

Mucosal Healing Is Associated With the Reduced Disabling Disease in Crohn's Disease

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OBJECTIVES: Mucosal healing (MH) is the goal of the “treat to target” strategy in Crohn's disease (CD), which seeks to prevent disability. However, evidence is limited regarding whether achieving MH can reduce disability in CD. We aimed to estimate the probability of disabling disease and to investigate the association between MH and disabling disease in CD.

METHODS: This was a retrospective case-control study of 319 consecutive CD patients. The primary outcome was disabling disease occurrence (defined as surgery, hospitalizations, steroid dependency, or disease complications). The secondary endpoint was disabling disease recurrence. The Kaplan-Meier method and Cox proportional hazards model were used to calculate cumulative rates and for multivariate analysis, respectively.

RESULTS: Of 319 CD patients (median follow-up time: 42.4 months, interquartile range: 24.7–60.0 months), 105 (32.9%) progressed to disabling disease and 20 (6.3%) had the recurrence of disabling disease. The cumulative rates of disabling disease were 11.3%, 30.2%, and 44.9% at 1, 3, and 5 years, respectively, after diagnosis. MH was associated with a significantly lower frequency of surgery, new penetrating event, and new stenosis ($P = 0.004$, $P = 0.001$, $P = 0.002$, respectively). Univariate and multivariate analyses revealed that MH was an independent protective factor of disabling disease occurrence (hazard ratio: 0.166, 95% confidence interval: 0.084–0.329).

CONCLUSIONS: Disabling disease was common in Chinese CD patients and increased during follow-up. Moreover, MH was significantly associated with a reduced occurrence of disabling disease in CD.

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/CTG/A11>

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INTRODUCTION

Crohn's disease (CD) is a chronic, relapsing, and progressive inflammatory disease of the gastrointestinal tract (1,2). Although the inflammatory phenotype is predominant at diagnosis among patients with CD, more than half of patients will experience progressive bowel damage over time, culminating in intestinal complications and surgery (3,4).

The concept of disabling disease was first introduced in 2006 (5). Although this definition fairly varies between authors, in CD, the term “disabling disease” denotes a progressive disease with burdening health-related events (4–7). To our knowledge, there is no validated definition of “disabling disease” in any consensus or guideline of CD to date.

As CD features mucosal chronic inflammation and ulceration, mucosal healing (MH) is the reconstruction and repair of

mucosa in the bowel. There is no consensus on the definition of MH to date; however, MH features a regression or disappearance of endoscopic lesions in CD (8). Understanding the importance of MH has led to the introduction of the “treat to target” strategy, where MH is set as the goal for therapy, with the aim of altering the disease's natural history (9). This strategy has been widely accepted by physician experts in inflammatory bowel disease (10). Moreover, MH has been used as an important indicator of therapeutic success in the latest guideline (11) and the primary endpoint in clinical trials, such as the recently published effect of tight control management on CD study (12). In a Norwegian population-based prospective cohort study, the achievement of MH led to significantly less endoscopic inflammation and decreased future steroid treatment in the long term (13). Moreover, a study demonstrated that MH

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Table 1. Baseline demographic and characteristics of the study

	Total [N = 319]	Disabling CD [n = 105]	Non-disabling CD [n = 214]	P value ^a
Gender: Male, n (%)	213 (66.8)	71 (67.6)	142 (66.4)	0.899
Age at diagnosis, n (%)				0.648
A1	51 (16.0)	19 (18.1)	32 (15.0)	
A2	232 (72.7)	76 (72.4)	156 (72.9)	
A3	36 (11.3)	10 (9.5)	26 (12.1)	
Location, n (%)				0.093
L1: Ileal	77 (24.1)	20 (19.0)	57 (26.6)	
L2: Conlonic	31 (9.7)	7 (6.7)	24 (11.2)	
L3: Ilealcolonic	211 (66.1)	78 (74.3)	133 (62.1)	
Upper tract involvement, n (%)	68 (21.3)	16 (15.2)	52 (24.3)	0.080
Disease behavior, n (%)				0.006
B1: Non-stricturing, non-penetrating	232 (72.7)	65 (61.9)	167 (78.0)	
B2: Stricturing	48 (15.0)	20 (19.0)	28 (13.1)	
B3: Penetrating	39 (12.2)	20 (19.0)	19 (8.9)	
Perianal disease, n (%)	98 (30.7)	32 (30.5)	66 (30.8)	1.000
Smoker, n (%)	31 (9.7)	14 (13.3)	17 (7.9)	0.158
Surgery within 6 months at diagnosis, n (%)	47 (14.7)	23 (21.9)	24 (11.2)	0.018
Follow-up time, median months [IQR]	42.4 [24.7–60.0]	49.5 [35.6–60.0]	36.4 [21.9–59.3]	0.001 ^b
CRP, median [IQR]	13.8 [6.9–29.6]	13.5 [8.2–28.1]	13.9 [6.7–31.0]	0.641 ^b
ESR, median [IQR]	44.0 [26.0–68.0]	48.0 [28.5–73.5]	41.0 [26.0–65.0]	0.095 ^b

5-ASA, 5-aminosalicylic acid; CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range.
^aFisher's exact probabilities.
^bMann-Whitney *U*-test.
 Italic values, *P* < 0.05, difference was statistically significant.

was associated with a lower need for abdominal surgery in CD patients receiving infliximab treatment (14). Other studies also noted the effect of MH on higher steroid-free remission rates and lower rates of hospitalization and surgery (15,16). Nevertheless, evidence is still limited regarding whether achieving MH can reduce disability in CD.

We, therefore, aimed to evaluate the probability of disabling disease in Chinese CD patients and to investigate the association between MH and disabling disease in CD. Here, we hypothesize that MH might be negatively associated with disabling disease in CD.

METHODS

Study population

This was a retrospective case-control study of consecutive patients with CD in the Inflammatory Bowel Disease Center, the First Affiliated Hospital, Sun Yat-sen University, China. Between May 2004 and March 2016, patients with CD who met all the inclusion criteria and none of the exclusion criteria were included in this study. The inclusion criteria were (i) a diagnosis of CD according to the European Crohn's and Colitis Organization guidelines (17); (ii) completion of endoscopy and radiology examinations at our center at diagnosis; (iii) undergoing, at least, 2 endoscopies during the follow-up period; and (iv) follow-up for more than 12 months. The exclusion criteria included (i) prior bowel resection; (ii) non-consecutive patient

status; (iii) missing patient information in the medical records; and (iv) patients with isolated proximal small bowel lesions at the time of diagnosis. The study protocol was approved by the Clinical Research Ethics Committees of The First Affiliated Hospital of Sun Yat-sen University.

Data collection

The medical charts of patients were reviewed, and baseline demographic and clinical information was collected, including diagnosis, therapy, achievement of MH, and adverse events. Baseline was defined as the time of diagnosis. Age at diagnosis, location, disease behavior, and perianal disease were used to classify patients according to the Montreal classification of CD (18). Medications were recorded. For the effect of medication on MH, we only considered medicines that were used for 2 months or longer, including immunosuppressive drugs (azathioprine or 6-mercaptopurine or methotrexate), thalidomide, and anti-tumor necrosis factor (anti-TNF) drugs (infliximab or adalimumab). Futile treatment meant 5-aminosalicylic acid monotherapy or the prescription of any drug mentioned above for less than 2 months. Combined therapy was determined as the combination of an immunosuppressive drug with thalidomide or anti-TNF drug. Endoscopies were performed by skilled endoscopists. MH was defined as the absence of ulceration at a colonoscopy performed more than 1 month before any disabling event (14).

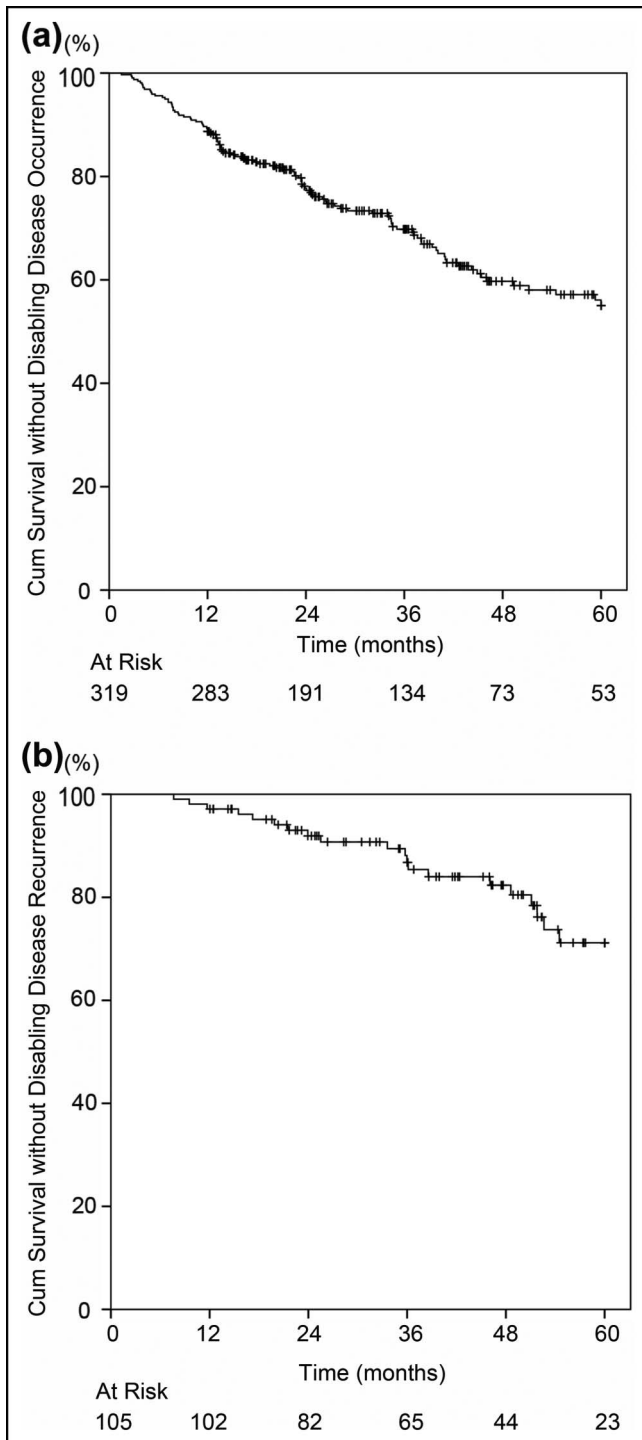


Figure 1. The accumulative rates of remaining free from the occurrence and recurrence of disabling disease in Crohn's disease. (a) The occurrence of disabling disease in Crohn's disease patients. (b) The recurrence of disabling disease in Crohn's disease patients with disabling disease occurrence.

Outcomes analyzed

The primary outcome was the occurrence of disabling disease, which was defined according to Beaugerie and Dias (4,5), with some modifications. Precisely, the occurrence of disabling

disease was defined as, at least, one of the followings (4): (i) one or more bowel surgeries (defined as the resection of the colon and/or small intestine) or perianal surgeries (determined as perianal abscess drainage, setons placement, fistulectomy, or fistulotomy) after the initial 6 months at diagnosis; (ii) at least 3 hospitalizations for disease flare or disease complication; (iii) steroid dependency; and (iv) new disease complication events such as intestinal stenosis (defined as intestinal obstruction observed by computed tomography enterography/magnetic resonance enterography/radiography or the inability to pass the scope in a colonoscopy), penetrating disease (defined as intestinal fistula), or perianal disease. Steroid dependency was defined as being unable to reduce steroids below the equivalent of prednisone 10 mg per day within 3 months of starting steroids, without recurrent active disease, or having disease relapse within 3 months of stopping steroids (17). The secondary outcome was the recurrence of disabling disease, defined as a different disabling event occurring 3 months after the first disabling event.

Statistical analysis

Frequencies were used to describe categorical variables, while the median and interquartile range (IQR) were used to describe continuous variables. A Bayesian network was built to demonstrate the relationship between variables (4,19). The Bayesian network is a probabilistic model that represents dependencies and independencies of a set of variables *via* a directed acyclic graph. The classifier model is the Tree Augmented Naive Bayesian networks (see Supplementary Methods, Supplementary Digital Content 1, <http://links.lww.com/CTG/A11>) (20).

Comparison between groups was performed using Fisher's exact probabilities for categorical variables, Kruskal-Wallis H-test for polynomial classification variables, and the Mann-Whitney *U*-test for non-normally distributed continuous variables. The Kaplan-Meier method was used for survival data to estimate the cumulative rates of disabling disease. Univariate analysis using the Log-rank test was performed to identify independent predictive factors, and factors with $P < 0.1$ in the univariate analysis were integrated into the Cox proportional hazards model to perform multivariate analysis. The threshold for statistical significance was set at $P < 0.05$. Data were analyzed with SPSS 22.0 (IBM, Chicago, IL).

RESULTS

Patients' characteristics at baseline

We reviewed the charts of 1,261 patients with CD treated in our department between 2004 and 2016. A total of 942 cases were excluded: 446 (35.4%) for a follow-up time of less than 12 months, 166 (13.2%) for only one endoscopy during follow-up, 166 (13.2%) for missing endoscopy or radiology records at diagnosis, 69 (5.5%) for prior bowel surgery, 55 (4.3%) for missing detailed medical records, and 40 (3.17%) for loss to follow-up.

The remaining 319 patients were included in the study, with a median follow-up time of 42.4 months (IQR: 24.7–60.0 months). Table 1 shows the baseline characteristics of this cohort, with a breakdown into disabling and non-disabling sub-groups. No significant difference was found between the groups at baseline regarding gender, location, and perianal disease. However, significant differences were noted for disease behavior, surgery within 6 months at diagnosis, and median follow-up time.

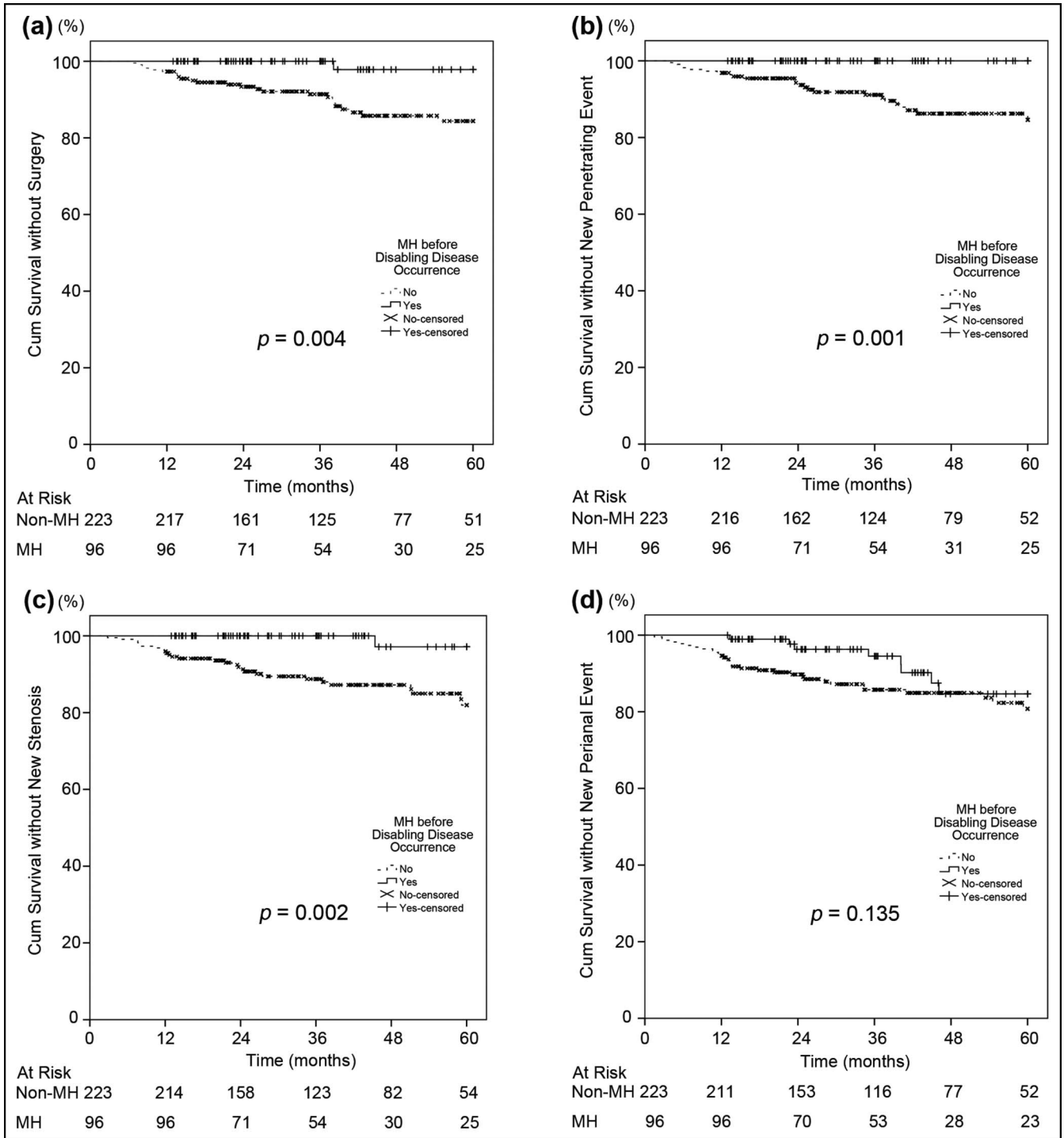


Figure 2. Kaplan-Meier analysis showing time to disabling events according to mucosal healing (MH) before disabling disease occurrence. Disabling events: surgery (a), new penetrating event (b), new stenosis (c), and new perianal event (d).

Before any disabling event, 134 (42.0%) patients received azathioprine/6-mercaptopurine/methotrexate/thalidomide monotherapy. Anti-TNF (infliximab/adalimumab) monotherapy was introduced only in 4 (1.3%) patients, while 56 (17.6%) patients received futile treatment. A combined therapy of immunosuppressive agent and thalidomide or TNF antagonist was prescribed to 125 (39.2%) patients (data not shown).

The occurrence of a disabling course: rate and predicting factors

Among the consecutive 319 patients, 105 (32.9%) progressed to disabling disease within a 14.2-month median follow-up time (IQR: 8.2–27.0 months). The cumulative rates of disabling disease were 11.3%, 30.2%, and 44.9% at 1, 3, and 5 years, respectively, after diagnosis (Figure 1a). The common disabling events were new perianal fistula/abscess (38.1%), new intestinal stenosis

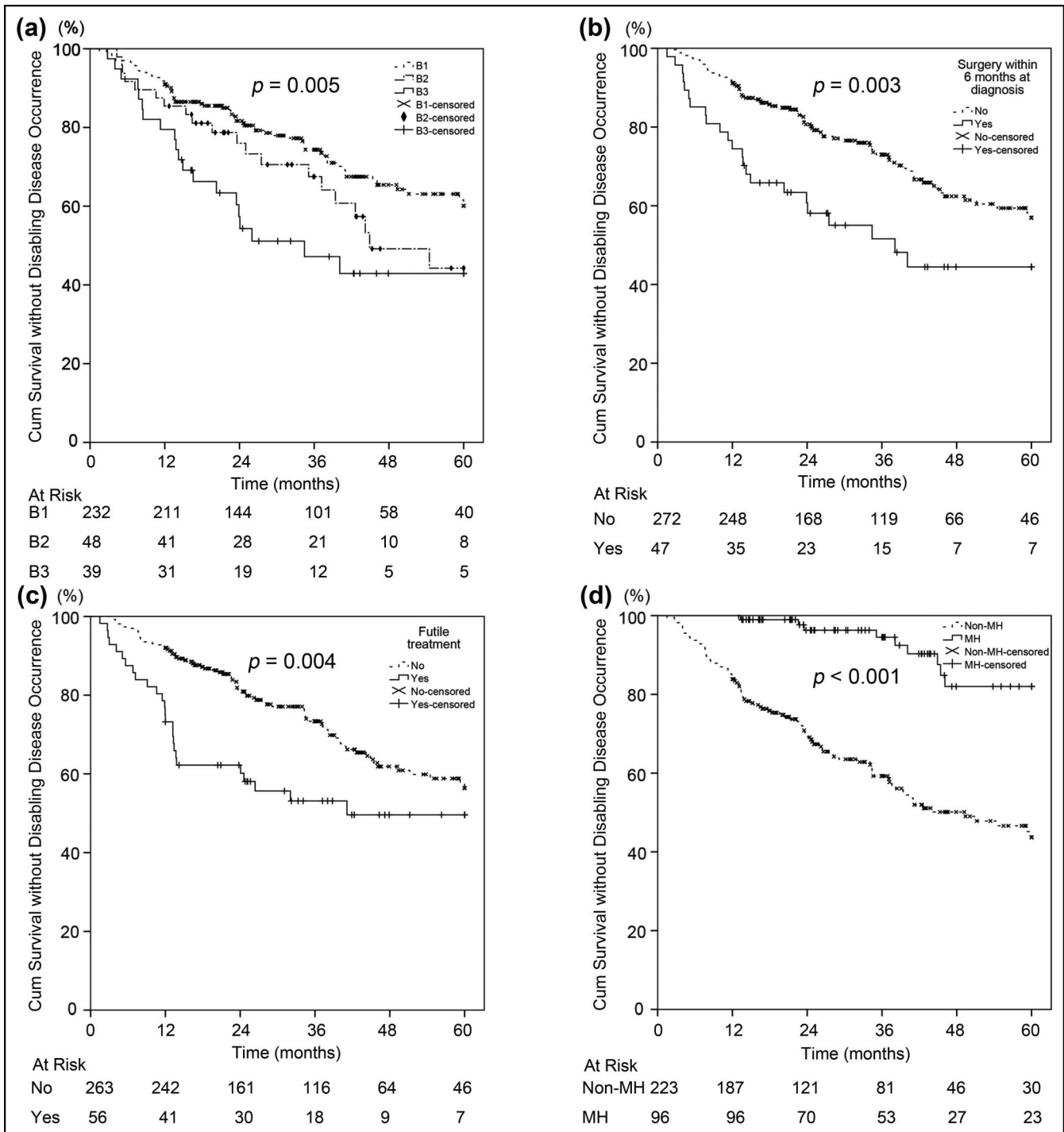


Figure 3. Kaplan-Meier analysis showing time to disabling disease occurrence according to different factors. Factors: disease behavior (a), surgery within 6 months at diagnosis (b), futile treatment (c), and mucosal healing (MH) (d).

(27.6%), and surgery (24.8%). Steroid dependency appeared to be the earliest disabling event and hospitalization for, at least, 3 times was the latest disabling event (see Supplementary Table 1, Supplementary Digital Content 1, <http://links.lww.com/CTG/A11>).

MH as evidenced by colonoscopy was achieved in 96 (30.1%) patients at a median time of 12.3 months (IQR: 6.8–23.8 months) after diagnosis. Within a median time of 22.9 months (IQR: 8.1–31.4 months) after the endoscopy, 9 (9.4%) of them

progressed to disabling disease. Moreover, significantly fewer patients experienced the occurrence of disabling disease in the MH group than in the non-MH group (8.6% vs 40.7%, $P < 0.001$). Notably, no patient with MH progressed to a new penetrating event. More importantly, MH was associated with a significantly lower frequency of surgery, new penetrating event, and new stenosis (see Supplementary Table 2, Supplementary Digital Content 1, <http://links.lww.com/CTG/A11>; $P = 0.001$, hazard ratio

Table 2. Predictors of disabling disease occurrence by univariate and multivariate analyses

	Univariate analysis		Multivariate analysis	
	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)
Gender: Male	0.726	1.076 (0.715–1.619)		
Age at diagnosis	0.417	0.782 (0.543–1.126)		
Location	0.084			
L1: Ileal	0.173	0.714 (0.439–1.162)		
L2: Conlonic	0.148	0.572 (0.265–1.232)		
L3: Ilealcolonic	<i>0.030</i>	<i>1.618 (1.044–2.509)</i>	0.059	1.534 (0.983–2.394)
Upper tract involvement	0.170	0.690 (0.405–1.175)		
Disease behaviour	<i>0.005</i>			
B1: Non-stricturing, non-penetrating	<i>0.004</i>	<i>0.561 (0.378–0.832)</i>	0.077	0.620 (0.366–1.053)
B2: Stricturing	0.273	1.312 (0.806–2.136)		
B3: Penetrating	<i>0.004</i>	<i>2.017 (1.239–3.286)</i>	<i>0.049</i>	<i>1.873 (1.004–3.496)</i>
Perianal disease	0.504	1.153 (0.759–1.750)		
Smoker	0.181	1.465 (0.834–2.573)		
Surgery within 6 months at diagnosis	<i>0.003</i>	<i>1.975 (1.244–3.138)</i>	<i>0.040</i>	<i>1.740 (1.025–2.956)</i>
Drug category before disabling	<i>0.009</i>			
Futile treatment	<i>0.004</i>	<i>1.898 (1.218–2.958)</i>	<i>0.001</i>	<i>2.260 (1.422–3.594)</i>
Mono-immunosuppression/thalidomide	0.629	1.099 (0.748–1.615)		
Mono-biotherapy	0.272	0.049 (0.000–157.807)		
Combined therapy	<i>0.020</i>	<i>0.610 (0.401–0.928)</i>	0.312	0.790 (0.501–1.247)
Mucosal healing	<i><0.001</i>	<i>0.169 (0.086–0.336)</i>	<i><0.001</i>	<i>0.166 (0.084–0.329)</i>

CI, confidence interval; HR, hazard ratio.
Italic values, *P* < 0.05, difference was statistically significant.

[HR]: 0.093, 95% confidence interval (CI): 0.013–0.687; *P* < 0.001, HR: 0.026, 95% CI: 0.001–0.816; and *P* < 0.001, HR: 0.081, 95% CI: 0.011–0.598, respectively). Further, patients with MH progressed more slowly to these disabling events compared to those without MH (Figure 2, *P* = 0.004, *P* = 0.001, and *P* = 0.002, respectively).

The Bayesian network was built to reveal the interdependent relationship between disabling disease and clinical variables at baseline (see Supplementary Figure 1, Supplementary Digital Content 1, <http://links.lww.com/CTG/A11>). Associations (arc between variables) were found between behavior and index surgery/perianal disease, perianal disease and gender/age, and age and upper tract involvement (L4).

Univariate and multivariate analyses were performed to verify the association between MH and the occurrence of disabling disease. On univariate analysis, MH achievement (HR: 0.169; 95% CI: 0.088–0.336), non-stricturing and non-penetrating (B1) disease behavior at diagnosis (HR: 0.561; 95% CI: 0.378–0.832), and combined therapy (HR: 0.610; 95% CI: 0.401–0.928) were negatively associated with the occurrence of disabling disease. In contrast, penetrating (B3) disease behavior at diagnosis (HR: 2.017; 95% CI: 1.239–3.286), ileocolonic (L3) disease location at diagnosis (HR: 1.618; 95% CI: 1.044–2.509), surgery within 6 months at diagnosis (HR: 1.975; 95% CI: 1.244–3.138), and futile treatment (HR: 1.898; 95% CI: 1.218–2.958) were positively associated with the occurrence of disabling disease (Figure 3 and Table 2). Multivariable analysis

revealed that MH (HR: 0.166; 95% CI: 0.084–0.329) was an independent protective factor for the occurrence of disabling disease, while penetrating (B3) disease behavior at diagnosis (HR: 1.873; 95% CI: 1.004–3.496), futile treatment (HR: 2.260; 95% CI: 1.422–3.594), and surgery within 6 months at diagnosis (HR: 1.740; 95% CI: 1.025–2.956) were independent risk factors for disabling disease occurrence (Table 2).

The recurrence of disabling disease: rate and predicting factors

Twenty (17.4%) subjects experienced a recurrence of disabling disease (median follow-up time: 48.9 months, IQR: 43.0–58.6 months) among 105 patients with a disabling event. The cumulative probabilities of disabling disease recurrence were 2.9%, 13.2%, and 28.8% at 1, 3, and 5 years, respectively, after diagnosis (Figure 1b). Unlike in the occurrence of disabling disease, surgery (35%) and new intestinal stenosis (35%) were the predominant recurrent disabling events (see Supplementary Table 1, Supplementary Digital Content 1, <http://links.lww.com/CTG/A11>).

In these patients with disabling CD, there was no significant difference in baseline variables between groups with or without the recurrence of disabling disease (see Supplementary Table 3, Supplementary Digital Content 1, a). MH before a disabling event was achieved in 9 patients, and none of them experienced the recurrence of disabling disease. However, 20 (20.8%) of 96 patients without MH before a disabling event developed new disabling events (*P* = 0.145) (Figure 4a).

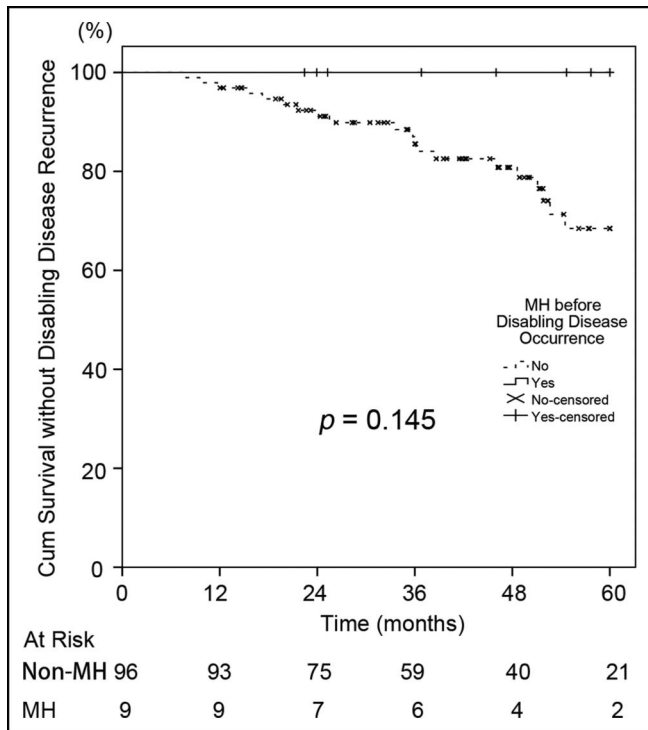


Figure 4. Kaplan-Meier analysis of disabling disease recurrence according to mucosal healing (MH) before disabling disease occurrence in disabling Crohn's disease patients.

Univariate and multivariate analyses were conducted to find out the predictive factors of disabling disease recurrence. On univariate analysis, surgery within 6 months at diagnosis (HR: 4.273; 95% CI: 1.775–10.284), male sex (HR: 3.872; 95% CI: 1.132–13.250), and smoker (HR: 2.927; 95% CI: 1.060–8.083) were positively associated with the recurrence of disabling disease. The analysis also showed that MH before a disabling event was not a protective factor for disabling disease recurrence (HR: 0.043; 95% CI: 0.000–29.751). Moreover, 2 independent risk factors, surgery within 6 months at diagnosis (HR: 4.378; 95% CI: 1.810–10.588), and male sex (HR: 3.991; 95% CI: 1.160–13.731) were identified in the multivariate analysis (Table 3).

DISCUSSION

This retrospective study demonstrated the negative association between MH and disabling disease in CD, providing clear evidence of the impact of MH on long-term outcomes in CD. Generally, 32.9% of consecutive patients with CD progressed to disabling disease within a median follow-up period of 14.2 months in this study. Notably, MH before a disabling course was an independent protective factor for the occurrence of disabling disease.

In this study, the rate of a disabling disease in Chinese CD patients was 32.9%, which is much lower than reported in other studies (57.9%–85.2%) (5–7). The definition of disabling events, such as the exclusion of surgery within 6 months at diagnosis and the prescription of immunosuppressive agents, might account for this difference. In a recent study with a similar definition in Portugal, the rate of disabling disease was 64% in early treated CD patients (4). The modifications of the definition of disabling

disease, in which therapy switch and steroid resistance were discarded, should be responsible for the lower rates in our study. Further work is needed to compare the rate of disabling disease with the same inclusion criteria and definition between the West and China.

Little is known about the protective factors for disabling disease in CD. A recent study reveals that neither early surgery nor immunosuppression therapy could prevent disabling disease (21). However, our study found that MH was protective against the occurrence of disabling disease. Further, MH was associated with a significantly lower frequency of surgery, new penetrating event, and new stenosis. Previous studies reveal that MH predicts a more favorable clinical remission (13,15,22), decreased future steroid treatment (13), and fewer unfavorable long-term outcomes, including surgeries (13,14,16,23), hospitalizations for disease flare (16,23), and disease relapse (13). In our study, however, MH was not associated with a lower need for hospitalizations (≥ 3 times). This finding may be related to an inadequate statistical power resulting from the small number of patients with hospitalizations (≥ 3 times). Controversially, a retrospective study of 252 CD patients in Europe demonstrated that MH at 2 years after treatment was not associated with any unfavorable long-term outcome, including surgery, hospitalization, and a new fistula (24). Because unfavorable events might occur within 2 years, this result would have been more convincing if an accurate assessment of MH before adverse events was performed during follow-up.

In previous studies with a different definition of disabling disease, the predictive risk factors were perianal disease (5–7), initial requirement for steroids at diagnosis (5–7), age below 40 years (5), and ileocolonic disease location at diagnosis (7). In the earlier-mentioned Portugal study, penetrating disease behavior, perianal disease, and intestinal stenosis were risk factors (4). The independent risk factors for disabling disease in our study were penetrating (B3) disease behavior, futile treatment, and surgery within 6 months at diagnosis. Perianal disease and stricturing (B2) disease behavior, unexpectedly, were not risk factors in our study. The main reason for this might be the exclusion of early perianal or intestinal surgery done within 6 months of diagnosis as a disabling event. Moreover, in a 10-year retrospective study in Korea, no significant associations were found between perianal disease and surgery or hospitalizations (25). However, surgery and hospitalizations were considered as disabling events in our study.

There are several explanations for our study's design and some confusing results. First, we arbitrarily set 5-aminosalicylic acid monotherapy as futile treatment. This is because 5-aminosalicylic acid is not recommended as a first-line treatment (17) and controversial clinical improvements were observed with 5-aminosalicylic acid over placebo in CD (26,27).

Second, the median follow-up time at baseline differed significantly between patients with and without disabling disease. It is highly probable that disabling events aroused the attention and improved the compliance of patients, thus, prolonging follow-up time. To figure out whether this might bias the main result, a sensitivity analysis restricting the follow-up time to 42 months was conducted. This sensitivity analysis incorporating patients with a similar median length of follow-up yielded similar results to the main analysis (data not shown).

Third and unexpectedly, even though none of the disabling patients with MH before a disabling event experienced the

Table 3. Univariate and multivariate analyses on predictors of disabling disease recurrence in disabling Crohn's disease patients

	Univariate analysis		Multivariate analysis	
	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)
Gender: Male	0.020	3.872 (1.132–13.250)	0.028	3.991 (1.160–13.731)
Age at diagnosis	0.282	1.599 (0.700–3.653)		
Location	0.422			
L1: Ileal	0.197	1.859 (0.714–4.841)		
L2: Conlonic	0.907	1.128 (0.150–8.476)		
L3: Ilealcolonic	0.211	0.560 (0.223–1.407)		
Upper tract involvement	0.950	0.961 (0.281–3.282)		
Disease behavior	0.739			
B1: Non-stricturing, non-penetrating	0.454	0.715 (0.296–1.726)		
B2: Stricturing	0.774	1.174 (0.392–3.516)		
B3: Penetrating	0.523	1.389 (0.505–3.824)		
Perianal disease	0.559	0.721 (0.240–2.166)		
Smoker	0.030	2.927 (1.060–8.083)	0.611	1.325 (0.448–3.924)
Surgery within 6 months at diagnosis	<0.001	4.273 (1.775–10.284)	0.001	4.378 (1.810–10.588)
Drug category ^a	0.604			
Futile treatment	0.196	0.044 (0.000–62.176)		
Mono-immunosuppression/thalidomide	0.969	0.983 (0.407–2.373)		
Mono-biotherapy	0.967	1.043 (0.139–7.811)		
Combined therapy	0.471	1.379 (0.573–3.318)		
MH before a disabling event	0.145	0.043 (0.000–29.751)		

CI, confidence interval; HR, hazard ratio; MH, mucosal healing.
^aDrug category after the first disabling event but before disabling recurrence.
 Italic values, *P* < 0.05, difference was statistically significant.

recurrence of disabling disease, MH before a disabling event was not protective against the recurrence of disabling disease. This might be related to the small number of patients with disabling disease who achieved MH before a disabling event. Nonetheless, this finding emphasizes the importance of achieving MH before a disabling event. Further work with a larger number of subjects is needed to clarify this phenomenon.

Our study has certain limitations. Its retrospective nature resulted in the lack of standardized endoscopic assessment for inflammation and ulceration. As there is no consensus on the validated definition of MH, MH was defined according to different criteria in different studies, such as CD endoscopic index of severity, simplified endoscopic score for CD, the absence of ulceration, and so on (14,15,28). To minimize bias, we defined MH as the absence of ulceration rather than as a simplified endoscopic score for CD of zero (15), and also refrained from trying to classify retrospectively ulcers into deep ulcers or not, as endoscopic records are not reliably detailed enough for both purposes. Second, we cannot exclude the possibility of inaccessible proximal small bowel lesions being misclassified as having MH by ileocolonoscopy. However, with the implementation of imaging and evaluation of transmural inflammation by the computed tomography enterography/magnetic resonance enterography in all patients, such proportion of misclassification is likely small. Finally, as in any long-term longitudinal study with extended follow-up, it is hard to exclude definitely the impact of

changing clinical practices during the study period on the observed results.

In conclusion, this study provides retrospective evidence regarding the rates of disabling disease in CD. Moreover, it revealed that MH is an independent protective factor for disabling disease in CD. MH may be a crucial target to achieve a better prognosis in CD and might help physicians make medical decisions in difficult cases.

Study Highlights

WHAT IS KNOWN

- ✓ MH is the goal of the “treat to target” strategy in CD.
- ✓ Evidence is limited regarding whether achieving MH can reduce disability in CD.

WHAT IS NEW HERE

- ✓ Disabling disease is common in Chinese patients with CD.
- ✓ MH appears to be associated with a reduced occurrence of disabling events.

TRANSLATIONAL IMPACT

- ✓ Achieving MH can reduce disabling disease in the clinical practice of CD patients.

CONFLICTS OF INTEREST

Guarantor of the article: Shenghong Zhang, MD, PhD.

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