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MINIREVIEWS

Clinical relevance of endoscopic assessment of inflammation in ulcerative colitis: Can endoscopic evaluation predict outcomes?

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel condition characterised by a relapsing and remitting course. Symptom control has been the traditional mainstay of medical treatment. It is well known that histological inflammatory activity persists despite adequate symptom control and absence of endoscopic inflammation. Current evidence suggests that presence of histological inflammation poses a greater risk of disease relapse and subsequent colorectal cancer risk. New endoscopic technologies hold promise for developing endoscopic markers of mucosal inflammation. Achieving endoscopic and histological remission appears be the future aim of medical treatments for UC. This review article aims to evaluate the use of endoscopy as a tool in assessment of mucosal inflammation UC and its correlation with disease outcomes.

Key words: Ulcerative colitis; Inflammation; Endoscopy; Disease activity indices; Mucosal healing

Core tip: Endoscopy is the mainstay of assessing disease activity in ulcerative colitis. Mucosal healing (MH) is an accepted end point in clinical trials. Recent data suggest that complete MH is associated with lower relapse rates and better long term outcomes. Advanced imaging techniques like high definition endoscopy, narrow band imaging, magnification endoscopy, chromoendoscopy and endomicroscopy help in detailed assessment of mucosa and the submucosal vasculature. In this review article we aim to look at the correlation

between these endoscopic assessment modalities and clinical outcomes.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel condition characterised by mucosal inflammation of the rectum and colon. It is associated with a relapsing and remitting disease course. The exact aetiology of the disease remains elusive although genetic linkage, auto immune causes and environmental influences have been postulated. Approximately 25% of patients with UC experience acute exacerbation of their disease activity during the course of their disease[1]. Colectomy rate increases with more than one hospital admissions with acute severe UC, reaching up to 40% after two admission[1]. Truelove and Witts criteria established over 60 years ago, estimates the severity of the disease and predicts the need for colectomy using clinical and biochemical scores[2]. Current treatment goals in UC focus on keeping the disease in remission and a colectomy free survival.

There have been significant scientific advances in both diagnosis and management of UC in the last two decades. The use of Immunomodulators like Azathioprine, Cyclosporine, and biologic agents like Anti-Tumour necrosis factors alpha has changed the way patients with UC are managed in modern day practice. Advances in medical management of UC have seen a fall in colectomy rates[3].

A flare up in disease activity in UC is difficult to predict but a reliable biomarker would be important in guiding appropriate therapy. Commercially available serum and faecal biomarkers have been ineffective in positively predicting disease relapse in UC. Serological markers available for clinical and research use includes C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells, Platelets, 1-acid glycoprotein, serum amyloid A-protein, 2-globulin, lactoferrin, orosomucoid and thrombopoietin. Faecal biomarkers are thought to be non-invasive and are relatively inexpensive. Available faecal biomarkers include a1-antitrypsin excretion, lysozyme excretion, calprotectin, lactoferrin, Myeloperoxidase. Faecal calprotectin has generated the most interest among researchers and clinicians. However, in a meta-analysis consisting of 6 prospective studies looking at the use of faecal calprotectin in predicting clinical flares in inflammatory bowel disease (IBD), Mao *et al*[4] report a pooled sensitivity of only 78% and specificity of 73%. Endoscopy is the main tool used by physicians in assessing severity and extent of the disease in UC in clinical practice. It is a reliable tool in assessment of disease activity during flare up of symptoms. But in inactive disease persistent microscopic inflammation is often seen despite the normal appearance of colonic mucosa on standard white light endoscopy (WLE)[5]. Histologically active disease is associated with greater risk of subsequent relapse[6-8]. Studies using standard WLE fail to predict relapse in quiescent UC[5,7,8], whereas studies using advanced endoscopic imaging modalities seem to hold promise[9-11].

In this review article we aim to discuss the use of endoscopic modalities in assessment of disease activity in UC, its correlation with clinical outcomes, and endoscopic predictors of relapse.

ENDOSCOPY IN UC

Endoscopy is essential in diagnosing UC, obtain biopsies and distinguishing from Crohn's disease. Direct mucosal visualisation allows physicians to assess extent and severity of the disease during flare ups and observe effectiveness of treatment during follow up. In addition to this it is the only available test to identify and resect dysplastic lesions during surveillance for colorectal cancer in patients with long standing colitis.

Endoscopic assessment of the mucosa for pathological diagnosis is largely operator dependant. Although agreement among beginners was good at the extremes of the disease, concordance for certain endoscopic features like granularity, erosions and friability was still poor and identified the need for training to improve endoscopic diagnosis[12,13]. Training has shown to improve diagnostic yield in endoscopy in trainee endoscopists. Studies suggest that among experienced endoscopists there is a good inter-observer agreement in UC related endoscopic findings[13].

There are at least ten scoring systems designed to assess the disease activity in UC since the development of first such score by Baron *et al*[14] in 1964. Table 1 provides details of scores using endoscopic activity alone and Table 2 details of scores with mainly clinical and biochemical parameters with or without endoscopic features. Many of these scoring systems use clinical, biochemical and endoscopic components in an attempt to grade the disease activity[15]. Endoscopic parameters of assessment include mucosal vascular pattern (MVP), friability and mucosal damage. Mayo endoscopic sub score is an endoscopic component of full Mayo score[16]. Both Baron score and Mayo endoscopic sub score have been used in clinical trials; however these scores have not been validated rigorously[15]. Recently Travis *et al*[13,17] have designed and validated a new scoring system using endoscopic "descriptors" called ulcerative colitis endoscopic index of severity (UCEIS). Ten IBD experts evaluated sigmoidoscopic videos of varying degree of endoscopic inflammation seen in UC. Inter and intra-investigator reliability was tested using

Table 1 Disease activity indices with endoscopic component alone

Disease activity index	Endoscopic variables
Baron score[14] 1964	Bleeding and MVP
Rachmilewitz endoscopic index[18] 1989	Granulation, MVP, Mucosal vulnerability, Mucosal damage
UC colonoscopic index of severity (UCCIS)[19] 2013	MVP, Granularity, Ulceration, Bleeding, Segmental assessment of endoscopic severity, Global assessment of endoscopic severity
UC endoscopic index of severity (UCEIS)[13] 2013	MVP, Bleeding, Erosions and Ulcers

MVP: Mucosal vascular pattern; UC: Ulcerative colitis.

Table 2 Disease activity indices with endoscopic and non-endoscopic components

Disease activity index	Endoscopic variables	Non-endoscopic variable
Powell-Tuck score[20] 1982	Bleeding	Wellbeing, Abdominal pain, stool frequency and consistency, Bleeding, Anorexia, nausea and vomiting, EIM, Temperature
Sutherland index[21] 1987	Friability, Bleeding	Stool frequency, Bleeding, Physician's rating of disease activity
Mayo score[16] 1987	Erythema, MVP, Friability, erosions, ulcers, spontaneous bleeding	Stool frequency, Bleeding, Physician's global assessment
Improvement based on individual symptom scores[22] 2002	Mucosal oedema, MVP, Granularity, Friability, Petechiae, Ulceration, Spontaneous bleeding	Rectal bleeding, Stool frequency, Abdominal pain, PFA, PGA

EIM: Extra-Intestinal Manifestations; MVP: Mucosal vascular pattern; PGA: Physician global assessment; PFA: Patient functional assessment.

Kappa statistics. In the validation phase they report a satisfactory intra and inter-investigator reliability using this score. No significant difference was observed when investigators were tested with or without the knowledge of clinical details of the subjects.

ENDOSCOPY IN ACUTE SEVERE COLITIS

Endoscopy plays a vital role is disease assessment in acute flares of UC. Limited examination of the colon by flexible sigmoidoscopy is enough to establish the diagnosis and obtain biopsies. Radiological examinations like abdominal X-rays and sometimes computed tomography (CT) scans are carried out prior to endoscopic examinations. Minimal air insufflation is used during endoscopic procedure to avoid misinterpretation of subsequent X-ray images as toxic megacolon.

Sigmoidoscopy is commonly performed during UC flare ups and it is thought to be sufficient for assessing disease severity. Colonoscopy is avoided until the disease is settled, mainly due to fear of complications such as perforation during severe flare. However there are few prospective studies to validate this widely used practice. In the only published study to date, Carbonnel *et al*[23] demonstrated that colonoscopic examination is safe in acute flare up of UC, and helps in identifying patients at high risk of colectomy. In their cohort of 85 consecutive patients with acute sever colitis, extensive deep ulcerations were found in 46 patients. Forty-three/forty-six patients with deep ulceration underwent colectomy and histology in 42/43 patients showed deep ulcerations extending up to muscular layer. Thirty of thirty-nine patients with moderate colitis responded to medical therapy. They did not report any major complications apart from one dilated colon in their cohort. The authors conclude that a full colonoscopy was safe in acute severe flare of colitis and also helped in predicting course of the disease and short term outcome. It is important to know that all endoscopic procedures in this study group were performed by an experienced colonoscopist; hence care must be taken in generalising these findings to all endoscopists. Secondly this study was conducted in the pre-biological treatment era which could account for the high rates of colectomy.

ENDOSCOPY IN DISEASE REMISSION

The aims of endoscopy performed during clinical disease remission are to assess if there is reduction of endoscopic activity after a flare, ascertain if mucosal healing (MH) is achieved, to obtain biopsies and screen for dysplastic lesions.

MH is increasingly recognised as a therapeutic endpoint in clinical trials. Although there is no consensus definition of MH, the International organisation of IBD proposed the following criteria to define MH: absence of friability, blood, erosions and ulcers in all visualised segments of the colonic mucosa[15]. Essentially disappearance of endoscopic lesions such as erosions and ulcers is called as MH. Drugs such as 5-aminosalicylates, immunomodulators like azathioprine, methotrexate and biological agents

Table 3 Correlation of endoscopic activity with clinical symptoms

Ref.	Study characteristics	Results
Karoui *et al*[35] 2011 Tunisia	Prospective observational study. 101 patients with UC in remission. CRP, Disease activity index and Rachmilewitz scores used	CRP correlated well with DAI and Rachmilewitz score Correlation between DAI and Rachmilewitz was not statistically significant
Osada *et al*[36] 2008 Japan	Prospective observational study. 54 patients with UC. CRP, ESR, Mayo endoscopic subscore, Lichtiger's clinical activity scores used.	Clinical symptoms correlated with left sided disease activity. CRP and ESR correlated well with right sided inflammation.
Turner *et al*[37] 2009 Canada	Prospective observational study. 86 patients with UC. Disease activity was measured using 9 different activity indices	Disease activity was best assessed by Walmsley and PUCAI followed by Partial Mayo score and Rachmilewitz

CRP: C-reactive protein; DAI: Disease activity index; ESR: Erythrocyte sedimentation rate; PUCAI: Paediatric ulcerative colitis activity index; UC: Ulcerative colitis.

(infliximab, adalimumab, golimumab, vedolizumab, *etc.*) are used in the induction of remission and maintenance of MH in UC[24-30]. MH is associated with favourable short and long term clinical outcomes like reduced hospitalisation due to flares of disease, decreased colectomy rates and lower incidence of subsequent colorectal cancers[6,31-34].

DOES ENDOSCOPY CORRELATE WITH CLINICAL SYMPTOMS?

Generally it is considered that clinical symptoms, biochemical markers of inflammation, endoscopic findings and histological grading help in assessing the severity of the disease in UC. It is not uncommon to find that clinical symptoms and endoscopic findings do not correlate. Table 3 contains the studies comparing endoscopic activity with clinical symptoms. Karoui *et al*[35] compared the endoscopic findings of patients in remission whereas Osada *et al*[36] examined patients with varying grades of severity. In both the studies serological markers (CRP and ESR) correlated well with the disease activity. However conflicting results were noted when comparing clinical symptoms with endoscopic findings (Table 3). Osada *et al*[36] reported that clinical symptoms correlated well with the disease of left colon whereas CRP and ESR reflected well with right sided disease. No significant association was noted by Karoui *et al*[35]. Different clinical activity indices used in the above two studies (Rachmilewitz score and Lichtiger index respectively) may have contributed to the differences. However, in a prospective study Turner *et al*[37] compared different clinical activity indices and their respective abilities to assess disease activity. They noted that the Rachmilewitz score and Lichtiger index had comparable "discriminative average" which is the ability to differentiate patients in clinical remission with those patients with active disease [Rachmilewitz score- 0.92 (95%CI: 0.87-0.98) and Lichtiger index- 0.90 (95%CI: 0.84-0.97)].

DOES STANDARD WLE CORRELATE WITH HISTOLOGICAL ACTIVITY?

The presence of deep ulcerations, extensive disease, higher median inflammation seen on WLE corresponds to more severe disease and are associated with higher colectomy rates[23,38]. MH is associated with better outcomes such as decreased relapse rates and the need for surgical interventions[6,30,31,33,39]. Use of conventional colonoscopy is restricted to assessment of disease activity and extent of the disease during disease flare; however colonoscopic findings in remission does not correlate well with the histological activity nor are they predictive of relapses. Table 4 provides details of studies comparing white light endoscopic activity and histological activity and their potential in predicting disease outcomes in UC.

Histological inflammation has been shown to persist despite normal endoscopic findings in both prospective and retrospective studies[5-8,40,41]. Histological markers of inflammation such as basal plasmacytosis, basal lymphocytosis and chronic inflammatory infiltrates were found in biopsies from endoscopically normal looking mucosa. These histological markers were associated with increased risk of subsequent relapse. The rate of relapse was reported to be between 20%-57.7% among UC patients with quiescent disease (Table 4).

DOES ENDOSCOPY PREDICT DISEASE RELAPSE?

In a recent prospective study involving 41 patients with UC who had undergone colonoscopy before and after receiving Tacrolimus, Ikeya *et al*[43] studied the outcomes of patients assessed by two of the disease activity score; the Mayo endoscopic subscore and the UCEIS. They reported better correlation of endoscopic assessment of disease activity using UCEIS and also in predicting relapse free survival. In another prospective

Table 4 Correlation between white light endoscopy and histology in ulcerative colitis

Ref.	Study characteristics and aims	Results
Bitton *et al*[8]	Prospective observational study	36.4% patients relapsed
2001	74 patients in clinical and endoscopic remission were included	Younger age, multiple previous relapses (women), and basal plasmacytosis on histology predicted relapse.
United States	Followed up for a year or until the patients relapsed.	CRP, ESR, IL-1b, -6, 15, ANCA was non-predictive of relapse.
Azad *et al*[41]	Prospective observational study	57.7% patients relapsed
2011	26 patients with clinical and endoscopic remission were included	Increased Eosinophils and Neutrophils were predictors of relapse.
India	Monthly follow up for a year or until the patients relapsed.	Hb, CRP, ESR, IL-6 were not predictive of relapse.
Bessissow *et al*[7]	Retrospective study	Microscopic inflammation was found in 40% of patients.
2012	75 patients with endoscopically inactive disease (Mayo score 0)	Basal plasmacytosis and histological activity (Geboes score ⩾ 3.1) predicted relapse.
Belgium	Time to relapse was noted	
Lemmens *et al*[40]	Retrospective study	Significant correlation with Mayo endoscopic subscore and histology noted in extremes of disease (inactive and acute severe disease)
2013	131 patients with known UC	
Belgium	Correlation of endoscopy and histology	
Rosenberg *et al*[5]	Prospective observational study	54% of patients with quiescent disease had signs of histological inflammation.
2013	103 UC patients in clinical remission	
United States	Correlation of endoscopy and histology	
Feagins *et al*[6]	Retrospective study of 51 patients.	20% of patients had flare up within 12 mo.
2013	colonoscopy for surveillance	Basal lymphocytosis, disruption of crypt architecture, erosions and ulcers predicted relapse.
United States	Correlation of endoscopic and histological activity	
Zenlea *et al*[42]	Prospective study	23% of patients relapsed
2016	179 patients included	Histological activity with Geboes score ⩾ 3.1 was strongest predictor of relapse.
United States	Baseline Mayo endoscopic score and Geboes score for histology noted Follow up period was 12 mo	

UC: Ulcerative colitis; Hb: Haemoglobin; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; ANCA: Anti-nutrophil cytoplasmic antibody.

study of 82 patients with UC, a score of 0-1 on UCEIS after treatment with Infliximab had favourable long term outcomes[44].

Does advanced imaging modalities predict relapse

Advanced imaging modalities such as magnification colonoscopy (MC), narrow band imaging (NBI), iScan, Fujinon intelligent colour enhancement (FICE), autofluorescence imaging (AFI), chromoendoscopy, confocal laser endomicroscopy (CLE) and endocytology, *etc.* enable real time mucosal assessment in greater detail. Imaging modalities such as NBI, MC and magnification chromoendoscopy have been evaluated, mainly by Japanese investigators, for their ability to predict relapse in UC (Table 5). Figure 1A-D shows the appearances of inflamed colonic mucosa in patients with colitis using standard definition, high definition, NBI and chromoendoscopy respectively. Image enhanced endoscopic techniques appear to improve the visualization of inflammation in colonic mucosa but large scale clinical studies are needed to ascertain the relevance of these findings to clinical outcomes.

MC: Optical enhancement of image from six to 150 fold occurs due to a moving camera at the tip of the endoscope[45]. In MC the image undergoes optical enhancement and hence the pixels are not distorted and the image quality is not compromised. Hence the image appears sharp and allows assessment of surface pattern in detail. Regular pit pattern seen under MC is associated with a significantly reduced risk of relapse[9,10]. Patients with distorted MVP, abnormalities in epithelium or pit pattern have a higher grade of inflammation on histology and relapse subsequently[9-11,46,47]. In one recent study MC with NBI-lead target biopsies seems to predict long term outcomes[48].

Chromoendoscopy and NBI: Chromoendoscopy is examination of the colonic mucosa after spraying dye which contrast enhances and highlights mucosal abnormalities allowing precision biopsies. NBI, also called as "virtual chromoendoscopy" or "dye-less chromoendoscopy", utilises optical filters and uses shorter wavelengths of light (between 415-540 nm) which intensely absorbed by haemoglobin. This allows examination of the vasculature and surface pattern in detail. Use of NBI in predicting relapse is controversial. Kudo *et al*[46] in their prospective study evaluated the MVP observed under WLE and NBI. NBI findings of obscure MVP correlated well with the histological markers of inflammation. Although this study did not report any outcome data on relapse, we know that the histological inflammation leads to subsequent relapse. More recently a prospective study from Spain of 67 patients with UC in sustained clinical

Table 5 Relapse prediction using advanced imaging techniques

Ref.	Imaging modality	Study characteristics	Results
Watanabe *et al*[9] 2009 Japan	Magnification colonoscopy with chromoendoscopy	Prospective study 57 patients with clinical and endoscopic remission were enrolled for MC examination and followed up for 12 mo	70% of patients with mucosal defects identified by MC had a flare up within 12 mo
Nishio *et al*[10] 2006 Japan	Magnification colonoscopy with chromoendoscopy	Prospective study 113 patients with UC in remission were enrolled. Pit pattern in rectal mucosa assessed using MC. Followed up for 12 mo	29% of patients relapsed. Significant correlation seen between pit pattern abnormalities and relapse rate.
Fujiya *et al*[11] 2002 Japan	Magnification colonoscopy	18 patients with UC in remission underwent MC and follow up	7 out of 9 (77.7%) with minute epithelial defect had a flare.
Kudo *et al*[46] 2009 Japan	NBI	Prospective study 157 colonic segments among 30 patients were examined under WLE and NBI	Obscured MVP had good correlation with the histological activity.
Jauregui-Amezaga *et al*[49] 2014 Spain	Chromoendoscopy and NBI	Prospective study 64 patients with clinical and endoscopic remission for at least 3 mo were included. 1 year follow up.	27% relapsed during follow up Neither NBI nor chromoendoscopy predicted relapse
Osada *et al*[55] 2011 Japan	AFI	Retrospective study 572 images from 42 patients were correlated with histological activity	The green component of AFI correlated closely with the inflammatory activity

MC: Magnification colonoscopy; MVP: Mucosal vascular pattern; AFI: Autofluorescence imaging; NBI: Narrow band imaging.

remission investigated chromoendoscopy, NBI and faecal calprotectin in predicting clinical flares. In this study advanced endoscopy suing NBI failed to predict relapse within one year[49].

CLE: CLE allows visualisation of cellular structures and assessment of their function in real time. Contrast agent such as fluorescein is administered systemically and laser light is emitted *via* CLE. The reflected endoscopic image is reprocessed for microscopic examination in such a way that the resultant image is enhanced to a 1000 fold magnification. CLE detects barrier dysfunction in the epithelium in patients with IBD[50]. Mucosal inflammation in IBD results in barrier dysfunction which is seen as increased fluorescence leak and widening of crypt diameter along with intercept distance on CLE. A composite score developed by Buda *et al*[51] using fluorescence leak, and crypt diameter have shown predictive capabilities for disease outcomes in quiescent UC patients during 12 mo follow up[50-52]. A recent study from Karstensen *et al*[53] reported parameters for distinguishing active and inactive UC with CLE. In this prospective study the authors examined colonic mucosa from twenty two patients with clinical symptoms of relapse and 7 patients with inactive disease referred for surveillance purposes served as controls. This study demonstrated that fluorescein leak, microerosions, tortuosity of crypts, distortion of crypt opening, decreased crypt density and presence of inflammatory infiltrates were significantly higher in active compared to inactive colitis. They also noticed improvement in the crypt architecture was associated with histological improvement following treatment of active colitis.

Endocytoscopy: Data on use of endocytoscopy (EC) in prediction of relapse in UC is limited. Maeda *et al*[54], in a retrospective study of patients who underwent endocytoscopic-NBI (EC-NBI) compared the images with histological inflammation. EC-NBI was found to be highly useful in assessing histological activity with a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of EC-NBI for diagnosis of acute inflammation to be 84%, 100%, 87.1%, 100% and 92.3%. There was not data on relapse rate provided in this study.

Endoscopic assessment with AFI and iScan have been found to correlate well with histological activity, they have not been used to assess relapse prediction in UC[55,56]. The FICE was however found not helpful in improving and further characterisation of endoscopic findings in IBD[57].

Spectroscopy: More recently we studied the use of Raman spectroscopy to identify MH and inflammation in UC. We observed that three carotenoid peaks were twice as intense in the inflamed mucosa and two phospholipid peaks were significantly lower in the normal mucosa. These five peaks seen on the spectroscopy could be used reliably to distinguish

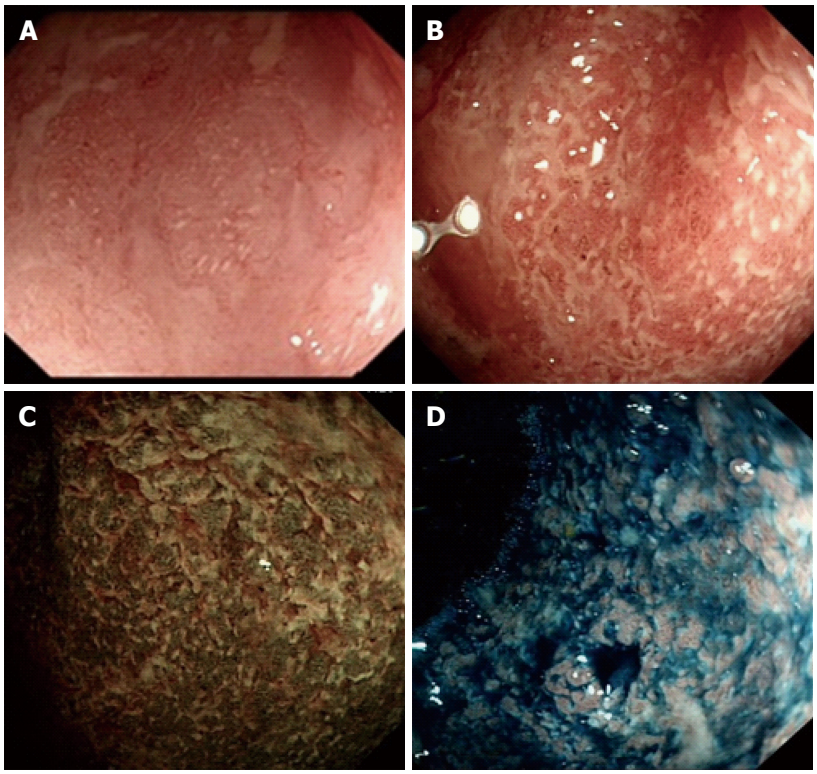

Figure 1 Assessment of inflamed colon with white light endoscopy, narrow band imaging and chromoendoscopy. A: White light assessment with standard definition endosocpe reveals areas with superficial ulceration interspersed with areas of patchy obliteration of mucosal vascular pattern; B: High resolution endoscope allows more detailed assessment including crypt openings and disrupted vascular architecture; C: NBI assessment of moderately active UC shows obscured vascular pattern; white mucosal spots which represent mucous exudates giving the characteristic appearance of "Coral reaf" like mucosa; D: Chromoendoscopy shows the mucosal damage with disruption of pit pattern and complete destruction of vascular pattern. Ulcer margins are seen more prominent with contrast enhancement.

active from quiescent UC[58].

CONCLUSION

Endoscopy is a useful tool in the clinical management of UC. Although standard WLE is the commonly used in day to day practice, it has its limitations in assessing disease activity and predicting disease course. Advanced imaging modalities show promising results but they are expensive, involve a steep learning curve and are time consuming. Endoscopic modalities such as CLE and EC are still restricted to research use and cannot be advocated for routine assessment of IBD. Advanced endoscopy improves visualisation of mucosal surface structure and vascularity and hold promise for predicting disease outcomes. Development of endoscopic markers using these advanced technologies in well-designed prospective clinical studies is essential to develop robust markers for predicting disease course in patients with UC.

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