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Histological remission as a reliable predictor of clinical outcomes in patients with ulcerative colitis after conventional therapy: a 5-year analysis

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Abstract

Purpose Histological remission has emerged as a promising target that may improve long-term outcomes in patients with ulcerative colitis (UC). The aim of this study was to investigate correlations between clinical, endoscopic, and histological remissions and the predictive value of histological remission on long-term outcomes in patients with UC receiving conventional therapy.

Methods A retrospective study was conducted involving 183 patients with UC who underwent histological assessment between August 2004 and May 2018. Concordance among clinical, endoscopic, and histological remissions was evaluated using Fleiss kappa statistics. Cox multivariate regression analysis was performed to identify independent factors associated with long-term outcomes, including corticosteroid use, biologics requirements, hospitalization, and composite outcome of disease progression.

Results At baseline, 84.7% of patients were treated with 5-aminosalicylic acid and 15.3% with immunosuppressants. Histological remission exhibited fair agreement with endoscopic remission (κ = 0.280, 95%CI = 0.276–0.285, $P < 0.001$). Cox multivariate analysis revealed histological remission served as an independent protective factor against the need for corticosteroid (HR: 0.242, 95%CI = 0.087–0.675, $P = 0.007$), biologics requirements (HR 0.323, 95%CI = 0.114–0.914, $P = 0.033$), hospitalization for acute severe UC (HR 0.270, 95%CI = 0.083–0.875, $P = 0.029$), and disease progression (HR 0.340, 95%CI = 0.164–0.708, $P = 0.004$) over a median 5-year follow-up period.

Conclusion Histological remission showed fair agreement with endoscopic remission and independently predicted better clinical outcomes, including reduced corticosteroid use, decreased biologics requirement, and lower rates of hospitalization and disease progression in patients with UC receiving conventional therapy.

Keywords Ulcerative colitis, Histological remission, Endoscopic remission, Clinical outcome.

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by relapsing and remitting symptoms, including bloody diarrhea and abdominal pain [1, 2]. First-line therapy for induction and maintenance of remission in mild to moderate UC is 5-aminosalicylic acid (5-ASA) [3–5]. However, moderate to severe UC may require oral corticosteroid for induction of remission, and a small proportion of patients choose immunosuppressives as maintenance therapy instead of biological agents owing to economic or accessibility reasons [6]. Traditionally, owing to the absence of a curative treatment, the goal of conventional therapy for patients with UC has been to achieve and maintain clinical symptomatic relief and endoscopic mucosal healing [7]. Recently, treatment strategies for UC have evolved from simple symptom control to a treat-to-target paradigm focused on mucosal healing, leading to improved long-term clinical outcomes [8]. While both mucosal healing and histological remission can benefit patients with UC, they may not always align. Despite mucosal healing and clinical symptoms being under control, histological activity, particularly the presence of acute inflammatory cells in the lamina propria, can persist [9–13]. Not all patients with UC who exhibit a healed mucosa on endoscopy undergo biopsy for further histological assessment. This finding suggests that histological remission may not be receiving adequate attention in clinical practice. Furthermore, the relationship between clinical, endoscopic, and histological remissions following conventional therapy is not well understood.

Histological remission indicates the microscopic normality of the colonic mucosa, with the resolution of any abnormalities in the crypts and the absence of inflammatory infiltration [14]. Recent evidence has revealed histological remission as a superior treatment target than endoscopic mucosal healing, correlating with decreased rates of hospitalizations, surgeries, and colorectal neoplasia; moreover, it could be achieved using conventional therapies, biological agents, and novel drugs with varying reported success rates [15–19]. Although the STRIDE consensus does not prioritize histological healing as a primary outcome, they are recognized as additional exploratory findings [7]. However, the predictive value of histological remission for long-term clinical outcomes after conventional treatment remains unclear. Therefore, the primary objective of this study was to evaluate potential correlations between clinical, endoscopic, and histological remissions. Additionally, a secondary endpoint aimed to assess the impact of histological remission on various clinical outcomes in patients with UC undergoing conventional therapy, including systemic corticosteroid use, transition to biological agents, hospitalization for acute severe ulcerative colitis (ASUC), UC-related colectomy, and disease progression.

Methods

Study population

This retrospective cohort study included patients diagnosed with UC at the Gastroenterology Department of the First Affiliated Hospital, Sun Yat-sen University, China, between August 2004 and May 2018. Inclusion criteria were: (1) established diagnosis of UC; (2) age ≥ 18 years; (3) receipt of conventional therapy for UC baseline treatment, including 5-ASA and immunosuppressants, with or without oral corticosteroid; (4) availability of a baseline histological assessment and completion of at least one year of follow-up; and (5) sufficient follow-up data for analysis, defined as having complete medical records documenting clinical outcomes (including medication use, hospitalizations, and surgeries) for the entire follow-up period, without any gap in care exceeding 6 months. Patients were excluded from the study if they met any of the following criteria: (1) baseline coinfection with cytomegalovirus or *Clostridioides difficile*; [9, 16] (2) biological agents use at baseline; (3) irregular follow-up, defined as no clinical visit for >6 months after baseline colonoscopy; (4) loss to follow-up, defined as no visit for >1 year; or (5) total follow-up duration of < 1 year.

The reporting of our study conformed to the STROBE statement, and the details of all patients were de-identified to ensure confidentiality. In addition, this study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (Number of approval: [2024]392), and a waiver of informed consent was granted for this retrospective study.

Data collection

UC was diagnosed on the basis of a combination of clinical, radiologic, endoscopic, and histological criteria. The term 'baseline' in this study refers to the time point at which the patient underwent the index histological assessment, not the initiation of therapy, which was not at a fixed interval after treatment initiation but was determined by clinical need. In this study, clinical activity was assessed using the Simple Clinical Colitis Activity Index (SCCAI), with an SCCAI score of ≤ 2 indicating clinical remission [7]. Endoscopic activity was evaluated using the Mayo Endoscopic Subscore (MES), with an MES score of ≤ 1 indicating endoscopic remission [20]. Histological activity was evaluated by an independent, blinded senior gastrointestinal pathologist using Nancy's histological index (NHI), with an NHI ≤ 1 indicating histological remission [21]. Demographic characteristics, clinical features, and endoscopic and histological data were retrieved and collected from electronic medical records at our hospital. Data on the following clinical

outcomes were collected: systemic corticosteroid use, need for biological therapy, hospitalization for ASUC, and UC-related colectomy. The occurrence of any of these events was analyzed as a composite outcome of disease progression. The decision to initiate biological therapy was based primarily on clinical and endoscopic disease activity, with treatment choices determined through shared decision-making between gastroenterologists and patients [5]. ASUC is diagnosed combining a bloody stool frequency ≥ 6 per day with at least one sign of systemic toxicity such as a pulse rate >90 bpm, temperature >37.8 °C, hemoglobin level of < 105 g/l and/or an erythrocyte sedimentation rate >30 mm/h [22]. The Truelove and Witts Severity Index was employed to assess acute colitis severity, diagnose ASUC, and determine hospitalization necessity.

Outcomes

The primary outcome of this study was to evaluate potential correlations among clinical, endoscopic, and histological remissions. The second outcome was to assess connections between endoscopic or histological remission and important clinical outcomes, including the use of systemic corticosteroid, the requirement for biologics, hospitalization for ASUC, UC-related colectomy, and composite outcome of disease progression.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges (IQRs), whereas categorical variables are reported as frequencies. Differences between the two groups were compared using independent sample t test (for parametric data) or Mann-Whitney test (for nonparametric data). The Bonferroni correction was applied to adjust for multiple comparisons. Agreement between clinical, endoscopic, and histological remissions was assessed using the Fleiss kappa test. Fleiss kappa values were categorized as follows: slight agreement (0.01–0.20), fair agreement (0.21–0.40), moderate agreement (0.41–0.60), substantial agreement (0.61–0.80), and almost complete agreement (0.81–1.0). Kaplan–Meier analysis was conducted to evaluate clinical outcomes based on baseline assessments. A multivariate Cox regression model with backward stepwise elimination was employed to identify independent risk factors for clinical outcomes. Variables incorporated into the model were limited to those that achieved statistical significance or exhibited a trend ($P<0.1$) in prior univariate analyses. Before performing the multivariate analysis, key model assumptions were verified, including satisfaction of the proportional hazards assumption and absence of significant multicollinearity as assessed by variance inflation factors. A P-value < 0.05 was considered statistically significant. For comparisons involving clinical outcomes stratified by endoscopic and histological remission, a Bonferroni-corrected significance level of $P<0.025$ (0.05/2) was applied. The analyses were performed using SPSS v.26 and R v.4.2.1.

Results

Baseline characteristics

A total of 183 patients with UC were included in this study with a median follow-up of 5.0 years (IQR 2.7–8.3 years) (Fig. 1). Baseline characteristics of the patients and treatments administered are summarized in Table 1. The total disease duration was 34.7 months (IQR 9.0–77.0 months) at baseline. The median age was 40.9 years (IQR 29.8–51.6 years), with 61.7% (113/183) being men. At the baseline assessment, 23 patients (12.6%) were presented with proctitis, 78 (42.6%) with distal colitis, and 82 (44.8%) with pancolitis. A total of 155 patients (84.7%) received 5-ASA (including 31 patients who received it in combination with corticosteroid), whereas 28 patients (15.3%) were administered immunosuppressants (including 7 patients who received it in combination with corticosteroid).

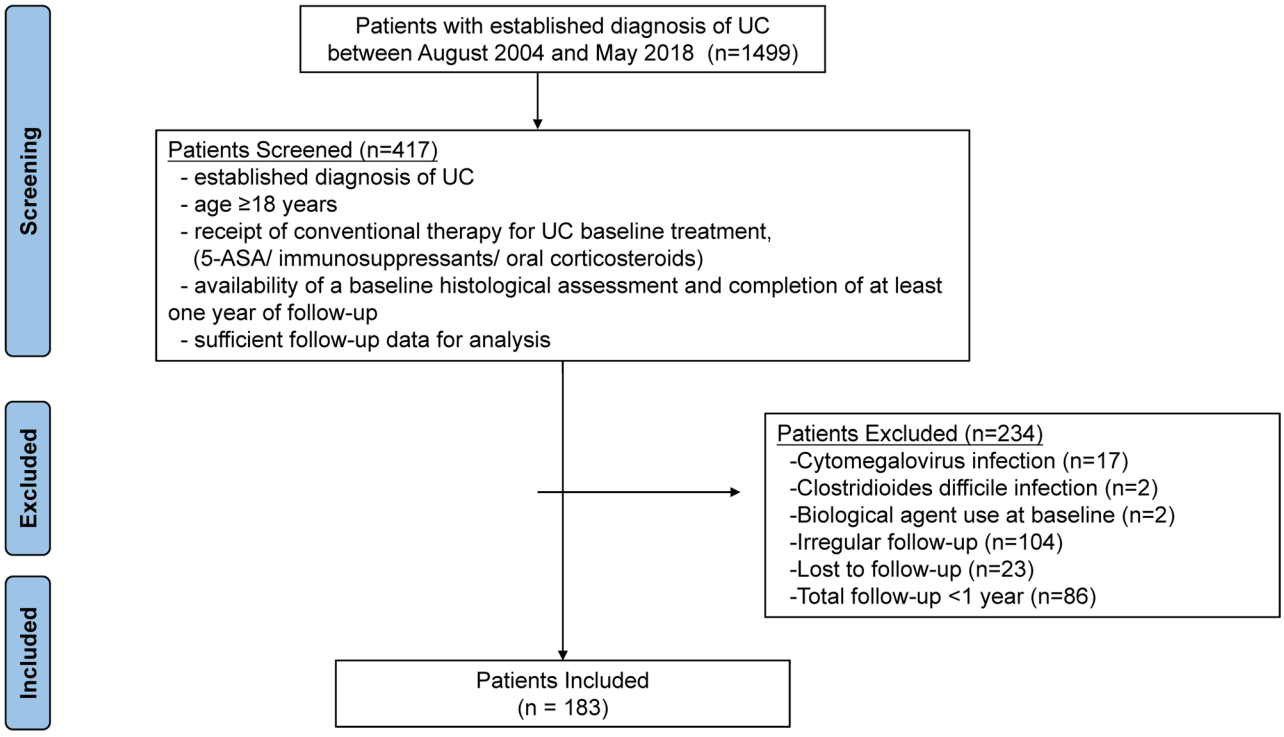
Concordance between clinical, endoscopic, and histological remissions

Clinical, endoscopic, and histological remissions were achieved in 18.6% (34/183), 19.7% (36/183), and 15.3% (28/183) of the patients, respectively (Fig. 2). Only ten patients achieved remission in all three assessment dimensions. Overall, agreement among the three measures of remission assessment was fair ($\kappa=0.292$, 95% CI 0.289–0.295, $P<0.001$). Histological remission had moderate agreement with clinical remission ($\kappa=0.417$, 95% CI 0.413–0.422, $P<0.001$) and fair agreement with endoscopic remission ($\kappa=0.280$, 95% CI 0.276–0.285, $P<0.001$). The greatest disparity was observed between clinical and endoscopic remission ($\kappa=0.187$, 95% CI 0.183–0.192, $P=0.011$).

Endoscopic versus histological remission in predicting clinical outcomes

Corticosteroid requirements

During the follow-up period, 69 (37.7%) patients received an induction dose of systemic corticosteroid. Among patients who achieved histological remission, only 14.3% required corticosteroid for subsequent treatment. In contrast 25.0% of patients in endoscopic remission required corticosteroid (Table 2). Patients in histological remission did not require an induction dose of systemic corticosteroid for a longer duration than those without histological remission [71.6 (IQR 56.8–112.1) months vs. 46.4 (IQR 30.4–89.5) months, $P=0.007$] (Table 3; Fig. 3A). Furthermore, multivariate analysis indicated that achieving histological remission was significantly and negatively



Note: 5-ASA, 5-aminosalicylic acid. Irregular follow-up, no visit in 6 months after histological assessment. Lost to follow-up, no visit after 12 months.

Fig. 1 Study flowchart

associated with the use of systemic corticosteroid (HR 0.242, 95% CI 0.087–0.675, $P = 0.007$). (Fig. 4A; Table 4)

Biologics requirements

During follow-up treatment, 42 (23.0%) patients transitioned to biological agents, with 30 patients opting for infliximab and 12 patients for vedolizumab. Notably, only four patients in histological remission required biological agents, whereas nine patients in endoscopic remission did (Table 2). Patients achieving histological remission experienced a significantly longer duration of maintenance on conventional therapy without requiring biological agents than those who did not achieve histological remission [81.5 (IQR 52.6–118.4) months vs. 45.0 (IQR 30.1–85.6) months, $P = 0.003$] (Table 3; Fig. 3B). This difference was not observed in patients in endoscopic remission ($P = 0.515$). Multivariate analysis indicated that histological remission was associated with a substantially reduced risk of biologics requirements, although the estimate was imprecise due to the limited number of events (HR 0.323, 95% CI 0.114–0.914, $P = 0.033$). Conversely, endoscopic remission did not predict the need to escalate treatment to biologics (HR 0.985, 95% CI 0.469–2.067, $P = 0.968$) (Fig. 4B; Table 4).

Hospitalization for ASUC

Forty-nine patients (26.8%) were hospitalized for ASUC during the follow-up period. Only 3 (10.7%) patients in histological remission experienced ASUC, compared with 5 (13.9%) patients in endoscopic remission (Table 2). The duration of disease progression without ASUC was significantly longer in patients who achieved histological remission compared to those who did not achieve histological remission [74.0 (IQR 53.0–113.6) months vs. 46.5 (IQR 28.1–88.0) months, $P = 0.008$] (Table 3; Fig. 3C). Multivariate analysis identified histological remission as the sole protective factor against hospitalization for ASUC, with an HR of 0.270 (95% CI 0.083–0.875, $P = 0.029$) (Fig. 4C; Table 4).

UC-related colectomy

Colectomy was a rare event, and only nine patients underwent this procedure during follow-up. And it was performed in only one patient in histological remission and in another patient with endoscopic remission. (Table 2)

Composite outcome of disease progression

Eighty-eight patients (48.1%) experienced a disease progression during follow-up. Among those with endoscopic remission, 14 patients (38.9%) had a progression;

Table 1 Baseline characteristics of patients with ulcerative colitis

Item	Patients (*n* = 183)
Sex, *n* (%)	
Male	113 (61.7)
Female	70 (38.3)
Age, median (IQR), years	40.9 (29.8, 51.6)
Disease duration, median (IQR), months	34.7 (9.0, 77.0)
Disease extent (Montreal classification), *n* (%)	
Proctitis (E1)	23 (12.6)
Distal (E2)	78 (42.6)
Extensive (E3)	82 (44.8)
Clinical disease activity (SCCAI), *n* (%)	
0–2	34 (18.6)
3–5	70 (38.3)
6–10	75 (41.0)
>10	4 (2.2)
Mayo endoscopy subscore (MES), *n* (%)	
0	4 (2.2)
1	32 (17.5)
2	70 (38.3)
3	77 (42.1)
Histological disease activity (NHI), *n* (%)	
0	6 (3.3)
1	22 (12.0)
2	64 (35.0)
3	48 (26.2)
4	43 (23.5)
Baseline therapy, *n* (%)	
5-ASA	155 (84.7)
Corticosteroids	38 (20.8)
Immunosuppressants	28 (15.3)

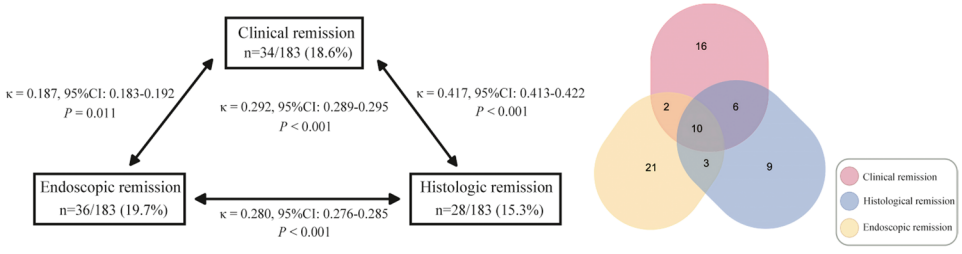
SCCAI Simple Clinical Colitis Activity Index, *NHI* Nancy's histologic index, *5-ASA* 5-Amino Salicylic Acid agents

however, only 8 patients (28.6%) in histological remission required treatment escalation due to progression (Table 2). Patients with histological remission had a significantly longer progression -free period than those without [70.0 (IQR 52.6–112.1.6.1) months vs. 45.0 (IQR 25.7–76.8) months, $P = 0.009$]. (Table 3; Fig. 3D). Multivariate analysis identified histological remission as the only independent protective factor against disease progression (HR 0.340, 95% CI 0.164–0.708; $P = 0.004$) (Fig. 4D; Table 4).

A total of 10 patients achieved simultaneous clinical, endoscopic, and histological remissions at baseline. During the subsequent follow-up period, two of these patients experienced relapse and required induction therapy with biologics, while one patient was hospitalized for ASUC. None of the patients required systemic corticosteroid or underwent surgery.

Discussion

While early intervention with advanced therapies is a compelling strategy in Crohn's disease, its definitive role in fundamentally altering the long-term natural history of UC, particularly in reducing colectomy rates, remains a subject of ongoing investigation and is not yet fully supported by all evidence [23, 24]. Although not a standard treatment target in clinical practice, histological remission has demonstrated superiority over endoscopic remission and is associated with better clinical outcomes, such as lower rates of relapse, hospitalization, and surgery [25]. Studies evaluating histological remission in UC are notably heterogeneous, frequently including patients on varied treatment regimens and hampered by limited follow-up. To our knowledge, this study represents the longest follow-up study of histological remission in an Asian UC cohort, with a specific focus on patients receiving conventional therapy, thereby offering clearer insight into histological outcomes in this understudied population. This design was necessary to isolate the effect of conventional therapy but limits our findings' generalizability to patients on advanced treatments.



Measure of remission	Concordance with other measures of remission		
	Clinical	Endoscopic	Histological
Clinical (n=34)	100.0% (n=34)	35.3% (n=12)	47.1% (n=16)
Endoscopic (n=36)	33.3% (n=12)	100.0% (n=36)	36.1% (n=13)
Histological (n=28)	57.1% (n=16)	46.4% (n=13)	100.0% (n=28)

Fig. 2 Concordance between clinical, endoscopic, and histological measures of remission in patients with ulcerative colitis

Table 2 Risks of clinical outcomes in patients with ulcerative colitis over a median of 5 years of follow-up

	Corticosteroid requirement, *n* (%)	Biologics requirement, *n* (%)	Hospitalization for ASUC, *n* (%)	Colectomy, *n* (%)	Composite outcome of disease progression, *n* (%)
Overall (*n* = 183)	69 (37.7%)	42 (23.0%)	49 (26.8%)	9 (4.9%)	88 (48.1%)
Endoscopic					
Remission (*n* = 36)	9 (25.0%)	9 (25.0%)	5 (13.9%)	1 (2.8%)	14 (38.9%)
Active disease (*n* = 147)	60 (40.8%)	33 (22.4%)	44 (29.9%)	8 (5.4%)	74 (50.3%)
Histological					
Remission (*n* = 28)	4 (14.3%)	4 (14.3%)	3 (10.7%)	1 (3.6%)	8 (28.6%)
Active disease (*n* = 155)	65 (41.9%)	38 (24.5%)	46 (29.7%)	8 (5.2%)	80 (51.6%)

ASUC acute severe ulcerative colitis

Table 3 Comparison of corticosteroid-free, biologics-free, hospitalization-free, and disease flare–free survival by endoscopic and histological activity status in patients with ulcerative colitis

Clinical Outcome	Endoscopic remission	Endoscopic activity	*P*	Histological remission	Histological activity	*P*
Corticosteroid-free, months	59.3 (39.9–103.5.9.5)	53.9 (31.1–94.0)	0.758	71.6 (56.8–112.1.8.1)	46.4 (30.4–89.5)	0.007*
Biologics-free, months	53.0 (37.5–103.5.5.5)	47.1 (30.4–87.7)	0.515	81.5 (52.6–118.4.6.4)	45.0 (30.1–85.6)	0.003*
Hospitalization-free, months	65.9 (41.7–111.1.7.1)	47.5 (29.6–88.5)	0.167	74.0 (53.0–113.6.0.6)	46.5 (28.1–88.0)	0.008*
Disease flare–free, months	51.1 (33.9–93.7)	49.0 (30.3–88.0)	1.000	70.0 (52.6–112.1.6.1)	45.0 (25.7–76.8)	0.009*

Values were presented as median and interquartile range. *P*-values were adjusted using the Bonferroni correction

*The significance threshold was set at $P < 0.025$

Our study revealed a fair correlation between histological and endoscopic remissions, suggesting that histological remission should be distinguished from endoscopic remission. Notably, histological activity often persists in patients with endoscopic remission, while some patients achieving histological remission may still exhibit endoscopic activity. This discrepancy can be partially explained by the heterogeneous distribution of inflammatory cells in the lamina propria across different biopsy sites [16, 26]. Such spatial heterogeneity can lead to grading variability due to inter-observer variation and inherent limitations in biopsy sampling [13]. Additional contributors to histo-endoscopic discordance include patchy microscopic inflammation, suboptimal bowel preparation, and variability in biopsy timing relative to disease activity fluctuations [27, 28]. The absence of standardized guidelines for optimal biopsy timing remains a significant methodological challenge. The complexity and time requirements of histological severity grading present challenges in clinical practice. With the rapid advancement of artificial intelligence (AI), the emergence of standardized and validated automated histological AI scoring systems has provided pathologists with an effective tool for assessing the severity of pathological disease activity [29]. This innovation has the potential to eliminate the barriers that have hindered the widespread use of histological scoring in clinical practice. Currently there are no standardized procedures for histological assessment in clinical practice. Over the past years, numerous attempts have been made to build reliable and reproducible indices and scores to evaluate histological activity, with the three most used scores being the Geboes Score, Robarts Histopathology Index, and Nancy Index [8]. In this study, we used the Nancy index, a well-established and validated histological scoring system that emphasizes the assessment of eosinophils and neutrophils in lamina propria and epithelium, and is recommended by the European Crohn's and Colitis Organization (ECCO) for observational research [30–32]. The inconsistencies observed among clinical symptoms, endoscopic findings, and histological assessments underscore the need for a comprehensive evaluation of disease activity in patients with UC. Symptoms consistent with irritable bowel syndrome, consequences of longstanding colonic fibrosis, and changes to the gut microbiota due to persistent bowel inflammation may all contribute significantly to the clinical presentation of the disease [33–35].

Modern UC management prioritizes achieving treatment targets—particularly endoscopic and histological remission—over selecting specific therapies. Advanced agents are valuable tools for this purpose, not ends in themselves. Our study demonstrates that among patients maintained on conventional first-line treatment for mild to moderate disease, histological remission, rather than endoscopic remission, was associated with improved clinical outcomes. These benefits included a reduced need for corticosteroid, decreased escalation to biologics, and lower rates of hospitalization and disease progression, all while enabling patients to remain on their original treatment regimen. The majority of patients had established UC rather than being newly diagnosed in this study. It suggests that pursuing histological healing remains a valuable treatment goal even in patients with longer-standing disease, potentially altering the

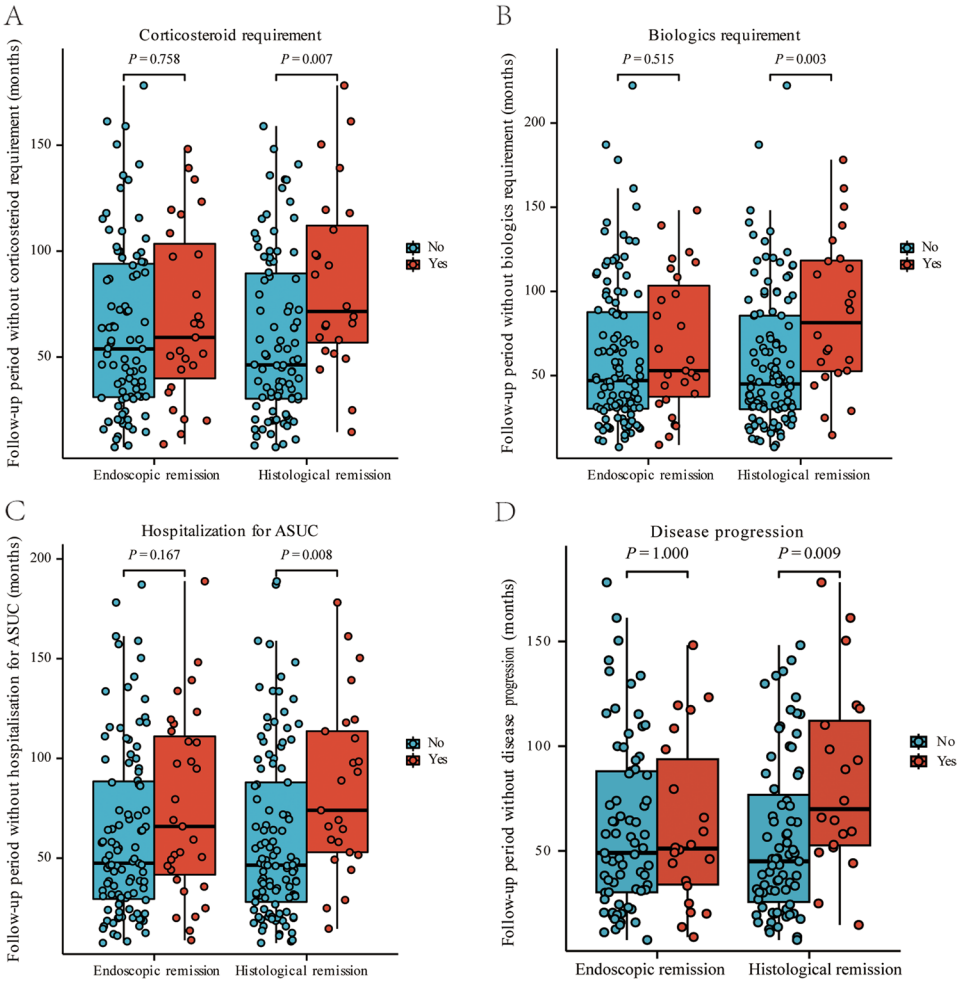


Fig. 3 The comparison follow-up duration without the need for (**A**) corticosteroid therapy, (**B**) biologics requirement, (**C**) hospitalization for ASUC, and (**D**) disease progression in patients with and without endoscopic and histological remission. ASUC, acute severe ulcerative colitis. *P*-values were adjusted using the Bonferroni correction

long-term disease course and reducing the cumulative burden of complications. However, we acknowledge that patterns and predictors of achieving remission might differ between newly diagnosed and established diseases. Our findings extended the established long-term benefits of histological remission to patients receiving conventional therapies, not only those on advanced regimens. Given the lack of a clear "window of opportunity" for therapy escalation in UC, patients who achieved histological remission through standard treatments can maintain their current regimen with less concern regarding disease progression [23].

The International Organization for the Study of Inflammatory Bowel Disease (IOIBD), in their latest consensus, has introduced the concept of disease clearance, defining it as the simultaneous achievement of clinical, endoscopic, and histological remissions [36]. In our study, the patients were already receiving conventional therapy at the time of the baseline histological assessment. Therefore, the remission rates we report (clinical 18.6%, endoscopic 19.7%, histological 15.3%) are lower than *de novo* induction rates in contemporary UC cohorts receiving conventional therapy. However, our results showed that achieving histological remission, even at a single time point, carries significant prognostic value for long-term outcomes, irrespective of the duration of prior treatment. Within the framework of modern treat-to-target strategies, these findings support a management approach in which treatment intensity is adjusted according to histological response: patients who attain histological remission with conventional therapy may maintain this regimen, whereas those who do not should be escalated to biologic agents to improve their chances of reaching this treatment target. Furthermore, our results underscore the difficulty of attaining complete remission with conventional therapies alone and indicate that more advanced treatment options are often necessary to achieve endoscopic and histological

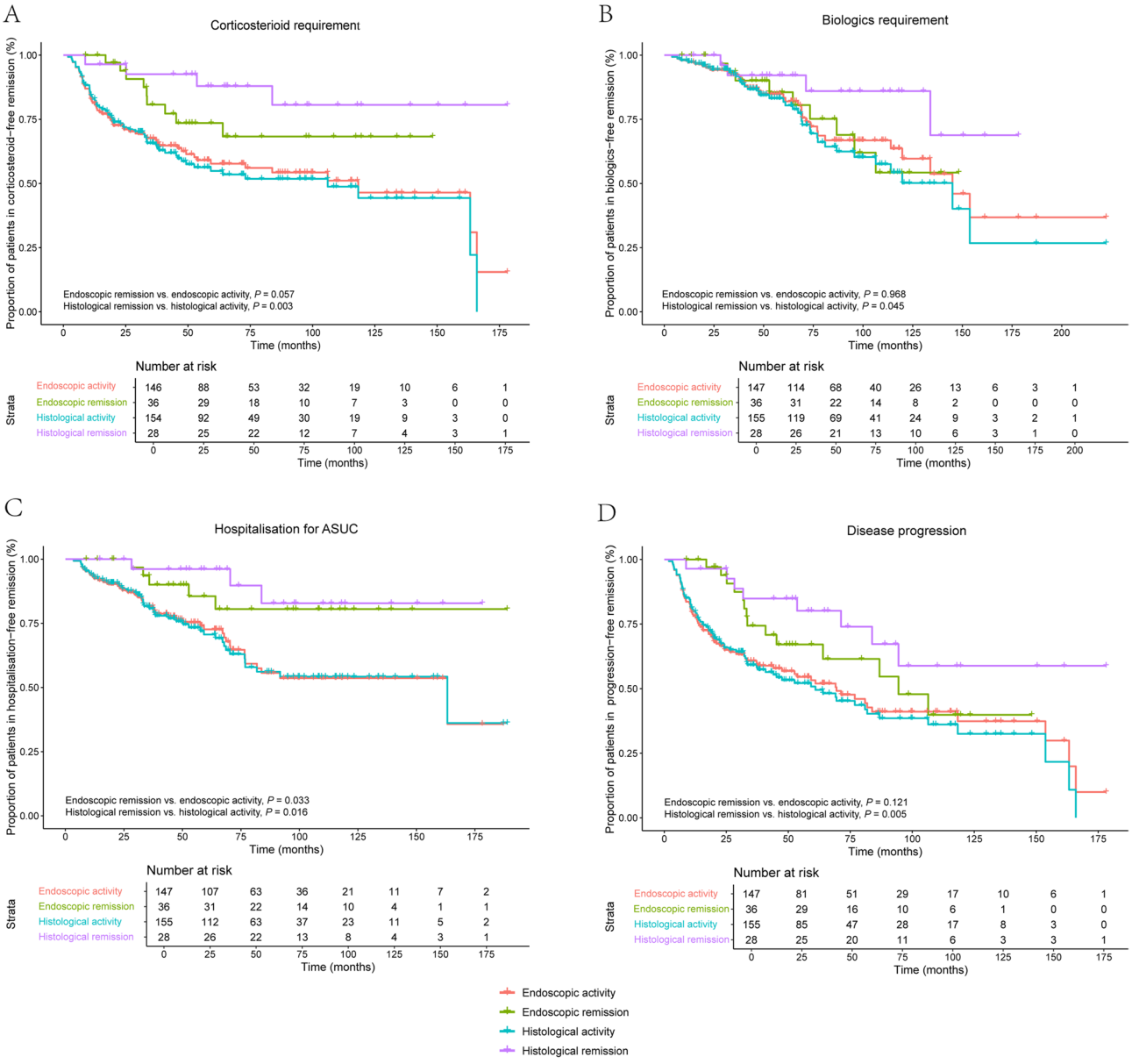


Fig. 4 Kaplan–Meier analyses of endoscopic and histological remission on clinical outcomes in patients with ulcerative colitis. (**A**) Corticosteroid requirement; (**B**) Biologics requirement; (**C**) Hospitalization for ASUC; (**D**) Disease progression. ASUC, acute severe ulcerative colitis

remission, or even disease clearance [37–39]. Nevertheless, the cost-effectiveness of advanced therapies, along with the need for repeated biopsies, and the potential for adverse effects, requires careful consideration by clinical practitioners.

This study has several limitations. As a retrospective cohort study rather than a randomized controlled trial, this analysis may be subject to selection bias in the inclusion of patients with UC. As the research was conducted at a regional IBD center and exclusively included Chinese patients from a single tertiary hospital, the generalizability of our findings to other populations may be inherently limited. The retrospective design of the study and the high cost of repeated biopsies also restricted our ability to reassess histological activity during follow-up and some missing data in other covariates were inevitable. However, given the very low rate of missing data (< 2%), it is unlikely to alter the direction or significance of our primary conclusions. In addition, all histopathological evaluations were conducted by a single, blinded senior pathologist. While this ensured consistency, it precluded assessment of inter-rater reliability and may have led to non-differential misclassification, likely biasing effect estimates toward the null rather than increasing false-positive rates. The absence of formal reliability assessment, such as through second-pathologist review

Table 4 Cox regression multivariate analyses on clinical outcomes in patients with ulcerative colitis

	Corticosteroid requirement		Biologics requirement		Hospitalization for ASUC		Disease flare	
	Univariate analysis HR (95% CI), *P*	**Multivariate analysis HR (95% CI), *P***	**Univariate analysis HR (95% CI), *P***	**Multivariate analysis HR (95% CI), *P***	**Univariate analysis HR (95% CI), *P***	**Multivariate analysis HR (95% CI), *P***	**Univariate analysis HR (95% CI), *P***	**Multivariate analysis HR (95% CI), *P***
Sex, female	1.224 (0.755–1.986), 0.413		0.890 (0.473–1.673), 0.717		1.021 (0.576–1.808), 0.944		1.199 (0.780–1.842), 0.408	
Age	0.991 (0.973–1.009), 0.330		0.996 (0.972–1.021), 0.749		0.996 (0.974–1.018), 0.701		0.997 (0.981–1.014), 0.738	
Disease duration	1.000 (0.996–1.005), 0.893		1.001 (0.996–1.007), 0.630		1.001 (0.995–1.006), 0.800		1.001 (0.998–1.005), 0.465	
Disease extent, *n* (%)								
E1	Reference		Reference		Reference		Reference	
E2	1.570 (0.650–3.794), 0.316		0.776 (0.321–1.877), 0.574		1.149 (0.461–2.862), 0.765		1.176 (0.582–2.378), 0.651	
E3	1.938 (0.811–4.633), 0.137		0.897 (0.372–2.168), 0.810		1.303 (0.528–3.217), 0.565		1.398 (0.699–2.798), 0.344	
5-ASA	0.596 (0.330–1.075), 0.085		**0.430 (0.215–0.860), 0.017***	**0.402 (0.201–0.805), 0.010***	0.771 (0.361–1.650), 0.503		0.542 (0.321–0.914), 0.022	0.526 (0.311–0.889), 0.016
Endoscopic remission	0.506 (0.250–1.021), 0.057	0.638 (0.314–1.298), 0.215	0.985 (0.469–2.067), 0.968		**0.364 (0.144–0.920), 0.033***	0.427 (0.168–1.084), 0.073	0.635 (0.358–1.128), 0.121	
Histological remission	**0.219 (0.079–0.605), 0.003***	**0.242 (0.087–0.675), 0.007***	**0.346 (0.123–0.975), 0.045***	**0.323 (0.114–0.914), 0.033***	**0.237 (0.074–0.765), 0.016***	**0.270 (0.083–0.875), 0.029***	**0.347 (0.167–0.722), 0.005***	**0.340 (0.164–0.708), 0.004***

Variables entered in the multivariable models before backward selection was performed included those with $P < 0.1$

5-ASA 5-aminosalicylic acid

**A P*-value <0.05 was regarded as significant

of a sample of slides, constitutes a methodological limitation. Variations in treatment decisions, influenced by physician preferences, patient-specific factors and institutional protocols, represent another important source of heterogeneity in observed outcomes. Another limitation pertains to the dichotomization of endoscopic and histological indices into remission or active disease, as the cut-off values for defining remission have not been robustly validated and vary across studies and trials. The statistical precision of our hazard ratio estimates, as reflected by the wide confidence intervals for some outcomes (e.g., biologics requirement), is limited by the sample size and the relatively low number of events for these endpoints. Despite these limitations, the biological rationale that histological healing predicts better long-term outcomes is likely to be universal. Our findings contribute to the growing body of evidence supporting this concept, specifically within the context of conventional therapy. However, the absolute rates of remission and outcomes we observed should be extrapolated with caution to populations where access to advanced therapies is more prevalent or where disease phenotypes and management strategies differ. Future prospective studies with extended follow-up, larger samples, and multiple pathologists are warranted to validate these results.

In conclusion, our study has demonstrated that concordance among clinical, endoscopic, and histological assessments of remission was fair. Notably, histological remission emerged as a reliable predictor of favorable long-term outcomes with conventional treatment, including a reduced need for corticosteroid and biological agents, as well as a lower frequency of hospitalizations for ASUC.

Abbreviations

5-ASA	5-aminosalicylic acid
AI	Artificial intelligence
ASUC	Acute severe ulcerative colitis
CI	Confidence interval
ECCO	European Crohn's and Colitis Organization
IBD	Inflammatory bowel disease
IOIBD	International Organization for the Study of Inflammatory Bowel Disease
IQR	Interquartile range
MES	Mayo Endoscopic Subscore
NHI	Nancy's histological index
SCCAI	Simple Clinical Colitis Activity Index
UC	Ulcerative colitis

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
T.L., Z.Z. and X.Z. conceived and designed this study. T.T., Y.Q., M.L., M.C., and J.L. collected and analyzed the data. T.T. and X.Z. wrote the original manuscript. T.L. and Z.Z. revised the manuscript. All authors have reviewed and approved the final version of the manuscript.

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Data availability
The data underlying this study will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The authors confirm that all procedures involving human participants were performed in accordance with the ethical standards of the relevant institutional and national research committees, as well as with the 1964 Helsinki Declaration and its later amendments (2008). This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (Number of approval: [2024]392), and a waiver of informed consent was granted for this retrospective study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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