Gut and Liver
https://doi.org/10.5009/gnl20078
pISSN 1976-2283 eISSN 2005-1212

Original Article

Clinical Significance of Residual Nonrectal Inflammation in Ulcerative Colitis Patients in Clinical Remission

Jongbeom Shin*, Sung Min Kong, Tae Jun Kim, Eun Ran Kim, Sung Noh Hong, Dong Kyung Chang, and Young-Ho Kim

Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Article Info
Received March 3, 2020
Revised July 3, 2020
Accepted July 4, 2020
Published online August 26, 2020

Corresponding Author
Young-Ho Kim
ORCID https://orcid.org/0000-0003-1803-2513
E-mail yhgi.kim@samsung.com

*Current affiliation: Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon, Korea.

Background/Aims: The treatment goal of ulcerative colitis (UC) has been changed to achieve endoscopic remission (ER). However, there is insufficient clinical evidence to determine whether a step-up treatment should be performed to achieve ER in clinical remission (CR) without ER, and there are inadequate data on the need to consider the distribution and severity of residual inflammation. This retrospective study aimed to evaluate the prognostic significance of the distribution and severity of residual inflammation in UC patients in CR.

Methods: A total of 131 UC patients in CR who underwent endoscopic evaluation for more than three times between January 2000 and December 2018 were reviewed. The patients were allocated by the endoscopic healing state and the distribution of inflammation to ER (n=31, 23.7%), residual nonrectal inflammation with patchy distribution (NRI) (n=17, 13.0%) or residual rectal involvement with continuous or patchy distribution (RI) (n=83, 63.3%) groups. We reviewed clinical characteristics, endoscopic findings, and factors associated with poor outcome-free survival (PFS).

Results: In UC patients in CR, PFS was significantly higher in the ER and NRI groups than in the RI group (p=0.003). Patients in the ER and NRI groups had similar PFS (p=0.647). Cox proportional hazard model showed only RI (hazard ratio, 5.76; p=0.027) was associated with a higher risk of poor outcome.

Conclusions: We suggest that escalation of treatment modalities may be selectively performed in consideration of the residual mucosal inflammation pattern, even if ER has not been achieved, in UC patients with CR. **(Gut Liver 2021;15:401-409)**

Key Words: Colitis, ulcerative; Clinical remission; Endoscopic remission; Therapy

INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory disorder that is confined to the mucosa and submucosa. It is generally accepted that UC involves the rectum and can continuously extend to more proximal portions of the colon.[1,2] In recent decades, remarkable advancements in therapeutic agents have made it possible to attain endoscopic remission (ER).[3-5] ER in UC is defined as recovery of mucosal inflammation, ulceration, and mucosal friability visible on endoscopy. ER is related to prolonged clinical remission (CR) and lower rates of colectomy.[6] For that reason, guidelines for clinical practice recommend the resolution of clinical symptoms and further acquisition of ER.[7-9]

In general, mucosal inflammation in UC patients who have not reached ER is either continuously distributed from the rectum or exhibits a patchy distribution that spares the rectum.[10] A patchy, rectal-sparing distribution is observed in one-third or more of treated patients.[11-13] According to the clinical practice guidelines, even in patients with CR status, patchy distribution is not defined as an ER state. Therefore, more aggressive treatment is required.[7,8,14] However, treatment escalation with immunosuppressive agents or anti-tumor necrosis factor agents to achieve ER involves the risk of potentially undesirable effects, such as the risk of infection and malignancy. It also increases the

economic burden due to high drug costs.[15-18]

There is insufficient clinical evidence regarding whether step-up treatment should be performed to achieve ER, especially in CR with residual patchy inflammation that is rectum sparing. There is also inadequate data on the need to consider the distribution and severity of residual inflammation in UC patients.

Therefore, we conducted this retrospective study to evaluate the prognostic significance of factors such as step-up therapy, hospitalization, and colectomy according to the distribution and severity of residual inflammation in UC patients in CR.

MATERIALS AND METHODS

1. Patient population

Patients with an established diagnosis of UC according to conventional criteria[19] treated at Samsung Medical Center (Seoul, South Korea) between January 2000 and December 2018 were included in this retrospective study (Fig. 1). All diagnosed UC patients met all three of the following criteria: a typical history of diarrhea or hematochezia and pus in the stool, or both, with five or more instances of diarrhea a week; colonoscopic findings showing diffusely granular, friable, or ulcerated mucosa; and characteristic histopathological signs of inflammation on biopsy.[19-21] The patients were retrospectively selected based on the following inclusion criteria: (1) aged over 18 years at the time of first colonoscopy; (2) underwent three or more total colonoscopies during the study period; and (3) achieved CR status in the first or second colonoscopy. The exclusion criteria were: (1) previous history of gastrointestinal surgery; (2) UC-associated dysplasia and/or adenocarcinoma; (3) severe comorbidity, such as malignancy or end-stage renal disease; (4) pregnant at the time of the first colonoscopy; or (5) involved in any clinical trial and (6) atypical distribution of inflammation with rectal-sparing at diagnosis.

All of the patients' medical records were reviewed to obtain clinical information and medical history. Medical history included the use of 5-aminosalicylic acid agents, corticosteroids, immunomodulators, and biologics. The patients were allocated by endoscopic healing state and distribution of inflammation into ER (n=31, 23.7%), residual nonrectal inflammation with patchy distribution (NRI; n=17, 13.0%), or residual rectal involvement with continuous or patchy distribution (RI; n=83, 63.3%) groups. For the analysis, the UC patients in CR were divided into two groups according to the occurrence of poor outcomes including hospitalization and colectomy. In this study, re-

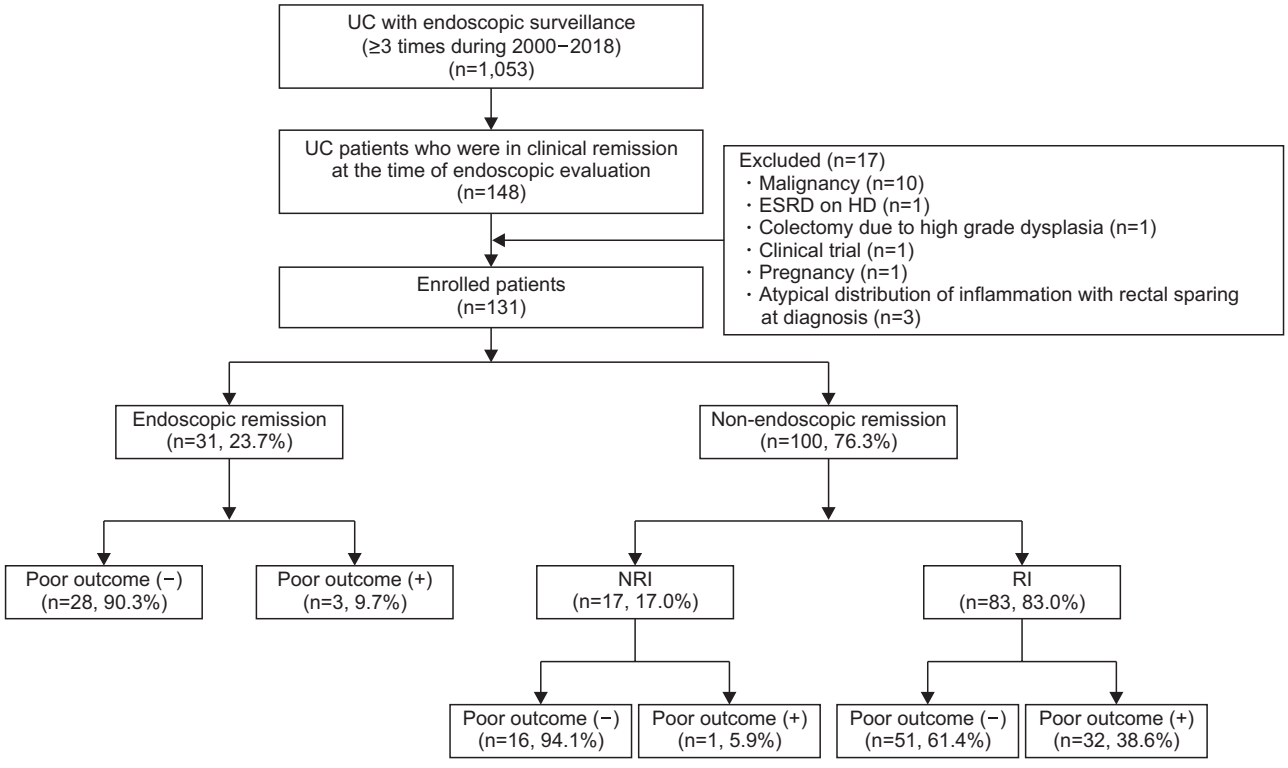

Fig. 1. Patient selection flowchart.
UC, ulcerative colitis; ESRD, end-stage renal disease; HD, hemodialysis; NRI, residual nonrectal inflammation with patchy distribution; RI, residual rectal involvement with continuous or patchy distribution.

gardless of colonoscopic findings, patients in CR did not receive other treatments. The study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, South Korea (IRB number: SMC 2019-09-057-002).

2. Endoscopic evaluation and assessment

The colon images used for analysis were taken by conventional white-light imaging from each segment of the bowel. Endoscopic score was assessed by two expert endoscopists (J.S. and S.M.K.) who were qualified by the subspecialty board of gastrointestinal endoscopy (>1,000 colonoscopies/year) to characterize the severity of UC and disease extent. We used the Ulcerative Colitis Segmental Endoscopic Index (UCSEI) to quantify endoscopic severity.[22] The UCSEI is scored using four different parameters, erythema (three levels), vascular pattern (three levels), friability (three levels), and erosions and ulcers (three levels), on a scale of 0 to 10. It can reflect segmental inflammation because each of the five colonic segments (ascending colon/cecum, transverse colon, descending colon, sigmoid colon, and rectum) are evaluated and the results are summed. The UCSEI was selected to evaluate residual inflammation because it can estimate distribution range and severity of inflammation. The rate of concordance in UCSEI score between the two endoscopists was 77.6%. The differences in UCSEI score between the endoscopists were always within 1 point. If a subject's score did not match after discussion, the worse score was taken as the final score in order to judge conservatively.

3. Definitions

Disease duration was defined as the duration from the time of diagnosis to the first colonoscopy. CR was defined as Simple Clinical Colitis Activity Index was ≤2 and ≤1 for stool frequency and rectal bleeding, respectively, for more than 3 months, as determined by clinical records.[23] The first colonoscopy was defined as the endoscopy performed at the earliest time point from 2000 to 2018, and the initial colonoscopy at diagnosis was not included in the first colonoscopy. The endoscopy that was performed after the first endoscopy was defined as the second endoscopy. ER was defined by completely normal mucosa (UCSEI=0). NRI was defined as discrete areas of patchiness visible endoscopically in any segment with frank rectal-sparing.[11] RI was defined as having only rectal inflammation or rectal inflammation with proximal involvement, continuously or discontinuously. Good drug adherence was defined by a medication possession ratio of at least 80%.[24,25] Poor outcome was defined as (1) requiring steroid administration including beclomethasone propionate and budesonide enema or step-up therapy including immunosuppressive agents and biologics for treatment of symptoms; (2) hospitalization because of a UC flare; or (3) receiving a colectomy for refractory UC. The poor outcome-free survival (PFS) was defined as the follow-up period to the first episode of poor outcome.

4. Statistical analyses

The primary study endpoint was PFS of UC patients in CR according to the distribution of mucosal inflammation. The secondary endpoints were (1) determination of the significant predictors of poor outcome in UC patients in CR and (2) identification of changes in the distribution pattern of residual inflammation according to the distribution of inflammation in UC patients in CR. The clinical characteristics of the study subjects are expressed as medians (ranges) for continuous variables and numbers (percentages) for categorical variables. The differences between categorical or continuous variables were analyzed using the Mann-Whitney U test, the Student t-test, the chi-square test, or Fisher exact test. PFS rates were estimated using the Kaplan-Meier method. Differences in PFS curves among the groups were assessed using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Two-tailed p-values of <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Baseline characteristics

During the observation period from January 2000 to December 2018, 1,053 patients received three or more colonoscopies. Of these, 131 patients were identified to be in CR at the time of the first or second colonoscopy between 2000 and 2018. The baseline clinical characteristics of the poor outcome-free and poor outcome patients are shown in Table 1. During a median period of 55.2 months, about one-quarter (n=36, 27.5%) of the patients had poor outcomes. All poor outcomes observed were steroid use (n=33) or step-up therapy (n=3). Except for the pattern of residual inflammation and UCSEI score, the two groups were generally similar in baseline characteristics and concomitant medications. In terms of the pattern of residual inflammation, ER (29.5% vs 8.3%, p<0.001) was greater in poor outcome-free patients. The median UCSEI scores of poor outcome-free and poor outcome patients were 5 (range, 0 to 17) and 8 (range, 0 to 20), respectively (p=0.031).

Table 1. Baseline Clinical Characteristics of the Study Subjects According to Poor Outcome

Variable	All (n=131)	Poor outcome free (n=95)	Poor outcome (n=36)	p-value*
Age, yr	42 (18–71)	44 (20–77)	38 (18–64)	0.383
Male sex	77 (58.8)	52 (54.7)	25 (69.4)	0.127
Duration of UC, mo	44.7 (5.7–256.9)	45.6 (5.7–256.9)	39.9 (6.0–156.0)	0.425
Disease extent				0.051
Ulcerative proctitis	24 (18.3)	16 (16.8)	8 (22.2)	
Left-sided UC	52 (39.7)	33 (34.7)	19 (52.8)	
Extensive UC	55 (42.0)	46 (48.4)	9 (25.0)	
Pattern of residual inflammation				0.001
ER	31 (23.7)	28 (29.5)	3 (8.3)	
NRI	17 (13.0)	16 (16.8)	1 (2.8)	
RI	83 (63.3)	51 (53.7)	32 (88.9)	
SCCAI	1 (0–2)	1 (0–2)	1 (0–2)	0.340
UCSEI	6 (0–20)	5 (0–17)	8 (0–20)	0.031
Hb, g/dL	14.1 (7.0–17.7)	14.1 (8.7–17.7)	14.4 (7.0–17.2)	0.921
Hct, %	42.1 (25.6–51.3)	41.4 (29.5–51.3)	43.1 (25.6–50.1)	0.467
Leukocyte, /μL	6,420 (2,080–14,410)	6,490 (2,080–14,410)	6,165 (3,600–11,830)	0.467
Platelet, $\times 10^3$/μL	245 (145–628)	243 (145–581)	261 (150–628)	0.414
Albumin, g/dL	4.5 (3.4–5.2)	4.5 (3.4–5.2)	4.4 (3.9–5.1)	0.556
ESR, mm/hr	13.5 (2.0–120.0)	14.0 (2.0–104.0)	13.0 (2.0–120.0)	0.575
CRP, mg/dL	0.06 (0.02–2.81)	0.06 (0.02–2.81)	0.06 (0.30–2.57)	0.622
BMI, kg/m^2	23.0 (17.2–31.2)	23.4 (17.2–31.2)	22.0 (19.3–29.4)	0.682
Medication				0.327
5-ASA	102 (77.8)	74 (77.8)	28 (77.7)	
Oral steroid	1 (0.8)	1 (1.1)	0	
Thiopurine	13 (9.9)	7 (7.4)	6 (16.7)	
Biologics	9 (6.9)	8 (8.4)	1 (2.8)	
No treatment	6 (4.6)	5 (5.3)	1 (2.8)	
Drug adherent (good)	89 (67.9)	67 (70.5)	22 (61.1)	0.165
Follow-up duration, mo	55.2 (1.4–142.8)	67.4 (7.5–142.8)	30.9 (1.4–104.2)	0.384

Data are presented as median (range) or number (%).
UC, ulcerative colitis; ER, endoscopic remission; NRI, residual nonrectal inflammation with patchy distribution; RI, residual rectal involvement with continuous or patchy distribution; SCCAI, Simple Clinical Colitis Activity Index; UCSEI, Ulcerative Colitis Segmental Endoscopic Index; Hb, hemoglobin; Hct, hematocrit; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BMI, body mass index; 5-ASA, 5-aminosalicylic acid.
*p-values were calculated using the t-test or Fisher exact test according to poor outcome.

2. PFS rates of UC patients in CR according to pattern of inflammation

PFS showed statistically significant differences according to the pattern of residual inflammation (p=0.003). The PFS rate was significantly higher in ER patients (p=0.028) (Fig. 2A). The PFS rates were significantly higher in the ER (p=0.011) and NRI (p=0.018) groups than in the RI group. In contrast, there was no difference in PFS rate between ER and NRI patients (p=0.647) (Fig. 2B).

3. Significant predictors of PFS in UC patients in CR

In univariable Cox proportional hazards models, pattern of residual inflammation (NRI HR, 0.58; 95% CI, 0.56 to 6.09, p=0.652 and RI HR, 5.86; 95% CI, 1.65 to 20.85; p=0.006) and UCSEI score (HR, 1.09; 95% CI, 1.01 to 1.17; p=0.034) were associated with risk of poor outcome. The pattern of residual inflammation was the only statistically significant predictor of PFS (RI HR, 5.76; 95% CI, 1.22 to 27.12; p=0.027) in multivariable analysis (Table 2).

4. Change in the distribution of residual inflammation according to the distribution of inflammation in UC patients in CR

Follow-up endoscopies in 95 patients without poor outcomes during the follow-up period were reviewed to determine whether the pattern of residual inflammation changed (Supplementary Fig. 1). The median interval between the first colonoscopy and the follow-up colonoscopy was 69.5 months (range, 7.5 to 142 months). No change in the pattern of residual inflammation was seen in 43.8% of the NRI group. In only three patients, NRI changed to RI. In patients with RI patterns, the pattern persisted in 64.7% of the patients.

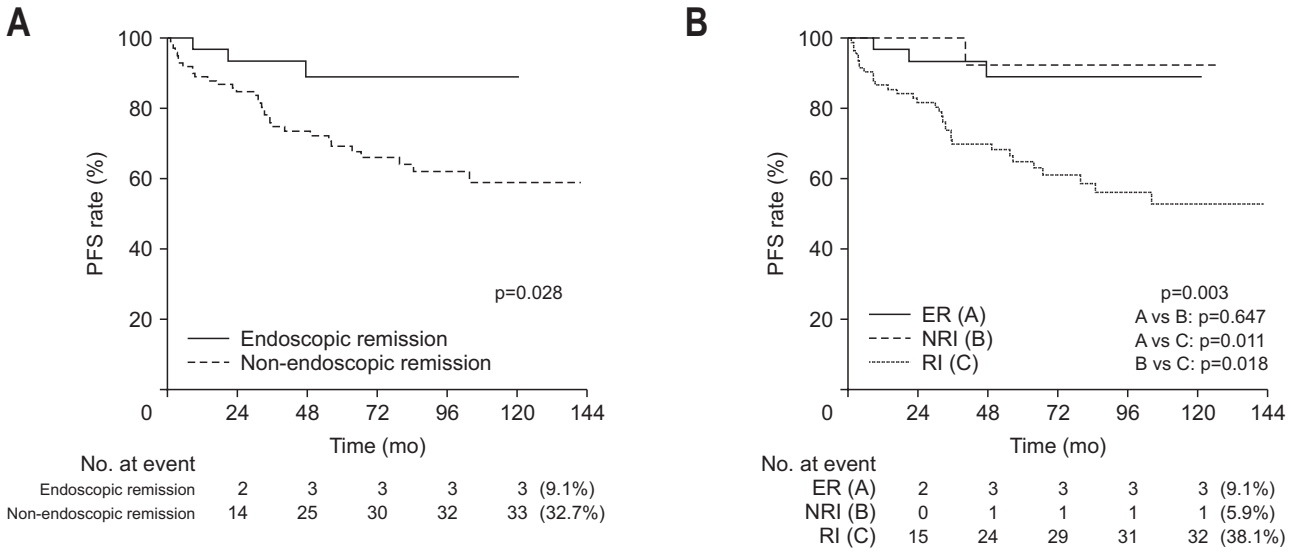

Fig. 2. Kaplan-Meier curves demonstrating poor outcome-free survival (PFS) according to endoscopic remission (ER) (A) and PFS according to residual inflammation (B).
NRI, residual nonrectal inflammation with patchy distribution; RI, residual rectal involvement with continuous or patchy distribution.

Table 2. Significant Predictors of Poor Outcome

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.98 (0.95–1.01)	0.206	0.98 (0.95–1.01)	0.294
Male sex	0.53 (0.24–1.20)	0.130	0.51 (0.22–1.22)	0.130
Pattern of residual inflammation				
ER	1		1	
NRI	0.58 (0.56–6.09)	0.652	0.60 (0.05–7.36)	0.690
RI	5.86 (1.65–20.85)	0.006	5.76 (1.22–27.12)	0.027
UCSEI	1.09 (1.01–1.17)	0.034	1.01 (0.91–1.12)	0.891

Event: poor outcome (n=36, 27.5%).
HR, hazard ratio; CI, confidence interval; ER, endoscopic remission; NRI, residual nonrectal inflammation with patchy distribution; RI, residual rectal involvement with continuous or patchy distribution; UCSEI, Ulcerative Colitis Segmental Endoscopic Index.

DISCUSSION

In this study, we evaluated the effect of the residual inflammation pattern and disease severity of UC patients in CR on poor outcomes, such as step-up therapy, hospitalization, and colectomy. The clinical characteristics, treatment modalities, and drug compliance of the two groups according to outcome (poor vs not poor) were similar. In contrast, there was a difference in the distribution of residual inflammation. An RI pattern was seen in the majority of patients with poor outcomes (88.9%) (Table 1) and most patients with NRI (94.1%) did not experience poor outcomes (Supplementary Table 1). The PFS rate was the lowest in the RI group (61.4%) and no statistically significant difference was found between the ER and NRI groups. In the Cox proportional hazard analysis, the distribution of residual inflammation was found to be a more significant predictor of poor outcomes than severity. To our knowledge, this was the first study to evaluate the pattern of residual inflammation in UC patients in CR and compare the effect of the patterns of residual inflammation on PFS.

Typical UC has a continuous distribution of inflammation from the rectum to the proximal part of the rectum, and both rectal-sparing or skipped inflammation have traditionally been associated with Crohn's disease. However, this atypical distribution of inflammation is not an uncommon event in UC patients. In one study,[26] an atypical distribution was observed in 19.2% of the patients at diagnosis; the figure reached 30% in another study.[10] The follow-up results of UC patients who had an atypical distribution of inflammation at the time of diagnosis showed

that two-thirds of the patients had changed to a typical distribution due to the appearance of rectal inflammation and/or the disappearance of skipped lesions.[26] Meanwhile, previous studies have shown that nonspecific distribution of inflammation can occur during the natural course of UC.[10,12,27] The prevalence of atypical distribution in treated UC is known to be 11% to 15%.[11,13] However, there have been no studies on the prevalence of atypical distribution in UC patients in CR. In our study, the rate of NRI was 12.7% among patients in CR. This result is similar to the results of studies examining the distribution of treated UC and slightly lower than that shown in studies examining distribution at the time of diagnosis.[11,13]

Several studies have been conducted on the effects of inflammation patterns on prognosis. Rajwal *et al.*[28] suggested that rectal-sparing inflammation in children with UC indicated a more aggressive disease that did not respond well to medical treatment. Adult UC patients with appendiceal skip lesions have frequent relapses and an aggressive disease course.[29,30] In contrast, Park *et al.*[26] found no prognostic implications of atypical distributions, such as patchy, segmental skip lesions, and rectal-sparing, in newly diagnosed UC patients. There is as yet no consensus on the prognostic implications of skip lesions or rectal-sparing inflammation. Previous studies provided information only on predicting the impact of patterns at the time of diagnosis on prognosis, and data on the distribution of inflammation during treatment is rare. In particular, there is no data on the prognostic implications of the remaining patterns of inflammation in patients in CR. These results have limited applications in determining further treatment plans in patients with UC during treatment. However, the current study provides data that could be used to determine treatment plans for UC patients in CR with NRI patterns.

ER has been associated with prolonged CR and lower hospitalization and colectomy rates.[6-9] Consensus guidelines for clinical practice recommend mucosal healing as the treatment target.[8] In contrast, Baars *et al.*[31] reported that the prevalence of endoscopic and/or mucosal inflammation in inflammatory bowel disease patients in CR was not low and concluded that mucosal healing was not more favorable in terms of disease course during 7 years of follow-up. These contradictory results for the prognostic effect of residual inflammation in patients in CR suggest that ER may not necessarily be required as a treatment target in specific patients in CR who have residual inflammation. In this study, the PFS rate of ER patients was the highest among the patients in CR. Only NRI patients showed a PFS rate similar to that of the ER group, although residual inflammation was observed rather than ER.

The cause of the differences in residual inflammation has not yet been identified. Some studies have reported that drug administration affects residual inflammation because rectal suppository agents may preferentially improve the rectal areas.[13] Other studies have suggested that the type of medication used and the method of administration did not significantly affect the distribution of residual inflammation.[32] In our study, the type of drug was not related to the distribution of residual inflammation. Furthermore, there was no difference in the use of suppositories between patient groups with different residual inflammation patterns (Supplementary Table 2). Drug adherence was also analyzed because it can influence the distribution of inflammation. However, in our study, drug adherence was not significantly different between the groups of patients with poor outcomes and those who were poor outcome-free. A well-designed prospective study is needed to elucidate the effect of drug-related factors on the distribution of residual inflammation.

The rate of ER observed in our study was 23.7%, which is lower than that seen in other recent studies.[33,34] This is because ER was strictly defined as an absence of mucosal inflammation on endoscopy. This strict definition was applied because prior studies found that the persistence of endoscopic activity in CR was a strong predictor of early relapse.[35,36]

In 60% of the patients without poor outcomes (57 patients; 17 in ER, seven in NRI, and 33 in RI), the distribution pattern of residual inflammation did not change between colonoscopies (Supplementary Fig. 1). Only three of the patients with an NRI pattern changed to an RI pattern, whereas more than 80% of the NRI patients maintained NRI or improved to ER. In contrast, in the case of RI, which was found to be associated with a high incidence of poor outcomes, it was observed that 64.7% of RI patients persisted with RI. Therefore, it is necessary to improve mucosal inflammation to reach ER in patients with RI patterns through aggressive treatment. Subgroup analysis was performed to examine the clinical characteristics of patients in whom residual inflammation was changed versus not changed (Supplementary Table 3); however, there were no meaningful clinical characteristics that affected changes in the pattern of residual inflammation.

This present study has several limitations. First, it is a retrospective study. It is inherently limited by the retrospective nature of the clinical data collected during follow-up. The endoscopic results were analyzed at a relatively constant time in patients in CR. There was a difference in the time between colonoscopy and Simple

Clinical Colitis Activity Index evaluation. However, the difference was less than 2 weeks. Although a consensus of the endoscopic findings was made by our endoscopists, some minor skip lesions may have gone unnoticed during image analysis. Therefore, the actual prevalence of NRI is likely to be slightly higher than reported. Second, the number of enrolled patients was relatively small. However, because this study was conducted in a single-center, it has the benefit of uniformity of endoscopic equipment and procedures and patient management. In addition, the long-term follow-up period may have alleviated this problem. Third, histopathological data analysis to confirm the non-inflammatory segments of skipped lesions and rectum sparing was not performed. Therefore, it is possible that NRI patients may be classified histologically as RI. However, this study analyzed the clinical significance of residual inflammation as classified by endoscopic findings. For this reason, histological differences did not affect the results of this study. In addition, the extent of UC as assessed by the Montreal classification is usually evaluated according to endoscopic findings rather than pathologic findings. Fourth, selection bias may have influenced the results because the study was conducted on patients who underwent colonoscopy during the observation period. This bias is hard to avoid in retrospective studies. To clearly assess the effects of residual inflammation, a well-designed, large-scale prospective study is needed. Despite these limitations, this was the first study to analyze the clinical significance of the distribution of residual inflammation in patients with UC in CR.

In conclusion, we showed that in UC patients in CR, residual inflammation may appear with an atypical distribution such as NRI, which is not unusual. Even though NRI was a persistent endoscopic inflammatory condition, we found no statistical difference in PFS compared to patients in ER. Therefore, we suggest that escalation of treatment modalities may be selectively performed in consideration of the residual mucosal inflammation pattern, even if ER has not been achieved, in UC patients in CR.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (no. NRF-2017R1A2B4006767).

AUTHOR CONTRIBUTIONS

Conceptualization: J.S., Y.H.K. Data curation: J.S., S.M.K., T.J.K., E.R.K., S.N.H., D.K.C. Formal analysis: J.S., S.M.K. Funding acquisition: Y.H.K. Methodology: J.S., S.M.K., T.J.K., E.R.K., S.N.H., D.K.C., Y.H.K. Project administration: J.S., Y.H.K. Visualization: J.S., S.M.K. Writing - original draft: J.S., Y.H.K. Writing - review & editing: J.S., S.M.K., Y.H.K. Approval of final manuscript: all authors.

ORCID

Jongbeom Shin https://orcid.org/0000-0001-6079-615X
Sung Min Kong https://orcid.org/0000-0001-7980-6303
Tae Jun Kim https://orcid.org/0000-0001-8101-9034
Eun Ran Kim https://orcid.org/0000-0002-0495-2565
Sung Noh Hong https://orcid.org/0000-0002-4140-3717
Dong Kyung Chang https://orcid.org/0000-0001-8925-4629
Young-Ho Kim https://orcid.org/0000-0003-1803-2513

REFERENCES

1. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet 2012;380:1606-1619.
2. Choi CH, Jung SA, Lee BI, et al. Diagnostic guideline of ulcerative colitis. Korean J Gastroenterol 2009;53:145-160.
3. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology 2007;132:763-786.
4. 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;110:1324-1338.
5. Choi CH, Moon W, Kim YS, et al. Second Korean guidelines for the management of ulcerative colitis. Intest Res 2017;15:7-37.
6. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut 2012;61:1619-1635.
7. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology 2011;141:1194-1201.

8. Vuitton L, Peyrin-Biroulet L, Colombel JF, et al. Defining endoscopic response and remission in ulcerative colitis clinical trials: an international consensus. Aliment Pharmacol Ther 2017;45:801-813.
9. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. J Crohns Colitis 2017;11:769-784.
10. Kleer CG, Appelman HD. Ulcerative colitis: patterns of involvement in colorectal biopsies and changes with time. Am J Surg Pathol 1998;22:983-989.
11. Bernstein CN, Shanahan F, Anton PA, Weinstein WM. Patchiness of mucosal inflammation in treated ulcerative colitis: a prospective study. Gastrointest Endosc 1995;42:232-237.
12. Joo M, Odze RD. Rectal sparing and skip lesions in ulcerative colitis: a comparative study of endoscopic and histologic findings in patients who underwent proctocolectomy. Am J Surg Pathol 2010;34:689-696.
13. Kim B, Barnett JL, Kleer CG, Appelman HD. Endoscopic and histological patchiness in treated ulcerative colitis. Am J Gastroenterol 1999;94:3258-3262.
14. Dignass A, Lindsay JO, Sturm A, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. J Crohns Colitis 2012;6:991-1030.
15. Jauregui-Amezaga A, Turon F, Ordás I, et al. Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening. J Crohns Colitis 2013;7:208-212.
16. Nakase H, Honzawa Y, Toyonaga T, et al. Diagnosis and treatment of ulcerative colitis with cytomegalovirus infection: importance of controlling mucosal inflammation to prevent cytomegalovirus reactivation. Intest Res 2014;12:5-11.
17. Khan N, Abbas AM, Lichtenstein GR, Loftus EV Jr, Bazzano LA. Risk of lymphoma in patients with ulcerative colitis treated with thiopurines: a nationwide retrospective cohort study. Gastroenterology 2013;145:1007-1015.
18. Di Sabatino A, Liberato L, Marchetti M, Biancheri P, Corazza GR. Optimal use and cost-effectiveness of biologic therapies in inflammatory bowel disease. Intern Emerg Med 2011;6 Suppl 1:17-27.
19. Magro F, Gionchetti P, Eliakim R, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis 2017;11:649-670.
20. Tysk C, Järnerot G. Ulcerative proctocolitis in Orebro, Sweden: a retrospective epidemiologic study, 1963-1987. Scand J Gastroenterol 1992;27:945-950.
21. Yang SK, Hong WS, Min YI, et al. Incidence and prevalence of ulcerative colitis in the Songpa-Kangdong district, Seoul, Korea, 1986-1997. J Gastroenterol Hepatol 2000;15:1037-1042.
22. Suzuki Y, Uchiyama K, Kato M, et al. Potential utility of a new ulcerative colitis segmental endoscopic index combining disease severity and the extent of inflammation. J Clin Gastroenterol 2015;49:401-406.
23. Walmsley RS, Ayres RC, Pounder RE, Allan RN. A Simple Clinical Colitis Activity Index. Gut 1998;43:29-32.
24. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006;333:15.
25. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value Health 2008;11:44-47.
26. Park SH, Yang SK, Park SK, et al. Atypical distribution of inflammation in newly diagnosed ulcerative colitis is not rare. Can J Gastroenterol Hepatol 2014;28:125-130.
27. Moum B, Ekbom A, Vatn MH, Elgjo K. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. Am J Gastroenterol 1999;94:1564-1569.
28. Rajwal SR, Puntis JW, McClean P, et al. Endoscopic rectal sparing in children with untreated ulcerative colitis. J Pediatr Gastroenterol Nutr 2004;38:66-69.
29. Anzai H, Hata K, Kishikawa J, et al. Appendiceal orifice inflammation is associated with proximal extension of disease in patients with ulcerative colitis. Colorectal Dis 2016;18:O278-O282.
30. Kim B, Park SJ, Hong SP, Kim TI, Kim WH, Cheon JH. Proximal disease extension and related predicting factors in ulcerative proctitis. Scand J Gastroenterol 2014;49:177-183.
31. Baars JE, Nuij VJ, Oldenburg B, Kuipers EJ, van der Woude CJ. Majority of patients with inflammatory bowel disease in clinical remission have mucosal inflammation. Inflamm Bowel Dis 2012;18:1634-1640.
32. Odze R, Antonioli D, Peppercorn M, Goldman H. Effect of topical 5-aminosalicylic acid (5-ASA) therapy on rectal mucosal biopsy morphology in chronic ulcerative colitis. Am J Surg Pathol 1993;17:869-875.
33. Rosenberg L, Lawlor GO, Zenlea T, et al. Predictors of endoscopic inflammation in patients with ulcerative colitis in clinical remission. Inflamm Bowel Dis 2013;19:779-784.
34. Fefferman DS, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. Clin Gastroenterol Hepatol 2005;3:11-24.
35. Meucci G, Fasoli R, Saibeni S, et al. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: a prospec-

tive, multicenter study. Inflamm Bowel Dis 2012;18:1006-1010.
36. Nakarai A, Kato J, Hiraoka S, et al. Ulcerative colitis patients in clinical remission demonstrate correlations between fecal immunochemical test results, mucosal healing, and risk of relapse. World J Gastroenterol 2016;22:5079-5087.