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ORIGINAL RESEARCH

Predicting Mucosal Healing in Crohn's Disease: A Nomogram Model Developed from a Retrospective Cohort

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Purpose: Mucosal healing (MH) has become a therapeutic end point for Crohn's disease (CD). The purpose of this study was to identify potential risk factors responsible for a lower probability of mucosal healing in CD. It also aimed to create and validate a noninvasive tool for predicting mucosal healing in CD to aid clinical decision-making.

Patients and Methods: We established a derivation cohort diagnosed with CD, in which endoscopic examination was performed before and after treatment at the First Affiliated Hospital of Nanjing Medical University between January 2010 and June 2021. Patient data including demographic and clinical characteristics and treatment details were collected. The achievement of mucosal healing (without ulceration on endoscopic examination) after treatment was the endpoint observed during follow-up. We performed logistic regression analysis to identify factors associated with mucosal healing. These factors were used to develop a model (CD mucosal healing prediction nomogram) to predict mucosal healing in CD. External validation was performed using a new cohort of 60 patients from the Second Affiliated Hospital of Soochow University between January 2012 and June 2021.

Results: A total of 331 patients were included in the derivation cohort. We found the following factors to be independently associated with mucosal healing after treatment: disease course <11 months, ulcer size <0.5 cm, Harvey-Bradshaw Index score <9, infliximab treatment, and non-exclusive use of 5-aminosalicylic acid. The model incorporating these factors achieved good discrimination, calibration, and clinical decision curve analysis results on internal validation (C-index: 0.788, 95% confidence interval [CI]: 0.74–0.84). The external validation cohort also demonstrated good discrimination (C-index: 0.785, 95% CI: 0.68–0.90) and calibration.

Conclusion: The CD mucosal healing prediction nomogram model demonstrated good reliability and validated. It can potentially be developed into a simple and clinically useful tool for predicting mucosal healing in CD.

Keywords: disease course, HBI scores, ulcer size, infliximab

Introduction

Crohn's disease (CD) is incurable and can cause characteristic mucosal injury in the entire gastrointestinal tract.[1–3] Treatment strategies aimed solely at resolution of clinical symptoms do not eliminate long-term bowel damage in patients with CD.[4,5] Mucosal healing (MH) is therefore preferred over clinical remission as a therapeutic end point in CD, because of the reliable association with durability of remission.[6,7] Evolving studies indicate that using MH as an endpoint improves long-term outcomes with diminished rates of relapse, hospitalization, and surgery; it is therefore cost-effective.[8,9]

At present, the evaluation of MH in patients with CD mainly relies on endoscopy. However, endoscopy has the disadvantages of invasiveness, high risk, high cost and so on. Clinically, non-invasive methods are needed to assist or replace endoscopy to assess MH in patients with CD. Identifying predictors of MH (a proposed treat-to-target strategy) is of considerable significance in guiding treatment strategies for CD.[10] Anti-tumor necrosis factor α (TNF-α) agents in

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combination with immunosuppressive (IS) agents, shorter disease duration, and repeated endoscopic procedures are reported to be associated with MH in patients with CD.[11,12] The presence of prior enteric fistulas and perianal diseases at diagnosis are associated with a lower rate of MH.[13] However, none of these factors have been found to be independent predictive factors of MH in multivariate models.

In clinical practice, the ability to identify patients at lower probability of MH through reliable and noninvasive methods may be useful for guiding management;[14] it may help initiate the most appropriate treatment earlier.[15] The prediction model previously constructed by our team could be used after treatment and before endoscopic assessment to predict whether MH has reached, so as to guide the timing of endoscopic examination.[16] But that model was unable to predict the effect of drug before treatment is administered. This study aimed to derive and validate a prediction algorithm, by determining the factors to be incorporated into the model; this was expected to improve predictive ability for MH in patients with CD before treatment.

Materials and Methods

Study Design and Patients

This retrospective multicenter observational cohort study included consecutive patients with CD who underwent treatment at the Inflammatory Bowel Disease Center of the First Affiliated Hospital of Nanjing Medical University between January 2010 and June 2021. Each patient underwent consecutive endoscopic procedures at least twice during the study period. Data for verification were obtained from the Second Affiliated Hospital of Soochow University, China. Diagnoses of CD were determined according to internationally accepted criteria based on a combination of clinical presentation, endoscopic findings, or macroscopic appearance at surgery, radiology, histology, or serology.[17]

The study was approved by the Clinical Research Ethics Committee of the hospital (ref: 2021-SR-235) and it was performed in compliance with the principles of the Declaration of Helsinki. All patients in the study provided informed consent for review of their clinical data.

Predictor Variables and Data Source

The following demographic and clinical characteristics were extracted from the electronic medical records and endoscopic image system of the patients: gender; date of birth; age, age at diagnosis; disease course of CD; history of surgery; smoking habit; family history of inflammatory bowel disease (IBD); clinical manifestations such as stool frequency; CD phenotype including site of lesion, ulcer size, lumen stenosis, intestinal wall penetration, abdominal mass, and rectal bleeding; CD-related extraintestinal complications such as erythema nodosum, uveitis/iritis, arthralgia, and ankylosing spondylitis, among others; therapeutic management; and interval between endoscopy procedures. The Harvey-Bradshaw Index (HBI) was then calculated for clinical evaluation.[18,19] Data regarding medical therapies administered before and during the study period, and any treatment adjustment, were collected; these included treatment exclusively with 5-aminosalicylic acid (5-ASA) or systemic corticosteroids at first flare; introduction of immunomodulators (methotrexate, tripterygium, azathioprine, or thalidomide); and introduction and regular use of biologics including infliximab, adalimumab, and vedolizumab, among others.

Endoscopic Documentation and Outcomes

All endoscopic procedures were performed by skilled endoscopists based on the standard protocol. Digital versions of static endoscopic images that were saved in the endoscopy registry were reassessed retrospectively by two experienced gastroenterologists. The endoscopic score system was adopted from that of af Björkesten and et al.[20] The primary outcome of the study was MH, defined as remission or mild inflammatory mucosal activity in the most affected area of the gastrointestinal tract, without ulcerations.[20] Disease phenotype was established according to the Montreal classification.[21,22] Patients were followed up until MH has been achieved or final endoscopy was performed before June 2021.

Statistical Analysis

Demographic and clinical parameters were compiled and summary statistics were calculated. Data were described as medians with interquartile ranges (IQRs) for continuous variables and percentages for discrete data. Chi-square or Fisher's exact tests were used to compare the nonparametric categorical data between groups. The univariate influence of different predictive parameters for the risk of failing to achieve MH was analyzed using logistic regression analysis. As the effect of one parameter may be influenced by others, an additional multivariate regression analysis was performed.

All parameters including the risk factors were subsequently included in a full multivariate model. Based on the results of the univariate and multivariate analyses, all factors were examined in the final model. Following stepwise forward selection, only the statistically significant factors remained in the optimized final model ($p < 0.05$). SPSS 26.0 software (SPSS, Chicago, IL, USA) was used to perform all appropriate statistical analyses. R software (version 3.3.2) was used to perform all analyses and to build the nomogram (rms package).

Results

Clinical Characteristics of All Included Patients and Patient Characteristics of Those with MH

A total of 331 patients (219 male and 112 female; median age: 29 years; IQR: 21–39 years) with CD were included; the ages ranged from 12 to 70 years. The flow chart for screening of the patients with CD during the study period is presented in Figure 1. The baseline demographic characteristics are shown in Table 1. The mean age at diagnosis of the included patients was 31.4 years; the cohort was predominantly male (66.2%). Overall, 42 (12.7%) patients had a history of smoking or active smoking. Only 5 (1.5%) patients had a family history of IBD. A total of 177 (53.5%) patients had a history of abdominal or perianal surgery or both. During follow up, 57 (17.2%) patients were initially treated with glucocorticoids, 78 (23.6%) patients were treated with IS. The TNF-α antagonist, infliximab, was administered regularly to 116 (35.0%) patients, while 97 (29.3%) patients received only 5-ASA. After the initial endoscopy procedure at our IBD center, endoscopic investigation for evaluation of MH was performed after 3–122 months, with a mean interval of 22.6 months (median [range]:15 [9, 29] months).

Univariate Logistic Regression for Prediction of MH

We identified 138 patients who achieved MH; this corresponded to 41.7% of the present cohort with CD. Compared with controls who failed to achieve MH, patients who achieved MH were more often males (male vs female: 47.5% vs

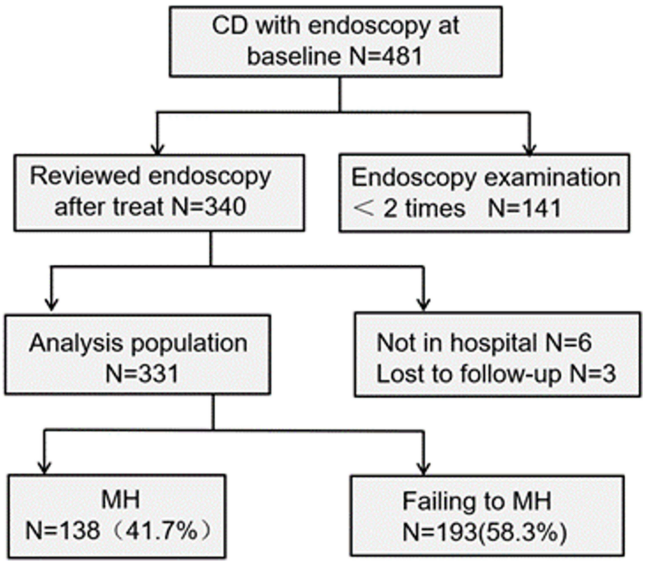

Figure 1 Flow chart showing screening of patients with Crohn's disease.
Abbreviations: CD, Crohn's disease; MH, mucosal healing.

Table 1 Comparison of Demographic and Clinical Characteristics Between Derivation and Validation Cohorts

Characteristics	Derivation Cohort (n=331)	Validation Cohort (n=60)	*P* value
Age at diagnosis, mean (range), y	31.4 (12–70)	28.0 (14–59)	0.052
Gender (M/F), number	219/112	48/12	**0.034**
Smoking, number (%)	42 (12.7)	7 (11.7)	0.826
IBD family history, number (%)	5 (1.5)	2 (3.3)	0.652
Median disease duration, m (IQR)	15 (8–33)	21 (10–43)	0.177
Abdominal operation, number (%)	88 (26.6)	9 (15.0)	0.821
Perianal operation, number (%)	104 (31.4)	36 (60)	**<0.001**
Harvey-Bradshaw score, mean	7.1 (0–19)	5.74 (1–14)	0.585
Disease location, number (%)			**<0.001**
L1 Ileal	66 (19.9)	7 (11.7)	
L2 Colonic	68 (20.5)	10 (16.7)	
L3 Ileocolonic	193 (58.3)	41 (68.3)	
L4 upper gastrointestinal	72 (21.8)	2 (3.3)	
Disease behavior, number (%)			**0.001**
B1, Non-stricturing/penetrating	198 (59.8)	49 (81.7)	
B2, Stricturing	122 (36.9)	8 (13.3)	
B3, Penetrating	31 (9.4)	5 (8.3)	
P, Perianal	144 (43.5)	43 (71.7)	
Ulcer size			**0.031**
≤0.5 cm	30 (9.1)	11 (18.3)	
>0.5 cm	301 (90.9)	49 (81.7)	
Therapy, number (%)			**0.004**
Initial glucocorticoid	57 (17.2)	3 (5.0)	
Immunomodulators	78 (23.6)	12 (20.0)	
Infliximab	116 (35.0)	30 (50.0)	
Exclusive 5-ASA	97 (29.3)	8 (13.3)	

Note: Bold indicates $P < 0.05$.
Abbreviations: IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid.

30.4%, $p = 0.003$). In patients with MH, there were significant differences between different age groups (age ≤ 16 years: 22.2%; 17–40 years: 45.6%; and >40 years: 33.8%, $p = 0.045$). We also found that the group with a disease course of less than 11 months had a higher percentage of MH than that with a disease course exceeding 11 months (50.8% vs 36.0%, $p = 0.008$). HBI scores lower than 9 (50.4% vs 21.2%, $p<0.001$), stool frequency less than four times per day (46.3% vs 31.7%, $p = 0.013$), and ulcer size less than 0.5 cm (63.3% vs 39.5%, $p=0.012$) were all associated with MH (Table 2). Patients who received treatment with infliximab had a higher rate of MH (67.2% vs 27.9%, $p<0.001$). On the contrary, patients treated exclusively with 5-ASA demonstrated a relatively low rate of MH (16.5% vs 52.1%, $p<0.001$).

Combined Predictive Index for MH

We then adjusted a multivariable model containing previously identified predictive variables (including collected demographic, clinical, treatment, and analytical variables) to assess their utility in predicting MH. Variables identified to be associated with MH included gender, age at diagnosis, disease course, HBI scores, stool frequency, ulcer size, and treatment with infliximab or only 5-ASA; the latter had considerable impact on outcomes of MH.

On multivariate analysis, the risk factors predictive of a lower rate of MH included a disease course of more than 11 months, HBI score of more than 9 points, ulcer size greater than 0.5 cm, and exclusive treatment with 5-ASA; on the contrary, regular use of infliximab was identified as the only protective factor (Table 3). The remaining variables analyzed in our cohort did not show significant association with the risk of failing to achieve MH.

Table 2 Univariate Logistic Regression for MH Prediction in Derivation and Validation Cohorts

	Derivation Cohort			Validation Cohort		
	MH	**Fail to MH**	***P* value**	**MH**	**Fail to MH**	***P* value**
Patients Number	138 (41.7)	193 (58.3)		29 (48.3)	31 (51.7)	
Gender			**0.003**			0.272
Male	104 (47.5)	115 (52.5)		21 (43.8)	27 (56.3)	
Female	34 (30.4)	78 (69.6)		8 (66.7)	4 (33.3)	
Age at diagnosis			**0.045**			0.477
A1 <17years	4 (22.2)	14 (77.8)		5 (62.5)	3 (37.5)	
A2 17–40years	109 (45.6)	130 (54.4)		21 (48.8)	22 (51.2)	
A3 >40years	25 (33.8)	49 (66.2)		3 (33.3)	6 (66.7)	
Smoking			0.243			0.104
Non-smoker	117 (40.5)	172 (59.5)		28 (52.8)	25 (47.2)	
Smoker	21 (50.0)	21 (50.0)		1 (14.3)	6 (85.7)	
IBD family history			0.593			0.933
No	137 (42.0)	189 (58.0)		28 (48.3)	30 (51.7)	
Yes	1 (20.0)	4 (80.0)		1 (50.0)	1 (50.0)	
Disease duration			**0.008**			0.106
<11months	65 (50.8)	63 (49.2)		11 (68.8)	5 (31.3)	
≥11 months	73 (36.0)	130 (64.0)		18 (40.9)	26 (59.1)	
Surgical history			0.448			0.439
No	63 (40.9)	91 (59.1)		9 (60.0)	6 (40.0)	
Abdominal	33 (37.5)	55 (62.5)		3 (33.3)	6 (66.7)	
Perianal	46 (44.2)	58 (55.8)		17 (47.2)	19 (52.8)	
HBI score			**<0.001**			**0.001**
≥9	21 (21.2)	78 (78.8)		6 (23.1)	20 (76.9)	
<9	117 (50.4)	115 (49.6)		23 (67.6)	11 (32.4)	
Stool frequency			**0.013**			0.533
>3 times/day	33 (31.7)	71 (68.3)		9 (42.9)	12 (57.1)	
≤3 times/day	105 (46.3)	122 (53.7)		20 (51.3)	19 (48.7)	
Complication			0.437			0.557
≤2	128 (41.2)	183 (58.8)		26 (46.4)	30 (53.6)	
>2	10 (50.0)	10 (50.0)		3 (75)	1 (25)	
Disease location			0.354			0.961
L1 Ileal	27 (40.9)	39 (59.1)		4 (57.1)	3 (42.9)	
L2 Colonic	24 (35.3)	44 (64.7)		5 (50.0)	5 (50.0)	
L3 Ileocolonic	84 (43.5)	109 (56.5)		19 (46.3)	22 (53.7)	
L4 upper	33 (45.8)	39 (54.2)		1 (50.0)	1 (50.0)	
Stricturing			0.526			0.781
No	92 (44.0)	117 (56.0)		26 (50.0)	26 (50.0)	
Yes	46 (37.7)	76 (62.3)		3 (37.5)	5 (62.5)	
Penetrating			0.462			0.938
No	127 (42.3)	173 (57.7)		26 (47.3)	29 (52.7)	
Yes	11 (35.5)	20 (64.5)		3 (60.0)	2 (40.0)	
Perianal lesion			0.816			0.111
No	79 (42.2)	108 (57.8)		11 (64.7)	6 (35.3)	
Yes	59 (41.0)	85 (59.0)		18 (41.9)	25 (58.1)	
Ulcer size			**0.012**			**0.005**
>0.5cm	119 (39.5)	182 (60.5)		19 (38.8)	30 (61.2)	
≤0.5cm	19 (63.3)	11 (36.7)		10 (90.9)	1 (9.1)	

(*Continued*)

Table 2 (Continued).

	Derivation Cohort			Validation Cohort		
	MH	**Fail to MH**	***P* value**	**MH**	**Fail to MH**	***P* value**
Medical treatment						
Steroids			0.715			0.107
No	113 (41.2)	161 (58.8)		26 (45.6)	31 (54.4)	
Yes	25 (43.9)	32 (56.1)		3 (100)	0 (0)	
Immunomodulator			0.690			0.897
No	107 (42.3)	146 (57.7)		23 (47.9)	25 (52.1)	
Yes	31 (39.7)	47 (60.3)		6 (50.0)	6 (50.0)	
Infliximab			**<0.001**			**0.020**
No	60 (27.9)	155 (72.1)		10 (33.3)	20 (66.7)	
Yes	78 (67.2)	38 (32.8)		19 (63.3)	11 (36.7)	
5-ASA Exclusively			**<0.001**			0.781
No	122 (52.1)	112 (47.9)		26 (50.0)	26 (50.0)	
Yes	16 (16.5)	81 (83.5)		3 (37.5)	5 (62.5)	

Note: Bold indicates $P < 0.05$.
Abbreviations: MH, mucosal healing; IBD, inflammatory bowel disease; HBI, Harvey-Bradshaw; 5-ASA, 5-aminosalicylic acid.

The multivariable model showed reliability for predicting the risk of MH failure, with an area under the receiver operating characteristic curve of 0.788 (95% CI, 0.74–0.84) (Figure 2), sensitivity of 60.6%, and specificity of 85.5%. The calibration curve showed good fit indicating high accuracy of the model (Figure 3A). Decision curve analysis

Table 3 Univariate and Multivariate Logistic Regression Model for Prediction of MH

Outcome: MH	**Univariate**		**Multivariate**	
	OR [95% CI]	***p* value**	**OR [95% CI]**	***p* value**
Disease duration ≥		0.008		0.010
11months	Ref		Ref	
<11months	1.837 [1.172–2.881]		2.044 [1.184–3.529]	
HBI score		<0.001		<0.001
≥9	Ref		Ref	
<9	3.779 [2.188–6.525]		3.054 [1.677–5.562]	
Ulcer size		0.012		0.003
>0.5 cm	Ref		Ref	
≤0.5 cm	2.642 [1.214–5.749]		3.869 [1.561–9.591]	
IFX treatment		<0.001		0.004
No	Ref		Ref	
Yes	5.303 [3.252–8.647]		2.367 [1.323–4.234]	
Exclusive 5-ASA		<0.001		<0.001
No	Ref		Ref	
Yes	0.181 [0.1–0.329]		0.225 [0.109–0.464]	
Gender		0.003		
Male	Ref			
Female	0.482 [0.298–0.781]			
Age at diagnosis		0.045		
A1 ≤16 y	Ref			
A2 17–40 y	2.94	0.054		
A3 >40 y	1.78	0.344		
Stool frequency		0.013		
>3 times/day	Ref			
≤3 times/day	1.852 [1.136–3.018]			

Abbreviations: MH, mucosal healing; HBI, Harvey-Bradshaw; IFX, Infliximab; 5-ASA, 5-aminosalicylic acid.

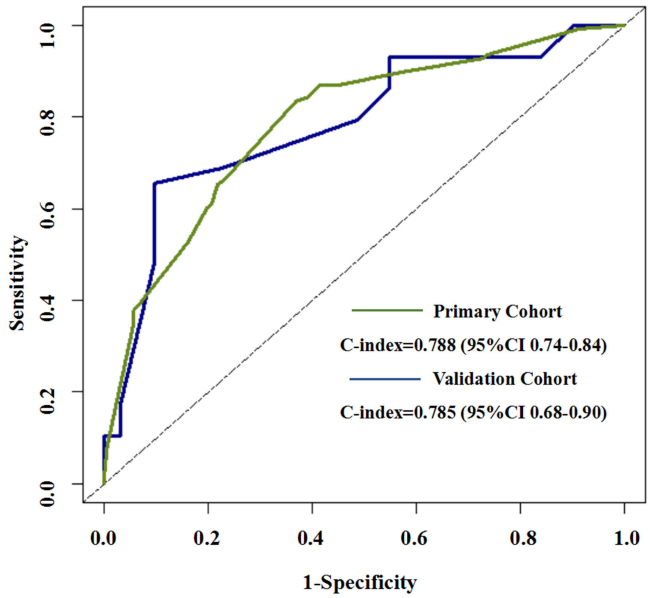

Figure 2 Receiver operating characteristic (ROC) curves of five predictors for predicting mucosal healing. The green line represents the primary group while blue line represents the validation cohort. The area under the ROC curve in the training cohort was 0.788 (95% CI, 0.74–0.84). The area under the ROC curve in the validation group was 0.785 (95% CI, 0.68–0.90).

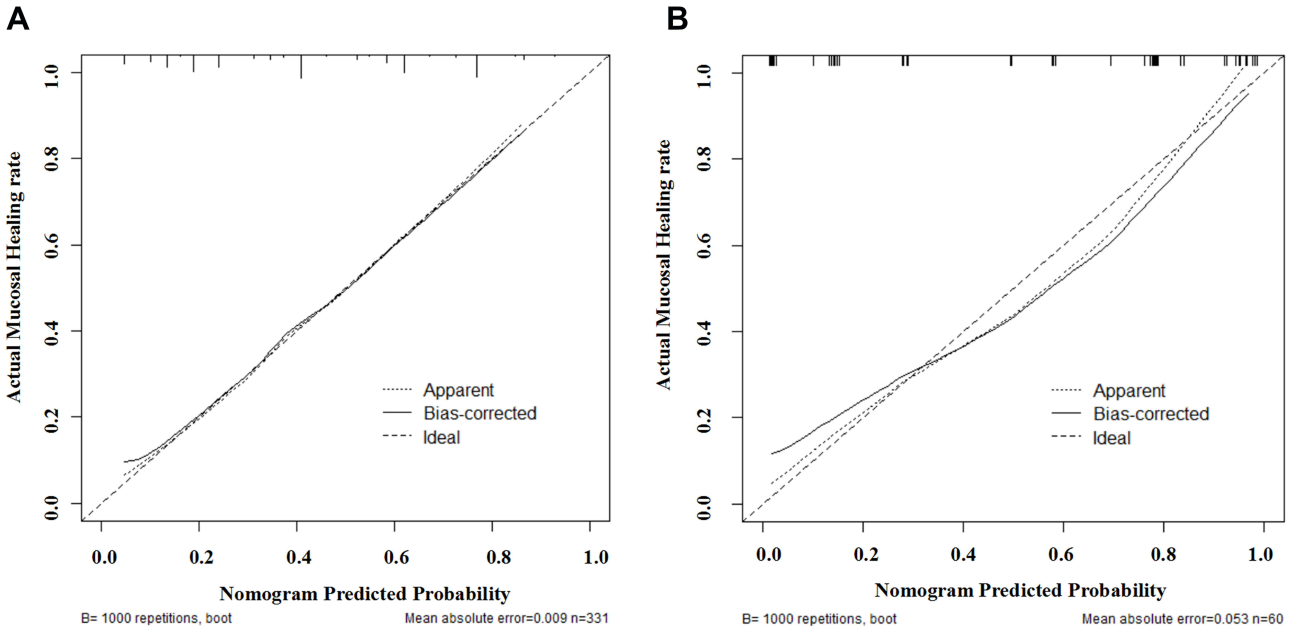

Figure 3 Calibration curves for the (**A**) training model in the training cohort and (**B**) validation cohort. The x-axis represents the predicted mucosal healing (MH) risk while the y-axis represents the actual MH rate. The solid line represents the performance of the prediction models. The 45-degree dotted lines represent a perfect prediction. The closer the solid line fits to the dotted line, the better the accuracy of the model.

showed achievement of a good fit in the training group (Figure 4). The results indicated that in cases where the threshold probability of MH ranged from 20–90%, use of the nomogram could yield more benefit than either the treat-all-patients or treat-none strategies.

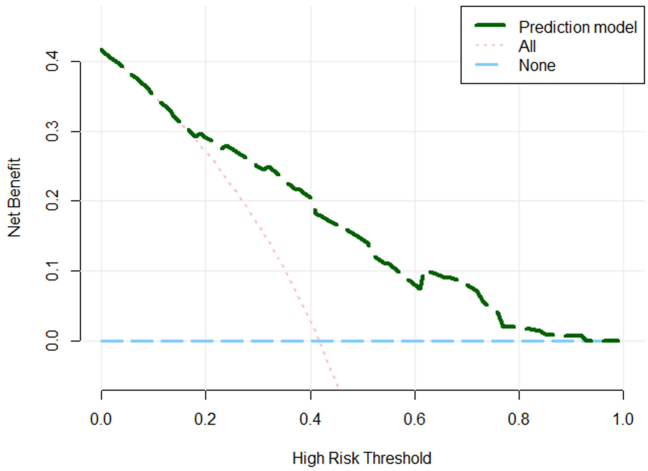

Figure 4 Decision curve analysis: curve of the established models in the training cohort. The y-axis represents the net benefit. The green line represents the performance of the training model. The pink dotted line represents the hypothesis that all patients achieve mucosal healing (MH) and the dotted light blue line represents the hypothesis that all patients fail to achieve MH. The curve shows the threshold probability of MH to range from 20–90%. If a patient's possibility of MH is lower than the threshold probability, an upgrade treatment strategy needs to be selected.

Establishment and Validation of the MH Prediction Nomogram

To further simplify the logistic regression results and to create a practical tool, the coefficients derived from the multivariate analysis were used as weights to establish a nomogram (Figure 5), that could facilitate practical application of the model for making predictions and determining the expected risk for a given patient.

A total of 60 patients with CD with a mean interval of 25.8 months between endoscopy procedures were included in the external validation cohort. There were some differences in baseline demographic characteristics between the validation and derivation groups, as shown in Table 1. The mean HBI score in the validation cohort was lower than that of the derivation group (5.74 vs 7.1); however, the difference was not statistically significant. Based on the Montreal

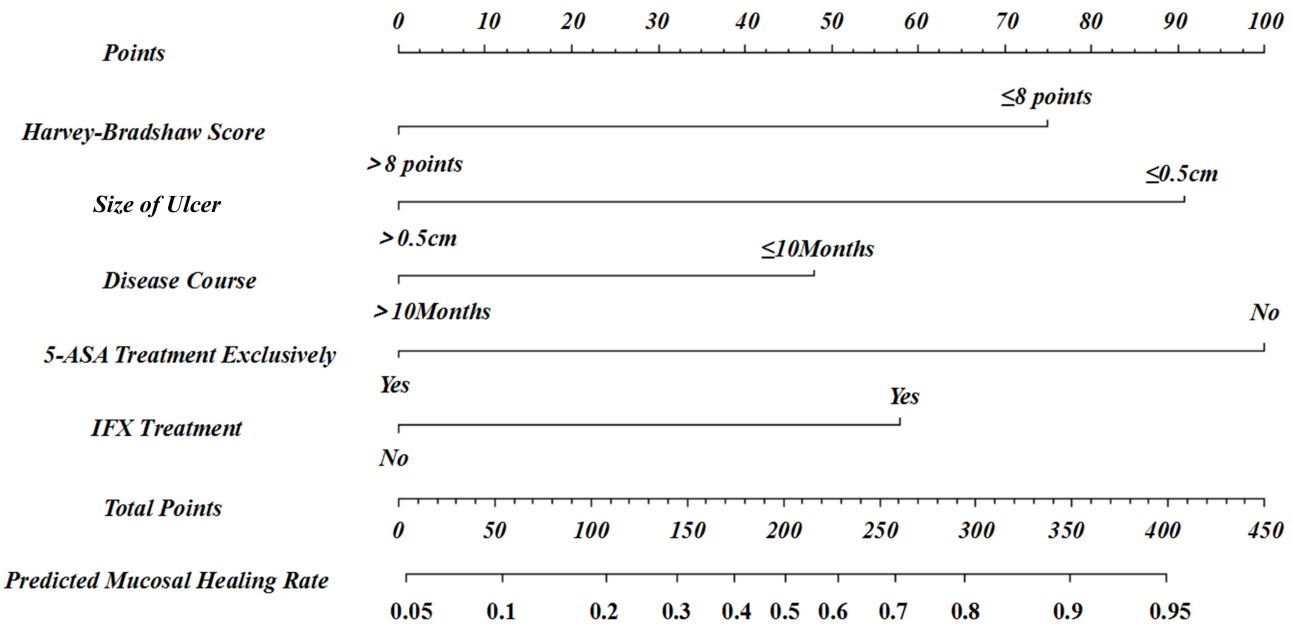

Figure 5 Nomogram for prediction of mucosal healing (MH) rate in a given patient, constructed using the coefficients derived from multivariate analysis as weights. To calculate the probability of MH, the value of each predictor was obtained by drawing a vertical line straight upward from that factor to the point axis; the points achieved for each predictor were summated and this sum was located on the total point axis of the nomogram, where the probability of MH could be located by drawing a vertical line downward.

Abbreviations: 5-ASA, 5-aminosalicylic acid; IFX, Infliximab.

classification, a larger proportion of patients in the validation group showed type B1 (non-stricturing non-penetrating type) lesions on endoscopy (81.7% vs 59.8% in the validation and derivation groups, respectively). A higher proportion of patients received infliximab in the validation cohort (50% vs 35% in the validation and derivation groups, respectively). The MH rates and *P*-values in the training and validation sets are summarized in Table 2. Overall, 29 patients (corresponding to 48.3%) in the validation cohort achieved MH. The variables identified to be associated with MH ($p<0.05$) included the HBI scores, ulcer size, and treatment with infliximab.

Using the algorithm for predictions of MH, the area under the receiver operating characteristic curve was 0.785 (95% CI: 0.68–0.90) in the validation set; this was close to the value in the training set (Figure 2); the sensitivity and specificity were 63.2% and 83.3%, respectively. Although the calibration curve for the validation cohort showed reasonable fit, it was not as good as that of the model (Figure 3B).

Discussion

The natural history of CD represents a progression from inflammatory disease to the development of complications including strictures, fistulas, and abscesses that ultimately necessitate surgery in a majority of patients.[23–25] Reports indicate that MH is associated with improved clinical outcomes.[26] In the proposed treat-to-target strategy, it is important to determine whether the patient is able to achieve MH.[27] The aim of this study was to identify reliable clinical predictors of MH, that are easy to assess immediately after diagnosis of CD. Cumulative probabilities of MH at 26 weeks and 52 weeks have been reported to be 10% and 22%, respectively, while the rates of MH have been reported to rise to 46%, 63%, and 72% at 2, 3, and 4 years, respectively.[12] In our study, 138 of 331 (41.7%) patients in the derivation cohort (with a mean follow-up of 22.6 months) achieved MH; this finding is consistent with that of previous studies.

In our study, CD duration of less than 11 months was found to be associated with a higher MH rate. Receipt of infliximab was significantly associated with an increased rate of MH, while treatment exclusively with 5-ASA was strongly associated with a lower rate of MH. The EXTEND trial showed that patients who had CD for less than 2 years and had received adalimumab had a higher rate of MH.[28] Bouguen et al found that repeated endoscopic procedures and adjustments in medical therapy after each endoscopic procedure were associated with MH.[29] Other studies have reported on treatment associated with endoscopic MH in patients with CD; these include early introduction of TNF-α antagonists, particularly in combination with IS agents.[30] However, the present data failed to demonstrate a positive association between repeated endoscopic procedures and subsequent MH.

On univariate logistic regression analyses, smoking, surgical history, and family history of IBD were not found to affect MH in our cohort. In addition, perianal disease did not have significant association with MH in this study. This may be attributed to the limited number of cases in the present study. A higher MH rate was found in male patients, those aged 17 to 40 years, and in those with loose stools occurring not more than thrice daily. Parameters with statistical significance in the MH model were selected for the optimized risk model in a stepwise manner. Unfortunately, none of these factors were included in the final multivariate logistic regression model. The differences between groups for the following factors remained statistically significant in the optimized model: disease course, HBI, ulcer size, and treatment with infliximab or with 5-ASA alone. Combined values of these factors were used to create a prognostic index with high predictive capacity for assessing the possibility of MH.

Since publication of the National Cooperative Crohn's Disease Study trial in 1979, the clinical disease activity index (CDAI) has been the primary outcome measure for clinical trials.[31] The HBI was derived to simplify calculation of the CDAI. The HBI score has been reported to be consistent with the CDAI score; a 3 point change in the HBI correlates with a 100 point change in the CDAI score and an HBI score of ≤4 corresponds to a CDAI score of ≤150.[32] The HBI index consists of five descriptors: general well-being, abdominal pain, number of liquid stools in the previous day, abdominal mass, and complications. The disease has been classified according to the score obtained: remission is defined by a score of < 5, >9 indicates severe disease activity, and 5–8 implies mild to moderately active disease.[19] In our study, we found that patients with an HBI score of less than 9 were more likely to achieve MH, in both the derivation and external validation cohorts. To our knowledge, this has not been reported in previous studies.

Regarding the association between endoscopic lesion characteristics and MH, previous studies have drawn certain meaningful conclusions with respect to certain risk factors. The presence of internal fistulas, perianal disease, and

stenoses, suggestive of a type B2/3 disease behavior, were found to be indicative of more aggressive disease progression.[33] Mao et al reported a lower rate of MH among patients who had prior enteric fistulas and perianal disease at diagnosis.[12] A correlation between endoscopic lesion features and MH was also observed in our study. Ulcers smaller than 0.5 cm were found to be associated with MH. The other factors including disease location, and presence of internal fistulas, perianal disease, stenosis, and complications did not affect the rate of MH.

We confirmed that a disease course of less than 11 months is suggestive of a good prognosis in terms of MH. An HBI score of less than 9 is a useful early noninvasive marker for predicting MH in CD. Our endoscopy characterization analysis provided new prognostic data; it showed that patients with CD having ulcer sizes of less than 0.5 cm achieved MH more easily. Furthermore, the association between achievement of MH and treatment with infliximab was significantly high; this was observed in contrast to the association with treatment with 5-ASA alone. Using these predictors, a simple and reliable risk model was developed for early risk stratification for MH in CD; particular emphasis was placed on parameters readily accessible without special diagnostic requirements, and therefore useful for daily clinical practice. Although some variables, such as disease location and behavior, differed significantly between the primary and validation cohorts, the performance of the nomogram model in the validation group was not affected. This indicates that our model may be applied widely across groups, even with different disease-related characteristics. This model we constructed in the study could be used before medical treatment. The probability of MH after one year treatment of biologics or 5-ASA can be respectively calculated in advance, aiming to help doctors choose the best therapeutic measure.

Our study has certain limitations. First, other biologic agents, including adalimumab, vedolizumab, and ustekinumab, were used in a total of 16 patients in the present study. Treatment with these biologics was not found to be associated with MH; this could be partly attributed to the limited number of patients in our study. Second, due to the retrospective design, certain details such as the medication dose, frequency, and medication compliance were not recorded in our study. Third, although we performed external validation, the sample size of the validation group was relatively small. Multicenter validation using large-scale samples will be needed to further confirm these results.

Conclusion

In conclusion, we used data from 331 consecutive patients with CD to successfully develop a simple and reliable tool, namely, the Crohn's disease mucosal healing prediction nomogram. We also validated the nomogram in an external cohort of 60 patients. Disease course, HBI scores, ulcer size, treatment with infliximab or only 5-ASA were found to be factors influencing MH. The CD mucosal healing prediction nomogram could be used as a clinical decision support tool for the management of patients with IBD.

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Disclosure

The authors report no conflicts of interest in this work.

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