INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disorder that affects the rectum and the colon to a variable extent and degree. Inflammation affecting the mucosa starts in the rectum and may extend proximally. The therapeutic targets for UC have been changing over the past few years. The initial treatment target used to be clinical remission. Following the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) consensus, the goal post shifted to endoscopic remission. Now there is literature accumulating favoring histologic remission as a treatment target. Disease relapse is greater in the presence of histologic activity even in patients who have attained endoscopic remission.

Colonoscopy with terminal ileum intubation along with biopsy is the standard of care for the diagnosis of UC and to assess the disease extent. Once diagnosed, to assess the therapeutic targets repeated sigmoidoscopy or colonoscopy is required. Colonoscopy is time-consuming, expensive, and needs...
preparation and sedation hence sigmoidoscopy is generally preferred for assessing disease activity in patients on treatment and when they suffer a symptomatic flare. When UC patients undergo clinical trials, sigmoidoscopy is considered the standard to assess disease activity. However, sigmoidoscopy for assessment of disease activity in the complete colon has not been prospectively evaluated.

We conducted a prospective observational study to evaluate the accuracy of sigmoidoscopy to predict endoscopic and histological disease activity in the complete colon in patients with disease extent beyond the sigmoid colon. The aim of the study is to show agreement between sigmoidoscopy and complete colonoscopy for endoscopic and histologic disease activity using various commonly used scoring systems in patients of UC undergoing follow-up colonoscopy.

METHODS

1. Patients
This was a single-center study performed at a tertiary care institute. It was a prospective observational study. The study was approved by the Institutional Ethics Committee (Reference number: E/2020/29) and we followed The Declaration of Helsinki guidelines. Written informed consent was obtained from all the patients before inclusion.

The diagnosis of UC was based on history and typical endoscopic and histological findings. Patients aged 18 years and above, diagnosed with UC with disease extent beyond the sigmoid colon were included in the study. Those with disease extending beyond the sigmoid colon on index colonoscopy, who underwent repeat complete colonoscopy and biopsy were included in the study. Patients with disease limited to the rectum and the sigmoid colon and those receiving local therapy were excluded. Patients with atypical UC were excluded.

The study duration was 1 year. Colonoscopies were done for indications including assessment of disease activity and remission. Patients were treated with mesalamine, steroids, immune modulators or biologicals as per the step-up management strategy. Patient identification and disease profile were kept anonymous prior to analysis. Complete enumeration sampling technique was used. In the previous 12 months, a total of 118 UC patients had visited the tertiary care center as per the hospital records. Taking the same into consideration, we have included consecutive patients (n = 100) who satisfied the inclusion criteria during the study duration of 1 year.

2. Endoscopic Assessment
Each patient underwent a complete colonoscopy with endoscopic score assessment separately for each segment including the rectum, sigmoid, descending, transverse and ascending colon and cecum. Colonoscopy/sigmoidoscopy was performed by either of 2 dedicated endoscopists (> 15 years of colonoscopy experience). The maximum endoscopic score for each segment was noted. The score was measured using the Mayo Endoscopic Score (MES) and Ulcerative Colitis Endoscopic Index of Severity (UCEIS). Each component of the UCEIS was scored separately for each segment and the total score for each segment was obtained. Endoscopic remission was considered as MES ≤ 1, as per the STRIDE II consensus. However, a comparison using MES less than or equal to 1 as remission criteria was also performed. As per UCEIS, endoscopic remission was defined by a score of less than or equal to 1. The maximum endoscopic score for the rectum and sigmoid colon was obtained (sigmoidoscopy). This was compared with the maximum endoscopic score for the complete colon (colonoscopy). It was done for both the endoscopic scoring systems of MES and UCEIS. A comparison between the highest sigmoidoscopy and colonoscopy scores was also done using remission criteria.

3. Histopathological Assessment
During colonoscopy, 4 biopsies from each segment were taken for assessment of histological activity. The biopsies were taken from areas of maximum endoscopic activity and in case of endoscopic remission, random biopsies were taken. Histopathological analysis was done by 2 dedicated gastrointestinal pathologists (> 15 years’ experience; Kamat R and Kini S) and any discrepancy in scoring was settled with mutual agreement. Nancy Index (NI), Robart Histopathology Index (RHI), and Simplified Geboes Score (SGS) were used for histological activity assessment. The NI consists of 3 components including acute inflammatory cells, chronic inflammatory cells, and ulceration. The score ranges from 0 to 9 and grade ranges from 0 to 4. Grade 0 or 1 represents the absence of acute inflammatory cells, chronic inflammatory cells, and ulceration. The score varies from 0 to 33, with a score ≤ 3 suggestive of histological remission. The RHI consists of 4 parameters including epithelial neutrophils, lamina propria neutrophils, chronic inflammatory cells, and erosions-ulceration. The score varies from 0 to 33, with a score ≤ 3 suggestive of histological remission. SGS consists of 4 grades, with grade 0 representing no inflammatory activity, grade 1 representing basal plasma cells, grade 2A representing eosinophils in lamina propria, grade 2B
representing neutrophils in lamina propria, grade 3 representing neutrophils in epithelium and grade 4 representing epithelial injury in crypts and surface epithelium. Histologic remission was defined as a Nancy grade of less than or equal to 1, SGS grade of less than 2B (absence of neutrophils) and a maximum RHI of 3 as long as lamina propria neutrophils, neutrophils in epithelium and erosion or ulceration are 0. For each of the 3 scoring systems, the maximum histological activity in the rectum and sigmoid colon (sigmoidoscopy) and the maximum histological activity in the complete colon (colonoscopy) were obtained and compared. A comparison between the histological scores for sigmoidoscopy and colonoscopy was done using remission criteria.

4. Outcomes
The primary outcome was the assessment of agreement between sigmoidoscopy and colonoscopy for endoscopic disease activity using MES and UCEIS. The secondary outcomes included an assessment of agreement of histologic activity between rectosigmoid biopsy and complete colonic biopsy using various histological scores (NI, RHI, and SGS).

5. Statistical Analysis
All the data were entered in Microsoft Excel format and then exported to SPSS version 23.0 (IBM Corp., Armonk, NY, USA). All continuous variables were reported as mean ± standard deviation while non-normal variables were reported as median (interquartile range). Agreement between sigmoidoscopy and colonoscopy was calculated by using Cohen kappa (κ) coefficient for both endoscopic and histologic scores. A coefficient of zero indicates that no linear relationship exists between 2 continuous variables, and a correlation coefficient of −1 or +1 indicates a perfect linear relationship. A kappa value between 0 and 0.19 was regarded as very weak, 0.20–0.39 as weak, 0.40–0.59 as moderate, 0.60–0.79 as strong, and 0.80–1.00 as very strong correlation. Spearman correlation was calculated between sigmoidoscopy and colonoscopy for MES, UCEIS, NI, RHI, and SGS. Diagnostic accuracy of sigmoidoscopy in detecting complete colonic disease activity status was presented as the area under the receiver operating characteristic curve, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and misclassification rate (proximal disease missed by sigmoidoscopy). A P-value of less than 0.05 was considered statistically significant.

RESULTS
1. Baseline Characteristics
A total of 100 patients of UC were included in the study. The study flowchart is shown in Fig. 1. Mean age was 36.36 ± 12.17 years and males constituted 68%. Baseline characteristics are shown in Table 1. Active disease (MES > 0) was present in 96 patients (96%) and disease was in remission (MES = 0) in 4 patients (4%). Considering active disease as MES > 1, active disease was present in 72 patients (72%) and disease was in remission in 28 patients (28%). Using UCEIS for endoscopic...
remission, active disease was present in 75 patients (75%) and disease was in remission in 25 patients (25%). The treatment taken by the patients included oral 5-aminosalicylic acid in 96%, steroids in 45%, azathioprine in 32%, and infliximab in 3% of patients.

2. Outcomes
The outcomes of the follow-up sigmoidoscopy and colonoscopy are shown in Table 2.

1) Primary Outcomes
(1) Comparison between sigmoidoscopy and colonoscopy using MES
First, sigmoidoscopy was adequate for assessment using MES in 97% of the patients (n = 97). This denoted that sigmoidoscopy missed proximal disease activity in only 3 patients (Misclassification rate of 3%). Strong agreement/correlation (κ = 0.96, r = 0.94) was observed in the MES findings between sigmoidoscopy and colonoscopy. The MES scores for sigmoidoscopy and colonoscopy are shown in Supplementary Table 1. Second, when MES ≥ 1 is used as activity criteria, sigmoidoscopy did not miss any proximal disease (misclassification rate of 0%). A sigmoidoscopy was adequate for assessing the presence of endoscopic activity in all the patients (n = 100). Perfect agreement/correlation (κ = 1.00, r = 1.00) was observed in the MES findings between sigmoidoscopy and colonoscopy considering MES ≥ 1 as the criteria for endoscopic activity. Sigmoidoscopy findings had perfect accuracy (100%) in predicting endoscopic activity in the colon, with an area under the curve (AUC) of 1.00 (Fig. 2A). Third, when MES > 1 is used as activity criteria, sigmoidoscopy missed proximal disease in only 3 patients (misclassification rate of 3%). A sigmoidoscopy was adequate for assessing the presence of endoscopic activity in 97% of patients (n = 97). Strong agreement/correlation (κ = 0.93, r = 0.93) was observed in the MES findings between sigmoidoscopy and colonoscopy considering MES ≥ 1 as the criteria for endoscopic activity.

Table 2. Primary and Secondary Outcomes Showing Comparison of Sigmoidoscopy with Colonoscopy Using Various Endoscopic and Histologic Scoring Systems

<table>
<thead>
<tr>
<th>Variable</th>
<th>Misclassification rate (%)</th>
<th>Kappa</th>
<th>Spearman correlation coefficient</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MES (0)</td>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>100</td>
</tr>
<tr>
<td>MES (1)</td>
<td>3</td>
<td>0.93</td>
<td>0.93</td>
<td>0.98</td>
<td>0.95</td>
<td>1.00</td>
<td>1.00</td>
<td>0.90</td>
<td>97</td>
</tr>
<tr>
<td>UCEIS</td>
<td>3</td>
<td>0.92</td>
<td>0.93</td>
<td>0.98</td>
<td>0.96</td>
<td>1.00</td>
<td>1.00</td>
<td>0.89</td>
<td>97</td>
</tr>
<tr>
<td>NI</td>
<td>2</td>
<td>0.86</td>
<td>0.87</td>
<td>0.99</td>
<td>0.97</td>
<td>1.00</td>
<td>1.00</td>
<td>0.77</td>
<td>98</td>
</tr>
<tr>
<td>RHI</td>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>100</td>
</tr>
<tr>
<td>SGS</td>
<td>1</td>
<td>0.92</td>
<td>0.92</td>
<td>0.99</td>
<td>0.98</td>
<td>1.00</td>
<td>1.00</td>
<td>0.85</td>
<td>99</td>
</tr>
</tbody>
</table>

MES, Mayo Endoscopic Score; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; NI, Nancy Index; RHI, Robarts Histopathology Index; SGS, Simplified Geboes Score; AUC, area under curve; PPV, positive predictive value; NPV, negative predictive value.
criteria for endoscopic activity. Sigmoidoscopy findings had excellent accuracy (97%) in detecting endoscopic activity throughout the colon, with an AUC of 0.98, sensitivity of 0.95, specificity of 1.00, PPV of 1.00, and NPV of 0.90 (Fig. 2B).

(2) Comparison between sigmoidoscopy and colonoscopy using UCEIS

First, sigmoidoscopy was adequate for assessment using UCEIS in 95% of the patients (n=95). This denotes that sigmoidoscopy missed proximal disease activity in only 5 patients (misclassification rate of 5%). Strong agreement/correlation ($\kappa = 0.94$, $r = 0.94$) was observed in the UCEIS findings between sigmoidoscopy and colonoscopy. Supplementary Table 2 shows the scores of UCEIS for sigmoidoscopy and colonoscopy. Second, when UCEIS > 1 is used as activity criteria, sigmoidoscopy missed proximal disease in only 3 patients (misclassification rate of 3%). Sigmoidoscopy was adequate for assessing the presence of endoscopic activity in 97% of patients (n=97). Strong agreement/correlation ($\kappa = 0.92$, $r = 0.93$) was observed in the UCEIS findings between sigmoidoscopy and colonoscopy considering UCEIS > 1 as the criteria for endoscopic activity. Sigmoidoscopy findings had

Fig. 2. Area under the curve (AUC) graph showing adequacy of sigmoidoscopy in comparison to colonoscopy using endoscopic scores as criteria for activity. (A) AUC graph showing adequacy of sigmoidoscopy in comparison to colonoscopy using Mayo Endoscopic Score > 0 as criteria for activity. (B) AUC graph showing adequacy of sigmoidoscopy in comparison to colonoscopy using Mayo Endoscopic Score > 1 as criteria for activity. (C) AUC graph showing adequacy of sigmoidoscopy in comparison to colonoscopy using Ulcerative Colitis Endoscopic Index of Severity > 1 as criteria for activity. PPV, positive predictive value; NPV, negative predictive value.

Fig. 3. Area under the curve (AUC) graph showing adequacy of sigmoidoscopy in comparison to colonoscopy using histological indices as criteria for activity. (A) AUC graph showing adequacy of sigmoidoscopy in comparison to colonoscopy using Nancy Index for activity. (B) AUC graph showing adequacy of sigmoidoscopy in comparison to colonoscopy using Roberts Histopathology Index for activity. (C) AUC graph showing adequacy of sigmoidoscopy in comparison to colonoscopy using Simplified Geboes Score for activity. PPV, positive predictive value; NPV, negative predictive value.
excellent accuracy (97%) in detecting endoscopic activity throughout the colon, with an AUC of 0.98, sensitivity of 0.96, specificity of 1.00, PPV of 1.00, and NPV of 0.89 (Fig. 2C).

2) Secondary Outcomes
(1) Comparison between histological grading obtained via sigmoidoscopic and colonoscopic biopsies using the NI
When NI grade > 1 is used as histologic activity criteria, sigmoidoscopy with biopsy missed proximal disease in only 2 patients (misclassification rate of 2%). A sigmoidoscopy with biopsy was adequate for the assessment of the presence of histologic activity in 98% of patients (n = 98). Strong agreement/correlation (κ = 0.86, r = 0.87) was observed in the histologic findings between sigmoidoscopy and colonoscopy considering NI grade > 1 as the criteria for histologic activity. Sigmoidoscopy with biopsy had excellent accuracy (98%) in detecting histologic activity throughout the colon, with an AUC of 0.99, sensitivity of 0.98, specificity of 1.00, PPV of 1.00, and NPV of 0.85 (Fig. 3C).

(2) Comparison between histological grading obtained via sigmoidoscopic and colonoscopic biopsies using RHI
Using RHI > 3 as histologic activity criteria, sigmoidoscopy with biopsy did not miss any proximal disease. A sigmoidoscopy with biopsy was adequate for the assessment of the presence of histologic activity in all the patients (n = 100). Perfect agreement/correlation (κ = 1.00, r = 1.00) was observed in the histologic findings between sigmoidoscopy and colonoscopy considering RHI > 3 as the criteria for histologic activity. Sigmoidoscopy with biopsy had perfect accuracy (100%) in predicting histologic activity in the complete colon, with an AUC of 1.0 (Fig. 3B).

(3) Comparison between histological grading obtained via sigmoidoscopic and colonoscopic biopsies using SGS
Using SGS ≥ 2B as activity criteria, sigmoidoscopy with biopsy missed proximal disease in only 1 patient (1%). Sigmoidoscopy with biopsy was adequate for the assessment of the presence of histologic activity in 99% of patients (n = 99). Strong agreement/correlation (κ = 0.92, r = 0.92) was observed in the histologic findings between sigmoidoscopy and colonoscopy considering SGS ≥ 2B as the criteria for histologic activity. Sigmoidoscopy with biopsy had excellent accuracy (99%) in detecting histologic activity throughout the colon, with an AUC of 0.99, sensitivity of 0.98, specificity of 1.00, PPV of 1.00, and NPV of 0.85 (Fig. 3C).

DISCUSSION
The study has important clinical implications in the evaluation of patients with UC. By doing just sigmoidoscopy with histopathological assessment an accurate prediction of the disease activity in the proximal colon could be made in more than 95% of patients. In fact, by doing only sigmoidoscopy, active disease in the proximal colon was missed in only 3% and 5% of the patients by MES and UCEIS respectively. Using MES > 0 and MES > 1 as criteria for endoscopic activity, sigmoidoscopy has excellent accuracy of 100% and 97% respectively in detecting disease activity in the complete colon. Using UCEIS > 1 as criterion of endoscopic activity, sigmoidoscopy has an excellent accuracy of 97% in detecting disease activity in the complete colon. When histopathological remission was assessed using the NI, RHI, and SGS using sigmoidoscopy with biopsies, active disease in the proximal colon was missed in 2%, 0%, and 1% respectively. Sigmoidoscopy with biopsy has an excellent accuracy of 98%, 100%, and 99% for NI, RHI, and SGS respectively for predicting histologic activity in the complete colon. Thus, sigmoidoscopy with biopsy is adequate for assessing disease activity in the proximal colon.

The first study by Kato et al. determined that 73% had maximum inflammation in the rectum and sigmoid colon and 27% had maximum activity proximal to the sigmoid colon. In addition, they found that 40% of patients had inflamed mucosa in the descending colon or in the more proximal portion of the colon, but showed no inflammation in the rectum and sigmoid. They had contradictory results and showed that a colonoscopic examination was warranted. The limitations of this study were its retrospective nature and lack of histologic assessment.

More recently published literature looking at the adequacy of sigmoidoscopy has found good agreement between sigmoidoscopy and colonoscopy. Jangi et al. found agreement for endoscopic improvement and in histologic findings in the left and the right colon at follow-up colonoscopy with a kappa of 0.58 and 0.67 respectively. Rate of misclassification if only left-sided endoscopic findings and histologic findings were considered was 3.5% and 5.9% respectively. This was the only study that assessed for histologic agreement, however, validated histological scores were not used.

Lin et al. in their retrospective study showed that according to MES in the most severely inflamed colonic and rectosigmoid segment, there were high degrees of correlation in the initial UC diagnosis (r = 0.90, P < 0.01) as well as during follow-up (r = 0.74, P < 0.01). Histological evaluation was not included.
They concluded that sigmoidoscopy was as effective as colonoscopy for detecting disease activity and evaluating therapeutic response in UC patients during follow-up.

The study by Colombel et al. was a multicenter phase 2 drug trial for etrolizumab. They found a high degree of correlation between sigmoidoscopy and colonoscopy in the assessment of disease activity based on MES ≥ 2 (κ = 0.83, r = 0.84), MES ≥ 1 (κ = 0.95, r = 0.96), and UCEIS (r = 0.92). In 230 out of 239 videos, findings from recto-sigmoidoscopy agreed with those from colonoscopy in detecting active disease (MES ≥ 2; n = 205) or healing (MES ≤ 1; n = 25). In 9 videos (2 taken at baseline, 7 after treatment), colonoscopy found proximal disease activity not detected by recto-sigmoidoscopy. They concluded that there was a high degree of correlation in the assessment of UC activity made by proctosigmoidoscopy and colonoscopy. The limitations of the study were that videos lacked annotations and boundaries for different segments were ambiguous. They did not assess histology. Only 239 out of 331 examinations were done beyond the sigmoid colon. As a complete colonoscopy was not performed in all patients it could have led to a bias.

In a recent retrospective study by Park et al. only 7.6% (κ = 0.893, r = 0.906, P < 0.001) cases of MES and 8.6% (κ = 0.890, r = 0.914, P < 0.001) cases of UCEIS scores were more severe in the proximal colon. Only colonoscopic images were analyzed and histologic assessment was not done. The study population included only 29.2% patients with extensive colitis, 29.6% having left-sided colitis and the majority of 41.2% having proctitis. Including disease limited to the rectum in the study would have led to a biased conclusion.

NI, RHI, and SGS are the most commonly used scoring systems in UC. NI and RHI are fully validated and recommended by the European Crohn’s and Colitis Organisation for research. NI is simple and suitable for clinical practice. In a comparative analysis by Peyrin-Biroulet et al. using data from a phase 3 clinical trial of Adalimumab they showed that regarding validity, week 52 correlations were moderate to strong between full and partial Mayo scores and Mayo subscale scores and the RHI and Geboes Score and were weak to moderate for the NI. They concluded that while the 3 indices had acceptable measurement properties, the Geboes Score and RHI performed better than the NI.

With the current treat-to-target strategy, stringent criteria are used to define endoscopic remission. Colonoscopy requires preparation and sedation, is more expensive and there is a loss of time from work. Complications of colonoscopy like perforation are more common in patients with inflammatory bowel disease. An accompanying person is also required as the patient is sedated. This makes repeated colonoscopies expensive, potentially risky and needs more planning and preparation.

Our study has demonstrated that sigmoidoscopy with biopsy can accurately predict the disease severity in the complete colon. Patients with disease extent proximal to the rectosigmoid need not undergo a complete colonoscopy to assess disease activity. This prospective study has validated the findings of previous retrospective studies which showed that sigmoidoscopy is as effective as colonoscopy for detecting disease activity in UC patients on follow-up. We used 3 commonly used histological scoring systems to support our findings.

However, pediatric patients and patients with primary scarring cholangitis could have rectal sparing. Patients on topical therapy could show distal improvement. These patients might need to undergo a colonoscopy. Patients with clinically active disease or raised fecal calprotectin and normal sigmoidoscopy should undergo a complete colonoscopy. Patients with long standing disease, undergoing an examination for dysplasia and malignancy surveillance will also require a complete colonoscopy.

The limitations of our study were that it was a single-center study with a lack of central reading and annotations. C-reactive protein and fecal calprotectin were not compared. The majority of our patients showed active disease and hence selection bias cannot be ruled out. However, this demonstrates real-world data from our part of the world of UC patients. The low number of patients on biologics and financial constraints are major challenges in ideal therapy for achieving remission.

In patients of UC with disease extent beyond the sigmoid colon, sigmoidoscopy showed strong agreement and excellent accuracy with colonoscopy for endoscopic and histologic disease activity. Misclassification of disease is very low when sigmoidoscopy with biopsy is performed. Sigmoidoscopy is adequate for the assessment of disease activity for UC patients during their follow-up.

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#### Conflict of Interest
No potential conflict of interest relevant to this article was reported.
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Data will be made available upon reasonable request to corresponding author.

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Supplementary Material
Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

REFERENCES