Development and reliability of the new endoscopic virtual chromoendoscopy score:

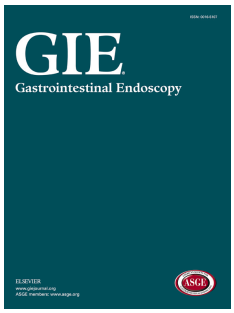
Iacucci, Marietta; Daperno, Marco; Lazarev, Mark; Arsenascu, Razvan; Tontini, Gian Eugenio; Akinola, Oluseyi; Gui, Xianyong Sean; Villanacci, Vincenzo; Goetz, Martin; Lowerison, Mark; Lethebe, Brendan Cord; Vecchi, Maurizio; Neumann, Helmut; Ghosh, Subrata; Bisschops, Raf; Kiesslich, Ralf

DOI:
10.1016/j.gie.2017.03.012

Document Version
Peer reviewed version

Citation for published version (Harvard):
Iacucci, M, Daperno, M, Lazarev, M, Arsenascu, R, Tontini, GE, Akinola, O, Gui, XS, Villanacci, V, Goetz, M, Lowerison, M, Lethebe, BC, Vecchi, M, Neumann, H, Ghosh, S, Bisschops, R & Kiesslich, R 2017, 'Development and reliability of the new endoscopic virtual chromoendoscopy score: the PICaSSO score (Paddington International Virtual ChromoendoScopy ScOre) in ulcerative colitis', *Gastrointestinal Endoscopy*. https://doi.org/10.1016/j.gie.2017.03.012

Accepted Manuscript



Development and reliability of the new endoscopic virtual chromoendoscopy score: the PICaSSO score (Paddington International Virtual ChromoendoScopy ScOre) in ulcerative colitis

Marietta Iacucci, Marco Daperno, Mark Lazarev, Razvan Arsenascu, Gian Eugenio Tontini, Oluseyi Akinola, Xianyong Sean Gui, Vincenzo Villanacci, Martin Goetz, Mark Lowerison, Brendan Cord Lethebe, Maurizio Vecchi, Helmut Neumann, Subrata Ghosh, Raf Bisschops, Ralf Kiesslich

PII: S0016-5107(17)30192-X

DOI: 10.1016/j.gie.2017.03.012

Reference: YMGE 10461

To appear in: *Gastrointestinal Endoscopy*

Received Date: 29 October 2016

Accepted Date: 5 March 2017

Please cite this article as: Iacucci M, Daperno M, Lazarev M, Arsenascu R, Tontini GE, Akinola O, Gui XS, Villanacci V, Goetz M, Lowerison M, Lethebe BC, Vecchi M, Neumann H, Ghosh S, Bisschops R, Kiesslich R, Development and reliability of the new endoscopic virtual chromoendoscopy score: the PICaSSO score (Paddington International Virtual ChromoendoScopy ScOre) in ulcerative colitis, *Gastrointestinal Endoscopy* (2017), doi: 10.1016/j.gie.2017.03.012.

Development and reliability of the new endoscopic virtual chromoendoscopy score: the PICaSSO score (Paddington International Virtual ChromoendoScopy ScOre) in ulcerative colitis

Marietta Iacucci[1,2], Marco Daperno[3], Mark Lazarev,[5] Razvan Arsenascu,[6] Gian Eugenio Tontini [7], Oluseyi Akinola[1,], Xianyong Sean Gui[9], Vincenzo Villanacci[10], Martin Goetz[8], Mark Lowerison[13], Brendan Cord Lethebe[13], Maurizio Vecchi[7], Helmut Neumann[12], Subrata Ghosh[1,2 *], Raf Bisschops [11*], Ralf Kiesslich [4*]

RB and RK contributed equally to the manuscript.

[1]Division of Gastroenterology, University of Calgary –Cumming School of Medicine Canada,

[2] Division of Gastroenterology& Institute translational Medicine University of Birmingham, UK

[3] Division of Gastroenterology University of Torino, Italy

[4] Division of Gastroenterology, Director of Internal Medicine II ,HSK Hospital, Wiesbaden ,Germany

[5] Division of Gastroenterology Johns Hopkins Hospital Baltimore, USA

[6] Division of Gastroenterology, Morristown Medical Center, Atlantic Health System, New Jersey USA

[7] Department of Biomedical Sciences for the Health Division of Gastroenterology IRCCS Policlinico San Donato , University of Milan Milan, Italy

[8] Division of Gastroenterology University Klinikum Tuebingen , Germany
[9]Department of Pathology University of Calgary, Calgary Canada
[10] Institute of Pathology ASST Spedali Civili Brescia Italy
[11]Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium
[12] Interventional Endoscopy Center, I. Medizinische Klinik und Poliklinik, University Hospital Mainz, Germany
[13] Department of Community Health Sciences, Clinical Research Unit, Cumming School of Medicine, University of Calgary, Canada

Correspondence to: Marietta Iacucci MD, PhD
Reader/Senior Associate Professor of Gastroenterology,
Institute of Translational Medicine,
University of Birmingham,
Adjunct Clinical Associate Professor of Medicine ,University of Calgary
Institute of Translational Medicine ,
Heritage Building Research & Development
University Hospital Birmingham NHS Foundation Trust,
Edgbaston B15 2TT Birmingham, UK.
Telephone +44(0)1213718119
email : m.iacucci@bham.ac.uk or miacucci@ucalgary.ca

No financial support was required for this manuscript

Development and reliability of the new endoscopic virtual chromoendoscopy score: the PICaSSO score (Paddington International Virtual ChromoendoScopy ScOre) in ulcerative colitis

Marietta Iacucci[1,2], Marco Daperno[3], Mark Lazarev,[5] Razvan Arsenascu,[6] Gian Eugenio Tontini [7], Oluseyi Akinola[1,], Xianyong Sean Gui[9], Vincenzo Villanacci[10], Martin Goetz[8], Mark Lowerison[13], Brendan Cord Lethebe[13], Maurizio Vecchi[7], Helmut Neumann[12], Subrata Ghosh[1,2 *], Raf Bisschops [11*], Ralf Kiesslich [4*]

RB and RK contributed equally to the manuscript.

[1]Division of Gastroenterology, University of Calgary –Cumming School of Medicine Canada,

[2] Division of Gastroenterology& Institute of Translational Medicine, University of Birmingham, UK

[3] Division of Gastroenterology University of Torino, Italy

[4] Division of Gastroenterology, Director of Internal Medicine II ,HSK Hospital, Wiesbaden, Germany

[5] Division of Gastroenterology, Johns Hopkins Hospital Baltimore, USA

[6] Division of Gastroenterology, Morristown Medical Center, Atlantic Health System, New Jersey, USA

[7] Department of Biomedical Sciences for the Health Division of Gastroenterology IRCCS Policlinico San Donato , University of Milan, Milan, Italy

[8] Division of Gastroenterology University Klinikum Tuebingen, Germany

[9]Department of Pathology University of Calgary, Calgary Canada

[10] Institute of Pathology ASST Spedali Civili, Brescia, Italy

[11]Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium

[12] Interventional Endoscopy Center, I. Medizinische Klinik und Poliklinik, University Hospital Mainz, Germany

[13] Department of Community Health Sciences, Clinical Research Unit, Cumming School of Medicine, University of Calgary, Canada

Correspondence to: Marietta Iacucci MD, PhD
Reader/Senior Associate Professor of Gastroenterology,
Institute of Translational Medicine,
University of Birmingham,
Adjunct Clinical Associate Professor of Medicine, University of Calgary
Institute of Translational Medicine ,
Heritage Building Research & Development
University Hospitals Birmingham NHS Foundation Trust,
Edgbaston B15 2TT, Birmingham, UK.
Telephone +44(0)1213718119
email : m.iacucci@bham.ac.uk or miacucci@ucalgary.ca

No financial support was required for this manuscript

Conflicts of Interest

MI: M .Iacucci received unrestricted research grant from Pentax USA

(2013-2016) and speaker's fee (2016); research support from Abbvie (204-2015); consultancy fees from Abbvie and Janssen (2015)

RB : R. Bisschops has received: consultancy fees from Boston Scientific (2015); speaker's fees from Covidien (2009–2016) and Norgine (2015); speaker's fee and hands-on training sponsorship from Olympus Europe (2013–2014); consultancy fees, speaker's fee, and research support from Pentax Europe (2008–2016) and Fujifilm (2013–2016); research support from Cook Medical (2015–2016); hands-on training sponsorship from ERBE (2013–2015); and an editorial fee from Thieme Verlag as co-editor of Endoscopy.

RA: R. Arsenascu haș received grant funding and consultant fees from Abbvie, Janssen , Shire and Takeda.

HN: H. Neumann has received Scientific support from Olympus, Pentax Medical, Fujifilm, EndoChoice, Abbvie, Siemens, SpectraScience, Smart Medical.

Lectures from Pentax Medical, Fujifilm, EndoChoice, Abbvie, SpectraScience, Aptalis, Mauna Kea Technologies, Eisai, Recordati, Takeda, MSD, Astra Zeneca, Falk, Smart Medical.

Consultant from Pentax Medical, Fujifilm, Smart Medical, EndoChoice, Fraunhofer, SpectraScience, Motus GI

SG: S.Ghosh has served as advisor to Pfizer, Janssen, Aerpio, Receptos, Takeda, Bristol Myers Squibb, Novo Nordisk, Shire , Ferring, Celgene and has received research support from Abbvie and speaker fee from Abbvie, Takeda and Janssen

None of the other authors have any conflict of interest to declare

Abbreviations

Ulcerative Colitis: UC

Mucosal Healing: MH

Federal Drug Agency: FDA

Mayo endoscopic subscore: Mayo

Ulcerative Colitis Endoscopic Index of Severity: UCEIS

The ulcerative colitis colonoscopic index of severity : (UCCIS)

Robarts Histological Index: RHI

New York Mount Sinai system developed by Harpaz : NYMS

White Light Endosocpy: WLE

High definition: HD

Virtual electronic Chromoendoscopy: VEC

The Paddington International Virtual Chromoendoscopy score **:**PICaSSO

High-definition white light =iSCAN 1

High-definition electronic virtual Chromoendoscopy =iSCAN 2 and 3

Key words : *Ulcerative Colitis , endoscopic scores , iscan, virtual Chromoendoscopy , Mucosal Healing*

Abstract

Introduction: Endoscopic inflammation and healing are important therapeutic endpoints in ulcerative colitis (UC). We developed and validated a new electronic virtual chromoendoscopy (EVC) score that could reflect the full spectrum of mucosal and vascular changes including mucosal healing in UC.

Methods: Eight participants reviewed a 60-minute training module outlining the three different i-SCAN modes demonstrating the entire spectrum of inflammatory mucosal and vascular changes in UC. Performance characteristics in endoscopic scoring and predicting the histologic inflammation with EVC (i-SCAN) by using 20 video clips before (pre-test) and after (post-test) were evaluated. Exploratory univariate factor analysis was performed on "PICaSSO" score covariates for mucosal and vascular score separately. Subsequently a proportional odds logistic regression model for the prediction of histological scores were analyzed.

Results: The interobserver agreement for Mayo endoscopic score in the pre-test (k=0.85; 95% CI, 0.78-0.90) and the post- test (k=0.85; 95% CI, 0.77-0.90) evaluation were very good. This was also true for UCEIS in the pre and post-test score interobserver agreement (k= 0.86;95% CI, 0.77-0.92 and k=0.84; 95% CI, 0.75-0.91). The interobserver agreement of the PICaSSO endoscopic score was very good in the pre and post-test evaluations (k= 0.92; 95% CI, 0.87-96 and k= 0.89; 95% CI, 0.84-0.94). The accuracy of the overall PICaSSO score in assessing histological abnormalities and inflammation by Harpaz score was 57% (95% CI, 48%-65%), by RHI 72% (95% CI, 64%-79%) and by ECAP (full spectrum of histologic changes) 83% (95% CI,76%-88%).

Conclusion: The EVC score "PICaSSO" showed very good interobserver agreement. The new EVC score may be used to define the endoscopic findings of the mucosal and vascular healing in UC and reflected the full spectrum of histological changes.

Introduction

Endoscopic assessment of mucosal inflammation and mucosal healing (MH) is a critically important component of determining the severity of ulcerative

colitis (UC) in clinical trials and in clinical practice (1,2). The Federal Drug Agency (FDA) is stipulating the use of endoscopic score combined with patient reported outcomes (PRO2 – rectal bleeding, bowel frequency) in evaluating the efficacy and outcome in the treatment of UC by novel emerging therapeutic agents. (3)

The Mayo endoscopic subscore is the most widely used endoscopic scoring system. Although never formally validated, the Mayo endoscopic score is simple and has operating characteristics that are easily applicable for scoring the degree of mucosal inflammation in UC by individual gastroenterologists and trained central readers reporting from video recordings (4-7). Mayo endoscopic score may vary from 0 to 3 and at each scoring level several features must be considered. Mayo score does not consider vascular changes but with the new generation of high-definition (HD) colonoscopes with or without electronic virtual chromoendoscopy (EVC), vascular patterns are often appreciated as abnormal, but not absent. Friability is another feature in the Mayo score that is open to subjective interpretation. Despite there are important endoscopic difference between Mayo score 0 and 1, both of these are considered mucosal healing in clinical trial and in clinical practice, but histological changes may still be present. It is also clear that there are clinically meaningful outcome differences between Mayo endoscopic subscore of 0 and 1. Although studies have established that mucosal healing (Mayo endoscopic score of 0 or 1) have reduced risk of flares or colectomy, it is important to note that recently Barrreiro –de Acosta et al (8) have shown that the risk of recurrence in UC patients with Mayo endoscopic score of 1 is higher (36.6%) compared with Mayo score 0 (9.4%) .

In order to overcome some of the limitations of Mayo endoscopic subscore, more detailed scoring systems have been recently developed and validated. It is not clear whether these new scores, Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS) are superior in their operating characteristics to Mayo endoscopic subscore. (9-11, 30)

In addition, no validated scoring systems for electronic virtual chromoendoscopy is available. These techniques are currently available on all endoscopic platforms and provide better mucosal and vascular details than conventional WL endoscopy. Iacucci et al (12) have recently described an endoscopic scoring system using i-SCAN electronic virtual chromoendoscopy to assess inflammation in UC. They have shown that measure of abnormal vascular pattern may correlate with histologic indices.

In this study, we aimed to develop a new electronic virtual chromoendoscopy score (EVC), which was more comprehensive in including details of subtle vascular and mucosal changes reflecting chronic and acute inflammation in UC patients using HD equipment with EVC. We wanted to better define the characteristics of endoscopic MH in UC patients and therefore we considered and included all the subtle chronic and acute inflammatory changes of vascular and mucosal pattern. We aimed to validate for the first time a new PICaSSO-Score (The Paddington International virtual ChromoendoScopy ScOre), by determining the intraobserver and interobserver agreement among international experts, to assess the correlation with standard endoscopic UC scores and the correlation to several histological scores.

Study Design & Methods

Ethical approval

The study was approved by the Conjoint Health Research Ethics Board (CHREB) of the University of Calgary, Alberta, Canada.
All authors had access to the study data and reviewed and approved the final manuscript.

Participants

A total of 8 gastroenterologists and 2 pathologists experienced in IBD and advanced endoscopic imaging techniques participated in the London consensus. The gastroenterologists had performed an average of 8000 colonoscopies in their lifetime and all of them were experienced in the i-SCAN virtual chromoendoscopy technology (Pentax, Japan) and 7 with NBI (Olympus, Japan). All of them were also familiar and experienced with endoscopic scoring systems currently in use in UC such as Mayo endoscopy subscore and Ulcerative Colitis Endoscopic Index of Severity Index (UCEIS) (4,9-11).

Training module (algorithm)

A 60-minutes Powerpoint training module was developed and presented at the consensus conference held at London. (MI, SG, MD).
The content of the module included an introduction to the study, an explanation of the existing endoscopic scores in use such as Mayo endoscopic subscore and UCEIS, the i-SCAN score developed by Iacucci *et al.* (4, 9-12), and the role of the histological score to assess inflammation

and mucosal healing in UC (SXG, VV).

The training module consisted of 70 endoscopic pictures and 5 videos and were assessed by all the participants with direct feedback and stepwise discussion. These illustrated the entire spectrum of inflammatory mucosal and vascular changes including mucosal healing in UC. Representative slides in Powerpoint from the training module and a video are shown (Figs 1 -2 and video supplement)

Video Library

Twenty high-quality video clips representing collections of different grades of inflammation were selected from an existing library. This anonymized library was collected by one investigator (M.I.) from surveillance colonoscopies or for assessing activity of the disease in UC patients.

The video clips had a duration of 90 to 120 seconds, showing the degree of inflammation by white light, followed by i-SCAN (EPKi 7000 Pentax EC-3490Fi in the 3 settings, High-definition white light i-SCAN 1, and electronic virtual chromoendoscopy i-SCAN 2 and 3). Two specimens of biopsies were taken in the rectum and in the sigmoid colon and were sent to a single expert pathologist (SXG), who was blinded to the endoscopic results. The histological examination were assessed according to the existing histological score – NYMS (New York Mount Sinai system) developed by Harpaz, (13) the newly validated Robarts Histological index (RHI) score (14) and the newly described Calgary (ECAP) score (12) which is more comphrensive in including the acute and chronic changes of inflammation in the colonic mucosa in UC. The videos were saved in audio video interleave (AVI) format. Of the twenty videos, 5 were severe UC, 5

moderate UC, 5 mild UC, and 5 were quiescient UC, as defined by Mayo endoscopy subscores.

Endoscopic form and data collection

Data was collected from each participant including years in practice after training, number of annual colonoscopies and in their lifetime, experience with NBI and i-SCAN techniques.

A structured Case Video Report Form (CVRF) was created for the participants to assess the different endoscopic scores (see supplement/appendix).

Development of the new virtual chromoendoscopy score in UC (PiCaSSO score)

The study was conducted in 4 phases: Phase 1, training module with pictures of the previous i-SCAN score developed by Iacucci et al and development of EVC classification system for endoscopic assessment of mucosal and vascular healing in UC after feedback and stepwise discussion between the experienced gastroenterologists ; phase 2 powerpoint training module of seventy i-scan pictures and 5 videos ; phase 3 (pre-test), evaluation of intraobserver and interobserver agreement between gastroenterologists experienced in EVC and IBD in scoring different endoscopic systems in UC (Mayo endoscopic subscore, UCEIS, i-SCAN virtual chromoendoscopy and the new PICaSSO score using video clips in the pre-test fashion for different grades of inflammation ; phase 4 (post-test), validation of the endoscopic findings criteria and the overall classification using the same videos in a post–test fashion after a second training module.

The videos included and considered in the teaching module were not included in the validation pre-test and post-test scores between the raters. All endoscopist raters were blinded to clinical history, clinical activity and number of videos in each category.

First and second phases (First day of the London consensus)

The new PICaSSO virtual chromoendoscopy score was developed by the consensus group in a stepwise fashion using videos and still pictures. We based our assessment on the framework of our endoscopic experience in virtual digital and optical chromoendoscopy, previous i-SCAN and NBI score which recently has been assessed and modified for mucosal inflammation that specifically characterizes vascular and mucosal changes which correlate well with histological scoring systems and clinical outcomes Table 1. (15-20).

Third phase (Pre-test)

All participants were provided with the pre-test videos and instructed to enter their responses in the CVRF. A total of 20 high-definition video clips was shown to the participants and on completion of the forms, these were handed over to the coordinator of the consensus. The endoscopists rated all the videos as high quality as part of their evaluation. The participants did not exclude any video because of concern about quality. All videos were from routine clinical practice.

Fourth phase (Post-test)

An additional teaching module of 10 videos of different grade of UC inflammation and with direct feedback and discussion, was presented on the

second day of the consensus. After that, the same 20 videos clips, in a different order, was provided to the participants – the period between pre-test and post test minimized recall bias.

Histologic assessment

An IBD histological grading scheme NYMS (New York Mount Sinai System) developed by Harpaz (13), and the Robarts Histological Index (RHI) were used for comparison (14) with endoscopic scores. A comprehensive and more detailed histological characterization, which reflected all the chronic and acute changes of inflammation, were independently performed by a single gastrointestinal histopathologist (SXG) who was blinded to the endoscopic findings. This scoring (ECAP system – **E**xtent, **C**hronicity, **A**ctivity, **P**lus additional findings) system was previously designed independently by SXG alongside the i-SCAN score to assess all, including even minimal chronic mucosal changes in UC (12). This grading/scoring, including (1) Extent of mucosal inflammation (**E**), (2) Chronicity (**C**), ie, changes indicative of a chronic inflammatory process, (3) Activity (**A**), ie, the degree of active (neutrophilic) inflammation, and (4) plus other additional findings (**P**), including eosinophilia and lymphoid follicles/aggregates, both being relatively nonspecific to any particular process. The details of the scoring system are shown in Supplementary Tables 1, 2, and 3, available online.

Statistical Analysis

Software

All the responses of the raters were transferred to a Microsoft Excel (Microsoft Inc, Redmond, Wash) database and exported to for statistical analysis.

Statistical Analysis was performed using the R system for statistical computing version 3.2.2 (R Core Team, 2015)

Analysis of Rater Agreement

Intraobserver and interobserver agreement was assessed for pre and post training time points for Mayo, UCEIS, i-SCAN Mucosal, i-SCAN Vascular, i-SCAN Total, Picasso Mucosal, Picasso Vascular and Picasso Total scores using Cohen's *Kappa* for Multiple Raters. Confidence intervals for each *Kappa* estimate were calculated using the adjusted bootstrap confidence interval procedure described in DiCiccio and Efron (1996) (21). Tests for equality of *Kappa* estimates pre and post training were performed using a non-parametric bootstrap p-value estimated using 1000 samples.

We obtained the sample size by considering the ability to detect 0.15 to 0.20 points of *Kappa* statistics difference with 2 tailed test at 80% power; fifteen to19 videos were sufficient for this purpose. In this study, a sample size of 160 observations (20 videos, 8 reviewers) was calculated to be adequate to detect this difference with 80% power and an alpha of 0.05.

Model Coefficient Selection

Exploratory univariate factor analysis was performed on Picasso co-variates for Mucosal, Vascular and Overall Score separately. Subsequently a proportional Odds Logistic Regression Models for the prediction of Histological Score (1-4), and Linear Regression Models of ECAP (1-26) and

RHI (1-33) scores were fit using co-variates indicated from the exploratory factor analyses.

Model Assessment

Model based predictions of histological Scores Harpaz, ECAP and RHI were assessed for prediction accuracy and correlation between predicted and true scores using a bootstrap sample based cross validation procedure. Accuracy and Kendal (Harpaz Score) or Pearson (ECAP or RHI Score) correlations are presented as measures of model quality. Accuracy was defined as 1-Misclassification Rate. Misclassification in the Histological Score was defined as any predicted value that did not equal the true histological score. In ECAP and RHI scores misclassification was defined as any model based prediction that fell outside of $\pm$ 1 minimum clinical important difference unit for each scale. ECAP and RHI minimal clinically important difference values were 4 and 6 units, respectively.

Results

Interobserver agreement between the endoscopic scores

The overall interobserver agreement for Mayo endoscopic subscore between the endoscopists in the pre-test (k=0.85; 95% CI, 0.78-0.90) and the post test (k=0.85; 95% CI, 0.77-0.90) evaluations was very good, as well as for UCEIS in the pre- and post test score (k= 0.86; 95% CI, 0.77-0.92 and k=0.84; 95% CI, 0.75-0.91). The overall interobserver agreement for i-SCAN score to assess inflammation was at baseline (k= 0.75; 95% CI, 0.66-0.83), and after training k= 0.76 (95% CI, 0.65-0.84). The interobserver

agreement of the new PICaSSO overall endoscopic score was considered very good in the pre- and post test evaluation (k= 0.91; 95% CI, 0.87-096 and k= 0.89; 95% CI, 0.84-0.94) Figure 3.

Intraobserver agreements of Mayo endoscopic subscore, UCEIS, i-SCAN mucosal, vascular and overall score, PICaSSO score are shown in Table 2.

Sensitivity analyses were carried out, and excluding most severe cases (Mayo 3), more remitting cases (Mayo 0) and selectively removing any subgroup of reads based on Mayo scoring classification, did not lead to any meaningful difference in interobserver agreement measured by means of *kappa* statistics.

Correlation between the existing endoscopic, histological scores and the new PICaSSO score

The correlation between Mayo, UCEIS, i-SCAN mucosal, vascular, overall and PICaSSO mucosal, vascular and overall with Harpaz, RHI and ECAP histological scores are showed in Supplementary Table 4, online. The new PICaSSO score correlated also well with all the histological scores but better with the ECAP than RHI score that includes acute but also chronic and subtle inflammatory changes of the colonic mucosa.

Multivariate logistic regression analysis and accuracy of the PICaSSO score

Exploratory statistical model analysis was performed and showed that the endoscopic mucosal features of continuous/regular crypts, crypts not visible (scar), discontinuous and or dilated/elongated crypts and vascular pattern

findings such as roundish after crypt architecture, vessels not visible (scar), sparse (deep) vessels without dilatation were associated with healing in UC whereas micro-erosions and crowded dilated vessels were associated with mild inflammation . Subsequently a proportional Odds Logistic Regression Models for the prediction of Histological Score (1-4), and Linear Regression Models of ECAP (1-26) and RHI (1-33) scores were performed for the final development of PICaSSO score and confirmed that these endoscopic features were predictors of mucosal healing and activity of the disease. Table 3.

The accuracy of the new PICaSSO score to predict mucosal healing and inflammation by using the 3 histological score (Harpaz, RHI and ECAP) was determined and is showed in Figure 4.

The PICaSSO mucosal, vascular and overall score predict better histological healing and inflammation abnormalities when it was used with the ECAP and RHI histological scores then compared with Harpaz score. The accuracy of the overall PICaSSO to assess histological abnormalities and inflammation by Harpaz score was 0.57% (95% CI, 0.48-065) by RHI 0.72% (95% CI, 0.64-079) and by ECAP 0.83% (95% CI, 0.76%-0.88) (Figure 4).

Discussion

To our knowledge, this is the first validated endoscopic score using the new generation of virtual chromoendoscopy endoscopes in UC. The PICaSSO score performed better than the previously published i-SCAN score by Iacucci et al. (12).

The newly developed PICaSSO score defined for the first time the endoscopic findings of the mucosal and vascular healing in UC using EVC and reflects the whole range of the endoscopic spectrum of inflammation. A precise endoscopic assessment of subtle inflammation may be further explored in future in terms of relationship to clinical outcomes. (22-24)

However, the endoscopic evaluation of MH in UC still remains an important challenge. Multiple endoscopic scores, partially validated, have been developed using the previous generation of WLE and have several limitations in the assessment of inflammation in UC accurately. In addition, the distribution of inflammation can be subtle, patchy and easily missed by WLE and random biopsies (15, 25-28).

On the other hand, the Mayo endoscopic subscore is widely used in clinical practice and in clinical trials, as it is easy to use by experienced gastroenterologists and has been found to have adequate interobserver and intraobserver agreement but is limited in the ability to be reproduced by less experienced gastroenterologists. In addition it is not ideal in detecting subtle inflammation at the lower end of the range and to differentiate well between mucosal healing and mild inflammation, as the range is a limited 0-3 score (4,30).

Recently, it has also been shown that patients with a Mayo endoscopic score of 1, which is considered in clinical trials as mucosal healing, have a high rate of recurrence compared with a score of 0 (8). In our article we have

confirmed a reproducibility and a good correlation between the Mayo subscore and all histological scores. The aim of the PICaSSO score was to distinguish between Mayo subscores 0 and 1 because Mayo 1 does not truly represent mucosal healing.

Iacucci et al have recently developed EVC score for UC that defines subtle inflammation and mucosal healing. They have also designed a new histologic grading/scoring system (ECAP system – Extent, Chronicity, Activity, Plus additional findings) to be fully reflective of every chronic or acute inflammatory histological changes in UC (12). These have shown a high degree of correlation between the i-SCAN scores and the Mayo subscore and Harpaz histological grading. However, complete MH defined by endoscopic Mayo subscore 0 still demonstrated abnormalities by using EVC and the histological ECAP score.

The London consensus developed and validated a more detailed endoscopic score, using the latest generation of high-definition virtual electronic chromoendoscopy endoscopes that could better define and characterize endoscopic mucosal healing and all the spectrum of mild and more severe inflammatory changes in UC patients. The new PICaSSO score embraced all the endoscopic findings of the inflammation in UC and performs better than the previous i-SCAN score developed by Iacucci et al. (12).

Previous studies have shown a large variance of intraobserver and interobserver agreement between gastroenterologists to assess the endoscopic activity in UC (5,29). The panelists of the London consensus had a very good intraobserver and interobserver variability in scoring endoscopic

inflammation in UC using all the endoscopic scores including the new PICaSSO score.

Our data suggest that the consistent evaluation of endoscopic inflammation between observers can most likely be attributed to the computer based training module, the stepwise feedback and the experience in advanced imaging techniques of the observers.

The PICaSSO score if further validated in multicenter studies, may turn out to be a reliable instrument for measuring endoscopic inflammation as mucosal and vascular changes in UC patients.
The endoscopic findings of mucosal and vascular healing such as continuous/regular crypts, crypts not visible (scar), discontinuous and or dilated/elongated crypts and vascular pattern findings such as roundish after crypt architecture, vessels not visible (scar), sparse (deep) vessels without dilatation predicted histological remission versus mild inflammation especially when these were used with the new more precise histological scores RHI and ECAP .(13-14)

Adding support to these results Hayashi et al have recently demonstrated that magnifying NBI observation of mucosa was effective for the assessment of UC follow-up. The endoscopic vascular pattern features were accurately assessed by NBI with magnification and were important predictors of UC relapse (20). Hayashi et al reported the vascular findings alone without the mucosal findings in the abstract. The vascular findings with NBI are similar to i-SCAN and it is likely that a common EVC score may be developed

irrespective of the exact EVC platform; ongoing studies will address this important issue.

We have introduced for the first time an integrated EVC score for mucosal and vascular patterns to better assess and grade inflammation and MH in UC. However, the experienced raters performed better in assessing mucosal pattern compared with the vascular pattern. This might be explained by the fact that the detailed electronic vascular endoscopic score is a new development concept, also for experienced observers. We are planning to do learning curve assessment in future using extended teaching phase divided into quartiles using endoscopists with varying levels of experience ; however, in this phase of development of the PICaSSO the participants were experts in i-SCAN and optical diagnosis technology and so we did not directly address the learning curve.

In the long term, the PICaSSO score needs to be validated in a multicenter prospective study. Multicenter real life studies are ongoing to validate the PICaSSO scores across different international centers under a variety of conditions. In this study, although the sample size in terms of videos read by the observers (n=20) might seem to be low, the sample size estimate mentioned above was accomplished. Moreover in some recently published papers the dataset of videos analysed did not exceed this number (5 to 11 videos) or the dataset was slightly larger, but readers concentrated on a smaller subset of videos (39 videos); (16 videos/reader). (31-33) A generalization to more than 2 categories was needed in order to obtain our results about multilevel non-dichotomous ratings. Asymptotic distributions of *kappa* statistics and their differences with many raters, many rating

categories and two conditions. (34). The raters did see the white light images and scored Mayo and UCEIS which may be considered a limitation in terms of scoring in the i-SCAN mode but this is also the real life situation.

Furthermore, it would be relevant to evaluate the reproducibility of the PICaSSO score in community centers and gastroenterologists with less experience in this technique. This would also allow assessing the educational training tool used in this study to assess the learning curve in new observers. More work is needed to converge to one simple and accurate EVC score that could be applied to all available and future endoscopic platforms. Indeed, adequate assessment of endoscopic healing may help in patient management and the outcome of the disease in our patients.

In conclusion, we have developed and validated new EVC score for UC incorporating more detailed mucosal and vascular findings on I-SCAN that holds the potential to better correlate with mucosal healing.

Figures

Figure 1: Endoscopic mucosal healing :a-d) High-definition i-SCAN 1and virtual chromoendoscopy i-SCAN 2 showed elongated crypts

Figure 2. Endoscopic vascular healing a-d) High-definition i-SCAN 1and virtual electronic chromoendoscopy i-SCAN 2 -3 showed sparse (deep) vessels without dilatation.

Figure 3. Interobserver variability between the endoscopic scores

Figure 4. Accuracy of the PICaSSO score to assess mucosal healing and inflammation in UC

ACKNOWLEDGEMENT

RB is supported by a grant from Foundation for Scientific Research Flanders.

References

1.Travis SP, Higgins PD, Orchard T, et al. Review article: defining remission in ulcerative colitis. Aliment Pharmacol Ther 2011;34:113-124.

2. Peyrin-Biroulet L, Sandborn W, Sands BE et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol. 2015;1324-38

3. Williet N, Sandborn WJ, Peyrin-Biroulet L.
Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. Clin Gastroenterol Hepatol. 2014 ;12:1246-56

4.Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625-9

-

5. Osada T, Ohkusa T, Yokoyama T, et al. Comparison of several activity indices for the evaluation of endoscopic activity in UC: inter- and intraobserver consistency. Inflamm Bowel Dis 2010;16:192-7

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

7. Feagan BG, Sandborn WJ, D'Haens et al.The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology. 2013;145:149-157

8 Barreiro-de Acosta M, Vallejo N, de la Iglesia D Evaluation of the Risk of Relapse in Ulcerative Colitis According to the Degree of Mucosal Healing (Mayo 0 vs 1): A Longitudinal Cohort Study. J Crohns Colitis. 2016 ;10:13-9

9.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;61:535–42.

10.Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology 2013;145:987–95.

11.Samuel S, Bruining DH, Loftus Jr EV, et al. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. Clinical Gastroenterology and Hepatology: Clin Gastroenterol Hepatol2013;11:49–54

12.M Iacucci, M Fort Gasia, C Hassan, Ret al . Complete mucosal healing defined by endoscopic Mayo subscore still demonstrates abnormalities by novel i-SCAN endoscopic and refined histological gradings. Endoscopy 2015;47:726-734

13. Hefti MM, Chessin DB, Harpaz NH et al. Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. Dis Colon Rectum 2009; 52: 193 – 197

14.Mahmoud H Mosli, Brian G Feagan, Guangyong Zou, et al Development and validation of a histological index for UC. Gut 2015;0:1–9.

15Iacucci M **,** Ghosh S Mucosal healing –How deep is enough? Dig Dis. 2016;34:160-4

16.Iacucci M, Ghosh S. Looking beyond symptom relief: evolution of mucosal healing in inflammatory bowel disease. Therap Adv Gastroenterol 2011; 4: 129 – 143

17.Kiesslich R, Goetz M, Hoffman A, Galle PR. New imaging techniques and opportunities in endoscopy. Nature Reviews Gastroenterol. & Hepatol. 2011;8:547-553.

18.Kodashima S, Fujishiro M. Novel image-enhanced endoscopy with i-scan technology. World J Gastroenterol 2010;16:1043-1049.

19.Kudo T, Matsumoto T, Esaki M, Yao T, Iida M. Mucosal vascular pattern in ulcerative colitis: observations using narrow band imaging colonoscopy with special reference to histologic inflammation. Int J Colorectal Dis 2009;24:495-501.

20.Seiko Hayashi, Shin-ei Kudo, Noriyuki Ogata et al Narrow-Band Imaging Efficiency for Evaluation of Mucosal Healing/ Relapse of Ulcerative colitis. Gastrointest Endosc 2016: 5 :154

21.DiCiccio, T.J. and Efron B. *Statistical Science 1996*; **11**, 189–228.

22.Bernstein CN, Shanahan F, Anton PA, et al. Patchiness of mucosal inflammation in treated ulcerative colitis: a prospective study. Gastrointest Endosc 1995;42:232–7.

23.Kim B, Barnett JL, Kleer CG, et al. Endoscopic and histological patchi ness in treated ulcerative colitis. Am J of Gastroenterol 1999;94:3258–62.

24.Bryant RV, Winer S, Travis SP, 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.

25.Mazzuoli S, Guglielmi FW, Antonelli E, et al. Definition and evaluation of mucosal healing in clinical practice. Dig Liver Dis 2013;45:969–77.

26.Annese V, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis 2013;7:982-1018

27.Daperno M, Castiglione F, de Ridder L, et al. Results of the 2nd part Scientific Workshop of the ECCO. II: measures and markers of prediction to achieve, detect, and monitor intestinal healing in inflammatory bowel disease. J Crohns Colitis 2011;5: 484-98

28. Tontini Ge, Bisshop R, Neumann H .Endoscopic scoring systems for inflammatory bowel disease: pros and cons.. Expert Rev Gastroenterol Hepatol. 2014 ;8:543-54.

29. Daperno M, Comberlato M, Bossa F, et al. Increasing interobserver agreement on IBD endoscopic scoring systems: results from the IGIBDEndo educational program. J Crohns Colitis 2014;8:S254–5.

30. Pagnini C, Menasci F, Desideri F et al
Endoscopic scores for inflammatory bowel disease in the era of 'mucosal healing': Old problem, new perspectives. Dig Liver Dis. 2016 48:703-8.

31. Daperno M, Comberlato M , Bossa F et al Training Programs on Endoscopic Scoring Systems for Inflammatory Bowel Disease Lead to a Significant Increase in Interobserver Agreement Among Community Gastroenterologists.J Crohns Colitis. 2016 Oct 4

32Marteau P, Laharie D, Colombel JF,et al. Interobserver Variation Study of the Rutgeerts Score to Assess Endoscopic Recurrence after Surgery for Crohn's Disease. J Crohns Colitis 2016; 10:1001-5

33. 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; 61:535-42

34 Grassano L, Pagana G, Daperno M, et al . Asymptotic distributions of kappa statistics and their differenceswith many raters, many rating categories and two conditions. Biom J 2017; in press.

Table 1 : The Paddington international virtual chromoendoscopy score (PICaSSO)in UC

PICaSSO MUCOSAL ARCHITECTURAL

- **0 - No mucosal defect**
  - A: Continuous/regular crypts
  - B: Crypts not visible (scar)
  - C: Discontinuous and or dilated/elongated crypts
- **I - Micro erosion or cryptal abscess**
  - 1 : discrete
  - 2: patchy
  - 3: diffuse
- **II- Erosions size <5 mm**
  - 1:discrete
  - 2:patchy
  - 3: diffuse
- **III -Ulcerations size >5 mm**
  - 1:discrete
  - 2:patchy
  - 3: diffuse
  -

PICASSO VASCULAR ARCHITECTURE

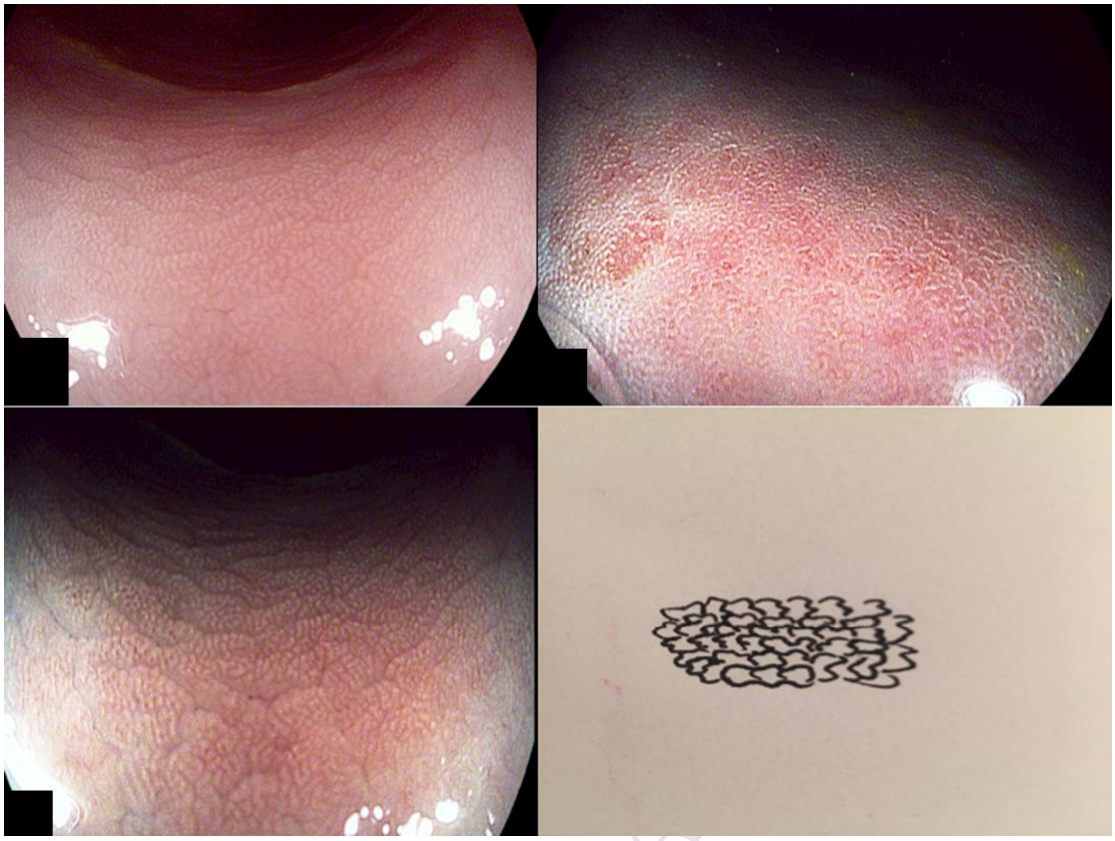
- **Vessels without dilatation**
  - A :Roundish following crypt architecture
  - B: Vessels not visible (scar)
  - C:Sparse (deep) vessels without dilatation
- **I Vessels with dilatation**
  - A roundish with dilatation
  - B crowded or tortuous superficial vessels with dilatation
- **II Intramucosal bleeding**
  - A roundish with dilatation
  - B crowded or tortuous superficial vessels with dilatation
- **III - Luminal bleeding**
  - A roundish with dilatation
  - B crowded or tortuous superficial vessels with dilatation

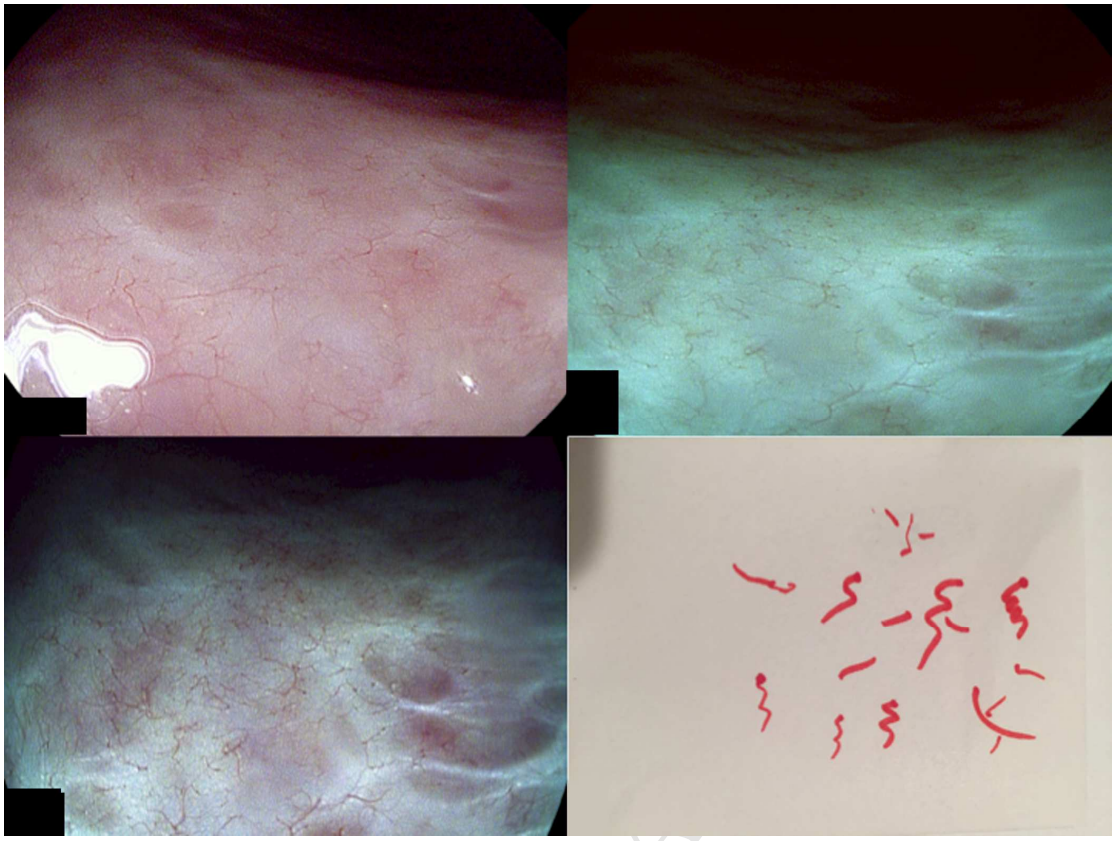
Table 2 : Intra-observer variability between endoscopic scores

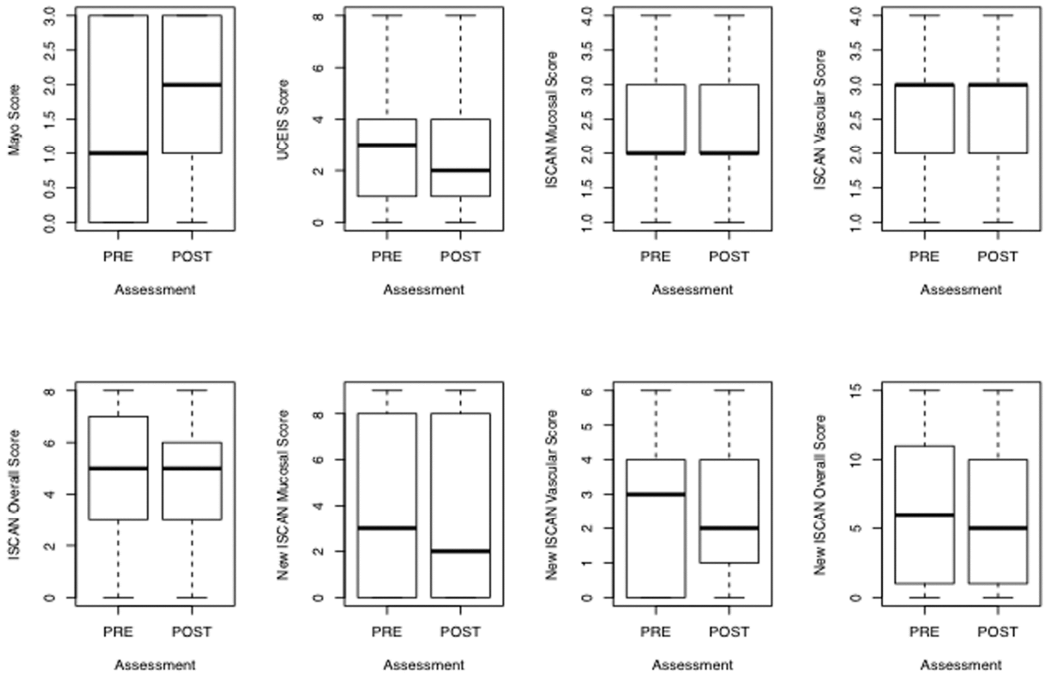
Endoscopic score	K pre-test	K post-test
Mayo (95% CI)	0.85 (0.786-0.909)	0.85 (0.781-0.913)
UCEIS (95% CI)	0.868 (0.783-0.925)	0.840 (0.749-0.917)
i-scan mucosal (95%CI)	0.732 (0.623-0.824)	0.713 (0.63.5-0.788)
i-scan vascular (95%CI)	0.632 (0.511 - 0.760)	0.664 (0.501- 0.795)
i-scan overall (95%CI)	0.757 (0.666- 0.845)	0.760 (0.647- 0.839)
PICaSSO mucosal (95% CI)	0.911 (0.849- 0.954)	0.90 (0.835- 0.947)
PICaSSO vascular (95%CI)	0.795 (0.675- 0.889)	0.640 (0.518- 0.809)
PICaSSO overall (95%CI)	0.917 (0.878- 0.962)	0.892 (0.848- 0.940)

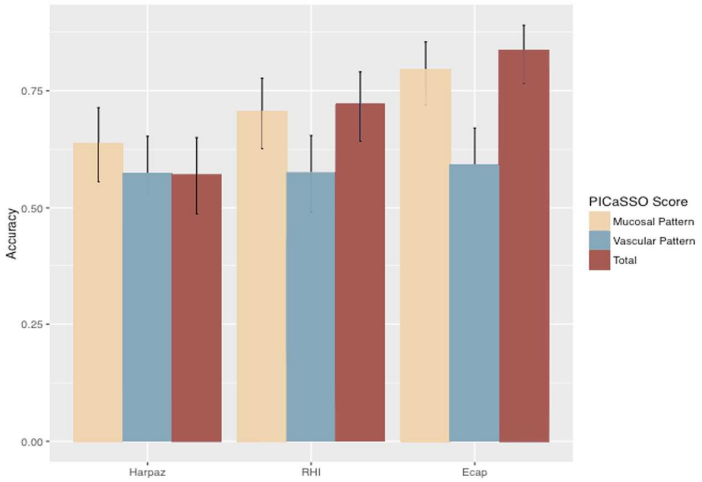
Table 3: Regression Model of PICaSSo endoscopic findings for the prediction of the Histological scores (Harpaz, RHI and ECAP)

	Harpaz score				**ECAP score**				**RHI score**			
PICaSSO Mucosal Findings	**Coeff.**	**Lower bound**	**Upper bound**	**P value**	**Coeff**	**Lower bound**	**Upper bound**	**P value**	**Coeff**	**Lower bound**	**Upper bound**	**P value**
Continuous/regular crypts	**-2.664**	**-3.47047**	**-1.8579**	**0**	**-8.643**	**-11.0686**	**-6.21751**	**0**	**-12.577**	**-16.3698**	**-8.783865**	**0**
Crypts not visible (scar)	**-7.229**	**-11.82646**	**-2.6324**	**0.002**	**-7.229**	**-11.8264**	**-2.63241**	**0.0020**	**-10.548**	**-17.658**	**-3.43773**	**0.0036**
Discontinuous dilated/elongated crypts	**-1.88**	**-2.655034**	**-1.1044**	**2.00E**	**-7.818**	**-10.66395**	**-4.97226**	**0**	**-12.154**	**-16.539**	**-7.7677**	**0**
Micro erosion or cryptal abscess 1. Discrete	-0.904	-1.88154	0.07381	0.069	-5.714	-9.9923	-1.4350	0.088	-9.704	-16.280	-3.1266	0.03
2.Patchy	0.521	-0.6347	1.677	0.376	2.969	-2.4906	8.428	0.2865	7.396	-0.9884	15.78	0.083
3. Diffuse	2.888	2.04	3.737	0	8.899	6.248	11.55	0	12.805	8.657	16.953	0
Erosions size <5 mm 1. Discrete	-0.767	-1.793324	0.25933	0.142	-4.632	**-9.293621**	**0.02955**	**0.0514**	**-6.412**	**-13.617**	**0.79395**	**0.081**
2. Patchy	**1.085**	**0.05559**	**2.1153**	**0.038**	**6.579**	**1.74227**	**11.415**	**0.0076**	**9**	**1.509023**	**16.4909**	**0.0185**
3. Diffuse	2.913	1.980457	3.84499	0	11.751	9.072063	14.4303	0	17.596	13.4175	21.774	0
Ulcerations size >5 mm 1. Discrete	0	-1.79847	1.7984	0.999	-2.69	-11.5088	6.128	0.549	-1.844	-15.460	11.7714	0.7906
2.Patchy	0.408	-0.52388	1.3402	0.390	3.475	-1.01645	7.9668	0.1294	5.514	-1.41354	12.4419	0.1187
3. Diffuse												
PiCaSSO Vascular Findings												
Roundish following crypt architecture	**-2.651**	**-3.784331**	**-1.5186**	**4.00E**	**-8.667**	**-12.0330**	**-5.3003**	**0**	**-11.5**	**-16.7801**	**-6.21988**	**2.00E**
Vessels not visible (scar)	**-3.958**	**-6.033903**	**-1.8822**	**0.00**	**-8.703**	**-12.5914**	**-4.81392**	**1.20E-**	**-10.901**	**-16.999**	**-4.8024**	**0.0004**
Sparse (deep) vessels	**-3.958**	**-6.033903**	**-1.8822**	**0.00**	**-8.703**	**-12.5914**	**-4.81392**	**1.20E-**	**-10.901**	**-16.999**	**-4.8024**	**0.0004**
IA Vessels with roundish with dilatation	**-1.723**	**-2.49248**	**-0.9534**	**1.10E**	**-7.078**	**-9.916723**	**-4.24013**	**1.00E-**	**-10.255**	**-14.665**	**-5.8446**	**5.00E-0**
IB Vessels with crowded or tortuous superficial vessels with dilatation	0.51	-0.12829	1.1473	0.11	**4**	**1.376304**	**6.62369**	**0.0028**	**5.813**	**1.75416**	**9.8708**	**0.0049**
IIA Intramucosal bleeding roundish with dilatation	-0.284	-0.99719	0.4283	0.434	-2.526	-5.75066	0.69923	0.124	-3.829	-8.8053	1.148168	0.1316
IIB Intramucosal bleeding crowded /tortuous superficial vessels with dilatation	**1.371**	**0.748326**	**1.99416**	**1.60E**	**6.468**	**4.0831738**	**8.853020**	**0**	**9.15**	**5.42896**	**12.8714**	**1.00E-0**
IIIA Luminal bleeding roundish with dilatation	1.772	-0.674129	4.21733	0.155	3.739	-5.071677	12.5505	0.4055	3.57	-10.0388	17.17932	0.6071
IIIB Luminal bleeding crowded /tortuous superficial vessels with dilatation	18.125	-1336.41	1372.6	0.979	8.171	5.133570	11.20928	0	11.12	6.36046	15.8795	5.00E-0









Abbreviations

Ulcerative Colitis: UC

Mucosal Healing: MH

Federal Drug Agency: FDA

Mayo endoscopic subscore: Mayo

Ulcerative Colitis Endoscopic Index of Severity: UCEIS

The ulcerative colitis colonoscopic index of severity : (UCCIS)

Rorbart histological index: RHI

New York Mount Sinai system developed by Harpaz : NYMS

White Light Endosocpy: WLE

High definition: HD

Virtual electronic Chromoendoscopy: VEC

The Paddington International Virtual Chromoendoscopy score **:**PICaSSO

High definition-white light =iSCAN 1

High definition electronic virtual Chromoendoscopy =iSCAN 2 and 3

Table 1 supplement : Histological scores

Table 1. IBD Histological Grading Proposal (ECAP System)

Histopatology	Grade/score
Extent of inflammation (E)	
Focal	1
Multifocal (patchy)	2
Diffuse	3
Chronicity (C)	
C1.Crypt Architectural Alteration	
None	0
Focal Alteration	1
Patchy Distortion (<50%)	2
Diffuse Distortion (>50%)	3
C2.Paneth Cell Metaplasia	
None	0
Present	1
Activity of Inflammation (A)	
A1.Surface Epithelium	
Normal	0
Reactive changes (mucin depletion/villiform)	1
Neutrophilic infiltration / probable erosion	2
Erosion	3
Ulceration	4
A2.Neutrophilic Cryptitis	
None	0
>5%	1
<50%	2
>50%	3
A3.Crypts Abscess	
None	0
Present	1
A4.Crypts Destruction	
None	0
Crypt Destruction	1
A5.Lamina Propria Mononuclear Cellularity	
Normal	0
Mild increase	1
Moderate increase	2
Severe increase	3
A6.Basal Plasmacytosis	
None	0
Focal	1
Diffuse	2
A7.Lamina Propria Neutrophilic Infiltration	
None	0
Rare	1
Scattered	2

Extensive	3
Plus/Others(P)	
P1.Lamina Propria Eosinophilic Infiltration	
None	0
Mild	1
Moderate	2
Severe	3
P2.Lymphoid Follicle /Aggregates	
None	0
Rare	1
Prominent	2
Total Score	

Table 2. Robarts Histologic index score

Component
Chronic inflammatory infiltrate
0=No increase
1=Mild but unequivocal increase
2=Moderate increase
3=Marked increase
Lamina Propria neutrophilis
0=No increase
1=Mild but unequivocal increase
2=Moderate increase
3=Marked increase
Neutrophils in epithelium
0=None
1=<5% crypts involved
2=<50% crypts involved
3=>50% crypts involved
Erosion or ulcerations 0=No erosions ,ulcerations or granulation tissue
1=Recovering epithelium+adjacent inflamamtion
1=probable erosion-focally stripped
2=unequivocal erosion
3=ulcer or granulation tissue

Table 3. New York Mount Sinai scoring system

Score	Description
0 – inactive colitis	No cryptitis
1 – mildly active colitis	Cryptitis in <50% of crypts
2- moderately active colitis	Cryptitis in >50% of crypts
3 – severely active colitis	Ulceration or erosion

Table4 supplement : Correlation(Kendall method) between endoscopic scores and histological scores

	Harpaz	ECAP	RHI	P value
Mayo 95%CI	0.79 (0.74-0.84)	0.69 (0.61-0.75)	0.62 (0.52-0.69)	P<0.001
UCEIS 95%CI	0.74 (0..67-0.79)	0.59 (0.49-0.67)	0.54 (0.44-0.64)	P<0.001
ISCAN Overall 95%CI	0.58 (0.48-0.66)	0.50 (0.39-0.60)	0.44 (0.32-054)	P<0.001
PICaSSO 95%CI	0.75 (0.69-0.81)	0.64 (0.55-0.72)	0.53 (0.42-0.62)	P<0.001

Appendix 1

CASE VIDEO REPORT FORM (CVRF)

Name (initials) …….. date ……

Number of years in practice after completion of training ……

Number of colonoscopies performed (approximate)

Lifetime ……Average Per Year…….

Experienced in NBI: YES/ NO

Experienced in iSCAN: YES/ NO

VIDEO NUMBER …….

High quality ☐Low quality ☐ (Choose one)

<u>MAYO Endoscopic Score Classification :</u> Mayo 0, Mayo 1, Mayo 2, Mayo 3 (Choose one from below)

0 = Normal or inactive disease ☐

1 = Mild disease (erythema, decreased vascular pattern, mild friability ☐

2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) ☐

3 = Severe disease (spontaneous bleeding, ulceration) ☐

UCEIS score (Choose one from each category)

1.Vascular pattern	**A.Normal (0)**	☐
	B.Patchy Obliteration (1)	☐
	C.Obliterated (2)	☐
2.Bleeding	**A.None (0)**	☐
	B.Mucosal (1)	☐
	C.Luminal mild (2)	☐
	DLuminal moderate/ severe (3)	☐
3.Erosions and ulcers	**A.None (0)**	☐
	B.Erosions (1)	☐
	C.Superficial ulcer (2)	☐
	D.Deep ulcer (3)	☐

Total score =

Descriptor (score of most severe lesions)	Likert scale anchor points	Definition
Vascular pattern	Normal (0)	Normal vascular patterns with arborization of capillaries clearly defined or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration 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 that can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of the endoscope or visibly oozing from the mucosa after washing intraluminal blood, or visibly oozing from a haemorrhagic 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 when compared with erosions but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa with slightly raised edge

iSCAN –UC score pictures

High quality ☐Low quality ☐

iSCAN-UC score videos

High quality ☐Low quality ☐

Mucosal pattern:
1 = normal
2 = mosaic pattern- Mild
3 = tubular-gyrus-erosions Moderate
4= nodular rosette- ulcers Severe
Vascular pattern:
1 = normal
2 = spiral isolated vessels-Mild
3 = crowded tortuous vessels-erythema- Moderate

4= irregular vessels- friability Severe

Mucosal pattern:
1 = normal
2 = mosaic pattern- Mild
3 = tubular-gyrus-erosions Moderate
4= nodular rosette- ulcers Severe
Vascular pattern:
1 = normal
2 = spiral isolated vessels-Mild
3 = crowded tortuous vessels-erythema Moderate
4= irregular vessels- friability Severe

Which was the best in your opinion?

HD ☐iSCAN 1 ☐SCAN 2 ☐SCAN 3 ☐
Choose one

Which was the best in your opinion?

HD ☐iSCAN 1 ☐SCAN 2 ☐SCAN 3 ☐
Choose one

The Paddington international virtual chromoendoscopy score (PICaSSO)in UC

PICaSSO MUCOSAL ARCHITECTURAL

- **0 - No mucosal defect**

  - A: Continuous/regular crypts
  - B: Crypts not visible (scar)
  - C: Discontinuous and or dilated/elongated crypts
- **I - Micro erosion or cryptal abscess**
  - 1 : discrete
  - 2: patchy
  - 3: diffuse
- **II- Erosions size <5 mm**
  - 1:discrete
  - 2:patchy
  - 3: diffuse
- **III -Ulcerations size >5 mm**
  - 1:discrete
  - 2:patchy
  - 3: diffuse
  -

PICASSO VASCULAR ARCHITECTURE

- **Vessels without dilatation**
  - A :Roundish following crypt architecture
  - B: Vessels not visible (scar)
  - C:Sparse (deep) vessels without dilatation
- **I Vessels with dilatation**
  - A roundish with dilatation
  - B crowded or tortuous superficial vessels with dilatation
- **II Intramucosal bleeding**
  - A roundish with dilatation
  - B crowded or tortuous superficial vessels with dilatation
- **III - Luminal bleeding**
  - A roundish with dilatation
  - B crowded or tortuous superficial vessels with dilatation