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Original Article

Pathology Section

Correlation of Clinical, Endoscopic and Histopathological Activity in Ulcerative Colitis: A Cross-sectional Analysis

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ABSTRACT

Introduction: There are several scoring systems in use to determine the endoscopic, clinical and histopathological activity in Ulcerative Colitis (UC) which helps in defining the optimal management strategy.

Aim: To understand the correlation between histological activity with simplified Geboes Score (GS), clinical activity with Truelove and Witts Score (TLWS) and endoscopic activity with Mayo Endoscopic Score (MES) in UC. The study also aimed at describing the common histopathological features of UC.

Materials and Methods: A cross-sectional analysis was conducted at a tertiary care hospital in Southern India for 1.5 years (November 2014 to May 2016). Consecutive colonoscopy biopsies of patients who presented with lower gastrointestinal symptoms and endoscopic findings suggestive of UC were included. Baseline characteristics including age, gender, symptoms, clinical signs and extent of disease were recorded. Disease severity was graded using TLWS, MES using endoscopy and GS. Spearman's correlations between the MES, GS and TLWS were calculated.

Results: A total of 62 cases of clinically diagnosed UC patients were evaluated based on endoscopy and histopathology findings. The mean age was 44.7 years and 42 (67.74%) were males in the study. Proctosigmoiditis was the most common extent (32.25%), followed by cases of proctitis (25.80%), pancolitis (22.58%), and left sided colitis (14.51%). There was a strong correlation between MES/TLWS with a rho=0.614 ($p<0.001$), followed by MES/GS with rho=0.421 ($p<0.001$) and GS/MES with a rho=0.375 ($p<0.01$). Basal plasmacytosis was found in 92.86% of moderate to severe disease.

Conclusion: The GS system strongly correlates with both MES and TWLS in patients with UC which could be used concurrently to determine the extent of healing and optimise treatment strategy. Findings of basal plasmacytosis, mucin depletion, dysplasia and pseudopolyps are associated with moderate to severe disease activity.

Keywords: Colitis, Crohn's disease, Goebes score, Mayo endoscopic score, Truelove and witts score

INTRODUCTION

The ulcerative colitis is the chronic inflammation of the colon often associated with waxing and waning pattern in the clinical presentation of symptoms. Over the years the treatment approaches have seen a paradigm shift from symptomatic relief to substantial mucosal healing with systemic immunosuppression [1]. To choose an optimal treatment strategy, it is pivotal to accurately evaluate the extent of the disease, including a clear assessment of the role of concomitant non inflammatory causes of symptoms [2]. The variation between observers in describing mucosal appearance in proctocolitis was described almost six decades ago [3]. Since then several groups have tried to establish a standardised endoscopic scoring system for determining the extent of disease of which MES is the most widely used [4].

The clinicians have defined acute severe colitis using TLWS. This grading system takes into account the frequency of blood stained stools, haemoglobin, Erythrocyte Sedimentation Rate (ESR), fever and pulse rate to assess the severity of the disease [5-7]. Albeit, these clinical and endoscopic scoring systems aide in evaluation of the extent of the disease. However, they are not reliable indicators of histological healing. Endoscopically, passive and subclinical UC have been observed to relapse or progress to cancer in patients with active histological activity [8,9]. GS is a comprehensive histopathological scoring system which encompasses evaluation of presence of architectural changes, mononuclear cells, eosinophils, neutrophils, crypt destruction and erosions or ulcerations [10,11].

Histological studies have established the role of basal plasmacytosis and dysplasia as predictors of UC relapse [7,11]. In addition, the severity of eosinophil infiltration in lamina propria has been reported to be directly proportional to the degree of relapse and non response to medical therapy [12]. These findings clearly establish the significance of histological evaluation in UC to assess disease severity and to optimise medical therapy.

Several attempts have been made to validate various clinical, histopathological and endoscopic scoring systems used to evaluate UC [4]. However, it is crucial to establish the correlation of histopathological scoring systems with clinical presentation and endoscopic evaluation of the disease but it has not been explored to a great extent. The primary objective of this study was to understand the correlation between histological activity (GS) and clinical (TLWS) and endoscopic activity (MES) in UC patients. The study also had an objective to describe the histopathological features in the UC biopsies in the study cohort.

MATERIALS AND METHODS

A single centre cross-sectional analysis was conducted at a tertiary care hospital in Southern India. All patients clinically diagnosed as UC during a time period of November 2014 to May 2016 were included. The study was approved by the Institutional Ethics Committee (IEC) (IEC no. IEC/MES/59/2014).

Inclusion and Exclusion criteria: Consecutive colonoscopy biopsies of patients who mainly presented with lower gastrointestinal symptoms and endoscopic findings suggestive of UC and gave informed consent were included in the study, while patients who had tiny inadequate biopsies and biopsies from anal region were excluded from the study.

A trained gastroenterologist who attended to the patients assessed the patient clinically and reported simplified modification of TLWS index of UC [Table/Fig-1] [5]. The presence of at least two out of

seven parameters was required to assign the disease to a particular category. Out of the parameters involved, if >2, the disease was categorised under the higher grade.

The gastroenterologist performing the endoscopy evaluated and noted the MES score [Table/Fig-2] [13].

Characteristic	Mild	Moderate	Severe
Frequency of stools (number per day)	<4	4-6	>6
Blood in stool	Intermittent	Frequent	Continuous
Temperature (°C)	Normal	>37.5	>37.5
Pulse (beats/min)	Normal	>90	>90
Haemoglobin (g/dL)	>11	10.5-11	<10.5
ESR (mm/h)	<30	>30	>30
Clinical signs	Nil	Abdominal tenderness	Abdominal distension and tenderness

[Table/Fig-1]: Modified Truelove and Witts Severity (TLWS) index of Ulcerative Colitis (UC).
Adapted from Truelove SC and Witts LJ [5]

Score	Endoscopic characteristic
Score 0	Normal mucosa or inactive disease.
Score 1	Mild disease with evidence of mild friability reduced vascular pattern, and mucosal erythema.
Score 2	Moderate disease with friability, erosions, complete loss of vascular pattern and significant erythema.
Score 3	Ulceration and spontaneous bleeding.

[Table/Fig-2]: Mayo Endoscopic Score (MES) for Ulcerative Colitis (UC).
Adapted from Tripathi K and Feuerstein J [13]

Biopsy was taken from the most affected area during endoscopic examination and was sent for histopathological examination. Colonoscopy biopsies were received at the pathology laboratory. Biopsies were fixed in 10% formalin for six hours. After routine processing and embedding in paraffin wax, tissue sections were taken and stained with Haematoxylin and Eosin (H&E) stain. Stained sections were studied under light microscopy. Assessment of histopathological severity in these sections was done by simplified modification of Geboes grading [Table/Fig-3] [11]. Primary evaluation was performed by the first histopathologist and confirmed by a second histopathologist to avoid any observational bias.

Score	Histopathologic features
Score 0	Normal mucosa or inactive disease.
Score 1	Architectural changes, focal or diffuse.
Score 2	Expansion of lamina propria by chronic inflammatory cells.
Score 3	Granulocyte infiltration of lamina propria (eosinophils and neutrophils).
Score 4	Neutrophils in epithelium (cryptitis and crypt abscess).
Score 5	Crypt destruction.
Score 6	Erosion or ulceration of surface epithelium.

[Table/Fig-3]: Modified Geboes Score (GS) for histological activity in Ulcerative Colitis (UC).
Adapted from Jauregui-Amezaga A et al., [11]

STATISTICAL ANALYSIS

All the data were entered in Microsoft Excel 2016 and then exported to Statistical Package for the Social Sciences (SPSS) version 19.0 (Chicago, Illinois, USA). Descriptive statistics were calculated as percentages for discrete data and medians with Inter Quartile Ranges (IQRs) for continuous data. Spearman's correlations between the endoscopic activity scores (MES), histological activity scores (GS) and clinical activity score (TLWS) were calculated. Significance was accepted at $p<0.05$.

RESULTS

A total of 62 cases of UC from the period of November 2014 to May 2016 were included. All clinically diagnosed cases of UC were endoscopically and histopathologically evaluated. The mean age of presentation was 44.7 years and the sample predominantly consisted of males 42 (67.74%). In the study group, 16 (25.80%) cases had proctitis, 20 (32.25%) had proctosigmoiditis. A total of 9 (14.51%) had left-sided colitis and 14 (22.58%) presented with pancolitis [Table/Fig-4].

Baseline characteristics	Frequency (%)
Mean age (years), (Range of ages)	44.7(17- 80)
Male, n (%)	42 (67.74)
Haemoglobin (g/dL), median (IQR)	11.6 (8.5-15.5)
ESR (mm/hr.), median (IQR)	27.5 (3-86)
Normal pulse, n (%)	62 (100)
Abdominal tenderness, n (%)	17 (27.42)
Constipation, n (%)	7 (11.29)
Raised body temperature, n (%)	3 (04.83)
Extent of disease, n (%)	
Proctitis	16 (25.80)
Proctosigmoiditis	17 (27.41)
Proctosigmoiditis, rectal polyp	1 (1.61)
Proctosigmoiditis, sigmoid colon polyp	1 (1.61)
Proctosigmoiditis, sigmoid colon, rectal polyp	1 (1.61)
Sigmoid colon polyps	2 (3.22)
Left sided colitis	9 (14.51)
Cecal diverticula	1 (1.61)
Pancolitis	13 (21.0)
Pancolitis with rectal polyp	1 (1.61)

[Table/Fig-4]: Baseline characteristics of patients with Ulcerative Colitis (UC) (n=62).
IQR: Interquartile range

Clinical Findings

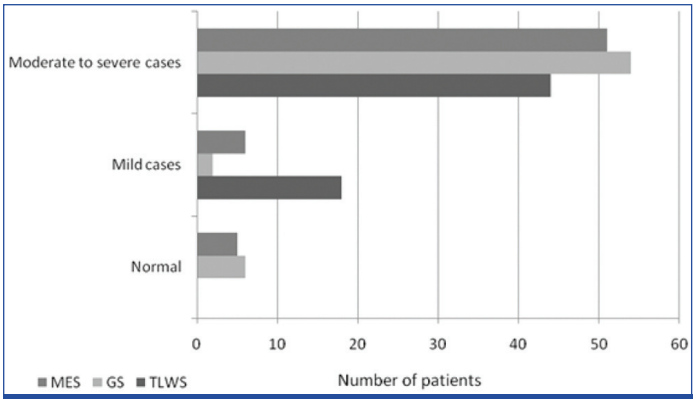
The severity of disease with TLWS was determined by the frequency of stools being <4 as mild, 4-6 as moderate and >6 as severe case of UC along with the presence of at least one or more factor amongst blood in stool, raised body temperature, pulse rate, haemoglobin values, ESR and presence of abdominal tenderness as a clinical sign.

The haemoglobin IQR was 11.6 g/dL with a range of 8.5 to 15.5 and 58.06% of the study population had haemoglobin value of >11g/dL. Fourteen (22.58%) of these patients had significantly low haemoglobin (<10.5 g/dL). The ESR Interquartile Range (IQR) was determined to be 27.5 with a range distribution of 3-86. Based on the ESR, 54.84% of the patients had mild disease and the rest of 45.16% had moderate to severe disease. There were no clinical signs in 45 out of 62 of the cases and only 27.42% had abdominal tenderness. None of the patients presented with abdominal distension.

In this study, 30 cases (48.39%) had mild disease with <4 stools/day and 8 out of these 30 cases (12.90%) had normal stools. 33.87% of cases had moderate disease with 4-6 stools per day. Severe disease with >6 stools per day was observed in 17.74% of cases [Table/Fig-5]. The median TLWS score was 2 with a range of 1-3 in these patients.

Endoscopic Activity

The MES score assesses the vascular pattern, presence of erythema, friability, erosions, ulcerations and bleeding to determine the severity of disease. Authors categorised the severity of disease based on the MES scores as mild, moderate and severe. The IQR for the MES score was 2 with a range of 1-3. Based on the MES, 8.1% cases had inactive disease, 9.7% cases had mild disease, 82.2% of the patients had moderate to severe disease. Proctosigmoiditis was the most common site of extent [Table/Fig-6]. In this study, cohort 6 cases (9.68%) presented with polyps either in sigmoid colon or in rectum. Multiple polyps in rectum are illustrated.



[Table/Fig-5]: Severity of Ulcerative Colitis (UC) as determined by different scoring systems.

Activity/Scoring system	n=62 (%)
Mayo Endoscopic Score	
Normal mucosa (Inactive disease)	5 (8.1)
Mild friability, decreased vascular pattern, mucosal erythema (Mild disease)	6 (9.7)
Friability, erosion, complete loss of vascular pattern, significant erythema (Moderate disease)	28 (45.1)
Ulceration and spontaneous bleeding (Severe disease)	23 (37.1)
Geboes Score (GS)	
Architectural change (Score 0)	0 (0)
Chronic inflammatory infiltrate (Score 1)	6 (9.7)
Lamina propria neutrophils and eosinophils (Score 2)	2 (3.2)
Neutrophils in epithelium (Score 3)	15 (24.2)
Crypt destruction (Score 4)	13 (21)
Erosion or ulceration (Score 5)	26 (41.9)

[Table/Fig-6]: Mayo Endoscopic Score (MES) and Geboes Score (GS) in the study population.

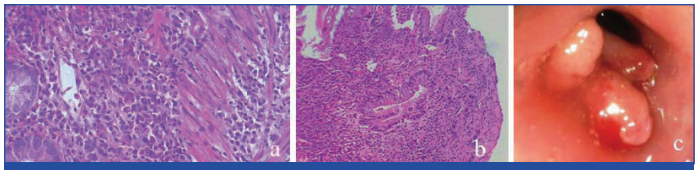
Histopathological Findings

Modified GS was used for histopathological assessment and the percentage distribution of cases is given in [Table/Fig-6]. Histological activity was observed in all the cases and no cases with a score-0 were observed. A significant proportion of the study population had a score of >3, with crypt destruction in 13 (21%) and erosion of ulceration in 26 (41.9%) patients. Mild disease with a score <3 was observed in 8 (12.90%) of the study population. Other features like basal plasmacytosis, mucin depletion, pseudopolyps and dysplasia were also assessed. Histopathology and endoscopic findings of three different cases are illustrated in [Table/Fig-7,8].

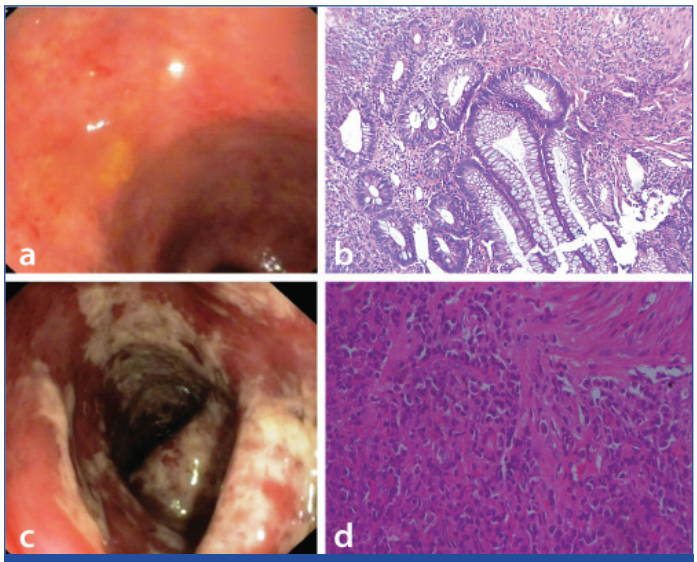
Basal plasmacytosis was seen in 22.58% cases [Table/Fig-9]. Out of 14 cases, four cases with basal plasmacytosis had severe disease, nine had moderate disease and one had mild disease. Basal plasmacytosis observed in one case is illustrated in [Table/Fig-7]. Mucin depletion was present in 24.19% cases. Majority cases with mucin depletion (9 out of 15) had moderate disease, three had severe disease and three had mild disease. Dysplasia was observed in 4 out of 62 cases and all of which had moderate disease activity. Out of the 9.68% cases which presented with polyps in endoscopic evaluation, 6.45% were pseudopolyps, 1.61% turned out to be tubular adenomas, and 1.61% turned out to be hyperplastic polyps. All cases with pseudopolyps and tubular adenomas had moderate to severe disease activity whereas one case with hyperplastic polyp had mild disease.

It was found that the proportion of moderate to severe disease was comparable between the three scoring systems with 70.97% in TWLS, 82.26% in MES and 87.10% in GS as shown in [Table/Fig-5].

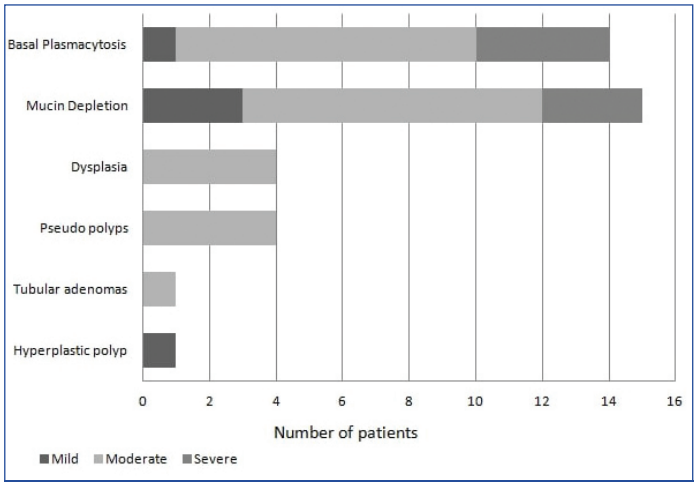
Spearman's correlation between TLWS, MS and GS are shown in [Table/Fig-10]. A strong positive correlation was found between



[Table/Fig-7]: Histopathological and endoscopic characteristics of Ulcerative Colitis (UC) in patient #43 (a,b-H&E Stain. a-40X, b-4X)



[Table/Fig-8]: Histopathological and endoscopic characteristics of Ulcerative Colitis (UC) (H&E stain, b-4X, d-10X).



[Table/Fig-9]: Histological features across disease severity in Ulcerative Colitis (UC).

MES and TLWS with a rho=0.614 (p<0.001) followed by GS with rho=0.421 (p<0.001). There was a strong correlation between GS and MES as well with a rho=0.375 (p<0.01).

	Geboes score	True love and Witts score
Mayo endoscopic score	0.375 p<0.01	0.614 p<0.001
Geboes score		0.421 p<0.001

[Table/Fig-10]: Spearman's correlations between clinical, endoscopic and histological activity.
*p-values >0.05 were considered significant

DISCUSSION

Accurate clinical, endoscopic, and histological assessments of disease activity are critical in UC patients to determine the further treatment modality and long-term prognosis. Several clinical grading systems have been in practice in the last four decades to measure the extent and severity of the disease. However, it has been seen that none of these scoring systems can independently provide accurate assessment of the disease as each has its own merits and demerits. This leads to the need for determining the relationship

between these scoring systems and establishing a management plan accordingly.

In the present study a strong correlation between clinical, endoscopic and histological activity in patients with UC is seen. In recent years, there has been a substantial shift towards determining mucosal healing to define the optimal management strategy in patients with UC. A recent surge of evidence has been observed that mucosal healing has been directly associated with reduced progression to colorectal cancer, lower rates of hospitalisation and reduced need for surgical intervention [14]. However, acute and chronic histological inflammatory activity is often seen to be associated with relapse of the disease even in the patients with clinically and endoscopically inactive disease [15]. This ascertains evaluation of histological activity in UC to be crucial in determining the further course of action for clinicians.

There exists a significant ambiguity with respect to the concordance between endoscopic mucosal healing and histological activity due to the use of different non validated indices to determine endoscopic extent of the disease [16-18]. A strong correlation was observed between TLWS and modified GS with a $p<0.001$. The clinical and endoscopic activity indices for UC correlated well in moderate to severe disease activity, but a poor correlation was observed between both indices in mild disease activity. This could be explained by the fact that only a small portion of the lesion was represented by histological sections. Reports from Rosenberg L et al., in their study of 103 patients revealed that 54% of their patients in clinical remission undergoing surveillance colonoscopy had histologic evidence of inflammation, and 34% had at least moderate histologic inflammation [19]. Similar findings have been reported by Baars JE et al., who observed the presence of histological inflammation without clinical symptoms [20].

However, there are a few studies where there is no correlation between endoscopic and histological activity. Simsek HD et al., who studied the concordance between the Rachmilewitz endoscopic activity index and the Harpaz histopathological activity scoring system in 106 UC patients, reported a poor correlation between histological and endoscopic activity [16].

Basal plasmacytosis, the infiltration of plasma cells in the deep layer of the mucosa have been frequently seen in severely inflamed mucosa in patients with UC [21]. In the present study cohort, basal plasmacytosis and mucin depletion were observed in a majority of cases which was classified as having moderate to severe disease activity. Dysplasia and pseudopolyps were also seen in moderate to severe disease. However, incidence of dysplasia appears to be lower in the present study, as authors have included only newly diagnosed cases. There have been several observations reported in the literature about presence of histological activity in endoscopically and clinically quiescent disease [18,21]. In a retrospective study of 75 patients it was found that the presence of basal plasmacytosis and a GS of >3.1 were directly significant in determining the disease relapse [22].

Despite the significant correlation, present study observed histological inflammation in biopsies done via endoscopy in patients with normal mucosa. This discrepancy could be due to mucosal healing and subclinical remission. Lemmens B et al., in a study of 263 biopsy sets, reported complete concordance amongst both extremes of histologic and endoscopic activity although significant misclassifications were observed in patients with mild disease [23]. This could be attributed to the higher sensitivity of microscopy to detect more severe disease in endoscopically quiescent cases. Narang V et al., observed that histological remission was a better predictor of clinical healing than endoscopic remission and also a better marker of treatment efficacy in patients with UC [24].

Limitation(s)

This study should be viewed in light of few limitations. Firstly, inter-observer variations in endoscopic scoring systems were not performed. Secondly, the study does not validate any of the three scoring systems for disease relapse and remissions, which was beyond the primary scope of the study. Also, reports of low incidence of dysplasia in the study could be attributed to the inclusion of only newly diagnosed cases of UC.

CONCLUSION(S)

The Geboes histological scoring system strongly correlates with both MES and TLWS in patients with UC. Findings of basal plasmacytosis, mucin depletion, dysplasia and pseudopolyps are associated with moderate to severe disease activity. Histological scoring is crucial to determine the extent of mucosal healing and thereby aid in optimising treatment strategies in these patients.

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