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How to assess endoscopic disease activity in ulcerative colitis in 2022

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Abstract

Endoscopic remission currently represents an important therapeutic goal to reach in the management of patients with ulcerative colitis (UC). The diagnostic and prognostic role of endoscopy, which remains the gold standard for the assessment of disease activity, has been widely reported. Despite being unvalidated and suboptimal at measuring remission, the most widely used scoring system is the Mayo endoscopic subscore (MES). The UC Endoscopic Index of Severity and the UC Colonoscopic Index of Severity represent recent performing indices for the assessment of endoscopic disease activity in the field of white-light endoscopy. However, their use is still very limited, both in trials and clinical practice. The most recent Paddington international virtual chromoendoscopy score was the first validated index to assess vascular and mucosal features in UC using a virtual chromoendoscopy technique and showed good performance. This narrative review aims to describe these validated endoscopic scoring indices, focusing on the development methodology, and the strengths and weaknesses of each one in comparison with the MES for the assessment of UC activity.

Keywords Ulcerative colitis, MES, UCCIS, UCEIS, PICaSSO

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Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by a recurrent, relapsing-remitting course [1]. The endoscopic assessment of disease activity and extent as well as the evaluation of treatment efficacy and the description of "mucosal healing" (MH) represent pivotal steps in the management of patients with UC, in both clinical trials and daily practice [2]. Endoscopic remission (ER) represents the primary long-term treatment goal in UC, as recently remarked in the update of the Selecting Therapeutic Targets in IBD (STRIDE) program [3]. Accumulating evidence does indeed show that MH is associated with better outcomes during the disease course, prolonged phases of steroid-free remission and a decreased risk of complications, such as hospitalizations, surgery and colorectal cancer [4-6]. Histological healing (HH) may also represent a desirable target with supporting evidence even better than that for MH; however, it is of little use in practice, given the lack of standardized, validated definitions and scores [7]. Therefore, endoscopy still represent a cornerstone in the management of UC.

In recent years, several scoring systems, most of them not formally validated, have been developed to assess endoscopic disease activity. Since 1987, the most commonly used score has been the Mayo endoscopic subscore (MES); it consists of a 4-point scale from inactive (grade 0) to a severely active disease (grade 3), based on endoscopic findings, such as erythema, vascular pattern, friability, bleeding, erosions and ulcerations, evaluated in the most inflamed colonic area (Table 1) [8].

However, the MES has shown some critical issues over the years: it has not yet been formally validated; it has moderate reproducibility and small sensitivity to change; it uses the "subjective" measure of friability; it may not appropriately describe erosions/ulcerations and the broad spectrum of mucosal inflammation; and some ambiguity remains as to which score correctly defines MH, if only 0 or ≤1, also given the increasing evidence of better disease outcomes among patients with MES=0, compared to these ones with MES=1 [9,10]. A recent systematic review has reported an overall interobserver correlation of MES score ranging from acceptable to good (kappa index [k] from 0.45-0.75) [11]. However, the MES continues to be used thanks to its simplicity and ease of use, although valid alternatives are available.

In 2012, Travis *et al* developed the first validated endoscopic scoring index, the UC Endoscopic Index of Severity (UCEIS) and, 5 years later, the International Organization for the Study of

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IBD (IOIBD) recommended it to define endoscopic remission and response in clinical trials [12,13]. The contemporary UC Colonoscopic Index of Severity (UCCIS), developed by Samuel *et al*, was the first validated score to assess the state of the entire colonic mucosa in UC [14]. However, despite the availability of these 2 endoscopic indices, their use in clinical trials and daily practice is still limited. Furthermore, the most recent Paddington International virtual ChromoendoScopy ScOre (PICaSSO) was the first validated index to assess endoscopic activity in UC using a virtual chromoendoscopy (VCE) technique, showing good preliminary performance [15].

This review aims to describe each validated endoscopic scoring index currently available for the assessment of UC, focusing on their strengths and weaknesses in comparison with the MES, based on the evidence in the literature.

Methods

An electronic web search of the English literature up to December 2021 was performed using Medline and the Cochrane Library. The search strategy used a combination of Medical Subject Headings (MeSH) and keywords, as follows: "inflammatory bowel disease", "ulcerative colitis", "endoscopy", "endoscopic disease activity", "disease assessment", "validated score", "endoscopic score", "endoscopic scoring system", "UCEIS", "UCCIS", "PICaSSO", "Mayo endoscopic subscore", "Ulcerative Colitis Endoscopic Index of Severity", "Ulcerative Colitis Colonoscopic Index of Severity" and "Paddington International virtual ChromoendoScopy ScOre".

A comprehensive and objective analysis of the abstracts was performed. Authors critically screened the abstracts and identified relevant articles. Fifty-five eligible studies were finally identified and fully analyzed. Data have been grouped according to each endoscopic index (Fig. 1).

Results

UCEIS

The UCEIS was constructed and validated using a rigorous methodology in a 2-phase study. Videosigmoidoscopies from 670 patients with mild-to-moderate UC, plus 5 patients with acute severe UC (ASUC) and 5 people without UC, were examined to describe features such as vascular pattern, presence of bleeding, erosions/ulcerations, in the area with the most severe colitis [12,16]. Each descriptor was scored individually and samples were assessed in greater detail, being more broadly stratified into ascending grades of severity. The UCEIS ranged from 3 (quiescent disease, as "1" assigned to normality for each variable) to 11 (most severely-active disease) in its original form. Subsequently, levels referring to "normality" were rebased to zero and the definitive score was a scale of 9 points, from 0-8 (Table 2) [16].

Table 1 The Mayo endoscopic subscore

Findings on endoscopy	0 = normal or inactive disease
	1 = mild disease (erythema, decreased vascular pattern and mild friability)
	2 = moderate disease (marked erythema, lack of vascular pattern, friability and erosions)
	3 = severe disease (spontaneous bleeding and ulcerations)

First reports showed high significant levels of correlation between the UCEIS and overall severity evaluation (correlation coefficient of 0.94), an intra-observer k value of 0.82 for vascular pattern, 0.72 for bleeding and 0.78 for erosions/ulcerations, an inter-observer k value of 0.83, 0.56 and 0.77, respectively, for the 3 descriptors. The inter-observer reliability ratio was 0.88. The intraclass correlation coefficient was 0.83, while the responsiveness was preliminarily reported as 0.49 and 0.58, according to Guyatt's measure and Cohen's effect size, respectively [16,17].

Multiple studies evaluating the correlation between the UCEIS and biomarkers or other UC scores have been published in recent years. Irani *et al* were the first to describe a very strong correlation between endoscopy and histology, using validated indices such as the UCEIS, the Nancy Histological Index (NHI) and the Robarts Histopathology Index (RHI). Spearman correlation analysis showed a rho coefficient (r) of 0.84 (95% confidence interval [CI] 0.76-0.89; P<0.001) between the UCEIS and the NHI, and 0.86 (95%CI 0.80-0.90; P<0.001) between the UCEIS and the RHI [18].

The UCEIS correlated strongly with the NHI (r=0.723; P<0.001), moderately with a clinical score, the Simple Clinical Colitis Activity Index (SCCAI) (r=0.671; P<0.001), but weakly with C-reactive protein (CRP) (r=0.279; P<0.001) in an analysis of 201 retrospectively reviewed endoscopies by De Jong *et al*. Substantial agreement was also demonstrated between the UCEIS and the MES (k=0.713; P<0.001) [19].

Previously, Theede *et al* had found high concordance between the UCEIS and the modified Harpaz Index, an unvalidated histological score (Kendall's $\tau\beta$=0.63, P<0.001) in a cross-sectional study of 120 UC patients with either active or inactive disease. A comparison of the MES and the UCEIS

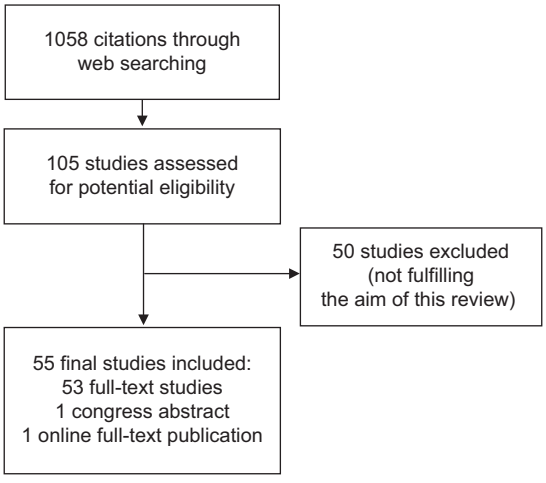

Figure 1 Flow diagram of literature review process

Table 2 The ulcerative colitis endoscopic index of severity

Descriptor	Likert scale anchor points	Definitions
Vascular pattern	Normal (0)	Normal vascular pattern with arborisation of capillaries clearly defined
	Patchy loss (1)	Patchy loss or blurring of vascular pattern
	Obliterated (2)	Complete loss of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood Or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (≤5 mm) defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa with a slighty raised edge

revealed a high degree of concordance (Kendall's τβ=0.89, P<0.001) [20].

The analysis of a cohort of 60 patients with quiescent UC by Mine *et al* showed a significant correlation between the UCEIS and fecal markers (fecal calprotectin [FC] r=0.54, P<0.001; lactoferrin r=0.56, P<0.001); the MES also showed significant though lower rates of correlation (for FC, r=0.34, P<0.01; for lactoferrin r=0.45, P<0.01) [21]. Similar results were described by Lee *et al*. FC levels from samples of 181 UC patients significantly correlated with the UCEIS (correlation coefficient r=0.430, P<0.001), significantly better than with the MES (Meng's z=-2.457, P=0.01) [22].

Significant associations between the UCEIS and the MES (r=0.704, P<0.001) and between the UCEIS and the Mayo Clinic score (r=0.762, P<0.001) were noted in a cohort of 92 consecutive patients with ASUC [23]. In a retrospective study that included 61 UC patients undergoing biological treatment, the correlation coefficient between the UCEIS and the MES was evaluated as very strong (r=0.94, P<0.001) considering both active and inactive disease [24].

In a study by Belvis Jiménez *et al*, videos from colonoscopies of 67 UC patients were analyzed and results were independently classified according to the MES, the UCEIS and the UCCIS by 3 endoscopists (A, B, C). For the UCEIS, the interclass correlation coefficient of average values was 0.92. Spearman's r was 0.87 between endoscopists A and B, 0.82 between A and C and 0.87 between B and C. The weighted k for the MES was 0.80 between endoscopists A and B, 0.52 between A and C and 0.49 between B and C. The relationship between the index of endoscopists A and B showed r=0.88, between A and C r=0.85, and between B and C r=0.80 [25].

Other studies analyzed the clinical performance of the UCEIS compared to the MES and showed a better short- and long-term prognostic role. A retrospective report by Corte *et al* suggested a strong likelihood of needing rescue therapy with cyclosporine or infliximab for patients with a UCEIS score ≥5, compared to a UCEIS score ≤4 (P=0.037), in a cohort of 89 UC patient with ASUC. The area under the receiver operating characteristic curve (AUROC) was 0.69 (95%CI 0.58-0.80), representing fair diagnostic accuracy of the UCEIS in ASUC [26].

In the scenario of ASUC, Xie *et al* also showed that the UCEIS could outperform the MES in predicting the need for colectomy in a multivariate analysis (odds ratio [OR] 3.25, 95%CI 1.77-5.97; P<0.001). The AUROC of the UCEIS was 0.85, with a sensitivity of 60.3% and a specificity of 85.5% using the cutoff value of 7. The predictive value of the MES was lower, with an AUROC of 0.65 (sensitivity 89.2%, specificity 43.6%, cutoff value 3) [23].

Ikeya *et al* found that lower UCEIS strata were significantly associated with a lower incidence of future colectomy (P<0.001) or relapse (P<0.001) in a cohort of 41 patients undergoing a colonoscopy before and after remission induction therapy with tacrolimus. They were also the first to stratify the UCEIS using the following thresholds: quiescent (score 0-1); mild (score 2-4); moderate (score 5-6); and severe (score 7-8) disease [27]. Recently, Pop *et al* prospectively followed-up 59 patients with quiescent UC and found an AUROC of 0.89 to predict relapse during the 12 months of the study using the UCEIS (P<0.001) [28].

Many studies also focused on stratification and thresholds of the UCEIS to use in practice. The analysis of Irani *et al* was performed using the same 4 strata mentioned above. It was assumed that UCEIS=1 in the remission stratum was a descriptor limited to partial obliteration of vascular pattern [18]. A UCEIS score ≥4 was proposed as the endoscopic threshold to consider treatment escalation (0.80 of sensitivity and 0.93 of specificity; AUROC of 0.93) in the above-referenced paper by De Jong *et al* [19]. Walsh *et al* used a UCEIS score ≥4 to define active UC in a study defining FC thresholds [29].

In 2017 the IOIBD performed a systematic review of the technical aspects of endoscopic scoring systems. The panel of experts arrived at a consensus using the Delphi method and chose a UCEIS score of 0 for the definition of endoscopic remission, while a decrease in UCEIS ≥2 was used to define endoscopic response in UC [13].

A recent report showed that a UCEIS ≥6 could predict patients lack of response to a biological treatment with an anti-tumor necrosis factor-α agent (AUROC 0.71; positive predictive value 100%; negative predictive value 31.7%). The same paper reported that UCEIS ≥7 showed the best performance in predicting the need for colectomy after treatment failure (AUROC 0.86; P=0.027). ER was defined as UCEIS=0 [24].

Another recent retrospective study of 283 UC patients, 80 of whom underwent surgery, reported that UCEIS ≥6 could be a value for predicting the need for ileal pouch-anal anastomosis (IPAA) [30]. Xu *et al* showed that UCEIS had a stronger correlation with pouchitis disease activity index. UCEIS ≥7 had the most significant AUROC of 0.747 in predicting post-IPAA pouchitis, representing an independent risk factor for it (OR 8.860, 95%CI 1.969-39.865; P<0.001), with a higher risk than MES of 3 (OR 5.200, 95%CI 1.895-14.273; P=0.001) [31].

UCCIS

The UCCIS was initially developed as a full colonoscopy severity scoring system. The analysis was performed on colonoscopy videos from 51 patients by 7 gastroenterologists [14]. Each colonic segment (right colon, transverse, descending, sigmoid, rectum) was described and scored, based on the following descriptors: vascular pattern (score 0-2), granularity (score 0-2), erosions/ulcers (score 0-4) and bleeding/friability (score 0-2). Segmental endoscopic severity (4-point scale) and global endoscopic severity (4-point scale and a 10-cm visual analog scale) were also assessed and the interobserver agreement was evaluated.

The UCCIS was derived from multivariate regression modelling of a segmental assessment of endoscopic severity as a function of descriptor scores, with coefficients averaged across segments and then approximated. The scores of the descriptors were entered into the following formula: UCCIS = 3.1 × SUM (vascular pattern across the 5 segments) + 3.6 × SUM (granularity across the 5 segments) + 3.5 × SUM (ulceration across the 5 segments) + 2.5 × SUM (bleeding/friability across the 5 segments). It ranged from 0-162 (Table 3).

The first analysis reported a correlation coefficient of 0.85 between the UCCIS and overall severity evaluation using the visual analog scale (P<0.001), and good interobserver agreement, with Lin's concordance correlation coefficients between 0.55 and 0.77, lower for bleeding/friability (between 0.34 and 0.66) [14]. The next report showed higher coefficients, between 0.70 and 0.85, again lower for bleeding/friability (between 0.56 and 0.77) [32].

Unfortunately, the UCCIS has only been tested in few studies in clinical practice. Samuel *et al* prospectively examined colonoscopies from 50 UC patients. The UCCIS showed a good correlation with clinical activity index (r=0.52, P<0.001) and SCCAI (r=0.62, P<0.001), also with CRP (r(s)=0.56, P<0.001), albumin (r=0.55, P<0.001), and hemoglobin (r=0.39, P<0.01) [14].

For the UCCIS an interclass correlation coefficient of 0.96 (95%CI 0.94-0.97) was reported in the study by Belvis Jiménez *et al*. Spearman's r was 0.97 between endoscopist A and B, 0.85 between A and C, and 0.86 between B and C [25].

A recent study to determine the cutoff values of the UCCIS for predicting 5-year clinical relapse in UC patients was performed by Ishida *et al*. The retrospective analysis of 157 patients in clinical remission showed that the relapse-free survival rate was significantly lower in patients with UCCIS ≥9.8 than in those with UCCIS <9.8 (log rank test P<0.001). A comparison between the UCCIS and the sum of MES (S-MES), a modified MES that takes into consideration the extent of endoscopic inflammation with segmental scoring of disease activity, was performed in the same study. A significant correlation was found between the 2 scores (r=0.726, P<0.001). The AUROC of the UCCIS was significantly higher than that of the S-MES, (0.772 and 0.677, respectively; P=0.004) to predict clinical relapse within 5 years of colonoscopy [33,34].

PICaSSO

PICaSSO, based on i-SCAN (PENTAX Medical, Japan) VCE technology to assess inflammation in UC, has recently been developed through a rigorous methodology (Table 4). The first study was conducted in 4 phases and involved 8 participants. Performance characteristics in endoscopic scoring and predicting the histologic inflammation with VCE, using 20 videos before (pre-test) and after (post-test), were analyzed. Mucosal architecture (crypt pattern, microerosions, erosions and ulcers) and vascular architecture (vascular pattern, vessel dilation, bleeding) were the descriptors evaluated in the area with the worst activity of disease. The interobserver agreement of the PICaSSO in the pre- and post-test evaluations was very good (k=0.92, 95%CI 0.87-96; and k=0.89, 95%CI 0.84-0.94; respectively). The accuracy of the overall PICaSSO in assessing histological abnormalities and inflammation by RHI was 72% (95%CI 64-79%). In the same study the interobserver agreement of the UCEIS was also analyzed, with similar but lower results (pre-test k=0.86, 95% CI 0.77-0.92; and post-test k=0.84, 95% CI 0.75-0.91) [15].

The next report by Trivedi *et al* on 15 participants undergoing a computerized training module showed a pre-training intraclass correlation coefficient of 0.754 for mucosal features and 0.622 for vascular components of PICaSSO. The coefficient was 0.786 for the overall UCEIS and 0.775 for the MES, also analyzed. Mucosal and vascular components of PICaSSO strongly correlated with the New York Mt. Sinai System, another unvalidated histological index (Spearman's rho 0.925 for mucosal and 0.715 for vascular; P<0.001). PICaSSO also showed the strongest accuracy in discriminating quiescent from mild disease, compared with both MES and UCEIS indices (AUROC of 0.781 and 0.715 for PICaSSO, 0.708

Table 3 The ulcerative colitis colonoscopic index of severity

Descriptor	Score	Definitions
Vascular pattern	0	Normal, clear vascular pattern
	1	Partially visible vascular pattern
	2	Complete loss of vascular pattern
Granularity	0	Normal, smooth and glistening
	1	Fine
	2	Coarse
Ulceration	0	Normal, no erosion or ulcer
	1	Erosions or pinpoint ulcerations
	2	Numerous shallow ulcers with mucopus
	3	Deep, excavated ulcerations
	4	Diffusely ulcerated with 30% involvement
Bleeding/friability	0	Normal, no bleeding, no friability
	1	Friable, bleeding to light touch
	2	Spontaneous bleeding
Grading of SAES and GAES (4-point scale)	0	Normal/quiescent: visible vascular pattern with no bleeding, erosions, ulcers, or friability (includes altered vascular pattern seen in quiescent disease)
	1	Mild: erythema, decreased or loss of vascular pattern, fine granularity, but no friability or spontaneous bleeding
	2	Moderate: friability with bleeding to light touch, coarse granularity, erosions, or pinpoint ulcerations
	3	Severe: spontaneous bleeding or gross ulcers
GAES VAS 10-cm scale	I - - - - - I - - - - - I - - - - - I - - - - - I - - - - - I - - - - - I - - - - - I - - - - - I - - - - - I - - - - - I Normal Extremely severe	

GAES, global assessment of endoscopic severity; SAES, segmental assessment of endoscopic activity; VAS, visual analog scale

Table 4 The Paddington international virtual chromoendoscopy score

Mucosal architecture	No mucosal defect (0)	a. Continuous/regular crypts b. Crypts not visible (scar) c. Discontinuous and/or dilated/elongated crypts
	Microerosions/ crypt abscess (I)	1. Discrete 2. Patchy 3. Diffuse
	Erosions size<5 mm (II)	1. Discrete 2. Patchy 3. Diffuse
	Ulcerations size>5 mm (III)	1. Discrete 2. Patchy 3. Diffuse
Vascular architecture	Vessels; no dilatation (0)	a. Roundish following crypts b. Vessels not visible (scar) c. Sparse (deep) vessels
	Vessels; with dilatation (I)	a. Roundish b. Crowded/tortuous superficial vessels
	Intramucosal bleeding (II)	
	Luminal bleeding (III)	

for MES and 0.705 for UCEIS) [35].

A prospective study by Iacucci *et al* that enrolled 82 UC patients compared the MES, a modified PICaSSO and probe-based confocal laser endomicroscopy in the prediction of HH, defined as RHI ≤3. The modified PICaSSO, simplified and structured by thresholds of severity from the original score, showed the best performances (AUROC 0.96, accuracy 91.5%) with a cutoff threshold of 4 [36].

In a study by Cannatelli *et al* that aimed to assess the FC thresholds to predict endoscopic remission, the reported correlation between FC and modified PICaSSO was 0.59 (95%CI 0.42-0.72) [37].

In a very recent multicenter prospective cohort study, 11 trained endoscopists performed both white-light endoscopy (WLE) and VCE in 307 patients with UC. Endoscopic disease activity was assessed using the MES, UCEIS and PICaSSO indices, while histological activity from targeted biopsies was assessed using multiple histological indices, including RHI and NHI. There was a strong correlation between PICaSSO and histological scores, with significantly superior correlation coefficients to those of the MES and the UCEIS. A PICaSSO score of ≤3 detected HH, defined as RHI ≤3 (AUROC 0.90, 95%CI 0.86-0.94) and NHI ≤1 (AUROC 0.82, 95%CI 0.77-0.87). The interobserver agreement for PICaSSO

was 0.88 (95%CI 0.83-0.92). At 6- and 12-month follow up, PICaSSO score ≤3 predicted outcomes such as clinical relapse better than PICaSSO >3 (hazard ratios 0.19, 95%CI 0.11-0.33 vs. 0.22, 95%CI 0.13-0.34, respectively), similar to HH, confirming prior observations [38].

MES 0 vs. 1: which one to define MH?

For many years MES ≤1 has been used to define MH and it has been considered the treatment goal to be achieved. However, an incorrect definition of MH could have contributed to a mis- or underestimation of results in past trials and observational studies. For example, in a *post hoc* analysis of infliximab trials, MES=0 discriminated from MES=1 with regard to symptoms and steroid-dependency; MES=0 at week 8 predicted symptom relief at weeks 30 and 54 in 71% and 74%, respectively, compared to 51% and 47% for MES=1. Patients with MES=0 at week 8 showed a higher steroid-free remission rate at week 54 than those with MES=1 (63% and 46%, respectively) [39,40]. In the study of Boal Carvalho *et al*, MES=1 was associated with a significant 3-fold increase in the risk of relapse compared with endoscopic MES=0 in 138 UC patients in steroid-free remission [41]. In a recent meta-analysis of 17 studies including 2608 UC patients in clinical remission, MES=0 was associated with a 52% lower risk of relapse compared to MES=1 (relative risk 0.48, 95%CI 0.37-0.62) [42]. Finally, in a cohort study on 55 UC patients with MES ≤1, MES=0 was significantly associated with a colectomy rate lower than that of MES=1 [43].

Discussion

The availability of biologics and small molecules holds out the prospect of achieving treatment goals that were previously inconceivable. Of these, ER currently represents a pivotal long-term target in the treatment of UC patients, as recently remarked [3].

The endoscopic assessment of activity is still crucial in the management of UC. Several endoscopic scoring systems have been developed in the era of WLE. Of these, the MES is still the most commonly used score but it has limits in the description of both active and inactive UC. Although the UCEIS was based on descriptors similar to those used in the MES, in most published studies it showed better performance, high reliability and a potential prognostic role. Many groups have studied the correlation between the UCEIS and biomarkers or clinical, endoscopic and histological scores and tested it with clinical relevance [16-31]. It is easy to use, and can reveal the most severe colitis area better and more precisely than the MES. It could be a useful tool in clinical practice and may be adopted in clinical trials, since ER was defined as UCEIS 0 in a previous consensus of the IOIBD [13]. However, prospective studies with larger cohorts of UC patients are required to clearly define thresholds for mild-to-moderate and severe disease and to confirm its clinical, and short- and long-term prognostic relevance.

The UCCIS was developed and proposed to include disease extension; it provides more detailed information about the inflammatory condition of the entire colonic mucosa [14]. This is relevant, since we know that patients with treated UC often show "patchy" inflammation or histologic rectal sparing. Some therapies may also result in a partial but substantial endoscopic response or a reduction of disease extent, which is a possible limitation, especially for patients involved in clinical trials [44,45]. The UCCIS is not widely used in practice and trials because of its complexity. Supporting evidence is currently scarce. Calculating the UCCIS requires time, effort and a complete colonoscopy, which is not to be preferred in cases of ASUC or short-term evaluation after treatment. Furthermore, studies are needed to compare the UCCIS with biomarkers or histological indices and to evaluate its potential prognostic role.

The PICaSSO, a recent VCE score that has been rigorously validated, showed the best performance in the definition of "healing" as well as a stronger correlation with histological activity. The latter, real-world study showed notable strengths and compared multiple validated indices, confirming the rigorous and valid methodology used for the development of PICaSSO and the high interobserver agreement and reliability [38]. The assessment of ER using PICaSSO may define a deeper form of remission, thanks to its stronger correlation with histology. This ability could lead to a greater use of VCE in the assessment of disease activity in clinical practice [46]. However, most previous studies showed a very strong correlation between PICaSSO and the UCEIS, with similar short-term prognostic performance. To our knowledge, there is no published study comparing the PICaSSO score with the UCCIS.

Most analyses involved expert endoscopists and highlighted the importance of a training phase, probably suggesting the need for a learning curve in the field of VCE among unexperienced endoscopists. Originally validated using the iSCAN platform, it is to be clarified whether PICaSSO could be reproducible when used with different VCE techniques, such as the narrow-band imaging near focus (Olympus) or blue-light imaging (Fujifilm) platforms, that are used to perform endoscopy at a global level. A preliminary unpublished report seems to confirm this [47].

Despite their weaknesses, mostly due to poor use in practice, the UCEIS, UCCIS and PICaSSO have been described as useful and reliable endoscopic scores with superior strength to the MES (Table 5). A MES ≤1 is still used in practice and trials to define MH, despite the growing evidence supporting different outcomes between MES 0 and 1 [39-43]. Thus, using validated scores and recommended definitions of remission could further reduce bias and increase interobserver kappa values. However, supporting evidence is needed.

It is known that the assessment of endoscopic disease activity is inevitably subjective and may lead to a lower interobserver agreement among unexperienced endoscopists [48]. To reduce the variability and the potential bias of local investigators, an independent "central reading" evaluation of videos by experienced and trained readers has been adopted, especially

Table 5 Endoscopic indices in ulcerative colitis

Index	Endoscopic technique	Validation	Strengths	Weaknesses
MES	WLE	No	Easy to use Used in trials and clinical practice	Subjective elements included Moderate reproducibility Small sensitivity-to-change Not appropriate description of inflammation and severity Ambiguous definition of ER
UCEIS	WLE	Yes	Easy to use Good reproducibility and agreement High correlation with clinical, histological indices and biomarkers Clear definition of ER/MH Clinical relevant outcomes	No thresolds for mild, moderate and severe disease No definition of superficial/deep ulcer
UCCIS	WLE	Yes	Good reproducibility and agreement Provides details about the inflammatory condition of the entire colonic mucosa	No definition of MH No thresolds for mild, moderate and severe disease Few supporting evidence
PICaSSO	VCE-iSCAN	Yes	High reproducibility and agreement Highest correlation with HH "Deeper "definition of MH	Endoscopy experience and training required No long-term clinical outcome Not yet tested on other VCE platforms

MES, Mayo endoscopic subscore; WLE, white-light endoscopy; UCEIS, ulcerative colitis endoscopic index of severity; UCCIS, ulcerative colitis colonoscopic index of severity; PICaSSO, Paddington International virtual ChromoendoScopy ScOre; VCE, virtual chromoendoscopy; HH, histological healing; MH, mucosal healing; ER, endoscopic remission

in clinical trials [49]. This approach reduced the bias in the interpretation of descriptors in UC and the placebo rate of remission or response.

Recently, artificial intelligence has also been proposed for the assessment of activity in UC, to overcome the interobserver variability and the subjectivity [50,51]. A computer-aided diagnosis system for predicting histological inflammation has been developed by Maeda *et al*. About 13,000 images obtained from 87 patients were examined. The reported sensitivity, specificity and accuracy in diagnosing active histological inflammation were 74%, 97% and 91%, respectively [52]. Ozawa *et al* developed a computer-assisted diagnosis system using a convolutional neural network, showing a AUROC of 0.86 and 0.98 to identify MES 0 and MES ≤1, respectively [53]. Takenaka *et al* constructed a deep neural network system, deep neural UC, and reported accuracies of 90.1% and 92.9% in rating ER and HH, respectively [54].

Increasing reports on molecular imaging to assess inflammation are also emerging, showing promising results. In the near future, the use of algorithms or neural networks may facilitate the reduction of the inevitable subjectivity deriving from the individual interpretation of inflammation and "healing", regardless of the score adopted [55]. However, this field of research is probably far from being applied in daily clinical practice.

Concluding remarks

Current studies confirm that reaching ER may improve outcomes in patients with UC, in a treat-to-target strategy. Validated and performing scoring systems for the assessment of endoscopic disease activity are available. The UCEIS, UCCIS and PICaSSO need to be used more and routinely in clinical trials and daily practice to strengthen the supporting evidence and to limit weaknesses, if possible. This "change of direction" could lead to correctly defining their impact on medical decision-making and prediction of outcomes in UC patients.

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