herzog D, Fournier N, Buehr P, et al; Swiss IBD Cohort Study Group. Prevalence of intestinal complications in inflammatory bowel disease: a comparison between paediatric-onset and adult-onset patients. *Eur J Gastroenterol Hepatol.* 2017;29:926–931.
23. Sturm A, Maaser C, Mendall M, et al. European Crohn's and Colitis Organisation topical review on IBD in the elderly. *J Crohns Colitis.* 2017;11:263–273.
24. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet.* 2017;389:1741–1755.
25. Bouguen G, Levesque BG, Feagan BG, et al. Treat to target: a proposed new paradigm for the management of Crohn's disease. *Clin Gastroenterol Hepatol.* 2015;13:1042–50.e2.
26. Klenske E, Bojarski C, Waldner M, Rath T, Neurath MF, Atreya R. Targeting mucosal healing in Crohn's disease: what the clinician needs to know. *Therap Adv Gastroenterol.* 2019;12:1756284819856865.
27. Lopes S, Andrade P, Cunha R, Magro F. Transmural healing in Crohn's disease: beyond mural findings. *Dig Liver Dis.* 2018;50:103–104.
28. Danese S, Sandborn WJ, Colombel JF, et al. Endoscopic, radiologic, and histologic healing with vedolizumab in patients with active Crohn's disease. *Gastroenterology.* 2019;157:1007–1018.e7.
29. Pineton de Chambrun G, Blanc P, Peyrin-Biroulet L. Current evidence supporting mucosal healing and deep remission as important treatment goals for inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol.* 2016;10:915–927.
30. Maconi G, Armuzzi A. Beyond remission and mucosal healing in Crohn's disease. Exploring the deep with cross sectional imaging. *Dig Liver Dis.* 2017;49:457–458.
31. Colombel JF, Sandborn WJ, Reinisch W, et al. Shorter disease duration is associated with higher rates of response to vedolizumab in patients with Crohn's disease but not ulcerative colitis. *Clin Gastroenterol Hepatol.* 2019;17:2497-2505 e1.
32. Helwig U, Mross M, Schubert S, et al. Real-world clinical effectiveness and safety of vedolizumab and anti-tumor necrosis factor alpha treatment in ulcerative colitis and Crohn's disease patients: a German retrospective chart review. *BMC Gastroenterol.* 2020;20:211.
33. Rackovsky O, Hirten R, Ungaro R, Colombel JF. Clinical updates on perianal fistulas in Crohn's disease. *Expert Rev Gastroenterol Hepatol.* 2018;12:597–605.
34. Eglinton TW, Barclay ML, Gearry RB, Frizelle FA. The spectrum of perianal Crohn's disease in a population-based cohort. *Dis Colon Rectum.* 2012;55:773–777.
35. Peyrin-Biroulet L, Cieza A, Sandborn WJ, et al; International Programme to Develop New Indexes for Crohn's Disease (IPNIC) group. Development of the first disability index for inflammatory bowel disease based on the international classification of functioning, disability and health. *Gut.* 2012;61:241–247.
36. Yu YR, Rodriguez JR. Clinical presentation of Crohn's, ulcerative colitis, and indeterminate colitis: symptoms, extraintestinal manifestations, and disease phenotypes. *Semin Pediatr Surg.* 2017;26:349–355.
37. Heyman MB, Kirschner BS, Gold BD, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr.* 2005;146:35–40.
38. Bruna-Barranco I, Lué A, Gargallo-Puyuelo CJ, et al. Young age and tobacco use are predictors of lower medication adherence in inflammatory bowel disease. *Eur J Gastroenterol Hepatol.* 2019;31:948–953.
39. Mosli M, Sabbahi H, Alyousef H, et al. Risk stratification of patients with Crohn's disease: a retrospective analysis of clinical decision making and its impact on long-term outcome. *Dig Dis.* 2018;36:49–55.
40. Albuquerque A, Cardoso H, Marques M, et al. Predictive factors of small bowel patency in Crohn's disease patients. *Rev Esp Enferm Dig.* 2016;108:65–70.
41. Auzolle C, Nancey S, Tran-Minh ML, et al; REMIND Study Group Investigators. Male gender, active smoking and previous intestinal resection are risk factors for post-operative endoscopic recurrence in Crohn's disease: results from a prospective cohort study. *Aliment Pharmacol Ther.* 2018;48:924–932.