ORIGINAL ARTICLE

INTESTINAL RESEARCH

pISSN 1598-9100 • eISSN 2288-1956
https://doi.org/10.5217/ir.2024.00058
Intest Res 2025;23(2):182-192

Histologic healing and clinical outcomes in ulcerative colitis

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Background/Aims: Growing evidence suggests histologic healing (HH) improves clinical outcomes in ulcerative colitis (UC) patients beyond endoscopic healing (EH). We hypothesize that HH is associated with better clinical outcomes in Asian UC patients, for whom data is lacking. **Methods:** We performed a retrospective study of UC patients in clinical remission (CR) with a follow-up colonoscopy and minimum 1-year follow-up post-colonoscopy. Primary outcome was clinical relapse (CRL), defined as either a Simple Clinical Colitis Activity Index score of >2, medication escalation, hospitalization or colectomy. Predictors of CRL and HH were assessed. **Results:** One hundred patients were included with a median follow-up of 22 months. At index colonoscopy, 80 patients were in EH. On follow-up, 41 patients experienced CRL. Of 80 patients in EH, 34 (42.5%) had persistent histologic activity (Nancy Index ≥2) and 29 (36.3%) relapsed during the follow-up period. Amongst patients in CR and EH, those with HH had lower CRL rate (26.1% vs. 50.0%, $P=0.028$) and longer CRL-free survival (mean 46.1 months vs. 31.5 months, $P=0.015$) than those with persistent histologic activity. On bivariable analysis of 100 patients in CR, HH, and Mayo endoscopic score (MES) of 0 were significantly associated with lower risk of CRL. On multivariable analysis, only MES 0 remained predictive of lower CRL risk. **Conclusions:** Above and beyond CR and EH, achieving HH improves clinical outcomes in Asian UC patients. However, HH may not confer incremental benefit if MES 0 has been achieved. Further prospective studies evaluating the benefit of histologically guided therapeutic decisions are needed. **(Intest Res 2025;23:182-192)**

Key Words: Ulcerative colitis; Intestinal mucosa; Histology

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease characterized by relapsing and remitting colonic mucosal inflammation. Inducing and maintaining steroid-free remission with resolution of rectal bleeding and diarrhea, as well as endoscopic healing (EH) are the current recommended long-term treatment targets.[1,2] Above and beyond EH, histologic healing (HH) is increasingly being explored as a therapeutic endpoint.

Microscopic inflammation persists in a significant proportion of UC patients with endoscopically quiescent disease and may predict clinical relapse (CRL).[3] The presence and severity of mucosal inflammation has also been linked to colorectal neoplasia risks.[4,5] Evidence of the associations of HH in UC with improved clinical outcomes such as reduced corticosteroid use, hospitalization, and colectomy rates is growing.[6,7]

Histologic targets have not yet, however, been endorsed as standard practice, given the paucity of prospective data demonstrating the benefit of histologically guided decisions on therapy. Standard definitions of histologic activity and remission are also lacking, with many different scoring systems existing in reported literature. Of these, the Nancy Index (NI) and the Robarts Histopathology Index have been the best validated.[8] There is also a lack of data for Asian UC patients.

The aim of this study was to evaluate the effect of HH on clinical outcomes in a Southeast Asian cohort of adult UC pa-

Received April 21, 2024. **Revised** June 30, 2024. **Accepted** July 22, 2024.
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https://doi.org/10.5217/ir.2024.00058 • Intest Res 2025;23(2):182-192

tients in clinical remission (CR), particularly those also with EH. Predictors of HH and CRL were also explored.

METHODS

1. Study Design

We performed a retrospective cohort study to evaluate the correlation between histologic activity and clinical outcomes in an adult UC cohort. The study was carried out in Tan Tock Seng Hospital, a tertiary-care hospital in Singapore with a dedicated inflammatory bowel disease (IBD) service. This study was approved by the Institutional Review Board of Tan Tock Seng Hospital (reference number 2021/00564) and conducted per the ethical standards of the Declaration of Helsinki. Waiver of informed consent was obtained for this study.

2. Study Population

Consecutive UC patients above 21 years old under the care of the Tan Tock Seng Hospital IBD Clinic who had undergone colonoscopy from January 2000 to April 2021 were identified from the institution's IBD patient registry. Patients were included if they had an established diagnosis of UC per standard clinical, endoscopic, and histologic criteria; were in CR, as defined by a Simple Clinical Colitis Activity Index (SCCAI) score of ≤2 and sub-score ≤1 for stool frequency or rectal bleeding; and had a subsequent colonoscopy and minimum follow-up period of 1-year post-colonoscopy after attaining CR. The SCCAI is a widely used scoring system to describe clinical disease activity in UC. It comprises 6 questions: daytime bowel movements (scored from 0–3), nocturnal bowel movements (scored from 0–2), urgency of defecation (scored from 0–3), amount of blood in stool (scored from 0–3), general well-being (scored from 0–4), and number of extra-colonic manifestations (scored from 0–4). The total score corresponds to the severity of disease activity.

The first colonoscopy performed after attainment of CR was termed the index colonoscopy. Patients were excluded if they had inadequate documentation in their medical records, concurrent infection (such as *Clostridioides difficile* or cytomegalovirus infection) or prior colectomy.

3. Study Outcomes

The primary outcome of the study was CRL, as defined by any of the following 4 criteria: (1) an SCCAI score of >2 with subscore >1 for stool frequency or rectal bleeding; (2) any escalation of medications related to active disease; (3) hospitalization for UC relapse; or (4) colectomy for refractory UC. Secondary outcomes were predictors of time to CRL and HH.

4. Data Collection

Relevant clinical data for the study were retrieved from the institution's IBD registry and summarized in a de-identified manner into an institution-approved Research Electronic Data Capture (REDCap) database. Patient demographics including age, sex, ethnicity, smoking status, SCCAI scores, biomarker levels (C-reactive protein [CRP], stool calprotectin), medications, as well as endoscopic and histologic activity and extent at the time of or within 3 months of index colonoscopy were recorded for each patient. Medication use was recorded for corticosteroids (oral, rectal or both), 5-aminosalicylates (oral, rectal or both), immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), biologic therapy (tumor necrosis factor [TNF]-α inhibitors, anti-integrins, anti-interleukin inhibitors) and small-molecules (Janus kinase inhibitors).

Disease duration was calculated as the time from UC diagnosis to index colonoscopy. Time to CRL was calculated as the time from index colonoscopy to the first recorded occurrence of any of the 4 aforementioned criteria for CRL. Duration of follow-up for each patient was taken as the time from index colonoscopy to either CRL or last recorded clinic visit if CRL had not occurred.

Endoscopic reports and images from all index colonoscopies were independently reviewed by 2 members of the study team and disease activity for each assigned a Mayo endoscopic score (MES).[9] In the event of discordant MES scores between both investigators, the opinion of a third investigator was sought. EH was defined as MES ≤1. Mucosal histopathology samples were reviewed by a senior gastrointestinal pathologist and assigned NI scores.[10] HH was defined as an NI of ≤1. The MES and NI assigned per colonoscopy were each based on that of the respective worst-affected segment. At baseline, the overall study cohort of patients in CR was stratified into those with and without EH. Patients in CR and EH were further stratified into those with and without HH.

The maximal extent of endoscopic activity (defined as MES >1) at index colonoscopy was described per the Montreal Classification (E1 for proctitis, E2 for left-sided UC [inflammation distal to the splenic flexure], E3 for extensive UC [inflammation proximal to the splenic flexure]).[11] Maximal extent of histologic activity (defined as NI >1) was described in an analogous fashion.

Medication escalation was defined as either increasing med-

ication dose within class, switching out of class, or adding corticosteroids within the first 6 months after index colonoscopy.

5. Statistical Analysis

Categorical variables were analyzed with the chi-square test or Fisher exact probability test and presented as percentages. Continuous variables were analyzed with the independent-samples *t*-test and presented as means with standard deviations if parametrically distributed, or the Mann-Whitney *U* test and presented as medians with interquartile ranges (IQR) if non-parametrically distributed. The Shapiro-Wilk test was used to determine whether continuous variables were parametrically or non-parametrically distributed.

For patients in CR and EH, cumulative incidence and incidence rates of CRL were compared between patients with and without HH. The Kaplan-Meier survival analysis was applied to compare CRL-free survival between patients with and without HH.

Clinical variables significantly associated with time to CRL were explored on bivariable and multivariable Cox proportional hazards regression analysis and reported with their respective hazard ratios (HR) and 95% confidence interval (CI). Clinical variables predictive of HH were explored on bivariable and multivariable logistic regression analysis and reported with their respective odds ratios (OR) and 95% CI. Two-sided *P*-values of <0.05 were considered statistically significant. IBM SPSS Statistics version 29.0 (Armonk, NY, USA) software was used for analysis.

RESULTS

1. Study Population

One hundred sixty-nine consecutive UC patients who had undergone colonoscopy from January 1, 2000 to July 30, 2019, were assessed for eligibility. A total of 100 patients in CR fulfilled the inclusion criteria and were entered into the study. Sixty-nine patients were excluded (11 with active disease, 50 with inadequate documentation or follow-up duration of less than 1 year, 8 with prior colectomy). Most were male (62%), with a median age at study enrolment of 56 years (IQR, 44–64 years) and median disease duration of 107 months (IQR, 50–176 months). Index colonoscopy with histological assessment was performed at a median duration of 2 months (IQR, 1–3 months) from attainment of CR. Ethnic distribution approximated that of the local Singapore population, with a majority being Chinese; 80% of patients were in EH, while 46% were in HH. Most were on 5-aminosalicylates, with approximately one-third of patients on corticosteroids (37%) and immunomodulators (31%) respectively. Two patients each were on TNF-α inhibitors and vedolizumab. Baseline patient characteristics are summarized in Table 1.

2. EH at Index Colonoscopy

Among patients in CR and EH, 57.5% (46/80) were in HH (30 with NI of 0, 16 with NI of 1), with 42.5% (34/80) remaining histologically active (27 with NI of 2, 4 with NI of 3, 3 with NI of 4). Among patients with MES 1, 35.1% (13/37) were in HH, with 64.9% (24/37) remaining histologically active. Among patients with MES 0, 76.7% (33/43) were in HH, with 23% (10/43) remaining histologically active.

3. HH at Index Colonoscopy

Comparing patients in CR with and without HH, no significant differences in patient demographics, CRP nor medication use were found. Patients without HH, however, had significantly higher stool calprotectin levels (median 183 μg/g vs. 44 μg/g, $P<0.001$), more left-sided or extensive disease and higher MES scores (Table 1). Among patients with HH, 71.7% (33/46) had an MES of 0, while 28.3% (13/46) had an MES of 1; 65.2% (30/46) of patients had an NI of 0, while 34.8% (16/46) had an NI of 1. Twenty-four percent of patients overall (24/100) had both MES 0 and NI 0.

4. Clinical Relapse

At the end of study follow-up, 41 patients (41%) overall experienced CRL, with 59 (59%) remaining in CR. Of the patients who relapsed, median time to CRL was 231 days (IQR, 46–545 days), while median time to follow-up for the remaining 59 patients was 784 days (IQR, 709–902 days).

Comparing all patients (n = 100) at index colonoscopy, patients with EH had longer CRL-free survival than those with persistent endoscopic activity (mean 40.5 months vs. 15.4 months, $P<0.001$) (Fig. 1). Patients with HH had longer CRL-free survival than those without HH (mean 46.0 months vs. 27.7 months, $P<0.001$).

Comparing patients with EH at index colonoscopy (n = 80); (1) CRL rates were significantly lower in patients with HH compared to those without HH at 1 year (10.9% vs. 29.4%, $P=0.036$) and 2 years (26.1% vs. 50.0%, $P=0.028$) of follow-up; (2) CRL-free survival was significantly longer in patients with HH than those with persistent histologic activity (mean 46.3 months vs. 31.7 months, $P=0.014$) (Fig. 2); (3) those with MES

https://doi.org/10.5217/ir.2024.00058 • Intest Res 2025;23(2):182-192

Table 1. Patient Characteristics at Index Colonoscopy

Variable	All patients (n = 100)	HH (n = 46)	No HH (n = 54)	*P*-value
Age (yr)	56 (44–64)	53.9 ± 13.3	54.0 ± 13.8	0.957
Disease duration (mo)	107.0 (50.0–176.0)	101.7 (55.7–210.3)	111.7 (46.5–163.4)	0.527
BMI (kg/m^2)	24.2 (22.0–26.7)	24.9 (22.3–27.2)	23.9 (21.9–25.6)	0.181
CRP (mg/L)	1.1 (0.6–3.0)	0.9 (0.6–2.5)	1.5 (0.6–4.0)	0.352
Stool calprotectin (μg/g)	104 (40–256)	44 (30–104)	183 (101–388)	< 0.001[a]
Sex				0.150
Female	38 (38)	14 (30.4)	24 (44.4)	
Male	62 (62)	32 (69.6)	30 (55.6)	
Ethnicity				0.529
Chinese	71 (71)	34 (73.9)	37 (68.5)	
Malay	10 (10)	3 (6.5)	7 (13.0)	
Indian	15 (15)	8 (17.4)	7 (13.0)	
Others	4 (4)	1 (2.2)	3 (5.6)	
Smoking status				0.828
Never	70 (70)	35 (76.1)	35 (64.8)	
Smoker	4 (4)	2 (4.3)	2 (3.7)	
Ex-smoker	19 (19)	8 (17.4)	11 (20.4)	
Endoscopic extent				< 0.001[a]
Normal	25 (25)	18 (39.1)	7 (13.0)	
Proctitis	37 (37)	20 (43.5)	17 (31.5)	
Left-sided	16 (16)	3 (6.5)	13 (24.1)	
Extensive	22 (22)	5 (10.9)	17 (31.5)	
Histologic extent				
Normal	19 (19)	19 (41.3)	-	
Proctitis	31 (31)	17 (37.0)	14 (25.9)	
Left-sided	17 (17)	4 (8.7)	13 (24.1)	
Extensive	33 (33)	6 (13.0)	27 (50.0)	
Mayo endoscopic score				< 0.001[a]
0	43 (43)	33 (71.7)	10 (18.5)	
1	37 (37)	13 (28.3)	24 (44.4)	
2	14 (14)	0	14 (25.9)	
3	6 (6)	0	6 (11.1)	
Nancy Index				
0	30 (30)	30 (65.2)	-	
1	16 (16)	16 (34.8)	-	
2	30 (30)	-	30 (55.6)	
3	12 (12)	-	12 (22.2)	
4	12 (12)	-	12 (22.2)	
Medications				
Steroids	37 (37)	17 (37.0)	20 (37.0)	0.993
5-ASA	98 (98)	45 (97.8)	53 (98.1)	0.909

(Continued to the next page)

Table 1. Continued

Variable	All patients (n = 100)	HH (n = 46)	No HH (n = 54)	*P*-value
Immunomodulators	31 (31)	12 (26.1)	19 (35.2)	0.327
Biologics	3 (3)	1 (2.2)	2 (3.7)	1.000[b]

Values are presented as median (interquartile range), mean ± standard deviation, or number (%).
[a]Statistically significant.
[b]Fisher exact test.
HH, histologic healing; BMI, body mass index; CRP, C-reactive protein; 5-ASA, 5-aminosalicylic acid.

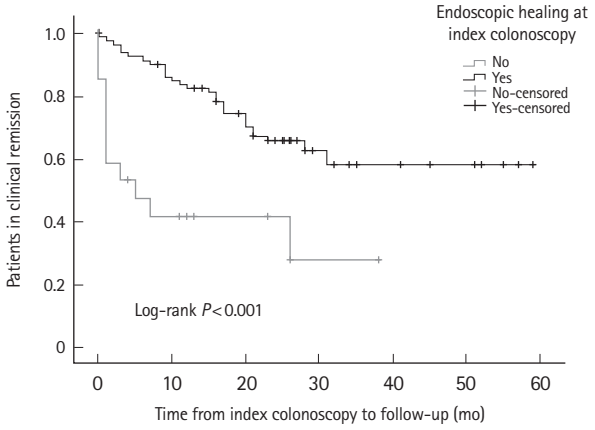

Fig. 1. Kaplan-Meier analysis of the effect of endoscopic healing on clinical relapse-free survival in patients with clinical remission.

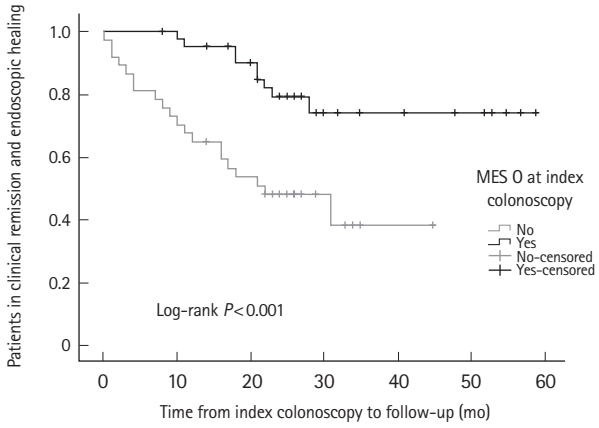

Fig. 3. Kaplan-Meier analysis of the effect of Mayo endoscopic score (MES) 0 versus MES 1 on clinical relapse-free survival in patients with clinical remission and endoscopic healing.

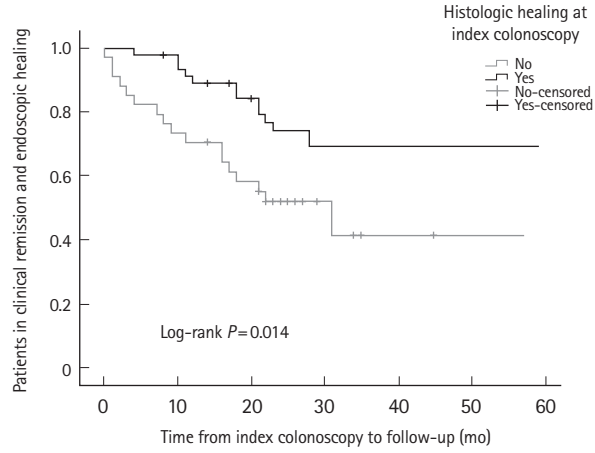

Fig. 2. Kaplan-Meier analysis of the effect of histologic healing on clinical relapse-free survival in patients with clinical and endoscopic healing.

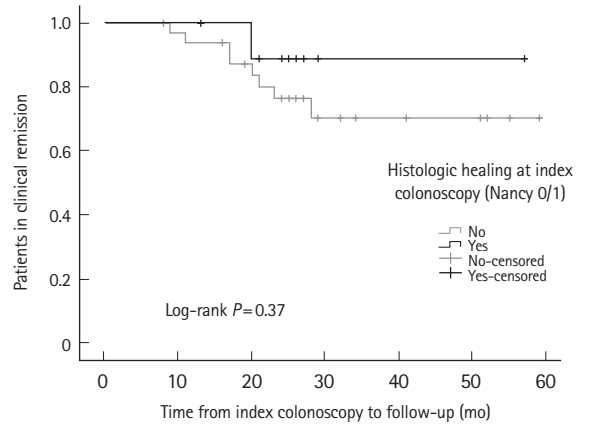

Fig. 4. Kaplan-Meier analysis of the effect of histologic healing on clinical relapse-free survival in patients with clinical remission and Mayo endoscopic score 0.

0 had longer CRL-free survival than those with MES 1 (mean 48.9 months vs. 25.3 months, $P<0.001$) (Fig. 3); and (4) those with an NI of 0 had a trend towards longer CRL-free survival than those with an NI of 1 (mean 49.0 months vs. 38.0 months, $P=0.142$). The relative risk (RR) of CRL for subjects with MES 0 compared with MES 1 was 0.39 (95% CI, 0.20–0.74). The RR for CRL of subjects with HH compared with no HH was 0.52 (95% CI, 0.29–0.94).

Comparing patients with MES 0 (n = 43) at index colonoscopy, HH and NI 0 status did not significantly lower CRL risk (RR 0.41; 95% CI 0.59–2.91 for HH; RR 0.63, 95% CI 0.20–2.04 for NI 0). On Kaplan-Meier analysis, however, we observed a

https://doi.org/10.5217/ir.2024.00058 • Intest Res 2025;23(2):182-192

trend towards significance for HH lowering the risk of CRL-free survival compared with non-HH (log-rank $P=0.37$) (Fig. 4). A similar trend was seen for NI 0 status. CRL rates for patients with EH are summarized in Table 2.

5. Predictors of CRL

On bivariable Cox regression analysis, duration of CR (HR, 1.04; 95% CI, 1.00–1.09; $P=0.034$), CRP (HR, 1.05; 95% CI, 1.01–1.10; $P=0.03$), stool calprotectin (HR, 1.001; 95% CI, 1.000–1.002; $P=0.049$), EH (HR, 0.28; 95% CI, 0.14–0.56; $P<0.001$), MES 0 status (HR, 0.25; 95% CI, 0.12–0.52; $P<0.001$) and HH (HR, 0.34; 95% CI, 0.17–0.67; $P=0.002$) were independently predictive of CRL-free survival at the end of study. On multivariable Cox regression analysis, accounting for duration of CR, CRP, and HH, only MES 0 status remained predictive of higher CRL-free survival (HR, 0.37; 95% CI, 0.15–0.94; $P=0.037$) (Table 3).

Table 2. CRL Rates at 2-Year Follow-up for Patients with Endoscopic Healing at Index Colonoscopy

	CRL	No CRL	*P*-value
MES 0 (n = 43)	9 (20.9)	34 (79.1)	0.002[a]
HH (n = 10)	1 (10.0)	9 (90.0)	0.330
No HH (n = 33)	8 (24.2)	25 (75.8)	
MES 1 (n = 37)	20 (54.1)	17 (45.9)	

[a]Statistically significant.
CRL, clinical relapse; MES, Mayo endoscopic score; HH, histologic healing.

6. Predictors of HH

On bivariable logistic regression analysis, stool calprotectin (OR, 0.99; 95% CI, 0.99–1.00; $P=0.004$), endoscopic extent (OR, 0.17; 95% CI, 0.07–0.43; $P<0.001$) and MES 0 status (OR, 11.17; 95% CI, 4.36–28.59; $P<0.001$) were significantly associated with HH. On multivariable logistic regression analysis, stool calprotectin (OR, 0.99; 95% CI, 0.989–0.999; $P=0.014$) and MES 0 status (OR, 19.12; 95% CI, 4.08–89.68; $P<0.001$) remained significantly associated with HH (Table 4).

Table 3. Cox Regression Analysis of Clinical Variables Associated with Time to Clinical Relapse

Variable	Bivariable regression		Multivariable regression	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age[a]	0.99 (0.97–1.01)	0.436		
Disease duration	1.00 (0.96–1.00)	0.310		
Duration of clinical remission	1.04 (1.00–1.09)	0.034[e]	1.05 (0.95–1.16)	0.336
BMI	0.95 (0.88–1.02)	0.168		
CRP	1.05 (1.01–1.10)	0.030[e]	1.04 (0.99–1.09)	0.108
Stool calprotectin	1.00 (1.00–1.00)	0.049[e]		
Sex[b]	0.93 (0.49–1.77)	0.834		
Current smoker[c]	0.55 (0.08–4.03)	0.557		
Endoscopic extent[d]	1.53 (0.82–2.87)	0.186		
EH	0.28 (0.14–0.56)	<0.001[e]		
MES 0	0.25 (0.12–0.52)	<0.001[e]	0.37 (0.15–0.94)	0.037[e]
HH	0.34 (0.17–0.67)	0.002[e]	0.59 (0.26–1.35)	0.209
Baseline medications				
Steroids	0.71 (0.36–1.39)	0.313		
5-ASA	0.90 (0.12–6.60)	0.920		
Immunomodulators	0.65 (0.31–1.36)	0.247		
Biologics	2.50 (0.60–10.42)	0.210		

[a]HR given per each year increase in age.
[b]HR for male sex, with female sex as comparator.
[c]HR for current smoking, with ex-smoking or non-smoking status as comparator.
[d]HR for left-sided or extensive disease, with proctitis or normal colon as comparator.
[e]Statistically significant.
HR, hazard ratio; CI, confidence interval; BMI, body mass index; CRP, C-reactive protein; EH, endoscopic healing; MES, Mayo endoscopic score; HH, histologic healing; 5-ASA, 5-aminosalicylic acid.

Table 4. Logistic Regression Analysis of Clinical Variables Associated with Histologic Healing

Variable	Bivariable regression		Multivariable regression	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age[a]	1.00 (0.97–1.03)	0.956		
Disease duration	1.00 (1.00–1.01)	0.373		
Duration of clinical remission	1.01 (0.95–1.09)	0.701		
BMI	1.05 (0.95–1.15)	0.355		
CRP	0.94 (0.84–1.06)	0.294		
Stool calprotectin	0.99 (0.99–1.00)	0.004[e]	0.99 (0.99–1.00)	0.014[e]
Sex[b]	0.55 (0.24–1.25)	0.152		
Current smoker[c]	1.07 (0.14–7.93)	0.947		
Endoscopic extent[d]	0.17 (0.07–0.43)	<0.001[e]	0.40 (0.10–1.53)	0.180
MES 0	11.17 (4.36–28.59)	<0.001[e]	19.12 (4.08–89.68)	<0.001[e]
Medications				
Steroids	1.00 (0.44–2.25)	0.993		
5-ASA	0.85 (0.05–13.96)	0.909		
Immunomodulators	0.65 (0.27–1.54)	0.328		
Biologics	0.58 (0.05–6.59)	0.659		

[a]OR given per each year increase in age.
[b]OR for male sex, with female sex as comparator.
[c]OR for current smoking, with ex-smoking or non-smoking status as comparator.
[d]OR for left-sided or extensive disease, with proctitis or normal colon as comparator.
[e]Statistically significant.
OR, odds ratio; CI, confidence interval; BMI, body mass index; CRP, C-reactive protein; MES, Mayo endoscopic score; 5-ASA, 5-aminosalicylic acid.

DISCUSSION

Clinical symptoms generally correlate well with endoscopic activity in UC, with the absence of rectal bleeding and normalization of stool frequency in particular correlating well with endoscopic remission.[12,13] A significant proportion of patients, however, may have persistent subclinical mucosal inflammation.[14,15] Our study results reflect this phenomenon, with a fifth of our patients in CR having persistent endoscopic activity. With increasing recognition of the benefits of mucosal healing on outcomes such as sustained CR, corticosteroid-free remission, and colectomy-free survival,[16] EH is now an aptly established long-term target in UC patients. In our study, patients with EH had expectedly lower CRL rates compared to those with endoscopic activity on follow-up.

About a third of patients in CR and EH, however, will have persistent histologic activity.[17,18] In our study, 42.5% (34/80) of clinically and endoscopically quiescent patients were histologically active at baseline and experienced higher CRL rates. Evidence is mounting of the accretive benefit of histologic remission beyond endoscopic remission. A systematic review and meta-analysis of 15 studies evaluating 1,573 UC patients showed patients in baseline histologic remission had lower pooled proportions of CRL compared to those in endoscopic remission (14 studies: RR, 0.83; 95% CI, 0.72–0.95) and to those in combined clinical and endoscopic remission (12 studies: RR, 0.81; 95% CI, 0.70–0.94). Patients in histologic remission also had reduced colectomy and corticosteroid requirements compared to those with histologic activity.[17] Another meta-analysis of 20 studies of UC patients in clinical and endoscopic remission showed a lower risk of CRL for patients in histologic remission compared to those with persistent histologic activity (RR, 0.39; 95% CI, 0.31–0.51). A significantly lower relative relapse risk for patients in histologic remission compared to those with histologic activity was seen in studies of relatively longer (greater than 1 year) duration.[18] In a similar vein, a third meta-analysis of 27 studies of UC patients in endoscopic remission (n=2,677) showed histologically active disease to be associated with an increased risk of disease relapse (OR, 2.41; 95% CI, 1.91–3.04), with an almost 2-fold greater odds of relapse seen with histologic activity in studies of at least 2-year follow-up compared to those of shorter dura-

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tion.[19] The latter 2 analyses suggest the full benefit of achieving histologic remission might only be appreciated on prolonged follow-up.

Forty-six percent of our study patients (46/100) achieved HH at baseline. This proportion is consistent with a systematic review and meta-analysis of 74 randomized controlled trials of UC patients showing a pooled histologic remission rate after induction with conventional therapies of 15.0% to 44.9%.[20] This 'therapeutic ceiling' of histologic remission has yet to be meaningfully overcome even with newer therapeutic agents,[21-26] though novel treatment paradigms may be able to achieve higher HH rates. For example, a phase 2, randomized, double-blind controlled trial comparing the combination of an interleukin-23 antagonist monoclonal antibody and a TNF-α inhibitor against each as monotherapy showed histologic remission rates of greater than 50% post-induction and at up to week 38 of maintenance treatment on combination therapy.[27] The concept of histo-endoscopic mucosal healing has now been incorporated into phase 3 UC clinical trials as an important study endpoint, with patients achieving this having significantly improved clinical outcomes.[21,26,28] It would be worthwhile for future clinical trials on UC therapeutics to continue to explore this outcome as a therapeutic goal.

The MES 0 sub-population deserves greater scrutiny. Two meta-analyses have demonstrated that MES 0 status clearly confers significantly lower CRL risk compared to MES 1 status, with risk reductions of up to 30%–50%.[18,29] MES 0 has now become the recommended target for UC EH in the Selecting Therapeutic Targets in Inflammatory Bowel Disease II guidelines.[30] Our study affirmed MES 0 status as predictive of CRL. In this group, we were unable to show a statistically significant difference in clinical outcomes with histologic activity versus quiescence. These results suggest the lack of incremental clinical benefit of HH once MES 0 is achieved, though a type 2 error cannot be excluded due to our relatively small numbers. Limited evidence exists on this topic. A prospective single-center study of 64 MES 0 histologically-active UC patients followed up for up to a year showed histology did not predict CRL.[31] Another single-center retrospective study of 411 active UC patients sequentially treated to target EH also showed no incremental clinical benefit of histologic remission in modified MES 0, though these patients had higher histologic remission rates compared to those with a score of 1, with this deeper level of EH independently predicting HH.[32] A meta-analysis incorporating these studies, however, showed an overall summary risk ratio of 0.37 favoring histologic remission for reducing CRL in MES 0 patients.[18] To what extent histological assessment, itself subject to inter-observer variability,[33] can help to mitigate the subjectivity of endoscopic assessment is unclear. The risks and costs of pursuing histologic remission once MES 0 has been achieved deserve further study.

Our study has several strengths. Firstly, it provides valuable real-world data on the effect of HH on clinical outcomes in Asian adult UC patients, particularly in a Southeast Asian context. There is a lack of data from this ethnically unique and diverse region. The superior clinical outcomes with HH demonstrated in our study are consistent with published data from Asian studies emerging in this field.[34-38] Secondly, our standardized use of validated endoscopic and histologic activity scores for all colonoscopies enabled consistency in data reporting and analysis. Thirdly, the routine use of stool calprotectin in our center allowed us to analyze its predictive effect on CRL and HH.[39,40]

Given our retrospective study design, however, inconsistencies in data quality and bias may be present. Pertinent to our study was the possible subjectivity in differentiating MES 0 and 1 scores as well as the lack of a standardized protocol for colonic biopsies to assess histologic activity. The retrieval of our data from an institutional database and standardized reporting of MES and NI scores by a team of experienced clinicians mitigates these limitations to a certain extent.

Being a single tertiary center study and considering the unique ethnic composition of our study population, our data may also not be fully generalizable to other Asian UC populations. We also did not explore if there were specific histologic characteristics such as basal plasmacytosis and neutrophilic infiltrates that may have predicted CRL, as has been previously reported.[17,19] Given the dearth of studies from this part of the world, however, our data nonetheless goes some way into filling an important knowledge gap.

There was also heterogeneity in medication titration for our patients, with this done reactively by physician discretion rather than per a pre-defined protocol. Prospective randomized-controlled trials evaluating the clinical outcomes of iterative optimization of therapy to target HH will be invaluable in helping clinicians weigh the benefits and risks of such an approach. To this end, the results of the VERDICT trial are eagerly awaited.[41]

Therapeutic targets in IBD have evolved from purely symptom resolution to incorporating EH in a treat-to-target fashion, with the intent to achieve the best possible long-term outcomes for patients with deeper levels of remission. Consider-

ing current evidence of its potential benefits, histologic remission could be considered the ideal target in appropriately selected UC patients. The practical limitation of achieving this target with current therapies, however, remains a challenge.

ADDITIONAL INFORMATION

Funding Source
This work was supported by Ferring Pharmaceuticals.

Conflict of Interest
This work was supported by Ferring Pharmaceuticals. Except for that, no potential conflict of interest relevant to this article was reported.

Data Availability Statement
All study-related data is included in the publication or provided as supplementary information.

Author Contributions
Conceptualization: Liang RFH, Lim WC. Data curation: Liang RFH, Lin H. Formal analysis: Liang RFH. Investigation: Liang RFH, Lin H, Chau CYP, Lim WC. Methodology: Liang RFH, Lim WC. Project administration: Liang RFH, Lin H, Lim WC. Supervision: Lim WC. Writing - original draft: Liang RFH, Lin H. Writing - review & editing: Liang RFH, Lin H, Chau CYP, Lim WC. Approval of final manuscript: all authors.

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