Normalization of C-Reactive Protein Predicts Better Outcome in Patients With Crohn's Disease With Mucosal Healing and Deep Remission

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OBJECTIVES: **Therapeutic targets for Crohn's disease (CD) have evolved from clinical and biological remission to mucosal healing (MH) and deep remission (DR). MH is defined as disappearance of ulceration, whereas DR is defined as a combination of clinical remission and MH. Limited data are available regarding differences in long-term outcomes of these patients reaching these targets. We thus aimed to evaluate patients' long-term clinical outcomes using different composite remission parameters.**

METHODS: **We performed a retrospective cohort study comparing long-term outcomes of patients with different remission parameters, including MH and DR with or without normalization of C-reactive protein (CRP_{norm}). The primary outcome was CD-associated intestinal surgery, and secondary outcomes included CD-related hospitalizations, clinical relapse (CR), or endoscopic recurrence (ER).**

RESULTS: **One hundred ninety-five patients with MH at follow-up endoscopy were divided into 3 groups: DR-only (n = 53), DR + CRP_{norm} (n = 106), and MH-only (n = 36). At the follow-up (median 46.0 months), 25 patients had undergone CD-related bowel surgery, 44 had CD-related hospitalizations, and 66 experienced CR. Of 151 patients who underwent follow-up colonoscopy after the index colonoscopy for MH, 96 experienced ER. Among the 3 groups, patients in the DR + CRP_{norm} group had the lowest risk of clinical or endoscopic relapse. The DR group had a lower rate of CR than the MH-only group ($P = 0.03$); there was no difference in the rate of CD-related surgery, hospitalizations, or ER.**

DISCUSSION: **Patients with DR combined with a normalized CRP showed better outcomes than those with DR only. The outcomes of patients with MH were similar to those of patients with DR, except for shorter flare-free survival.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A194 and http://links.lww.com/CTG/A195

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INTRODUCTION

Crohn's disease (CD) is a progressive condition of the gastrointestinal tract that requires long-term treatment and management (1). It has been reported that targeting clinical symptoms alone may be insufficient to reduce or prevent long-term disability in patients with CD. Biological biomarkers of inflammation, as well as endoscopic features, have proven to be candidate treatment targets. Mucosal healing (MH), defined as the disappearance of ulceration at endoscopy, correlates with improved outcomes in patients with CD (2) and is, thus, currently the most recognized treatment target. However, MH has limitations because of its invasiveness and inability to provide the full picture of transmural lesions. The treatment target should thus include less-invasive objective measures of inflammation (3). Moreover, the discordance between clinical symptoms and objective markers of intestinal inflammation such as fecal calprotectin, C-reactive protein (CRP), or endoscopy (4), indicates the necessity for new endpoints integrating these indices.

Goals are currently evolving toward deep remission (DR), which combines clinical remission with MH (5–8). Data from the EXTEND study demonstrated that the realization of DR, defined as the absence of mucosal ulceration and Crohn's disease activity index (CDAI) scores of <150, was associated with improved outcomes for adalimumab-treated patients with CD (9). Patients with early DR experienced fewer dose escalations and had lower healthcare costs (10).

A definition of treat-to-target has been proposed by the Selecting Therapeutic Targets in Inflammatory Bowel Disease program, aimed at achieving clinical and endoscopic remission in

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patients with CD (11). The landmark CALM study demonstrated that dosage adjustment of antitumor necrosis factors based on clinical symptoms combined with biomarkers resulted in better clinical and endoscopic outcomes than symptom-driven decisions alone (12). Although the treatment target of DR is appealing, there are still uncertainties regarding its clinical relevance. A unified definition is lacking, and the benefit to patients from a stricter definition of DR, which includes a decreased need for surgery or hospitalization, compared with clinical or endoscopic remission alone, needs to be clarified (13). This study was designed to assess long-term outcomes in a cohort of patients with CD having different degrees of remission with the aim of finding a more desirable endpoint that might ultimately affect the disease course.

METHODS

Study design

This was a retrospective, observational cohort study of patients with CD (from October 1, 2006, to September 30, 2016) using a prospectively maintained inflammatory bowel disease database at a tertiary medical center. Diagnosis of CD was determined according to the criteria of Lennard-Jones (14), based on patients' clinical, endoscopic, histopathological, and radiological findings. The location of the disease was identified by the criteria of the Montreal Classification (15).

Eligible patients had (i) established CD with MH detected by ileocolonoscopy, (ii) at least 1 cross-sectional imaging evaluation, and (iii) a minimal follow-up of 6 months. Exclusion criteria were (i) age younger than 16 years, (ii) incomplete endoscopic procedures, (iii) no endoscopic remission; (iv) isolated proximal small bowel disease (15), and (v) disease-modifying treatment, including immunomodulators (IMMs) and biologics switch.

The study protocol met the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Sun Yat-Sen University (No. 2015-47). A written informed consent was obtained from all patients.

Clinical follow-up and data collection

Clinical follow-up and additional pertinent patient data, the inflammatory bowel disease registers, and the endoscopy registers were reassessed by 2 experienced gastroenterologists (B.L.C. and Y.H.). The incidence of CD-related surgery, median CDAI scores, and CRP concentrations at successive visits throughout the follow-up were recorded. The number of patients remaining in MH and those who experienced an endoscopic recurrence (ER) were also recorded at the time of each endoscopic procedure. We used the Simple Endoscopic Score for CD (SES-CD) to assess a minimal level of active ileocolonic inflammation (16). MH was defined as a SES-CD of 0–2, with no signs of ulceration in any colonic segment or in the terminal ileum (17), and ER was defined as patients with MH experiencing a SES-CD of >2. Data of CDAI and SES-CD were recorded at each visit in our prospectively maintained database.

Definitions and outcomes

Our study defined the primary outcome as the proportions of CD-related intestinal surgery, including resection of a part of the gut, strictureplasty for stenosis, surgery for intraabdominal fistula complications, and fecal diversion (ostomy). Procedures such as abscess drainage or endoscopic dilatations were not counted as primary outcomes. Prespecified secondary outcomes were the proportion of CD-related hospitalizations, clinical relapse (CR), or ER during follow-up. CD-related hospitalizations were defined as those resulting from adverse events or CD-related treatment or complications (10). CR was defined as a CDAI score >150 with an increase of more than 70 points (18). MH was defined as disappearance of an ulcer at endoscopy. DR was defined as a combination of clinical remission and MH. Normalized CRP was defined as less than 3 mg/L. Serum CRP was tested with an immunoturbidimetric assay in our center, with a cutoff value for healthy subjects of 3 mg/L (19,20).

Statistical analysis

Demographic and clinical parameters were collected, and summary statistics were calculated. Continuous data were described using medians with interquartile ranges (IQRs). Analysis of variance was used to compare continuous parameters between groups, and Fisher's exact test and χ^2 tests were used for nonparametric categorical data.

Cumulative probabilities of ER, CR, and CD-related intestinal surgery were estimated using the Kaplan–Meier method. For each event, the time to ER, CR, CD-related intestinal surgery, or hospitalization was considered to end at the last known follow-up evaluation or at the date during which the event was first observed. SPSS 15.0 software (SPSS, Chicago, IL) was used to perform all appropriate statistical analyses. For all tests, statistical significance was defined as $P < 0.05$ and 2-tailed tests were used.

RESULTS

Demographic characteristics

A total of 195 patients (median age, 30 years; IQR, 23–40 years; median duration, 12 months; IQR, 0.3–2.4 years; male, 123) who presented with MH at the scheduled endoscopic follow-up evaluation were included in the study. The baseline characteristics (and concomitant medications) are listed in Table 1. The baseline endoscopic assessment showed normal endoscopic findings in 90 (46%) patients and mild mucosal erythema or granularity without ulcerations in 105 (54%) patients.

The total 195 patients were divided into 3 groups based on normalization of CDAI and/or CRP: the DR-only group (patients with CDAI < 150 at detection of MH, with abnormal CRP, n = 53), the DR + CRP_{norm} group (patients with DR with normalized CRP, n = 106), and the MH-only group (patients with CDAI > 150 at the detection of MH, n = 36) (Figure 1).

There was no significant difference in gender, age, disease duration, previous disease outcomes before referral, infliximab use, perianal lesion, erythrocyte sedimentation rate, steroid use, and simultaneous medication (Table 1).

After a median follow-up period of 46.0 months (IQR, 28.2–67.9 months), 25 (12.8%), 44 (22.6%), and 66 (33.8%) of the 195 patients experienced CD-related bowel surgery, CD-related hospitalizations, and CR, respectively. Of 151 patients, 96 experienced ER based on the follow-up colonoscopy.

No differences in major abdominal surgery ($P = 0.23$), CD-related hospitalizations ($P = 0.11$), or ER ($P = 0.36$) except for CR ($P = 0.006$) were observed when stratifying patients according to baseline endoscopic findings (entirely normal vs mild erythema without ulcers) (see Figure 1A–D, Supplementary Digital Content 1, http://links.lww.com/CTG/A194).

Table 1. Characteristics of the study population at inclusion in the follow-up cohort

Variable	DR + CRP_{norm} (n = 106)	DR only (n = 53)	MH only (n = 36)	*P* value
Gender, M:F	68:38	31:22	23:13	0.516
BMI, median (IQR75)	17.9 (15.8–20.3)	17.8 (16.3–19.1)	16.9 (16.5–18.1)	0.625
Median disease duration at referral, yr (IQR)	0.8 (0.3–2.04)	1.2 (0.8–3.3)	1.9 (0.3–4.3)	0.251
Median disease duration at MH, yr (IQR)	2.4 (1.2–4.3)	1.6 (0.8–4.7)	2.4 (0.6–4.7)	0.752
Age at referral, yr (IQR)	28 (23–37)	33 (20–38)	37 (26.9–42.3)	0.213
Age, <40 yr	73 (68.9)	44 (83)	19 (52.8)	
Montreal classification at CD diagnosis, n (%)				0.197[a]
L1: ileal	31 (29.2)	13 (24.5)	11 (30.6)	
L2: colonic	17 (16)	7 (13.2)	2 (5.6)	
L3: ileocolonic	53 (50)	30 (56.6)	17 (47.2)	
L4: upper digestive tract	5 (4.7)	3 (5.7)	6 (16.7)	
Small bowel involvement	25 (23.6)	22 (41.5)	16 (44.4)	
Montreal B classification at CD diagnosis, n (%)				**0.093**
B1: nonpenetrating nonstricturing	50 (47.2)	20 (37.7)	8 (22.2)	
B2: stricturing	36 (34)	24 (45.3)	20 (55.6)	
B3: penetrating	20 (18.9)	9 (17)	8 (22.2)	
P: perianal lesion	24 (22.6)	16 (30.2)	4 (11.1)	
Disease outcomes before referral, n (%)				0.541
Penetrating disease	5 (4.7)	8 (15.1)	4 (11.1)	
Stricturing disease	5 (4.7)	7 (13.2)	2 (5.6)	
Anal fistula	37 (34.9)	27 (50.9)	22 (61.1)	
Previous treatments, n (%)				0.402
Previous surgery	35 (33.0)	12 (22.6)	14 (38.9)	
Previous medical treatment				
Steroid	45 (42.5)	12 (22.6)	7 (19.4)	
IMM (AZA/6 MP or MTX)	54 (50.9)	15 (28.3)	7 (19.4)	
TNF-α antagonists	15 (14.2)	4 (7.5)	2 (5.6)	
Simultaneous medication				0.204
Steroid	17 (16)	7 (13.2)	12 (33.3)	
AZA/6 MP or MTX	64 (60.4)	30 (56.6)	16 (44.4)	
TNF-α antagonists	10 (9.4)	4 (7.5)	3 (8.3)	
CDAI, median at referral (IQR)	200 (144–250)	169.5 (117–278)	213 (180.8–268.5)	0.145
CDAI, median at MH (IQR)	76 (43–114)	89 (67–143)	230 (218–303)	**0.014**
Biologic variables at MH				
Hemoglobin level (g/L)	128 (121–140)	121 (109–129)	117 (95–128)	**0.065**
Leukocyte count (10^9/L)	6.7 (4.7–8.6)	7.1 (5.7–8.8)	6.12 (4.8–8.6)	0.19
Neutrophil granulocyte count (10^9/L)	3.5 (2.2–5.2)	4.1 (2.9–5.5)	2.87 (2.4–6.2)	0.728
Platelet count (10^9/L)	269 (231–331)	297 (232–364)	275 (231–354)	0.46
CRP (mg/L)	1.2 (0.5–2.2)	11.6 (3.1–13.6)	5.72 (1.7–12.6)	**0.001**
ESR (mm/hr)	18 (12–28.5)	38 (18–49)	23 (12–35)	0.115

Factors in bold have a *P* value less than or near 0.05.
6-MP, 6-mercaptopurine; AZA, azathioprine; BMI, body mass index; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein; CRP_{norm}, normalization of CRP; DR, deep remission; ESR, erythrocyte sedimentation rate; IMM, immunomodulator; IQR, interquartile range; MH, mucosal healing; MTX, methotrexate; TNF, tumor necrosis factor.
[a]The *P*-value refers to the comparison of 3 groups with small bowel involvement.

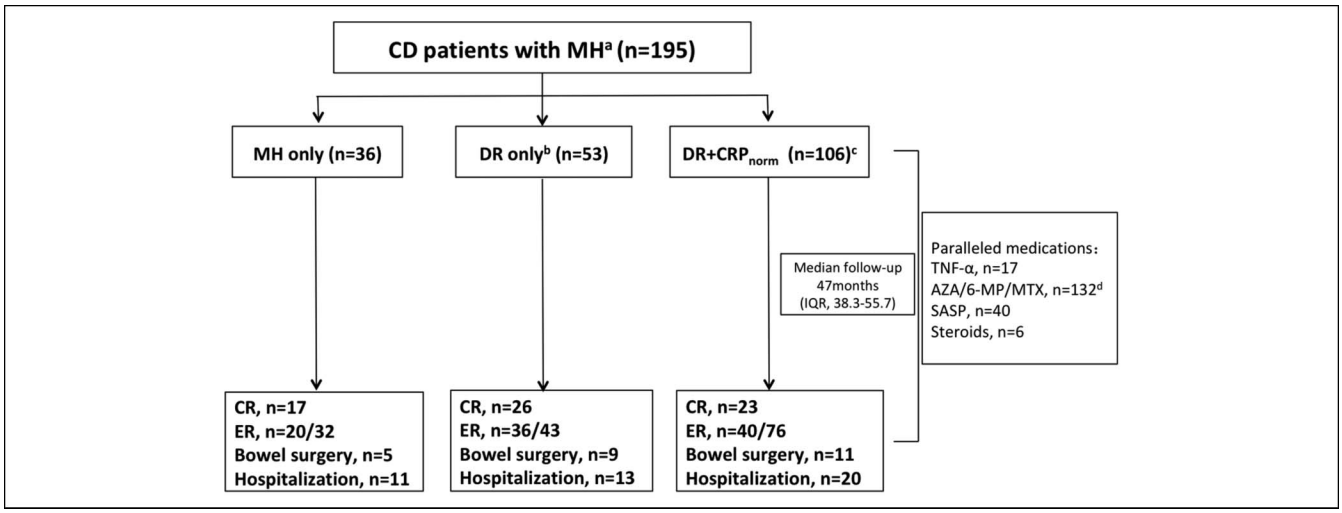

Figure 1. Flow chart of patient enrolment. [a]Adopted the definition used by Frøslie et al. (34), in which normal endoscopic findings and mild mucosal erythema or granularity without ulcerations were all regarded as MH; [b]defined as the absence of mucosal ulceration and CD activity index scores less than 150 (35); [c]among 195 patients, 159 patients were with available data of CRP; [d]AZA/6-MP (n = 102), MTX (n = 18). 6-MP, 6-mercaptopurine; AZA, azathioprine; CD, Crohn's disease; CR, clinical relapse; CRP_{norm}, normalization of C-reactive protein; DR, deep remission; ER, endoscopic recurrence; IQR, interquartile range; MH, mucosal healing; MTX, methotrexate; SASP, salazosulfapyridine; TNF, tumor necrosis factor.

Comparison of CD-related bowel surgery among the MH-only, DR-only, and DR + CRP_{norm} groups

During follow-up, 31 patients underwent intestinal resections: 9 (17.0%), 11 (10.4%), and 5 (13.9%) in the DR-only, DR + CRP_{norm}, and MH-only groups, respectively. Albeit not significant, there was a trend toward an increased proportion of patients remaining free of CD-related bowel surgery in the DR + CRP_{norm} group compared with the other 2 groups (85.3% ± 7.3% vs 67.8% ± 10.8% vs 37.5% ± 19%, $P = 0.09$), with the median time of CD-related bowel surgery-free survival of 181.4 ± 9.8 vs 80.2 ± 4.8 vs 101.4 ± 6.8 months (Figure 2a). Higher proportion of patients remained free of CD-related intestinal surgery in the DR + CRP_{norm} group at 5 years: 92.5% ± 2.8% vs 77.8% ± 6.8% of patients in the DR-only group vs 91.1% ± 6.2% of patients with MH only ($P = 0.087$) (Figure 2a).

Comparison of CD-related hospitalizations between the MH-only, DR-only, and DR + CRP_{norm} groups

During follow-up, 44 patients had CD-related hospitalizations: 13 (24.5%) in the DR-only group, 20 (18.9%) in the DR + CRP_{norm} group, and 11 (30.6%) in the MH-only group. A significantly higher proportion of patients remained free of CD-related hospitalizations in the DR + CRP_{norm} group at 5 years: 87.2% ± 4.2% vs 63.6% ± 7.8% in the DR-only group vs 74.6% ± 8.6% in the MH-only group ($P = 0.004$) (Figure 2b). The CD-related hospitalization-free survival was significantly longer in the DR + CRP_{norm} groups compared with the DR-only or MH-only groups (133.5 ± 17.1 vs 68.6 ± 5.1 vs 86.3 ± 8.6 months, $P < 0.01$).

Comparison of ER and CR among the MH-only, DR-only, and DR + CRP_{norm} groups

During follow-up, ER was observed in 96 patients: 36 (83.7%) with DR only, 40 (52.6%) in the DR + CRP_{norm} group, and 20 (62.5%) with MH only. A significantly higher proportion of patients maintained MH in the DR + CRP_{norm} group at month 60: 19.6% ± 6.7% vs 9.1% ± 5.8% in the DR-only group vs 24.5% ± 10% in the MH-only group (Figure 2c). The CR-free survival was significantly longer in the DR + CRP_{norm} group than in the DR-only or MH-only groups (33.4 ± 3.7 vs 20.3 ± 3.2 vs 33.7 ± 5.8 months, $P = 0.02$).

CR was observed in 66 (33.8%) patients: 26 (49.1%) in the DR-only group, 23 (21.7%) in the DR + CRP_{norm} group, and 17 (47.2%) in the MH-only group. A significantly higher cumulative proportion of patients remained CR-free in the DR + CRP_{norm} group at 5 years: 58.5% ± 10% vs 29.5% ± 11.9% in the DR-only group vs 36% ± 11.7% in the MH-only group (Figure 2d). The CR-free survival was significantly longer in the DR + CRP_{norm} group compared with the DR or MH-only groups (109.4 ± 12.1 vs 50.5 ± 6.5 vs 50.6 ± 9.3 months, $P = 0.01$).

Impact of DR on long-term outcomes

Of the 195 patients, 36 had MH and 159 achieved DR. There was no significant difference in 5-year long-term outcomes, including abdominal surgery, CD-related hospitalizations, and ER between patients with or without DR (Figure 3a–c), except for CR ($P = 0.027$; Figure 3d).

Impact of CRP normalization on long-term outcomes

Of the 195 patients with MH, 159 patients had data on CRP and 66.7% (106 of 159) had normalized CRP. Fewer patients with normalized CRP required bowel surgery than those with an elevated CRP level (10.4% vs 17.0%, $P < 0.01$). The CD-related hospitalization rate was lower in patients with DR + CRP_{norm} compared with those with elevated CRP (18.9% vs 24.5%, $P = 0.001$). Of patients with normalized CRP, 52.6% experienced an ER compared with 83.7% with elevated CRP ($P = 0.001$). Flares occurred in 21.7% of patients in the DR + CRP_{norm} group compared with 49.1% of those with an elevated CRP during follow-up ($P = 0.005$).

We further compared patients with MH and normal CRP with patients with abnormal CRP. No difference in major abdominal surgery ($P = 0.77$), CD-related hospitalizations ($P = 0.32$), and ER ($P = 0.62$), except for CR ($P = 0.007$), was observed (see Figure 2A–D, Supplementary Digital Content 1, http://links.lww.com/CTG/A195).

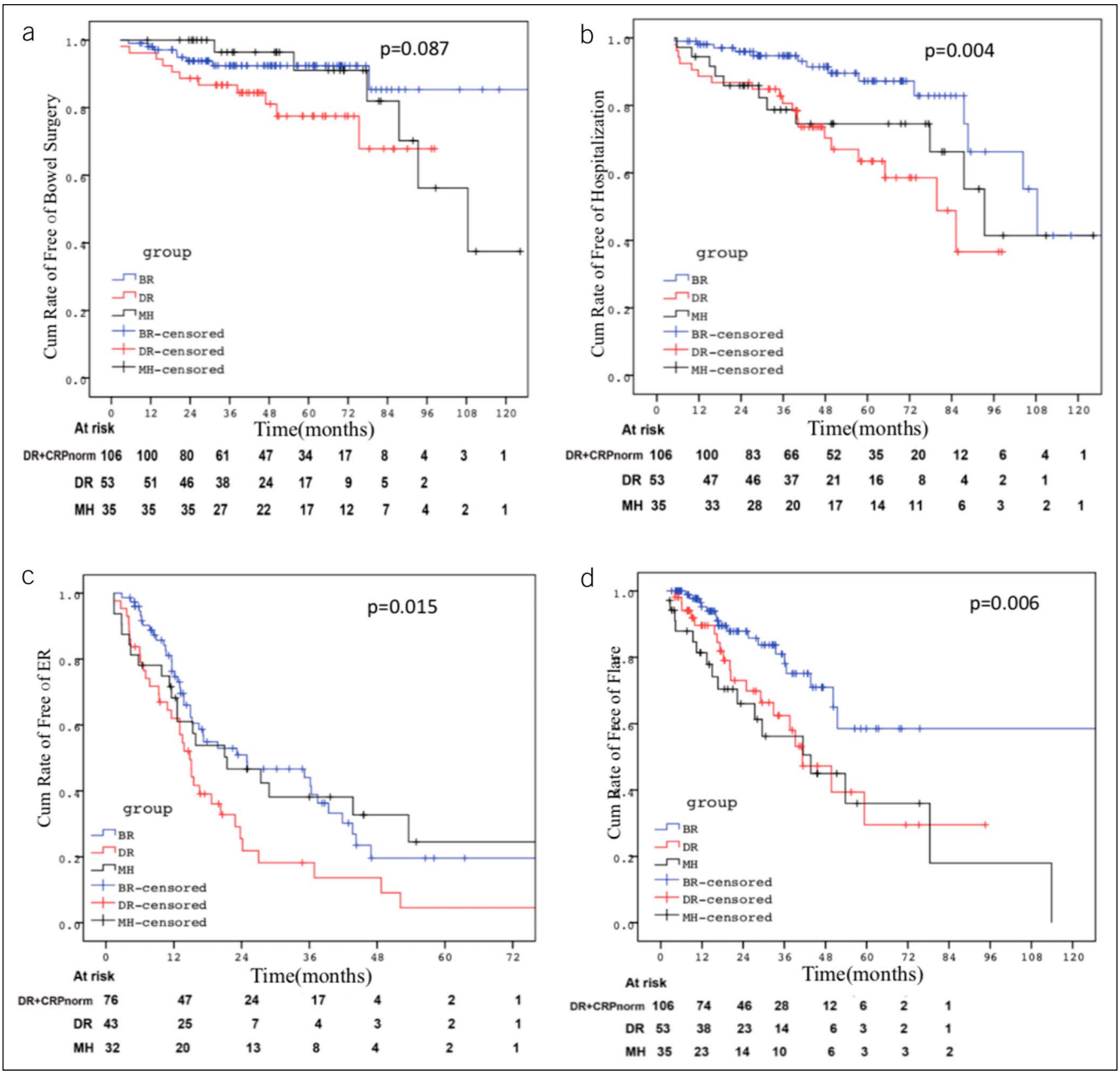

Figure 2. Comparison of long-term outcomes among CD patients with deep remission + CRP_{norm} vs deep remission only vs mucosal healing only. Comparison of cumulative probability of (**a**) CD-related bowel surgery, (**b**) CD-related hospitalizations, (**c**) ER, and (**d**) clinical relapse among patients with CD with DR + CRP_{norm} vs DR only vs MH only. BR, biological remission; CD, Crohn's disease; CRP_{norm}, normalization of C-reactive protein; DR, deep remission; ER, endoscopic recurrence; MH, mucosal healing.

DISCUSSION

This study focused on the comparison of long-term outcomes of patients with CD and DR compared with those with MH only. Our results suggest that CRP normalization is associated with better clinical outcomes for patients with CD in DR but that there was no difference in major abdominal surgery, CD-related hospitalizations, and ER; these results suggest that the combination of clinical remission and MH is insufficient to predict the long-term outcome. Overall, it may be helpful in the management of the disease to aim for DR and 1 or more objective measures of inflammation (endoscopy/biomarkers), rather than symptom control alone, to prevent further damage and disability.

The achievement of clinical remission is essential for patients with CD but, as a therapeutic goal, it alone does not provide optimal long-term outcomes or prevent disability. Evidence is accumulating on the limitations of CDAI. Approximately 40% of the index is derived from 3 subjective criteria (diarrhea, abdominal pain, and a sense of well-being) (21), whereas more objective measures of inflammation (such as CRP and endoscopic lesions) are not taken into account. The overall accuracy of clinical symptoms to predict MH is only 56% (22). In our cohort, cases with DR were not associated with less ER or CD-related operations compared with those with MH only. This was

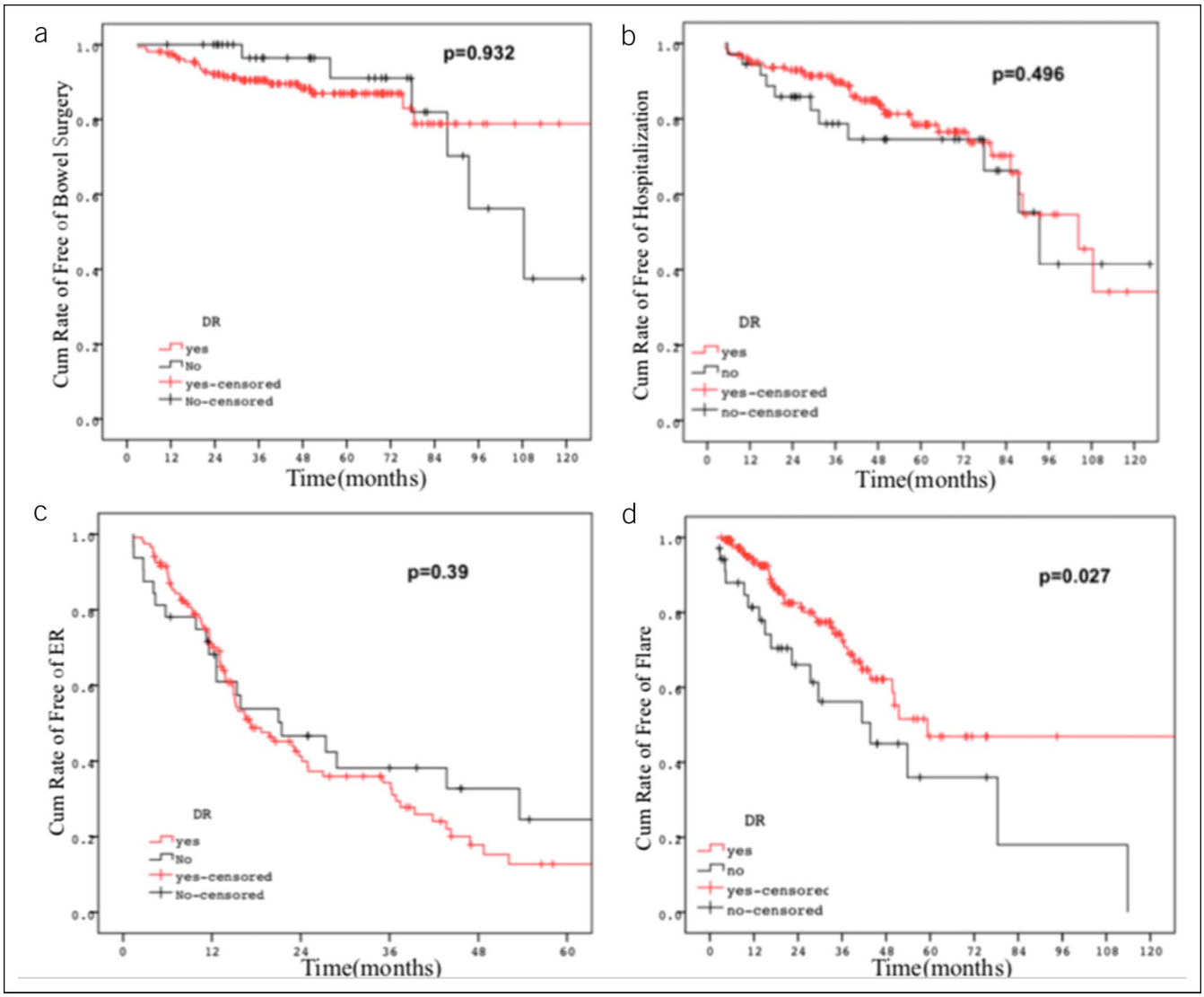

Figure 3. Comparison of long-term outcomes between CD patients with and without deep remission. Comparison of cumulative probability of (**a**) CD-related bowel surgery, (**b**) CD-related hospitalizations, (**c**) ER, and (**d**) clinical relapse between patients with CD with and without DR. BR, biological remission; CD, Crohn's disease; DR, deep remission; and ER, endoscopic recurrence.

consistent with results from EXTEND, in which patients with DR did not have better outcomes than patients with only MH (9).

As a treatment target, the definition of DR, combining symptoms with an objective index of inflammatory disease activity, is still evolving (23). Although there is no widely accepted definition, there is consensus that DR should be a state of remission with little or no risk of disease progression. Clinical and endoscopic remissions should be vital components of DR. Ileocolonoscopy is the best method of endoscopic evaluation (24), but its practical usage is limited because of its invasiveness. Moreover, ileocolonoscopy does not provide complete transmural information. The exploration of biomarkers, such as fecal biomarkers or CRP, may be options to enhance the practical assessment of DR. In the landmark STORI study, DR with a CDEIS of 0, calprotectin level < 250 mg/g, and CRP < 5 mg/L was associated with a decreased risk of relapse when infliximab was discontinued (25).

Fecal biomarkers (calprotectin or lactoferrin) are other indices that reflect bowel inflammation, but data showing the relationship between fecal biomarkers and clinical significance are limited (26–29). Elevated levels of CRP are closely associated with both endoscopic and histological evidence of inflammation. The CRP value as a noninvasive inflammatory marker for a long-term outcome has been widely investigated. Early normalization of CRP levels predicts a sustained long-term response ($P = 0.001$) (30,31). Increased CRP levels at remission were an independent predictor of relapse in patients with CD receiving thiopurines to maintain remission (32). CRP is also a predictor of surgery in patients with CD (33).

Of all the included patients in our study, 7 patients never had an elevated CRP during their disease course. One patient experienced CD-related hospitalization owing to a disease flare and eventually underwent bowel surgery. CRP has no or poor correlation with endoscopic activity of the small bowel (34) and may underestimate endoscopic activity in a significant proportion of patients (35). Furthermore, there is a poor correlation between CRP concentrations and symptoms (36). Although clinical remission was achieved, in some patients, the systemic inflammatory process could not be fully suppressed, and the remaining inflammatory

process ultimately led to early relapse. Moreover, in up to one-third of patients with CD with intestinal inflammation, no elevation in CRP concentration was observed (37). In our study, 4 of 7 patients showed small bowel involvement. A combination of objective signs of inflammation, CRP, and ileocolonoscopy findings may be a better predictor of long-term outcomes of patients with CD. In this cohort, patients with DR + CRP_{norm} predicted more favorable sustained long-term outcomes (longer time before CD-related operations or hospitalization, ER, and CR-free survival) than those with DR alone. In patients with small bowel involvement, biomarkers such as calprotectin, lactoferrin, and S100A12 levels, which correlated significantly with the capsule endoscopy scoring index rather than CRP, are preferred (38). Individual CRP profiles of patients with CD, which are important indicators of a long-term outcome, should be incorporated as a component of "deep" remission.

Our study has certain limitations. First, the retrospective design could induce selection bias and a bias in gathering information. Second, the interval to endoscopic follow-up could result in bias. In fact, we have a relatively strict endoscopic follow-up schedule in our center. For example, interval of less than 6 months is suggested to assess therapeutic response by endoscopy (39). For patients without endoscopic or CR, we suggest the patient to repeat colonoscopy every year. Third, because of the lack of standard criteria for MH, we adopted the definition of Frøslie et al. (40), in which endoscopic findings from normal to mild mucosal erythema or granularity without ulcerations were regarded as MH. In addition, because endoscopy could not define the extent of transmural damage, there was a need for integrated cross-sectional imaging such as computed tomography enteroclysis or magnetic resonance enterography into the treatment target. Currently, the Lémann Score (the Crohn's Disease Digestive Damage Score) has been developed for the evaluation of bowel damage (41). Prospective studies aiming to evaluate various treatment algorithms to achieve DR and the utility of DR to predict crucial outcomes related to disease progression and disability are ongoing (Clinicaltrials.gov numbers: NCT01235689 and NCT01698307). These studies will provide valuable insight regarding the optimal definition of DR and clarify its role as a treatment target in CD. Finally, our study only evaluated the effects of complete normalization of CRP but did not assess partial biological response defining as a decrease from baseline of at least 50% (42), for the latter may be able to distinguish between those who have not reached biological remission but have a biological response. Further study is needed to investigate the clinical implication of a partial biological response.

In conclusion, patients with DR combined with a normalized CRP generally achieved better outcomes than those with DR only. Outcomes in patients with MH only were similar to patients with DR only. Larger prospective studies are needed to confirm these preliminary results and to determine whether treatment aimed at a more objective combined target (CRP normalization combined with MH) could alter the long-term course of CD.

CONFLICTS OF INTEREST

Guarantor of the article: Ren Mao, MD.

Specific author contributions: Xiaoqin Lin, MD and Yun Qiu, MD, contributed equally to this work. X.L. and Y.Q. share the first authorship.

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Study Highlights

WHAT IS KNOWN

- ✓ Therapeutic targets for CD have been evolving.
- ✓ Limited data are available regarding differences in long-term outcomes of these patients reaching these targets.

WHAT IS NEW HERE

- ✓ Patients with DR combined with a normalized CRP were associated with better outcomes compared with patients with DR-only.

TRANSLATIONAL IMPACT

- ✓ Aiming for DR in managing disease with resolution of 1 or more objective measures of inflammation beyond symptom control might be helpful to prevent further damage and disability.

REFERENCES

1. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, et al. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol 2010;105:289–97.
2. Pineton de Chambrun G, Peyrin-Biroulet L, Lemann M, et al. Clinical implications of mucosal healing for the management of IBD. Nat Rev Gastroenterol Hepatol 2010;7:15–29.
3. D'Incà R, Caccaro R. Measuring disease activity in Crohn's disease: What is currently available to the clinician. Clin Exp Gastroenterol 2014;7:151–61.
4. af Björkesten CG, Nieminen U, Turunen U, et al. Surrogate markers and clinical indices, alone or combined, as indicators for endoscopic remission in anti-TNF-treated luminal Crohn's disease. Scand J Gastroenterol 2012;47:528–37.
5. Hommes D, Colombel JF, Emery P, et al. Changing Crohn's disease management: Need for new goals and indices to prevent disability and improve quality of life. J Crohns Colitis 2012;6(Suppl 2):S224–34.
6. Colombel JF, Louis E, Peyrin-Biroulet L, et al. Deep remission: A new concept? Dig Dis 2012;30(Suppl 3):107–11.
7. Sandborn WJ. The future of inflammatory bowel disease therapy: Where do we go from here? Dig Dis 2012;30(Suppl 3):140–4.
8. Panaccione R, Hibi T, Peyrin-Biroulet L, et al. Implementing changes in clinical practice to improve the management of Crohn's disease. J Crohns Colitis 2012;6(Suppl 2):S235–42.
9. Colombel JF, Rutgeerts PJ, Sandborn WJ, et al. Adalimumab induces deep remission in patients with Crohn's disease. Clin Gastroenterol Hepatol 2014;12:414–22.e5.
10. Sandborn WJ, Colombel J-F, Louis E, et al. Economic impact of deep remission in adalimumab-treated patients with Crohn's disease: Results from extend. Gastroenterology 2011;140:S-205.
11. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining therapeutic goals for treat-to-target. Am J Gastroenterol 2015;110:1324–38.
12. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): A multicentre, randomised, controlled phase 3 trial. Lancet 2018;390:2779–89.
13. Zallot C, Peyrin-Biroulet L. Deep remission in inflammatory bowel disease: Looking beyond symptoms. Curr Gastroenterol Rep 2013;15:315.
14. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol Suppl 1989;170:2–6; discussion 16–9.

15. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a working party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005;19(Suppl A):5A–36A.
16. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: The SES-CD. Gastrointest Endosc 2004;60:505–12.
17. Vuitton L, Marteau P, Sandborn WJ, et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. Gut 2016;65: 1447–55.
18. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: Results of the CLASSIC II trial. Gut 2007;56:1232–9.
19. Qiu Y, Chen BL, Mao R, et al. Endoscopy assessment at 1-year identifies long-term responders to thiopurines maintenance therapy in patients with Crohn's disease. Medicine (Baltimore) 2015;94:e1204.
20. Mao R, Chen BL, He Y, et al. Factors associated with progression to surgery in Crohn's disease patients with endoscopic stricture. Endoscopy 2014;46:956–62.
21. Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70:439–44.
22. Peyrin-Biroulet L, Reinisch W, Colombel JF, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. Gut 2014;63:88–95.
23. Travis S, Feagan BG, Rutgeerts P, et al. The future of inflammatory bowel disease management: Combining progress in trial design with advances in targeted therapy. J Crohns Colitis 2012;6(Suppl 2):S250–9.
24. Feagan BG, Lemann M, Befrits R, et al. Recommendations for the treatment of Crohn's disease with tumor necrosis factor antagonists: An expert consensus report. Inflamm Bowel Dis 2012;18:152–60.
25. Louis E, Mary JY, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology 2012;142:63–70.e5; quiz e31.
26. Gisbert JP, Bermejo F, Perez-Calle JL, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis 2009;15:1190–8.
27. Sipponen T, Karkkainen P, Savilahti E, et al. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. Aliment Pharmacol Ther 2008;28:1221–9.
28. Sipponen T, Savilahti E, Karkkainen P, et al. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. Inflamm Bowel Dis 2008;14:1392–8.
29. Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. Inflamm Bowel Dis 2004;10:661–5.
30. Jurgens M, Mahachie John JM, Cleynen I, et al. Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. Clin Gastroenterol Hepatol 2011;9:421–7.e1.
31. Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: Results from a single-centre cohort. Gut 2009;58:492–500.
32. Park JJ, Cheon JH, Hong SP, et al. Outcome predictors for thiopurine maintenance therapy in patients with Crohn's disease. Dig Dis Sci 2012; 57:133–41.
33. Henriksen M, Jahnsen J, Lygren I, et al. C-reactive protein: A predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. Gut 2008;57: 1518–23.
34. Ponte A, Pinho R, Rodrigues A, et al. Evaluation and comparison of capsule endoscopy scores for assessment of inflammatory activity of small-bowel in Crohn's disease. Gastroenterol Hepatol 2018;41: 245–50.
35. Mitselos IV, Katsanos KH, Tatsioni A, et al. Association of clinical and inflammatory markers with small bowel capsule endoscopy findings in Crohn's disease. Eur J Gastroenterol Hepatol 2018;30:861–7.
36. Solem CA, Loftus EV Jr, Tremaine WJ, et al. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. Inflamm Bowel Dis 2005;11:707–12.
37. Denis MA, Reenaers C, Fontaine F, et al. Assessment of endoscopic activity index and biological inflammatory markers in clinically active Crohn's disease with normal C-reactive protein serum level. Inflamm Bowel Dis 2007;13:1100–5.
38. Aggarwal V, Day AS, Connor S, et al. Role of capsule endoscopy and fecal biomarkers in small-bowel Crohn's disease to assess remission and predict relapse. Gastrointest Endosc 2017;86:1070–8.
39. Mao R, Qiu Y, Chen BL, et al. Factors associated with the achievement of mucosal healing in Crohn's disease: The benefit of endoscopic monitoring in treating to target. Therap Adv Gastroenterol 2017;10:453–63.
40. Frøslie KF, Jahnsen J, Moum BA, et al. Mucosal healing in inflammatory bowel disease: Results from a Norwegian population-based cohort. Gastroenterology 2007;133:412–22.
41. Peyrin-Biroulet L, Cieza A, Sandborn WJ, et al. Development of the first disability index for inflammatory bowel disease based on the international classification of functioning, disability and health. Gut 2012;61:241–7.
42. Ferrante M, Colombel JF, Sandborn WJ, et al. Validation of endoscopic activity scores in patients with Crohn's disease based on a post hoc analysis of data from SONIC. Gastroenterology 2013;145: 978–86.e5.