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Clinical value of using double balloon enteroscopy combined with endoscopic ultrasound to evaluate Crohn's disease of the small bowel: a retrospective study

Liu Zhongcheng[1,2,3†], Tang Chao[4†] and Guo Qin[1,2,3,5*]

Abstract

Background Diagnosing and assessing Crohn's disease, which involves only the small bowel, is challenging. This study investigated the clinical value of combining double balloon enteroscopy with endoscopic ultrasound to evaluate this disease.

Methods This single-center retrospective study included patients with Crohn's disease of the small intestine between October 2022 and October 2023. Relevant clinical data were collected. Double balloon enteroscopy and ultrasound endoscopy of the small intestine were performed.

Results Among the 50 patients, 10, 34, and 6 had mild, moderate, and severe active phase Crohn's disease, respectively. Ten patients scored between 1 and 4 points on the modified partial simple endoscopic score for Crohn's disease (mpSES-CD), 24 scored between 5 and 8 points, and 16 scored more than 8 points. Forty patients had thickening of the intestinal wall (total thickness, 4.14 ± 0.98 mm). Submucosal and intrinsic muscle layer thickening was primarily observed. Ten patients were in remission, and all mucosal–submucosal and submucosal–intrinsic muscle boundaries could be distinguished. Thirty-four patients had moderate-phase Crohn's disease, of whom 26 (76.47%) had distinguishable mucosal–submucosal boundaries, and 28 (82.35%) had distinguishable submucosal–intrinsic muscular boundaries. Of the six patients with severe phase Crohn's disease, four (66.67%) had distinguishable mucosal submucosal boundaries, and two (33.33%) had distinguishable submucosal–intrinsic muscular boundaries.

Conclusions The mpSES-CD and Harvey–Bradshaw Index correlate well. Endoscopic ultrasound can determine disease severity by measuring each bowel wall layer's thickness and observing the distinction between the layers. This combination of techniques can compensate for the shortcomings in diagnosing the depth of the vertical infiltration of Crohn's disease using white-light endoscopy.

Keywords Crohn's disease, Double balloon enteroscopy, Small intestine, Endoscopic ultrasound, Modified partial simple endoscopic score for Crohn's disease, Harvey–Bradshaw index

†Liu Zhongcheng and Tang Chao contributed equally to this work.

*Correspondence:
Guo Qin
guoq83@mail.sysu.edu.cn

Full list of author information is available at the end of the article

Background

Crohn's disease (CD) is an idiopathic inflammatory condition of the gastrointestinal tract with an unknown etiology and nonspecific clinical manifestations; the disease course is prolonged and recurrent [1]. CD must be diagnosed in conjunction with endoscopic, radiological, and histopathological results. However, diagnosing and assessing CD that involves only the small bowel is challenging. Various methodologies have been introduced to evaluate the activity of small-bowel CD. CTE and MRE provide valuable information about the severity and the extent of disease as well as the related adverse events. Intestinal ultrasound is widely promoted due to its absence of ionizing radiation, independence from bowel preparation, and higher cost-effectiveness. However, all these imaging techniques have many limitations: CTE exposes patients to ionizing radiations,, whereas MRE is restricted by a long examination time and methodical complexity. The limitations of intestinal ultrasound include high operator dependency, challenges in accurate detection in obese patients, and susceptibility to interference from intraluminal gas. White light endoscopy of structural changes in the mucosa can help determine the degree of inflammation. Still, the information it provides is limited to the basic histomorphology of the mucosal surface. This makes accurate determination of the severity of structural damage in the bowel wall and its associated clinical outcomes complex [2].

Endoscopic ultrasound combines the features of endoscopy and ultrasonography to determine the depth of inflammatory infiltration in CD and facilitates the evaluation of disease severity via endoscope-guided ultrasound of echogenic changes in the bowel wall [3]. In this study, we retrospectively analyzed the findings of double balloon enteroscopy with endoscopic ultrasound in patients with small bowel CD to investigate their correlation with disease severity.

Methods

General characteristics

Patients with CD who visited our hospital between October 2022 and October 2023 were eligible for evaluation.

Inclusion and exclusion criteria

We included patients if they (1) met the diagnostic criteria for CD [4], (2) had lesions involving only the small bowel, and (3) underwent both double balloon enteroscopy and endoscopic ultrasound. We excluded patients with (1) concomitant intestinal tumors and (2) other comorbid immunological diseases.

Examination methods

We observed the lesion site using enteroscopy, performed endoscopic scoring, and selected the site with the most severe inflammation for endoscopic ultrasound observation. The same highly trained physician performed the double balloon enteroscopy and endoscopic ultrasound procedures. The operating physician has extensive experience in performing enteroscopy (with at least 100 procedures) and endoscopic ultrasound (with at least 200 procedures). All patients underwent a double balloon enteroscopy (DBE; EN-450T, Fujifilm, Japan) and small bowel EUS (Endoscopic Ultrasound System IM-02P-202501, InnerMedical Co., Ltd, Shenzhen, China).

Observational indicators

We assessed the clinical activity of the disease using the Harvey–Bradshaw Index [5] and performed endoscopic scoring using the modified partial simple endoscopic score for CD (mpSES-CD) [6]. The mpSES-CD scores were classified as 0, no inflammatory activity; 1 to 4, mild inflammatory activity; 5 to 8, moderate inflammatory activity; or >8, severe inflammatory activity. Using endoscopic ultrasound, we measured the full thickness of the intestinal wall. The thinnest and thickest parts of the intestinal wall at the inflammation site were measured after injecting an appropriate amount of water, and the average value was calculated. We measured the thickness of each layer of the intestinal wall, including the mucosa, submucosa, and muscularis propria, and evaluated the distinction of the boundaries between the layers.

Statistical analysis

We performed statistical analysis using SPSS Statistics for Windows version 27.0 software (IBM Corp., Armonk, NY, USA). Image-Pro Plus 6.0 software (Informer Technologies, Inc., www.informer.com) was used to analyze and process endoscopic ultrasound images. Measurement data that conformed to a normal distribution are expressed as means ± the standard deviations and were compared using the *t*-test for independent samples. Absolute count data are expressed as frequencies, and the chi-square test was used to compare groups. Pairwise comparisons between groups were performed via chi-square partitioning. Spearman's rank correlation coefficients were used for correlation analysis. All *P*-values < 0.05 were deemed to indicate statistical significance.

Ethical considerations

The Ethics Committee of the Sixth Affiliated Hospital, Sun Yat-Sen University, approved this study (ethics number: 2023ZSLYEC-264). Before the formal interviews, each participant received a clear explanation of the study's objectives and provided informed consent.

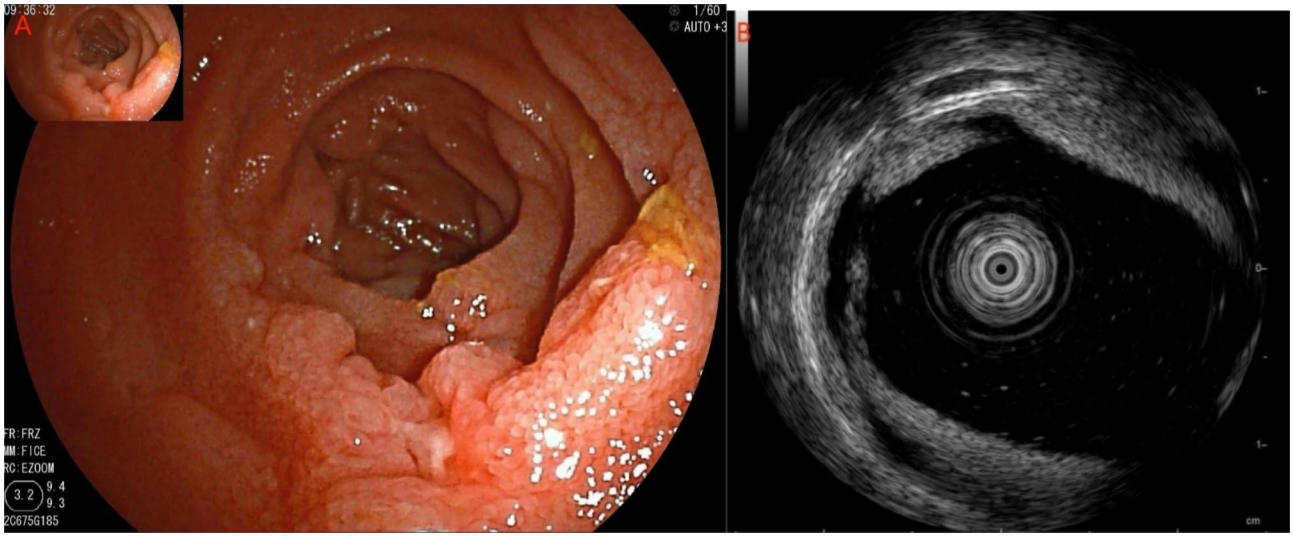

Fig. 1 **A**: Endoscopic findings showing a thin white coated ulcer with a diameter of about 0.6 cm, and nodular changes in the surrounding mucosa, indicating mild disease activity. **B**: Small intestinal endoscopic ultrasound showing clear differentiation of the layers of the intestinal wall and mild thickening of the intestinal wall

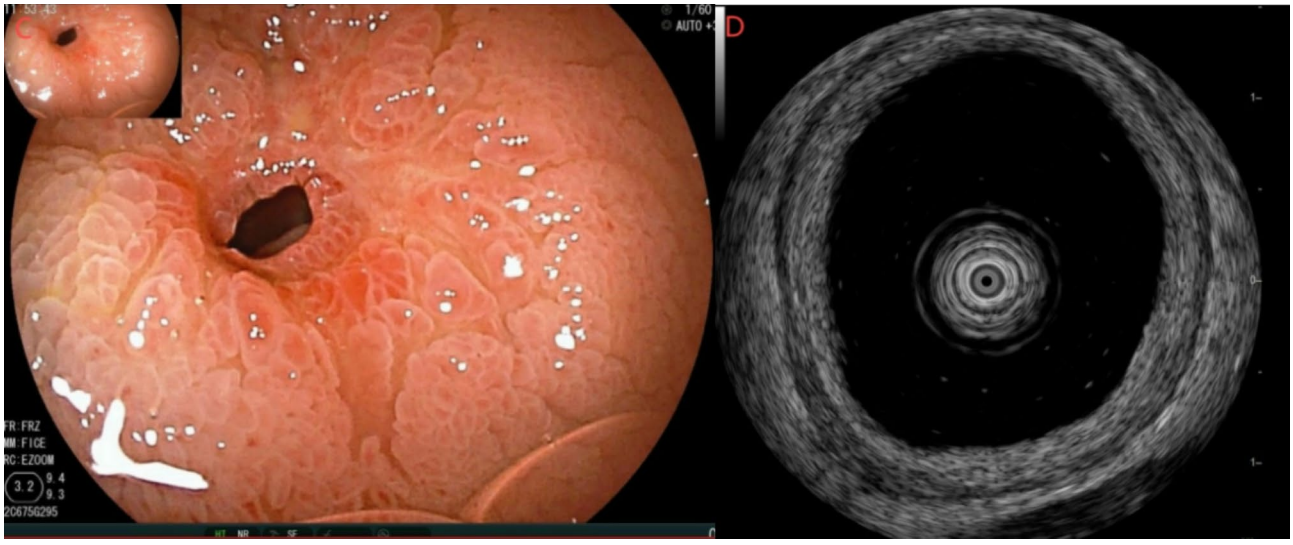

Fig. 1 **C**: Endoscopic findings showing concentric stenosis, with thin white coated ulcers around the stenosis, indicating moderate disease activity. **D**: Small intestinal endoscopic ultrasound showing clear differentiation of the layers of the intestinal wall and moderate thickening of the intestinal wall

Results

Patient characteristics

Fifty patients with CD participated in our study. Of the participants, 44 were male, and six were female; their mean age was 33.50 ± 12.00 years. We stratified the patients as having mildly active disease (10 patients, 20%, such as in Figure 1A-B), moderately active disease (34 patients, 68%, such as in Figure 1C-D), or severe disease (6 patients, 12%, such as in Figure 1E-F) using the Harvey–Bradshaw Index: 10 patients (20%) had mpSES-CD scores of 1 to 4, 24 (48%) had scores of 5 to 8, and 16 (32%) had scores of > 8.

Correlation between mpSES-CD scores and disease activity

Spearman's rank correlation analysis revealed a significant positive correlation between mpSES-CD scores and disease activity ($P < 0.05$; Table 1).

Correlation between serological markers and disease activity

There is no statistically significant difference in hemoglobin, Leukocytes, Erythrocyte sedimentation rate, and Albumin with respect to disease activity ($P > 0.05$; Table 2), whereas C-reactive protein shows a statistically significant difference in relation to disease activity ($P < 0.05$; Table 2).

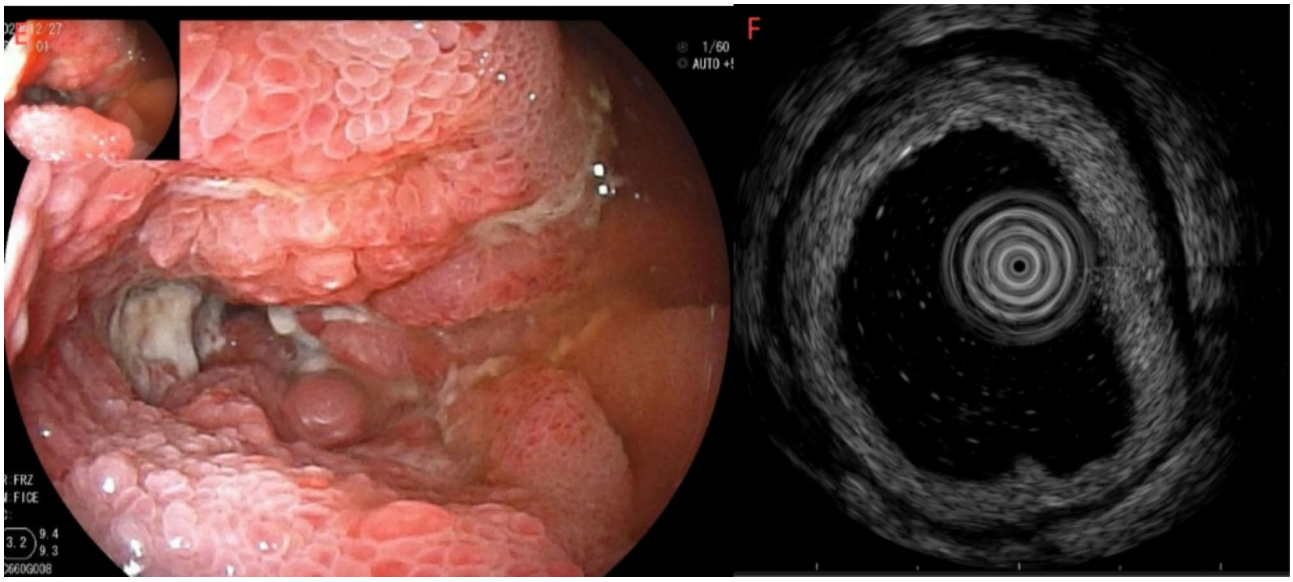

Fig. 1 **E**: Endoscopic findings showing a stenosis of approximately 0.3 cm in diameter, with irregular ulcers around the stenosis. The ulcer surface is white coated, indicating severe disease activity. **F**: Small intestinal endoscopic ultrasound showing poor intestinal layer differentiation and significant thickening of the intestinal wall

Table 1 Correlation between endoscopic scores and disease activity in patients with Crohn's disease

Endoscopic score	Disease activity			rs	*P*-value
	Mild	Moderate	Severe		
mpSES-CD	1.90 ± 0.88	5.33 ± 0.70	7.63 ± 0.89	0.834	0.000*

mpSES-CD, modified partial simple endoscopic score for Crohn's Disease

*$P < 0.001$

Characteristics of the endoscopic ultrasound findings

Of the patients with CD, 40 (80%) had thickening of the bowel wall, with a mean bowel wall thickness of 4.14 ± 0.98 mm, mean mucosal thickness of 1.45 ± 0.38 mm, mean submucosal thickness of 1.05 ± 0.45 mm, and muscularis propria thickness of 1.17 ± 0.58 mm. Thickening of the submucosa and muscularis propria were predominant.

Determining disease activity from thickness of the bowel wall on endoscopic ultrasound

In patients with CD, there was a notable trend of increased bowel wall thickness, particularly in the submucosa and muscularis propria, as disease activity escalated. The difference between groups was statistically significant ($P < 0.05$). Spearman's rank correlation revealed a significant positive correlation between bowel wall thickness on endoscopic ultrasound, excluding the mucosa, and disease activity ($P < 0.05$). The difference in mucosal thickness in the mildly active and moderately active disease groups was not statistically significant ($P > 0.05$). Mucosal thickness was significantly greater in the severe disease group than in the mildly active and moderately active disease groups ($P < 0.05$; Table 3).

Distinction between the layers of the bowel wall in patients with CD and different degrees of disease activity

All 10 patients in remission had distinct mucosa–submucosa and submucosa–muscularis propria boundaries. The frequency of a distinct submucosa–muscularis propria boundary decreased progressively with increasing disease activity. The frequency of a distinct mucosa–submucosa boundary did not differ significantly in patients with mild and moderate disease activity. Still, it was

Table 2 Correlation between serological markers and disease activity in patients with Crohn's disease

	Disease activity			rs	*P*-value
	Mild	Moderate	Severe		
Hb (g/L)	116.90 ± 16.76	115.62 ± 15.02	109.17 ± 8.84	220.463	0.568
WBC (10^9/L)	5.74 ± 1.61	6.49 ± 1.52	6.55 ± 1.18	2.275	0.369
ESR (mm/h)	12.90 ± 2.88	15.03 ± 5.35	16.50 ± 4.76	24.114	0.327
Alb (mg/L)	36.30 ± 3.89	34.21 ± 3.64	33.17 ± 2.14	12.691	0.174
CRP (mg/L)	8.67 ± 2.38	12.26 ± 5.59	15.23 ± 2.05	23.505	0.031*

Hb, Hemoglobin; WBC, Leukocytes; ESR, Erythrocyte sedimentation rate; Alb, Albumin; CRP, C-reactive protein

*$P < 0.001$

Table 3 Correlation of bowel wall thickness by endoscopic ultrasound with Crohn's disease activity

Bowel wall thickness parameters	Disease activity			rs	*P*-value	95% CI for OR	
	Mild	Moderate	Severe			Lower	Upper
Full bowel wall thickness (mm)	2.55 ± 0.45	4.36 ± 0.29	5.60 ± 0.77	0.162	0.000***	3.87	4.42
Mucosal thickness (mm)	1.39 ± 0.42	1.41 ± 0.33	1.79 ± 0.47	0.135	0.070	1.35	1.56
Submucosal thickness (mm)	0.51 ± 0.10	1.11 ± 0.36	1.65 ± 0.36	0.109	0.000***	0.92	1.18
Muscularis propria thickness (mm)	0.45 ± 0.14	1.23 ± 0.41	2.06 ± 0.37	0.136	0.000***	1.01	1.33

OR, odds ratio

*$P < 0.001$

Table 4 Comparing bowel wall distinction in patients with Crohn's disease with varying disease activity

Endoscopic ultrasound presentation	Disease activity			χ2	*P*-value
	Mild, $n = 10$	Moderate, $n = 34$	Severe, $n = 6$		
Boundary between mucosa and submucosa				3.431	0.180
Distinct (cases)	10 (100%)	26 (76.47%)	4 (66.67%)		
Indistinct (cases)	0	8 (23.53%)	2 (33.33%)		
Boundary between submucosa and muscularis propria				10.784	0.005*
Distinct (cases)	10 (100%)	28 (82.35%)	2 (33.33%)		
Indistinct (cases)	0	6 (17.65%)	4 (66.67%)		

*P-value < 0.01

significantly lower in patients with severe disease activity (Table 4).

Discussion

In clinical practice, diagnosing small bowel CD presents greater challenges than diagnosing colonic CD. Diagnosis relies primarily on clinical features and findings from imaging, laboratory tests, endoscopic examination, and histopathological analysis. Moreover, confirming small bowel CD necessitates the exclusion of other diseases. Enteroscopic manifestations of CD primarily include segmental lesion distribution, mucosal changes resembling paving stones during active phases, aphthous or longitudinal ulcers, bowel wall thickening and narrowing, and polypoid hyperplasia or scar-like alterations during remission. This study used a simple CD endoscopic scoring system to assess disease activity, revealing a significant correlation between derived scores and clinical disease severity. This underscores the system's effectiveness in determining the condition of patients with small bowel CD.

Endoscopic ultrasound is reportedly helpful for the diagnosis, activity assessment, and prognosis determination of CD [7]. Previous investigations have explored the diagnostic value of transabdominal ultrasound in CD, suggesting that bowel wall thickening (> 4 mm), indistinct bowel wall layers, focal vascularity of the intestinal wall, and internal fistulas and strictures can indicate disease activity [8]. However, transabdominal ultrasound accuracy is affected by intestinal gas and subcutaneous fat thickness, resulting in inferior echo clarity compared to endoscopic ultrasound. Close-up observation with an endoscopic ultrasound probe enables clear visualization of the bowel wall's layered structure. In addition, the staging of CD and the degree of inflammation can be predicted based on bowel wall thickening and infiltration depth of inflammatory cells. In this study, most CD lesions exhibited thickening of the bowel wall, primarily of the submucosa and muscularis propria, presenting as discontinuous and asymmetric segmental thickening. In contrast, thickening of the mucosa was less pronounced. This is consistent with CD's deep transmural inflammatory lesions and their segmental asymmetric distribution. Therefore, endoscopic ultrasound offers advantages over white light endoscopy for assessing inflammation depth.

Most CD lesions are located in the submucosa and muscularis propria of the bowel wall, are heavily infiltrated with cells associated with chronic transmural inflammation, and exhibit a thickened and edematous submucosa, focal abnormalities of the structural crypt and formation of non-caseating granulomas [9]. Although the depth of CD invasion can be indirectly assessed endoscopically and histopathologically, structural changes in the intestinal wall due to swelling, exudation, abscesses, or fibrosis are challenging to identify. In this study, patients with severe disease exhibited the highest mean thickness of the bowel wall, followed by those with moderately active and mildly active disease. This pattern was evident when comparing the thicknesses of the submucosa and muscularis propria. The observed correlation indicates that all thickness parameters of the bowel wall except the mucosa are significantly positively correlated with the degree of CD activity.

Consequently, determining bowel wall thickness using endoscopic ultrasound is valuable for evaluating CD activity levels. We did not observe a significant difference

in the thickness of the mucosa between patients with mild and moderate disease activity; however, we did observe a difference in patients with severe disease activity. This may be because inflammation associated with CD primarily involves the deeper layers of the bowel wall and thus, except in severe cases, has a lesser effect on the mucosa.

The distinction between the submucosa and muscularis propria decreased progressively with increasing disease activity. Although the differentiation between the mucosa and submucosa did not differ significantly between patients with mild and moderate disease activity, it significantly decreased in patients with severe disease activity. This may stem from CD's manifestation as an intramural inflammation, primarily affecting the deeper layers of the bowel wall, while inflammation predominantly occurs in the submucosa and below. The mucosa was affected in patients with severe disease, but this observation may be related to the small number of patients. Thus, future validation with larger sample sizes may be warranted.

For patients with moderate to severe Crohn's disease, endoscopic ultrasound can help identify those with deep inflammation, penetrating lesions, or high-risk complications, as these patients may be more suitable for early biological therapy. By accurately assessing lesion characteristics through endoscopic ultrasound, the overuse of biological treatments in patients with mild Crohn's disease can be avoided, thereby optimizing the allocation of medical resources. Additionally, endoscopic ultrasound can detect fibrotic strictures or penetrating lesions in the intestinal wall, which aids in determining whether surgical intervention or optimization of medical treatment is necessary.

CRP is one of the most widely used noninvasive biomarkers for monitoring CD activity, the diagnostic accuracy of this biomarker is inconsistent [10]. In our study, C-reactive protein shows a statistically significant difference in relation to disease activity.

This study has some limitations, such as the lack of follow-up with patients, which currently prevents the assessment of their prognosis. Additionally, it is a single-center study with a relatively small sample size. In the future, prospective multicenter studies could be conducted to obtain more substantial evidence to confirm the advantages of combining endoscopic ultrasound with double-balloon enteroscopy.

Conclusions

In summary, the diagnosis and disease evaluation of small bowel CD remains a focus of clinical work, and enteroscopy plays a pivotal role. The mpSES-CD correlates well with the degree of disease activity, serving as a valuable tool for evaluating clinical disease. Endoscopic ultrasound offers a means to determine disease severity by accurately measuring the thickness of the bowel wall of each layer and the distinction between the layers to be observed. Thus, it addresses how endoscopic ultrasound can compensate for the shortcomings of white-light endoscopy in diagnosing the vertical infiltration depth of CD. The combination of enteroscopy and endoscopic ultrasound can enhance diagnostic precision and provide improved clinical guidance for assessing CD severity and the development of treatment plans.

Abbreviations

Alb	Albumin
CD	Crohn's disease
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
Hb	Hemoglobin
mpSES-CD	Modified partial simple endoscopic score for Crohn's disease
WBC	Leukocytes

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Author contributions

Data curation: T.C. Writing–original draft: L.Z. Writing–review & editing: L.Z. and G.Q. Funding acquisition: G.Q. All authors approved the final version of the manuscript.

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Data availability

All relevant data are within the paper.

Declarations

Ethics approval and consent to participate

All patient samples in this study were collected with informed consent by the Declaration of Helsinki. The Ethics Committee of the Sixth Affiliated Hospital, Sun Yat-Sen University, approved this study (ethics number: 2023ZSLYEC-264).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Small Bowel Endoscopy, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China
[2]Biomedical Innovation Center, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
[3]Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
[4]Department of Gastroenterology, Fourth Hospital of Changsha, Changsha, China
[5]Department of Gastroenterology, the Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

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