Correlation between endoscopic and histological activity in ulcerative colitis using validated indices

Journal:	*Journal of Crohn's and Colitis*
Manuscript ID	Draft
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Irani, Nazneen; John Radcliffe Hospital, Translational Gastroenterology Unit Wang, Lai Mun; John Radcliffe Hospital, Department of Cellular Pathology Collins, Gary; University of Oxford, Centre for Statistics in Medicine Keshav, Satish; John Radcliffe Hospital, Translational Gastroenterology Unit Travis, Simon; John Radcliffe Hospital, Translational Gastroenterology Unit
Subject:	Biomarkers, Endoscopy, Pathology
Classifications:	Endoscopy, Biomarkers, Pathology

Title Page

Journal:	Journal of Crohn's and Colitis
Article type:	Original Article
Title :	Correlation between endoscopic and histological activity in ulcerative colitis using validated indices
Corresponding Author:	Professor Simon PL Travis Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom Email: simon.travis@ndm.ox.ac.uk Phone: +44 1865 228753
List of Authors:	Irani, Nazneen R; Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom Wang, Lai Mun; Department of Cellular Pathology, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom Collins, Gary S; Centre for Statistics in Medicine, University of Oxford, United Kingdom Keshav, Satish; Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom Travis, Simon P L; Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom
Short Title:	Endoscopic and histological activity in ulcerative colitis
Conference Presentation:	European Crohn's and Colitis Organisation, Barcelona 2017 Digestive Diseases Week, Chicago 2017
Keywords:	Ulcerative Colitis, UCEIS, Histopathology, Nancy Index, Robarts' Histopathology Index
Word count: **Number of tables:** **Number of figures:** **Number of references:**	2404 4 2 34

ABSTRACT

Background and Aims: Endoscopy and histopathology are pivotal for evaluating disease activity in ulcerative colitis (UC); correlation between validated endoscopic and histological indices has not been examined. We aim to correlate the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) with two new validated histological indices in patients with established UC.

Methods: Retrospective single centre cohort of patients with established UC who underwent flexible sigmoidoscopy or colonoscopy by a single endoscopist. The UCEIS was scored at the worst affected area in the distal colon, which was biopsied; histological disease activity using Nancy (NI) and Robarts' Histological (RHI) indices was scored by a pathologist blinded to the endoscopy. Spearman correlation between the UCEIS, NI and RHI, and between NI and RHI were performed.

Results: 125 patients, median age 37 years (range 16-81 years), with UCEIS scores (scale 0-8) 0=21; 1-3=48; 4-6=51; 7-8=5. Correlation coefficients between UCEIS and NI (scale 0-4) were r=0.84 (95% CI 0.76-0.89, p<0.001) and between UCEIS and RHI (scale 0-33) r=0.86 (95% CI 0.80-0.90, p<0.001). The difference in correlation was not significant (p=0.57). There was excellent correlation between the two histological indices (r=0.92, 95% CI 0.87-0.95, p<0.001). Quiescent disease activity defined as the absence of neutrophils (Nancy 0-1, Robarts 0-3) was most closely correlated with UCEIS=0.

Conclusions: The UCEIS strongly correlates with both NI and RHI. Complete mucosal healing is best defined as a UCEIS=0/8, since this correlates with the absence of microscopic disease activity.

1. INTRODUCTION

Therapeutic advances in the management of ulcerative colitis (UC) have changed treatment targets.[1-4] Mucosal healing is associated with improved clinical outcomes and is set to become a long term therapeutic goal.[5-6] Endoscopic mucosal healing is defined by resolution of visible mucosal inflammation and ulceration at endoscopy.[3] A Mayo Clinic endoscopic sub score (eMCS) has been associated with a higher rate of being corticosteroid free (eMCS 0) and lower rates of hospitalisation or colectomy (eMCS $\leq$ 1) over a 12 month period.[7-12] In a six year follow up study, concordance between endoscopic and histological remission was associated with better outcomes than endoscopic remission alone.[13] Nevertheless, endoscopic mucosal healing does not necessarily reflect quiescent microscopic disease.[14-15] Past attempts to correlate endoscopic activity and histological activity have been notable more for their disparity than correlation.[16-19] The likely reason for this disparity is that there have been no validated endoscopic or histological indices to compare.

In the past three years, the situation has changed. The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is now validated in three independent cohorts.[20-21] It accounts for 88% of the variation between observers and is unaffected by knowledge of clinical symptoms.[22]

Two validated histological indices were published in 2017.[23-24] The Nancy Index (NI) consists of three components, with five grades of histological activity defined from grade 0 (absence of significant histological disease activity) to grade 4 (severely active disease). Intra-reader reliability was 0.88 (95% CI 0.82-0.92) and the interclass correlation coefficient (ICC) for inter-reader reliability was 0.86 (95% CI 0.81-0.99).[23] The Robarts' Histopathology Index (RHI) uses similar descriptors, but breaks down acute inflammatory infiltrate into lamina propria and epithelial neutrophil components, so it has four components and a scale of 0 (no disease activity) to 33 (severe

disease activity). Intra-rater and inter-rater ICCs were 0.92 (95% CI 0.88-0.94) and 0.82 (95% CI 0.74-0.86) respectively.[24]

The primary aim of the current study was to correlate endoscopic (UCEIS) and histological (NI and RHI) assessment of disease severity in UC using these validated indices. A secondary aim was to determine whether a UCEIS of 0 or 1 best represents remission, based on the hypothesis that true mucosal healing should best correlate with quiescent histopathology.

2. METHODS

2.1 Study design

Single centre retrospective cohort study performed in between Oxford August 2015 to February 2016. Subjects enrolled had an established diagnosis of UC according to standard criteria.[25] Patients with UC who had an endoscopic assessment by a single specialist (SPLT) between March 2013 and August 2015 were enrolled. Patients were excluded if they had colitis yet to be classified, Crohn's colitis, diversion, diverticular, infectious, drug-induced or ischaemic colitis, or an ileal pouch-anal anastomosis. Subjects were recruited regardless of the extent of clinical disease activity.

2.2 Endoscopy

Patients underwent a flexible sigmoidoscopy or colonoscopy according to standard technique by a single clinician (SPLT) and the UCEIS score (table 1) in the worst affected area in the distal colon was documented at the time of endoscopy. Biopsies were taken from worst affected area in addition to other areas as clinically indicated by the treating physician at the time of the endoscopy. The treating clinician (SPLT) was not blinded to the patients' clinical symptoms at the time of endoscopy, and some patients had multiple biopsies taken from varying colonic segments all during a single endoscopy at the treating clinician's discretion. Endoscopy reports were retrieved for procedures performed between March 2013 and August 2015 from the endoscopic reporting database 'Endobase'. Patients were excluded if a UCEIS score was not documented at the time of endoscopy or if biopsies were not taken for histology. Data were collected on the subject's age at time of endoscopy, gender, type of endoscopic procedure performed (flexible sigmoidoscopy or colonoscopy), date of procedure, UCEIS score and component sub-scores. To protect patient confidentiality, no patient names, initials, or date of birth were recorded on the same spreadsheet as the data collected. Study subjects were part of the "Inflammatory Bowel Disease in Oxford:

prospective cohort for outcomes, treatment, and predictors" project, UK Research Ethics Committee reference: 09/H1204/30.

2.3 Histopathology

The Nancy Index (NI, table 2) and the Robarts' Histopathology Index (RHI, table 3), were scored by a single specialist gastrointestinal histopathologist (LMW), blinded to the subjects' clinical information and endoscopic findings, using the worst affected area.

2.4 Statistical Analysis

Descriptive statistics, histograms and scatterplots were used for describing patient demographics, distribution of UCEIS scores and histological indices. Spearman correlation between the UCEIS, Nancy Index and Robarts Histological Index was performed, with a p-value of <0.05 used for statistical significance. Confidence intervals for the Spearman correlation were obtained using bootstrapping. A correlation coefficient (r) of zero indicates that no linear relationship exists between two continuous variables, and a correlation coefficient of −1 or +1 indicates a perfect linear relationship. If we wish to label the strength of the association, for absolute values of r, 0-0.19 is regarded as very weak, 0.2-0.39 as weak, 0.40-0.59 as moderate, 0.6-0.79 as strong and 0.8-1.0 as very strong correlation, but these are rather arbitrary limits, and the context of the results should be considered.[26] Analysis was performed using R version 3.2.3.

3. RESULTS

3.1 Patients

A total of 126 UC patients were identified. One patient was omitted from the final analysis because biopsies could not be located for histological assessment. Therefore 125 patients were included in the final analysis, with a median age of 37 years (range 16-81 years) at the time of endoscopy; 64/125 (51%) were male. Baseline characteristics are shown in table 4.

3.2 Endoscopy

All UCEIS scores were represented, consistent with the full spectrum of disease activity (supplementary table 1). The UCEIS has been divided into four strata by some authors, to correlate with clinical activity: remission (UCEIS 0-1), mild (UCEIS 2-4), moderate (UCEIS 5-6) and severe (UCEIS 7-8).[27] Nevertheless, debate continues whether 'remission' is best defined as UCEIS=0 or 1.[28] It was assumed that UCEIS=1 in the remission stratum was a descriptor limited to partial obliteration of vascular pattern. Overall, 49/125 (39%) patients had a UCEIS score of 0-1 and 42/125 (34%) had mild colitis. A further 29/125 (23%) had moderately active colitis and 5/125 (4%) had severe colitis (figure 1).

3.3 Histopathology

All 5 grades of the Nancy Index were represented (supplementary figure 1). A total of 31% (39/125) of patients had absence of histological disease, 36% (45/125) mildly active disease, 4% (5/125) moderately active disease and 22% (28/125) severely active disease (supplementary table 2).

Almost all levels of the Robarts Histopathology Index were represented (supplementary figure 2), ranging from 0-31 with a median RHI score 10 and interquartile range 1-21 (supplementary table 3).

3.4 Correlation testing between endoscopy and histology scores

The correlation coefficient between the UCEIS and NI was r=0.84 (95% CI 0.76-0.89, p<0.001). The correlation and confidence intervals (CI) between the UCEIS and RHI were similar: r=0.86 (95% CI 0.80-0.90, p<0.001). These correlations are classed as very strong given r>0.8. The NI and RHI histological indices were very strongly correlated: r=0.92 (95% CI 0.87-0.95, p <0.001). All correlations between the UCEIS, NI and RHI were statistically significant p<0.001, but the difference in correlation between the two histological indices was not (p=0.57, figure 2).

3.5 What level of UCEIS correlates with histological remission?

Histological inactivity is defined by the absence of acute inflammation, neutrophils, erosions or ulceration, although a chronic inflammatory cell infiltrate may be present. Histological remission hence corresponds to a NI grade ≤1 and an RHI score ≤ 3, indicative of chronic inflammation but the absence of acute inflammatory changes.

To answer the question whether UCEIS=0 or UCEIS=1 best represents true remission, these UCEIS scores were evaluated against histological remission (NI grade ≤1 or RHI score ≤ 3). There were 21 patients with UCEIS=0, and 28 with a UCEIS=1 (all these only had partial obliteration of vascular pattern). 20/21 (95%) patients with a UCEIS=0 had an NI=0 in contrast to 18/28 (64%) patients with a UCEIS=1. The odds ratio (OR) was 11.1 (95% CI 1.3-95.6, p=0.0143), indicating that UCEIS=0 best matched NI grade 0. With regard to NI=1, the same 20/21 (95%) patients with a UCEIS=0 had also had NI grade ≤1, compared to 20/28 (71%) with a UCEIS=1; OR=8 (95% CI

0.9-70; p=0.059). With regard to RHI score ≤ 3, 18/21 (86%) with a UCEIS=0 had an RHI≤ 3, compared to 19/28 (64%) with a UCEIS=1; OR=2.5 (95% CI 0.6-11.1, p=0.304).

Since the trend favoured a UCEIS=0 to define endoscopic remission with histological remission, we analysed a combined NI grade ≤1 and RHI score ≤ 3. When UCEIS=0, 18/21 (86%) had a combined NI and RHI indicating histological remission, compared to 18/28 (64%) when UCEIS=1; OR=3.3 (95% CI 0.8-14.2, p=0.114).

4. DISCUSSION

This is the first time that validated indices for endoscopy and histopathology have been correlated in ulcerative colitis and the results are novel. First, there was a very strong correlation between endoscopy and histopathology, in contrast to that reported with unvalidated indices. Second, there was also a very strong correlation between the two histopathology indices that have been validated for disease activity in ulcerative colitis. Third, the UCEIS score that best correlates with absence of histological disease activity is 0/8 and this has prognostic implications.

Attempts to correlate endoscopic activity and histological activity in the past have been notable more for disparity than correlation.[16-19, 29] A plausible reason for this disparity is that there have, until now, been no validated endoscopic or histological indices to compare. When the Leuven group compared 263 biopsy sets from 131 patients with UC of differing activity[19], comparing the eMCS with the Geboes[30] and Riley[31] histological indices, it was noted that endoscopically mildly active disease (Mayo 1) was distributed over all different histologic grades (37% grade 0; 21% grade 1; 28% grade 2; and 14% grade 3). By comparing the 5 grade Nancy index (0-4) and the 9 grade UCEIS (0-8), we have shown that all correlations between the UCEIS and NI were highly statistically significant ($p<0.001$). When the disease was endoscopically mildly active (UCEIS 2-3/8), all patients with a UCEIS score of 3/8 had a Nancy score of 2 and when the UCEIS was 2/8, then the Nancy score was 1 or 2 (figure 2). The same was true for correlations between the UCEIS and RHI, but the range was wider, consistent with the wider scale (RHI: 34 levels, 0-33). The overall correlation between the UCEIS and RHI was numerically greater ($r=0.86$; 95% CI 0.80-0.90, $p<0.001$) than between the UCEIS and NI ($r=0.84$; 95% CI 0.76-0.89, $p<0.001$), but the difference was not statistically significant. The full range of UCEIS scores was represented, which earlier work has shown correlates closely with the entire range of severity of UC, from normal to worst ever seen on a 100 point visual analogue scale.[20]

The two histopathology indices performed similarly well, as might be expected since the principal difference between the two is that the RHI divides the acute inflammatory infiltrate of neutrophils into epithelial and lamina propria components, while the NI considers them together. Other components (chronic inflammatory infiltrate and ulceration) are the same, even if levels differ. The Nancy Index is considered (by our specialist GI pathologist, LMW) simpler to score in practice, but the close correlation means that either can be used confidently in clinical trials or clinical practice. The very strong correlation ($r=0.92$; 95% CI 0.87-0.95, $p<0.001$) is notable compared to studies of intra-observer and inter-observer variation for other indices.[32] During the development of the Geboes Index for assessing disease activity, initial agreement on the assessment of 99 samples by three pathologists was too low to be of value with κ values of 0.20, 0.42 and 0.26.[30] Subsequent agreement after careful definition of terms, aided by pictograms, raised κ values to 0.62, 0.70 and 0.59, indicating modest to good agreement. No assessment was made of intra-observer variation. There was complete agreement between pathologists on neutrophil infiltration, which is a key component of both the NI and RHI. The Geboes Index, used in clinical trials was designed only to evaluate activity and not to be responsive, so has limited value in evaluating response to therapy.[33] Response characteristics of the NI and RHI have been defined.

This study has also determined whether a UCEIS of 0 or 1/8 represents remission, since this had not been evaluated during the development of the UCEIS[20-21], even though others have speculated that it could be 0 or 1.[27-28] A UCEIS of 0/8 is most closely correlated with histological remission. In this regard, 20/21 (95%) patients with a UCEIS=0 had an NI=0, in contrast to 18/28 (64%) patients with a UCEIS=1. This matters in clinical trials and practice. When the first biomarker of non-response to anti-TNF therapy was established in 2017 (Oncostatin M) the definition used to establish response (or non-response to anti-TNF therapy) was that of histological remission.[34] Furthermore, histological

remission when concordant with endoscopic and clinical remission, predicts better patient-related outcomes with regard to steroid usage or hospitalisation than clinical and endoscopic remission alone.[13] Histopathology may yet prove the predictive biomarker that has eluded UC clinical trialists and regulatory authorities.

There are, however, limitations to this study. It was, by its nature, retrospective and larger prospective multi-centre studies are needed in the future to further corroborate our results. Furthermore, the number of patients at the severe end of the spectrum (16/125, UCEIS 6-8/8) were few. This matters less than it appears, since concordance between endoscopic and histological disease activity matters most in mild-moderately active disease. In addition, only a single endoscopist (SPLT) and a single specialist GI pathologist (LMW) were used to evaluate indices. Apart from being a pragmatic approach, it can reasonably be argued that this reduced variation, especially since SPLT led the development of the UCEIS, but we recognise the potential for bias.

What this study demonstrates is important for clinical practice, let alone trials. Very strong correlation between endoscopic and histological indices means that histopathology reports of activity when disease appears endoscopically inactive cannot be dismissed as aberrant, but requires attention to optimize (and potentially to escalate) treatment. Since histopathology reports arrive several days after endoscopy, it provides an opportunity to personalize therapy. The histopathologist can be confident that the Nancy and Robarts' Histological indices are as reliable as each other, even if the Nancy Index is simpler to score in practice. A UCEIS score 0/8 best defines a target for complete mucosal healing with no histological disease activity. This predicts a good clinical outcome over succeeding years.

Funding: The authors received no external funding for this work. Their institutional resources were used to carry out this investigation.

Conflict of Interest: There is no financial conflict of interest to declare for any of the authors in association with the publication of this manuscript.

Author Contributions: All authors had access to the study data. N. Irani, S. Travis and S. Keshav contributed to the study concept and design, data collection, data analysis and interpretation, and drafting of the manuscript. L.M. Wang and G. Collins contributed to the data collection, data analysis and interpretation, and drafting of the manuscript. All authors reviewed and approved the final version of the manuscript prior to submission.

Acknowledgements: We are most grateful to the patients who contributed to the study and our outstanding outpatient and endoscopy teams, as well as our clinical nurse specialists who helped co-ordinate the study. The research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

REFERENCES

1. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009;**361**:2066-78.

2. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007;**132**:763–86.

3. Travis SP, Higgins PD, Orchard T, et al. Review article: defining remission in ulcerative colitis. *Aliment Pharmacol Ther* 2011;**34**(2):113–24.

4. Peyrin Biroulet L, Sands B, Reinisch W, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015;**110**(9):1324-38.

5. Bessissow T, Lemmens B, Ferrante M, et al. Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. *Am J Gastroenterol* 2012;**107**:1684-92.

6. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. *Gut* 2012;**61**(11):1619-35.

7. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with Infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterol* 2011;**141**:1194-1201.

8. Baert F, Moortgat L, Van Assche G, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010;**138**(2);463-8.

9. Rutgeerts P, Diamond RH, Bala M, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006;**63**(3):433-42.

10. D'Haens G, Baert F, Van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomized trial. *Lancet* 2008;**371**(9613):660-7.

11. De Cruz P, Kamm MA, Prideaux L, et al. Mucosal healing in Crohn's disease: a systematic review. *Inflamm Bowel Dis* 2013;**19**(2);429-44.

12. Schnitzler F, Fidder H, Ferrante M, et al. Mucosal healing predicts long term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009;**15**(9):1295-301.

13. Bryant RV, Burger DC, Delo J, et al. Beyond endoscopic mucosal healing in UC: histological remission better predicts corticosteroid use and hospitalization over 6 years of follow-up. *Gut* 2016;**65**:408–414.

14. Korelitz BI. Mucosal healing as an index of colitis activity: back to histological healing for future indices. *Inflamm Bowel Dis* 2010;**16**(9);1628-30.

15. Rosenberg L, Nanda KS, Zenlea T, et al. Histologic markers of inflammation in patients with ulcerative colitis in clinical remission. *Clin Gastroenterol Hepatol* 2013;**11**(8):991-6.

16. Powell-Tuck J, Day DW, Buckell NA, et al. Correlations between defined sigmoidoscopic appearances and other measures of disease activity in ulcerative colitis. *Dig Dis Sci* 1982;**27**:533-7.

17. Gomes P, du Boulay C, Smith CL, et al. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. *Gut* 1986;**27**:92-5.

18. Bessho R, Kanai T, Hosoe N, et al. Correlation between endocytoscopy and conventional histopathology in microstructural features of ulcerative colitis. *J Gastroenterol* 2011;**46**:1197-202.

19. Lemmens B, Arijs I, Van Assche G, et al. Correlation between the endoscopic and histologic score in assessing the activity of ulcerative colitis. *Inflamm Bowel Dis* 2013;**19**:1194-201.

20. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gut* 2012;**61**(4):535-42.

21. Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *Gastroenterol* 2013;**145**(5):987-95.

22. Travis SP, Schnell D, Feagan BG, et al. The impact of clinical information on the assessment of endoscopic activity: characteristics of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS). *J Crohn's Colitis* 2015;**9**(8):607-16.

23. Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, et al. Development and validation of the Nancy histological index for UC. *Gut* 2017;**66**(1):43-49.

24. Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. *Gut* 2017;**66**(1):50-58.

25. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. *J Crohn's Colitis* 2012;**6**:965-90.

26. Brown RA, Swanson-Beck J. Medical Statistics on Personal Computers, 2nd edn. London: BMJ Publishing Group, 1993.

27. Ikeya K, Hanai H, Sugimoto K, et al. The Ulcerative Colitis Endoscopic Index of Severity more accurately reflects clinical outcomes and long-term prognosis than the Mayo Endoscopic Score. *J Crohn's Colitis* 2016;**10**(3):286-95.

28. Vuitton L, Marteau P, Sandborn WJ, et al. Defining endoscopic response and remission in ulcerative colitis clinical trials: an international consensus. *Aliment Pharmacol Ther* 2017;**45**:801-13.

29. Fluxá D, Simian D, Flores L et al. Clinical, endoscopic and histological correlation and measures of association in ulcerative colitis. *J Dig Dis* 2017;**18**:634-41.

30. Geboes K, Riddell R, Ost A, et al. A reproducible grading scale for histological assessment of inflammation in ulcerative colitis. *Gut* 2000;**47**(3):404-9.

31. Riley SA, Mani V, Goodman MJ, et al. Microscopic activity in ulcerative colitis: what does it mean? *Gut* 1991;**32**(2);174-8.

32. Langner C, Magro F, Driessen A, et al. The histopathological approach to inflammatory bowel disease: a practice guide. *Virchows Arch* 2014:**464**(5):511-27.

33. Bryant R, Weiner S, Travis SPL et al. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. *J Crohns Colitis* 2014;**8**:1582-97.

34. West NR, Hegazy AN, Owens BMJ, et al. Oncostatin-M drives intestinal inflammation in mice and its abundance predicts response to anti-tumour necrosis factor neutralizing therapy in patients with inflammatory bowel disease. *Nature Medicine* 2017;**23**:579-89.

FIGURE LEGENDS

Figure 1: Distribution of total UCEIS scores.

Figure 2: Distribution, scatterplot and correlation coefficient (r) between UCEIS, NI and RHI.

a) UCEIS & RHI (scale 0-33): r =0.86, 95% CI 0.80-0.90, p <0.001
b) UCEIS & NI (scale 0-4): r=0.84, 95% CI 0.76-0.89, p <0.001
c) RHI & NI: r=0.92, 95% CI 0.87-0.95, p <0.001

Supplementary Figure 1: Distribution of Nancy Index scores.

Supplementary Figure 2: Distribution of Robarts Histologic Index scores.

TABLES

Table 1: UCEIS descriptors, levels and definitions used for evaluating UC.

Descriptor	Score (points)	Definition
Vascular Pattern	Normal (0)	Normal vascular pattern
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Spots or streaks of coagulated blood on the mucosal surface which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Visible oozing of blood from haemorrhagic mucosa
Erosions & Ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (≤5mm) defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer (2)	Larger (>5mm) defects in the mucosa, which are discrete fibrin covered ulcers, but remain superficial
	Deep ulcer (3)	Deeper excavated ulcers in the mucosa, with a slightly raised edge

Adapted from ref 21, with permission.

Table 2: Description of the Nancy Index histological criteria and definitions.

Grade	**Acute inflammatory cell infiltrate**	**Chronic inflammatory cell infiltrate**	**Ulceration**
0	None (0 point)	None (0 point) Mild (1 point)	None (0 point)
1	None (0 point)	Moderate or marked increase (3 points)	None (0 point)
2	Mild (2 points)	Moderate or marked increase (3 points)	None (0 point)
3	Moderate (3 points) Severe (4 points)	Moderate or marked increase (3 points)	None (0 point)
4	Moderate (3 points) Severe (4 points)	Moderate or marked increase (3 points)	Yes (2 points)

Adapted from ref 23, with permission.

Table 3: Components of the Robarts' Histopathology Index.

Component	**Calculating the Robarts' Histopathology Index**
Epithelial neutrophils 0=None 1=<5% crypts involved 2=<50% crypts involved 3=>50% crypts involved	**RHI = 1 x Chronic inflammatory cell infiltrate level (4 levels)** **+ 2 x Lamina propria neutrophils (4 levels)** **+ 3 x Epithelial neutrophils (4 levels)** **+ 5 x Erosion or ulceration (4 levels)**
Lamina propria neutrophils 0=None 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	
Chronic inflammatory cell infiltrate 0=No increase 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase	
Erosion or ulceration 0=No erosion, ulceration or granulation tissue 1=Recovering epithelium + adjacent inflammation 1=Probable erosion—focally stripped 2=Unequivocal erosion 3=Ulcer or granulation tissue	

Adapted from ref 24, with permission.

Table 4: Baseline characteristics of patients with UC (n and % unless specified).

Baseline characteristics	n (%)
Patients with UC	125
Age (years), mean (sd)	39.2 (15)
Sex	
Men	64 (51)
Women	61 (49)
Procedure	
Flexible sigmoidoscopy	76 (61)
Colonoscopy	49 (39)
Number of biopsies taken per patient	
1	4 (3)
2	46 (36)
3	21 (17)
4	14 (11)
5	21 (17)
6	12 (10)
7	5 (4)
8	2 (2)

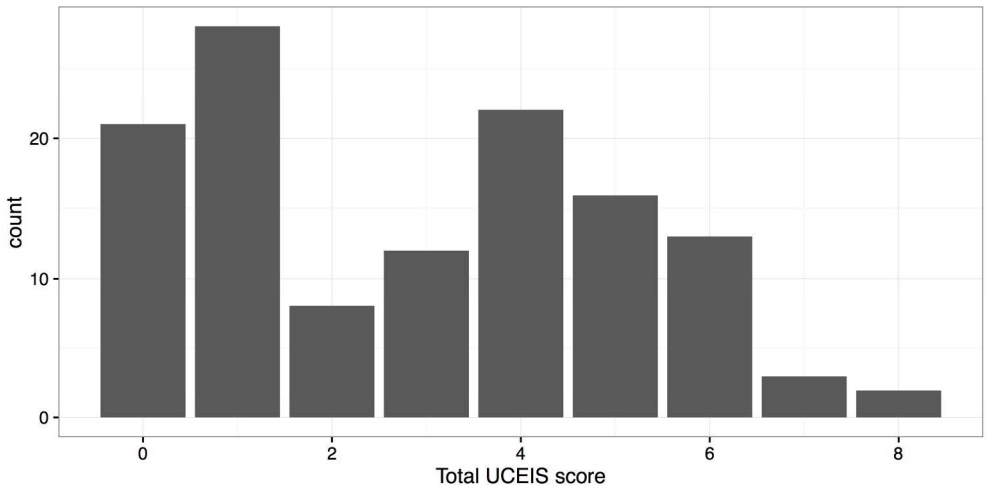


Figure 1: Distribution of total UCEIS scores.

203x101mm (300 x 300 DPI)

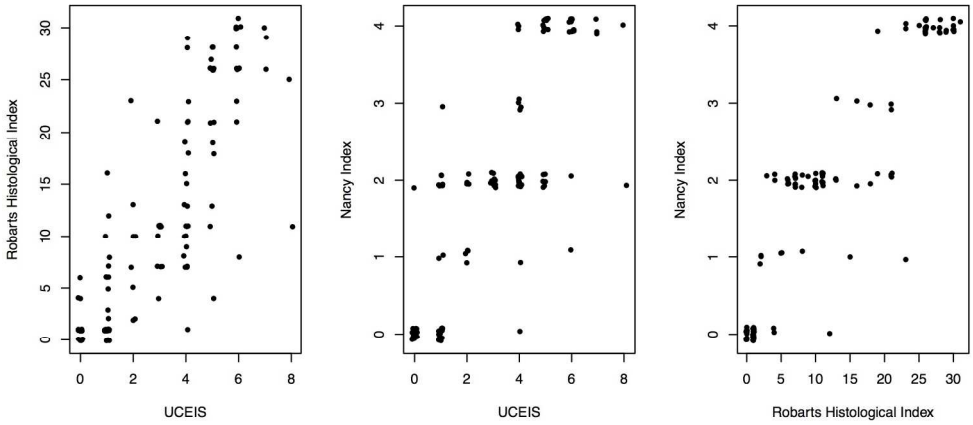
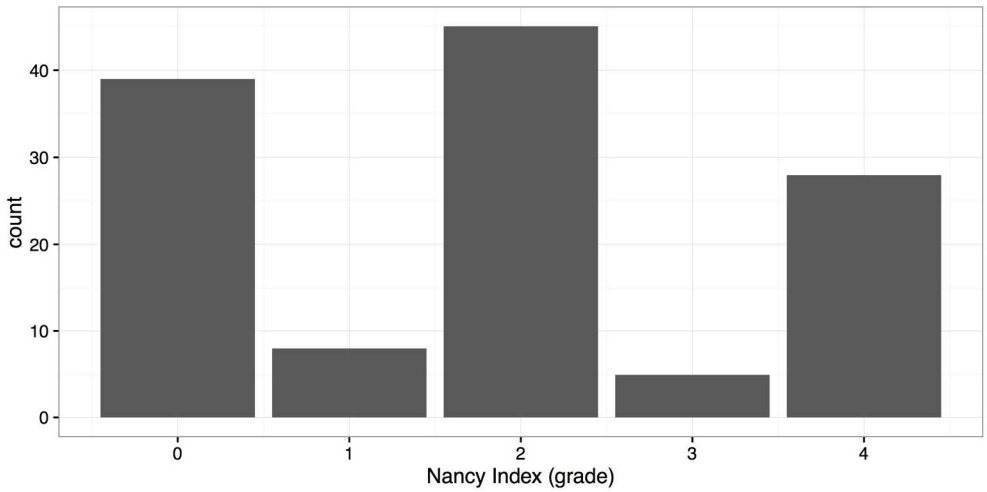
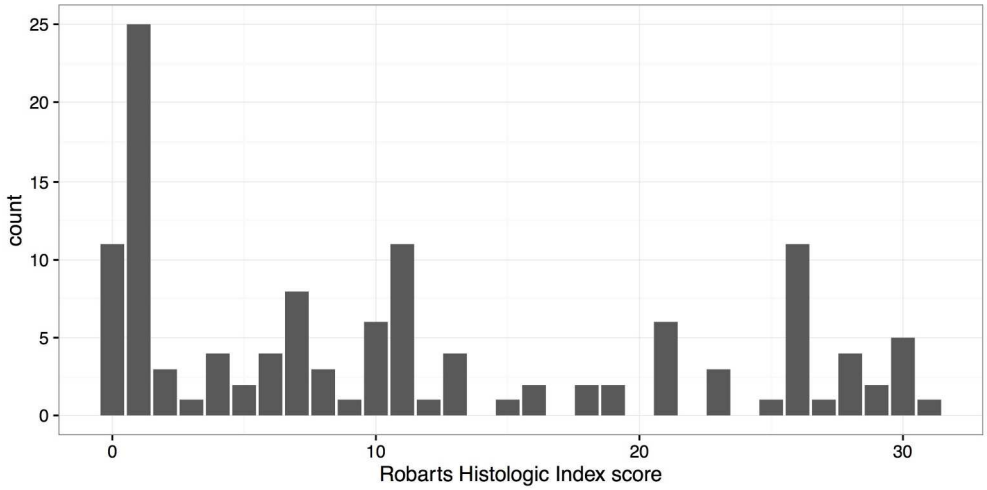


Figure 2: Distribution, scatterplot and correlation coefficient (r) between UCEIS, NI and RHI.
a) UCEIS & RHI (scale 0-33): r =0.86, 95% CI 0.80-0.90, p <0.001
b) UCEIS & NI (scale 0-4): r=0.84, 95% CI 0.76-0.89, p <0.001
c) RHI & NI: r=0.92, 95% CI 0.87-0.95, p <0.001

203x101mm (300 x 300 DPI)



203x101mm (300 x 300 DPI)



203x101mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL TABLES

Supplementary Table 1: Range of UCEIS scores according to individual components.

Component	n (%)
Vascular pattern	
Normal	21 (17)
Patchy obliteration	34 (27)
Obliterated	70 (56)
Bleeding	
None	63 (50)
Mucosal	44 (36)
Luminal mild	14 (11)
Luminal moderate or severe	4 (3)
Ulceration & Erosions	
None	61 (50)
Erosions 5mm or less	28 (22)
Superficial ulcer >5mm	31 (25)
Deep ulcer	5 (4)
Total UCEIS score	
0	21 (17)
1	28 (22)
2	8 (6)
3	12 (10)
4	22 (18)

5	16 (13)
6	13 (10)
7	3 (2)
8	2 (2)

Supplementary Table 2: Nancy Index range of scores.

Item	**n (%)**
Acute inflammatory cell infiltrate	
None	47 (37.6)
Mild	62 (49.6)
Moderate	12 (9.6)
Severe	4 (3.2)
Chronic inflammatory cell infiltrate	
None	11 (8.8)
Mild	34 (27.2)
Moderate or marked increase	28 (22.4)
Severe	52 (41.6)
Ulceration	
None	97 (77.6)
Yes	28 (22.4)
Grade	
0	39 (31.2)
1	8 (6.4)
2	45 (36.0)

3	5 (4.0)
4	28 (22.4)

Supplementary table 3: Robarts' Histopathology Index range of scores.

Item	**n (%)**
Epithelial neutrophils	
None	43 (34)
<5% crypts involved	27 (22)
<50% crypts involved	45 (36)
>50% crypts involved	10 (8)
Lamina propria neutrophils	
No increase	46 (37)
Mild but unequivocal increase	64 (51)
Moderate increase	11 (9)
Marked increase	4 (3)
Chronic inflammatory cell infiltrate	
No increase	11 (9)
Mild but unequivocal increase	34 (27)
Moderate increase	28 (22)
Marked increase	52 (42)
Erosion or ulceration	
No erosion, ulceration or granulation tissue	81 (65)
Recovering epithelium + adjacent inflammation or Probably erosion-focally stripped	9 (7)

Unequivocal erosion	6 (5)
Ulcer or granulation tissue	29 (23)
Robarts' Histologic Index (0-33)	
Mean (sd)	11.4 (10)
Median (IQR)	10 (1, 21)
(minimum, maximum)	(0, 31)