

Original Research Article

ASSESSMENT OF HISTOLOGICAL ACTIVITY IN PATIENTS WITH ULCERATIVE COLITIS USING NANCY INDEX AND ITS CORRELATION WITH ENDOSCOPIC SCORE (UCEIS) – A PROSPECTIVE STUDY

ABSTRACT

Aims: Assessment of histological activity in patients with Ulcerative Colitis (UC) using Nancy Index (NI) and determining its correlation with endoscopic grading using Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score.

Study design: Cross sectional prospective observational study.

Place and Duration of Study: Department of Medical Gastroenterology and Department of Pathology, Apollo Hospital Chennai, between March 2020 to October 2021.

Methodology: Consecutive patients with UC between the age 18-80 years undergoing endoscopic examination and biopsy were enrolled. Patients with infective colitis, toxic megacolon, perforation, hemodynamic instability and patients with previous colorectal surgery were excluded. Clinical disease severity was assessed using Truelove Witts score (TLW). Whereas, endoscopic and histologic activity was graded using UCEIS and Nancy Index into remission (UCEIS-0-1, NI-0-1), mild (UCEIS- 2-4, NI -2), moderate (UCEIS - 5-6, NI - 3) and severe (UCEIS - 7-8, NI - 4). Statistical analysis was performed using Spearman's correlation coefficient using SPSS v.25.0.

Results: Our study included 85 (M:F-1.5:1) patients. Mean age at presentation was 44.25(±13.44) years and age at onset of disease 39.68 (±1.32) with a median duration of disease 2(IQR – 2.5) years. Most common symptoms at the time of presentation were blood in stool followed by mucus in stool in 64.7% and 45.9%, respectively. Most of the patients were on oral ASA preparation, 43% were on AZA and 7% on steroids. Endoscopically – E1:E2:E3 disease was seen in 29%, 47% and 24%, respectively. Correlation between UCEIS and NI was found to be very strong with $r = 0.85(p < 0.001)$. 95.7% of patients in endoscopic remission also had histologic remission. No statistically significant difference was found when a UCEIS score of 0 or ≤ 1 was used to predict histological remission.

Conclusion: Significant correlation was observed between validated endoscopic and histologic indices of severity. A UCEIS score of 0 or ≤ 1 both predicted histological remission. Endoscopic remission can be used as surrogate marker for histological remission.

Keywords: *Ulcerative colitis, UCEIS – Ulcerative Colitis Endoscopic Index of Severity, Nancy index, correlation of endoscopy with histology and validated score.*

1. INTRODUCTION

UC is a chronic inflammatory condition with continuous mucosal inflammation usually without granuloma formation that affects the rectum and to a variable extent the colon in a continuous fashion.(1) India has the highest incidence of UC among the Asian countries. (2)(3) Targets of therapy has evolved alongside introduction of newer drugs from clinical remission to now Mucosal healing (MH) which is defined as absence of disease activity on endoscopy and is associated with higher clinical response, lower relapse rate, lower hospitalisation rates, reduced need for surgery and decreased risk of colorectal cancer.(4) Persistence of histological activity in patients with MH is associated with a 2-3 times increased risk of colitis relapse, corticosteroid use and hospitalization during a 12-month follow-up period and also increased risk of dysplasia.(5)(6) The STRIDE II consensus considers use of histological remission (HR) alongside endoscopic remission as a representative of deeper healing. (7) For endoscopic assessment – Mayo endoscopic score (MES) and UCEIS are the only ones which have undergone external validation. (8) MES has been shown to have poor concordance among trainee endoscopists and is unable to distinguish between deep and shallow ulcers. Stratification based on UCEIS is associated with lower colectomy and relapse rates.(9)(10) UCEIS has advantage over MES in terms of intra- and inter-observer variability.(11) Of the histological indices - The Nancy Index (NI) and Roberts Histological Index (RHI) are recently developed validated indices for histological evaluation.(12)(13) The main advantage of NI over its predecessor is that it has very good intraobserver and interobserver reliability, its good responsiveness to change and its simplicity and ease of use. This current study aims to find the relationship between validated endoscopic UCEIS and histological-NI. The secondary objective of the study was to look at the clinical profile of patients with UC and to determine what score of UCEIS - 0 or ≤ 1 better represents histological remission.

2. MATERIAL AND METHODS

2.1 Study design - All patients between the age of 18-80 years presenting to Apollo Main Hospital, Chennai with a diagnosis of UC (new and follow up case) and undergoing endoscopic evaluation (sigmoidoscopy/ colonoscopy) and biopsy taken from the worst affected area in the distal colon were consecutively enrolled in the study. Patients were excluded from the study if they had toxic megacolon, perforation or hemodynamic instability precluding endoscopic evaluation. Also patients who have undergone colorectal surgery with removal of the distal colon were excluded.

2.2 Technical information - Lower Gastrointestinal (GI) scopy was done as per standard technique using Olympus-CF-Q-150 series colonoscopes. All colonoscopy/ sigmoidoscopy videos (using - Skysoft Digital Hospital- Digital Mediscan ver. 2020) were assessed by single clinician and endoscopic severity score calculated using UCEIS score. The range in the UCEIS scores is from 0 to 8, which was stratified into four grades: remission (0–1); mild (2–4); moderate (5–6); and severe (7–8). At least 2 biopsy samples taken from the worst affected area in the distal colon in addition to other areas of colon (from varying colonic segments) as clinically indicated at the treating clinician's discretion. In case of patients in remission or endoscopically inactive disease – random samples were taken from sigmoid colon and rectum. Histopathological examination of all the biopsy samples was done (retrospectively by retrieving slides from the histopathology department) by an experienced pathologist (expert in the field of GI pathology) who was blinded to patient's history / examination / endoscopic findings. All examined slides were Haematoxylin and Eosin stained. Biopsy sample was graded according to NI using three key histological components which included- acute inflammatory cell infiltrate, chronic inflammatory cell infiltrate and ulceration into 5 grades from 0-4. **Grade 0** – Absent or mild increase in the number of chronic

inflammatory cells, **Grade 1** – Moderate to severe acute inflammatory infiltrates, **Grade 2** – Few or rare neutrophils in the epithelium or lamina propria, **Grade 3**- Presence of moderate to severe acute inflammatory infiltrate and **Grade 4** – presence of ulceration.

Table 1 - UCEIS score (14)

Descriptor	Score	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 ($\leq 5\text{mm}$) defects in the mucosa, of a white or yellow colour with a flat edge
	Superficial ulcer(2)	Larger ($>5\text{mm}$) 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
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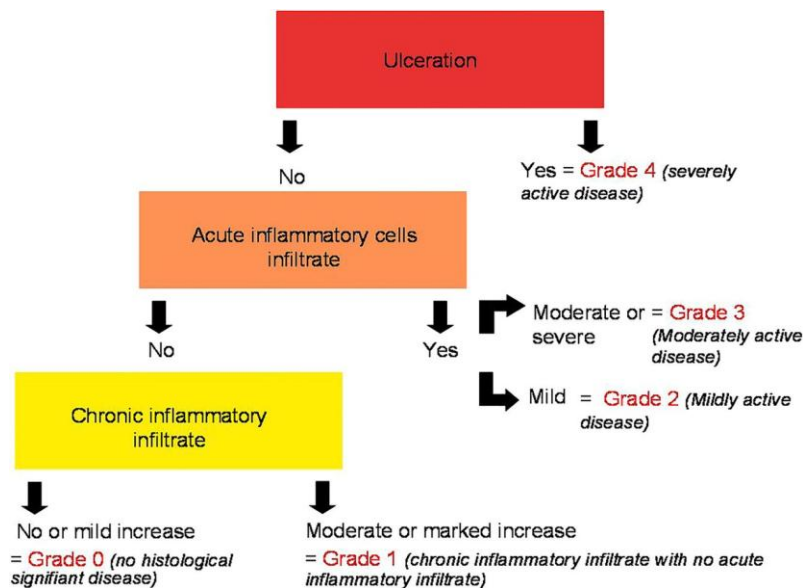


Figure 1 – Nancy Index (NI) (15)

2.3 Statistics - Data entry was done in MS excel spread sheet. Data analysis was carried out by SPSS version 25.0. Mean and standard deviations were used to summarize data for continuous variables whereas percentages were used for categorical variables. Spearman correlation was calculated between UCEIS and NI. Comparison of categorical variables was done by either chi square test or Fisher's exact test based on the number of observations. p values of <0.05 were considered significant. Spearman rank correlation (ρ) value between 0 and 0.19 was 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.

3. RESULTS

Total of 85 patients were enrolled in the study (15 new cases and 70 follow up cases). The baseline characteristics are described in Table no. 2.

Table 2 - Baseline characteristics

Number of patients	85
Male (%)	51(60%)
Age at presentation (years, mean + SD)	44.25 (\pm 13.44) years

Age at onset of disease (years, mean + SD)	39.68 (± 1.32) years
Duration of disease (years, Median - IQR)	2 (IQR – 2.5) years
Active Smokers (%)	5.9%
Extent of disease (E1/E2/E3)	25/40/20 (29.4%/ 47.1% / 23.5%)

Most common symptoms at the time of presentation included blood in stools followed mucus in stool, urgency and tenesmus. (Table no. 3)

Table 3 - Symptoms at the time of presentation

Symptoms	Number (%)
Blood in stool	55(64.7%)
Mucus	39(45.9%)
Urgency	38(44.7%)
Tenesmus	35(41.2%)
Nocturnal frequency	30(35.3%)
Abdominal pain	9(10.6%)
Fever	1(1.2%)

At the time of presentation 15 patients were treatment naïve (newly diagnosed cases) and remaining 70 patients were on treatment for UC. Most of the patients were on oral aminosalicylic acid (ASA) followed by azathioprine (AZA).

Table 4 – Medication history

Medication	No.	%
Topical ASA preparation	22	31.42%
Oral ASA preparation	68	97.14%

Topical steroids	1	1.33%
Oral steroids	5	7.14%
Azathioprine (AZA)	30	42.85%
Biologics	0	0%

Severity assessment: Clinical, endoscopic and histologic severity assessment was done using Truelove and Witts score (TLW), UCEIS and NI into remission, mild, moderate and severe disease, respectively. (Table no. 5)

Table 5 – Severity assessment using clinical, endoscopic and histological grading.

Severity of disease	Remission	Mild	Moderate	Severe
Clinical –TLW	30 (35.3%)	15 (17.6%)	24 (28.2%)	16 (18.8%)
Endoscopy – UCEIS score	23 (27.1%)	28 (32.9%)	26 (30.6%)	8 (9.4%)
Histology – NI	22 (25.9%)	9 (10.6%)	26 (30.6%)	28 (32.9%)

Correlation between UCEIS and NI- Using Spearman's correlation – a very strong correlation was observed between UCEIS and NI ($r=0.85$) (95% CI 0.78- 0.9; $p<.001$).

What score of UCEIS best represents histological remission –

Histological remission is defined by NI of 0 or 1. There were total of 6 patients with UCEIS score of 0 and 17 patients with UCEIS score of 1. All patients with UCEIS score of 0 had NI ≤ 1 and 16 out of 17 (94.1%) patients with UCEIS score of 1 had NI ≤ 1 .

Table 6 – Comparing endoscopic remission (0 or ≤ 1) vs histological remission.

	NI remission	NI – no remission	Total
UCEIS 0	6	0	6

UCEIS 1	16	1	17
UCEIS ≤1	22	1	23

Using Fishers exact test the two-tailed P value equals 1.00 for UCEIS score of 0 and ≤1 (Statistically not significant). So a UCEIS score of 0 or ≤1 both can be used to represent histological remission.

DISCUSSION -

MH in patients with UC is an established therapeutic goal for Treat-to-Target strategy as per STRIDE II since it is associated with higher clinical response, lower relapse rate, lower hospitalisation rates, reduced need for surgery and decreased risk of colorectal cancer.(4)(16) Whereas the concept of histological healing is still evolving and is yet not considered as treatment target but as an adjunct to endoscopic remission to represent a deeper level of healing. Histological remission though not considered as treatment target is associated with better outcomes as compared to endoscopic healing alone.(17) Whereas persistence of histological activity has been associated with increased risk of relapse, corticosteroid use, hospitalisation and increased risk of dysplasia.(5) (6)(17)(18) Most of the studies done in this regard using non-validated endoscopic indices have shown more of disparity than correlation between endoscopy and histology.(19)(20)(21)

In this study where we have used validated indices of severity the strength of correlation was found to be very strong between UCEIS and NI. Our findings are in concordance with study by Irani et al(22) comparing the UCEIS and NI where they found a very strong correlation with r value of 0.84. Another recently published study from India by Jimil Shah et al(23) which compared MES (Mayo Endoscopic Score) with NI in 96 patients of UC found a weak correlation of $r = 0.38$. The likely reasons for this discrepancy – might be the use of MES instead of UCEIS. UCEIS being more extensive (Score 0-8) scoring system provides better stratification of activity, is more extensively validated as compared to MES and none of the patients in the study by Jimil Shah had a MES score of 0 – which denotes remission as compared to our study which had 27.1% patients in remission, similar to the study by Irani et al which had 39% patients in endoscopic remission.

Other studies which compared MES with Geboes score (GS) includes the study published in 2019 by Kovach et al. (24) where they found a weak to moderate correlation with r value of 0.14-0.48. But two other study by D Fluxa et al (25) published in 2017 and DB Kim et al (26) published in 2016 showed a strong correlation between MES and GS with r value of 0.67 and 0.77 respectively. A similar study by Lemmens et al(27) found a moderate level of correlation ($r=0.428$). A recent Indian study published in 2020 by DK Bhagwani et al(28) also compared MES with GS and found a strong correlation with r value of 0.788. So there is a wide variation in the results ranging from weak to strong correlation when non-validated scores are used.

In this study, of all the patients in remission as per UCEIS, 95.7% also had histological remission as per NI. The remaining 4.3% had mild disease as per histology. Similarly, all patients who were classified as severe disease endoscopically also had severe disease histologically. Whereas, for mild and moderate disease as per UCEIS more than 50% had a higher grades of histological activity. UCEIS was able to correctly classify 95.7% patients in remission, 28.6% in mild, 42.3% in moderate and all 100% cases in severe category. The lack of concordance in the mild and moderate category matters less than it may appear

because concordance in the remission group is the one that matters the most, since it defines the eventual target of therapy in management of UC.

An international consensus published in 2017 by IOIBD (29) for defining endoscopic remission concluded that UCEIS score of 0 was the one which best defined remission. But the more recent STRIDE II(7) consensus recommended UCEIS score of ≤ 1 as endoscopic remission. Our study found that a UCEIS score of ≤ 1 is a good representative of histological inactivity.

Strengths and limitations –

In this study we have used only validated indices of severity. We have also included patients who were in remission as compared to other Indian studies.

There are certain limitations in the current study – Single center study with small sample size. Inter-observer variation could not be studied due to reporting of UCEIS and NI by single endoscopist and histopathologist. Participation by an expert histopathologist (with expertise in GI histopathology) may limit the generalisability in routine practice. We have used a single clinical, endoscopic and histological index of severity in our study for demonstration of correlation. So the good correlation seen in our study may be of use only in centers where the above indices of severity are used for reporting. Correlation with Fecal Calprotectin (FCal) for activity or severity assessment was not done in the current study due to unavailability of the same at the time of this study at our center. Effect of duration of treatment and effect of duration of clinical remission was not taken into account while comparing endoscopic and histologic index for severity assessment which could possibly change the results.

4. CONCLUSION

To conclude, this study showed that validated endoscopic score like UCEIS had a very strong correlation with NI and a UCEIS score of ≤ 1 can be used to represent histological remission which might become the eventual target in UC management in future.

It implicates that use of validated score must be adopted in clinical practice. Endoscopic remission using validated index like UCEIS can be considered as surrogate marker for histological inactivity. Large scale multicenter studies with more number of patients in remission group are required to confirm the same.

CONSENT

"All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.'"

ETHICAL APPROVAL

"All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

DISCLAIMER:

AUTHORS HAVE DECLARED THAT NO COMPETING INTERESTS EXIST. THE PRODUCTS USED FOR THIS RESEARCH ARE COMMONLY AND PREDOMINANTLY USE PRODUCTS IN OUR AREA OF RESEARCH AND COUNTRY. THERE IS ABSOLUTELY NO CONFLICT OF INTEREST BETWEEN THE AUTHORS AND PRODUCERS OF THE PRODUCTS BECAUSE WE DO NOT INTEND TO USE THESE PRODUCTS AS AN AVENUE FOR ANY LITIGATION BUT FOR THE ADVANCEMENT OF KNOWLEDGE. ALSO, THE RESEARCH WAS NOT FUNDED BY THE PRODUCING COMPANY RATHER IT WAS FUNDED BY PERSONAL EFFORTS OF THE AUTHORS.

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ABBREVIATIONS

ASA	Aminosalicilic acid
AZA	Azathioprine
GS	Geboes score
HR	Histological remission
IOIBD	International Organization for the Study of IBD
MES	Mayo endoscopic score
MH	Mucosal healing
NI	Nancy Index
RHI	Robarts histological index
TLW	Truelove and Witts score
UC	Ulcerative colitis
UCEIS	Ulcerative colitis endoscopic index of severity