Medical Principles
and Practice

Assessment of the Correlation between Endoscopic Activity and Histological Activity in Ulcerative Colitis Patients

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Abstract

Objective: The aim of this study was to assess the concordance between the Rachmilewitz endoscopic activity index (EAI) and the Harpaz histopathological activity scoring system (HSS), which are used for evaluating the disease activity of ulcerative colitis (UC). **Subjects and Methods:** This study included 109 patients with UC. Based on the disease extent, patients were divided into two groups as left-sided colitis and pancolitis. Patients were grouped as inactive, mild, moderate and severe depending on the Rachmilewitz EAI and Harpaz HSS. Kendal's tau and kappa (κ) statistics were used to assess the agreement between endoscopic and histopathological scores. A receiver operating characteristic (ROC) curve was also analyzed to evaluate the sensitivity and specificity of endoscopic scores to predict inactive histopathological disease. **Results:** In the left-sided colitis group, there were slight and poor agreements in the inactive endoscopic subscores (ESS) with inactive Harpaz HSS (κ: 0.598, p < 0.001) and moderate ESS with moderate Harpaz HSS (κ: 0.236, p = 0.046). There was no agreement between mild ESS and mild Harpaz HSS and between severe ESS and severe Harpaz HSS (κ: 0.071, p = 0.573 and κ: 0.160, p = 0.151, respectively). In the pancolitis group, there was no significant agreement between inactive, mild, moderate and severe ESS and the equivalent Harpaz HSS grades (κ: –0.194, p = 0.187; κ: 0.125, p = 0.397; κ: 0.148, p = 0.175 and κ: 0.174, p = 0.153, respectively). The ROC curve showed that the ESS indicating inactive disease had a low sensitivity to predict histologically inactive disease. **Conclusion:** The concordance between the endoscopic and histopathological indices was poor. Using both scores in the follow-up of patients with UC is necessary for treatment planning.

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Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease that is characterized by a chronic colonic mucosal inflammation process with relapse and remission episodes [1]. It is a chronic disease that requires long-term treatment with anti-inflammatory agents, such as 5-aminosalicylic acid (5-ASA), immunosuppressives and anti-tumor necrosis factor medications [2, 3]. A proper evaluation of the disease activity and prevalence is critical in

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determining an optimal treatment strategy. The diagnosis and evaluation of disease activity is done depending on the patient symptoms, as well as colonoscopic and histopathological findings [1].

The prognosis of the disease, treatment choice and treatment response differ across UC patients [4]. An evaluation of mucosal healing is one of the most important criteria in selecting an anti-inflammatory agent [4]. Histopathological and endoscopic activity assessments play important roles in deciding the most convenient treatment option and evaluating a patient's response to a treatment [4]. There is no standard investigative method to determine mucosal healing, and using endoscopic or histological examinations alone has not been commonly accepted [4].

There are different scoring systems that are used to evaluate endoscopic findings in UC patients [5, 6]. One of them is the Rachmilewitz endoscopic activity index (EAI), which is frequently used in a patient's treatment process [7]. The Rachmilewitz EAI uses scores that vary between 0 and 12 and is dependent on the mucosal appearance, vascular pattern, ulceration and fragility criteria [7].

Many scoring indices have been developed to evaluate the histopathological activity in UC patients [8]. Of these indices, the Harpaz histological scoring system (HSS) is one of the easiest to use and is the most reliable method [9]. In this scoring system, neutrophil infiltration, epithelial cells, cryptitis, crypt abscesses, ulceration and erosion are evaluated [9].

In cases of overwhelming endoscopic findings, pathological findings are expected to also be overwhelming. In cases with few endoscopic findings, pathological findings are also expected to be minimal. However, contradictory findings among clinical, endoscopic and pathological findings can be encountered when assessing the disease activity [10].

In UC cases, determining equivalent endoscopic findings on a histopathological examination is thought to play an important role in making decisions about changing or stopping treatment. After the administration of an effective treatment and during normal disease progression, histological disease severity is altered [11]. In addition to beginning a biological therapy, mucosal healing is currently used as a significant endpoint in clinical trials [2]. In addition, mucosal healing has recently been shown to be associated with better patient outcomes, which consist mostly of lower colectomy rates and a lower hospitalization risk [12, 13]. Active microscopic inflammation increases the risk of neoplasia [12, 13]. Therefore, the aim

Table 1. Endoscopic index

Endoscopic finding	Score
Granulation scattering reflected light	
Yes	0
No	2
Vascular pattern	
Normal	0
Faded/disturbed	1
Completely absent	2
Vulnerability of mucosa	
None	0
Slightly increased (contact bleeding)	2
Greatly increased (spontaneous bleeding)	4
Mucosal damage (mucus, fibrin, exudate, erosions, ulcer)	
None	0
Slight	2
Pronounced	4

Table 2. Harpaz HSS

Inflammatory activity	Score	Defining histopathological characteristics
Inactive/ quiescent/normal	0	No epithelial infiltration by neutrophils
Mildly active	1	Neutrophil infiltration of <50% of sampled crypts or cross-sections, no ulcers or erosions
Moderately active	2	Neutrophil infiltration of ≥50% of sampled crypts or cross-sections, no ulcers or erosions
Severely active	3	Erosion or ulceration, irrespective of other features

of this study was to evaluate the correlation between the Rachmilewitz EAI and Harpaz HSS scales, which are used to determine the degree of disease activity in UC cases receiving treatment.

Subjects and Method

Patients

One hundred and nine patients (aged 17–80 years) who were treated in the Department of Gastroenterology of our hospital were included in the study. A diagnosis of UC was made based on clinical, radiological, endoscopic and histopathological findings. Patient demographic data, routine biochemical serum inflammatory marker levels and medical histories were obtained from the medical records. The phone numbers of patients included in the study were gathered from the hospital records and the history of each patient's medication was compiled through phone calls to

Table 3. Distribution of cases according to and correlations between endoscopic and histopathological scores in the overall cohort and subgroups

Rachmilewitz endoscopic scores	Harpaz pathological scores, n (%)				Kendal's tau correlation coefficient	p value
	inactive	mild	moderate	severe		
Left colitis (n = 63)					0.445	<0.001
Inactive (n = 16)	12 (75)	2 (12.5)	2 (12.5)	0		
Mild (n = 10)	3 (30)	2 (20)	5 (50)	0		
Moderate (n = 19)	1 (5.3)	2 (10.5)	12 (63)	4 (21.1)		
Severe (n = 18)	2 (11.1)	3 (16.7)	9 (50)	4 (22.2)		
Pancolitis (n = 46)					0.039	0.706
Inactive (n = 8)	0	1 (12.5)	7 (87.5)	0		
Mild (n = 8)	2 (25)	2 (25)	2 (25)	2 (25)		
Moderate (n = 7)	1 (14.3)	0	5 (71.4)	1 (14.3)		
Severe (n = 23)	4 (17.4)	4 (17.4)	8 (34.8)	7 (30.4)		
Overall cohort (n = 109)					0.272	<0.001
Inactive (n = 24)	12 (48)	3 (18.8)	9 (18)	0		
Mild (n = 18)	5 (20)	4 (25)	7 (14)	2 (11.1)		
Moderate (n = 26)	2 (8)	2 (12.5)	17 (34)	5 (27.8)		
Severe (n = 41)	6 (24)	7 (43.8)	17 (34)	11 (61.1)		

each patient. Mesalazine treatment, immunosuppressive therapy and histories of previous steroid therapy were evaluated using a questionnaire. Patients were evaluated on the presence of steroid resistance and steroid addiction. Patients whose disease severity was determined with a colonoscopic examination were divided into two groups as left-sided colitis and pancolitis.

Evaluation of Disease Activity

An endoscopic evaluation was made by a trained gastroenterology specialist with at least 5 years of experience (M.K.). Colonoscopy findings were rated according to the Rachmilewitz EAI [4]. Rachmilewitz endoscopic subscores (ESS) were defined based on the Rachmilewitz EAI: inactive, 0–3; mild, 4–6; moderate, 7–9, and severe, 10–12. The criteria used in the endoscopic evaluations are summarized in table 1.

Biopsies obtained during each colonoscopic examination were evaluated by a trained pathologist (G.G.S.) with at least 5 years of experience who was blinded to the patient endoscopic activity scores or other clinical and medical data. The Harpaz HSS scoring was used in the histopathological evaluation and graded based on epithelial neutrophil infiltration, cryptitis, crypt abscesses, ulceration and erosion. The Harpaz HSS scoring was made according to the parameters shown in table 2, categorized as: inactive, 0; mild, 1; moderate, 2, and severe, 3.

Statistical Analysis

Statistical analyses were performed using SPSS 15.0 (Chicago, Ill., USA). Intergroup comparisons of categorical variables were performed using a χ^2 test. Concordance between the endoscopic activity and histological activity scores were investigated for all cohorts and separately for the left-sided colitis and pancolitis groups using Kendall's tau correlation analysis and kappa (κ) statistics. The degree of agreement between the scores was measured as described by Altman [14]: very poor agreement, 0.2; slight agreement, 0.2–0.4; moderate agreement, 0.4–0.6; substantial (good, high) agreement, 0.6–0.8, and excellent (almost perfect) agreement, >0.8. Receiver operating characteristic (ROC) curves were used to analyze the specificity and sensitivity of low Rachmilewitz endoscopic scores in predicting histopathologically inactive disease.

Results

The mean age of the patients was 46.2 ± 15.6 years. Sixty-three of the patients were male. Sixty-three patients were diagnosed with left-sided colitis and 46 had pancolitis.

In the left sided-sided colitis cohort (n = 63), Rachmilewitz ESS revealed that 16 (25.4%) patients had inactive ESS, 10 (15.8%) had mild ESS, 19 (30.2%) had moderate ESS and 18 (28.6%) had severe ESS. By comparison, Harpaz HSS revealed that 18 (28.6%) patients had inactive colitis, 9 (14.4%) had mild colitis, 28 (44.4%) had moderate colitis and 18 (28.6%) had severe colitis (table 3). The concordance of the Harpaz HSS with the Rachmilewitz ESS is shown in figure 1. In the left-sided colitis cohort, although there was a slight and poor agreement in the inactive and moderate scores, there was no agreement in the mild and severe scores: 4 (25%) of the 16 cases with inactive Rachmilewitz ESS were misclassi-

Fig. 1. Concordance of Harpaz histological scores with Rachmilewitz endoscopic scores.
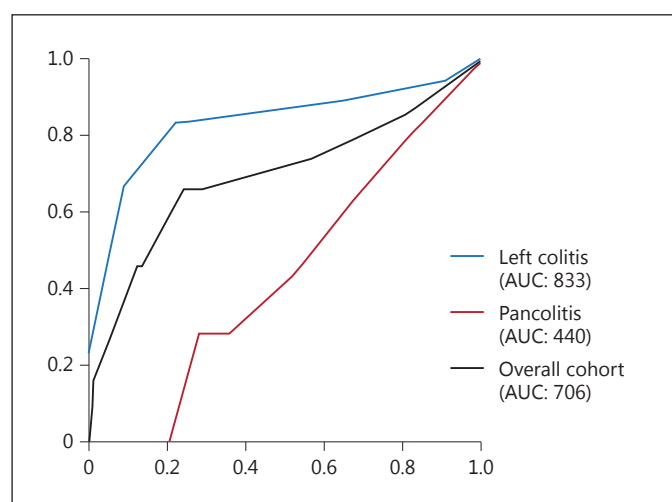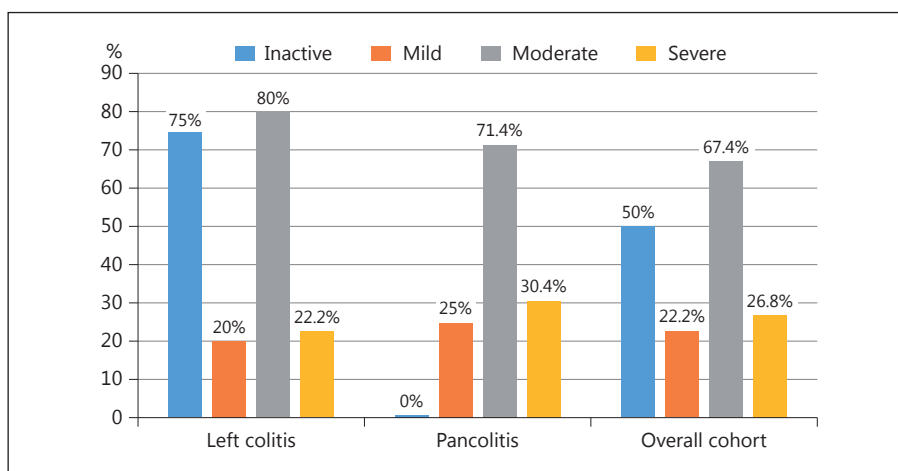

Fig. 2. ROC curves for Rachmilewitz endoscopic scores with the Harpaz histological scores as a state variable.

fied as mild, moderate or severe Harpaz HSS; 8 (80%) of the 10 cases with mild Rachmilewitz ESS were misclassified as inactive or moderate Harpaz HSS; 7 (20%) of the 19 cases with moderate Rachmilewitz ESS were misclassified as inactive, mild or severe Harpaz HSS, and 14 (77.8%) of the 18 cases with severe Rachmilewitz ESS were misclassified as inactive, mild or moderate Harpaz HSS (κ: 0.598, 95% CI 0.375 to 0.821, p < 0.001; κ: 0.071, 95% CI –0.203 to 0.345, p = 0.573; κ: 0.236, 95% CI 0.013 to 0.459, p = 0.046; κ: 0.160, 95% CI: –0.087 to 0.407, p = 0.151, respectively; table 3). The concordance between the Rachmilewitz ESS and Harpaz HSS was highest in the left-sided colitis group.

In the pancolitis cohort, Rachmilewitz ESS revealed that 8 patients had inactive ESS, 8 had mild ESS, 7 had moderate ESS and 23 had severe ESS. By contrast, HSS revealed that 7 patients had inactive colitis, 7 had mild colitis, 22 had moderate colitis and 10 had severe colitis (table 3). There was no agreement between the Harpaz HSS and Rachmilewitz ESS in the pancolitis cohort: all 8 cases (100%) with inactive Rachmilewitz ESS were misclassified as mild or moderate Harpaz HSS; 6 (75%) of the 8 cases with mild Rachmilewitz ESS were misclassified as inactive, moderate or severe Harpaz HSS; 2 (28.6%) of the 7 cases with moderate Rachmilewitz ESS were misclassified as inactive or severe Harpaz HSS, and 16 (69.6%) of the 23 cases with severe Rachmilewitz ESS were misclassified as inactive, mild or moderate Harpaz HSS (κ: –0.194, 95% CI –0.292 to 0.096, p = 0.187; κ: 0.125, 95% CI –0.206 to 0.456, p = 0.397; κ: 0.148, 95% CI –0.066 to 0.362, p = 0.175; κ: 0.174, 95% CI –0.061 to 0.409, p = 0.153, respectively).

In the overall patient cohort, Rachmilewitz ESS revealed that 24 patients had inactive ESS, 18 had mild ESS, 26 had moderate ESS and 41 had severe ESS. By contrast, HSS revealed that 25 patients had inactive colitis, 16 (17.4%) had mild colitis, 50 (54.5%) had moderate colitis and 18 (19.6%) had severe colitis (table 3). In the overall cohort there was a slight agreement between the endoscopic and histological activity scores in inactive cases: 12 (50%) of the 24 cases with inactive Rachmilewitz ESS were misclassified as mild or moderate Harpaz HSS; 14 (77.8%) of the 18 cases with mild Rachmilewitz ESS were misclassified as inactive, moderate or severe Harpaz HSS; 9 (34.6%) of the 26 cases with moderate Rachmilewitz ESS were misclassified as inactive, mild or severe Harpaz HSS, and 30 (73.2%) of the 41 cases with severe Rachmilewitz
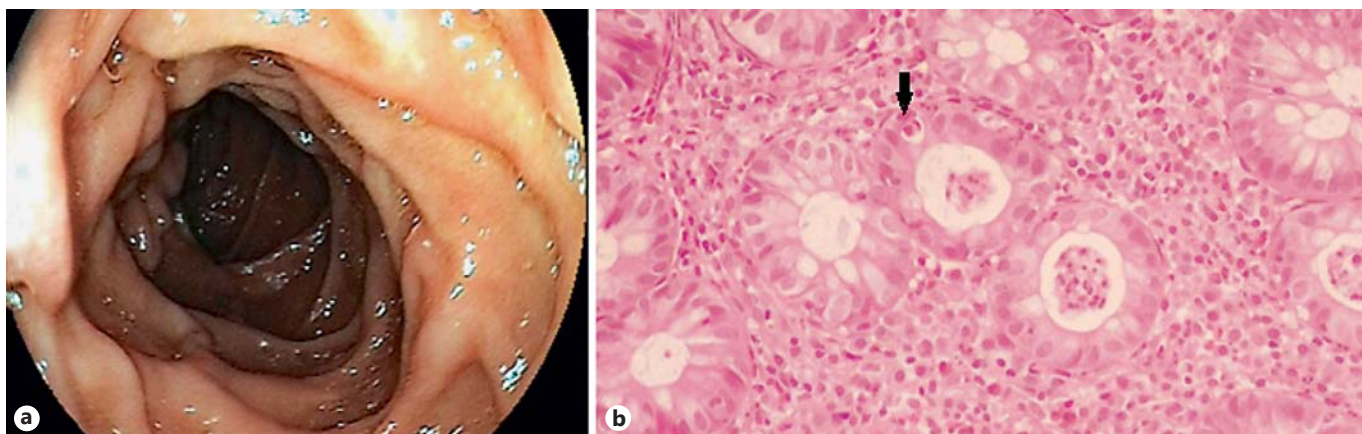
Fig. 3. a Mucosa appearing endoscopically normal and the lumen of the colon. **b** Harpaz grade 2: cryptitis, crypt abscess and neutrophils in the lamina propria. Original magnification ×200.
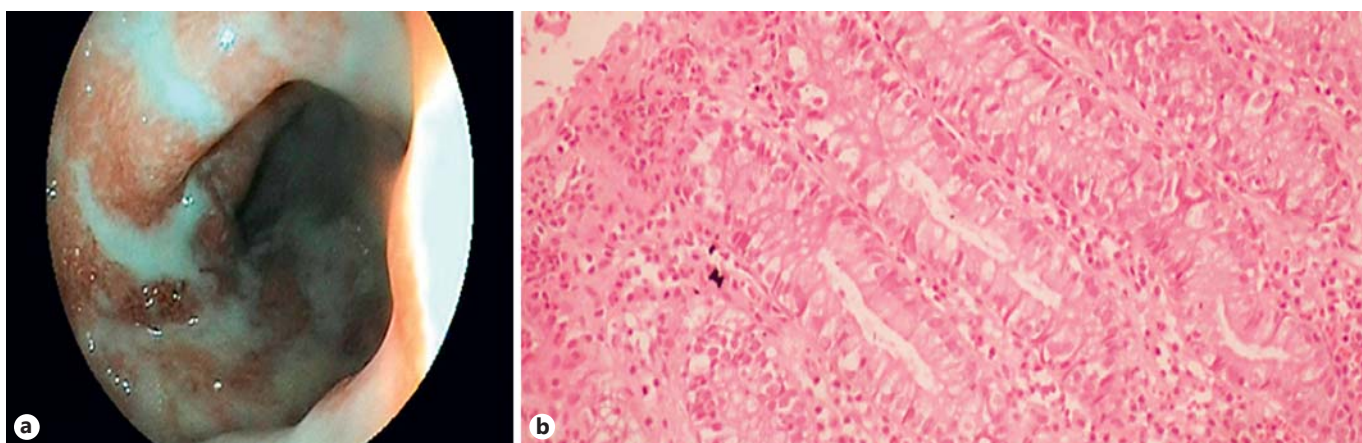

Fig. 4. a Rachmilewitz EAI 10: absent vascular pattern, mucosal friability, marked erosions and ulceration. **b** Harpaz grade 0 with no epithelial infiltration by neutrophils. Original magnification ×200.

ESS were misclassified as inactive, mild or moderate based on the Harpaz HSS (κ: 0.342, 95% CI 0.136 to 0.548, p < 0.001; κ: 0.095, 95% CI –0.117 to 0.306, p = 0.322; κ: 0.195, 95% CI 0.028 to 0.362, p = 0.022; κ: 0.186, 95% CI 0.016 to 0.357, p = 0.024; table 3).

The ROC curve showed that Rachmilewitz EAI scores ≤3, which indicated inactive disease, predicted an inactive Harpaz HSS with a sensitivity of 67% and specificity of 91% in the left-sided colitis cohort. However, in the pancolitis cohort, the ROC curve showed that Rachmilewitz EAI scores ≤3 predicted an inactive Harpaz HSS with a sensitivity below 1% and specificity of 80% (fig. 2).

Discussion

In this study, there was a very poor and slight agreement between the endoscopic and histopathological scores in cases with inactive and moderately active disease in the left-sided colitis group, and there was no significant agreement between the endoscopic and histological activity scores in the pancolitis group. In the overall cohort, there was a slight agreement between the endoscopic and histological activity scores in the inactive cases. Furthermore, the concordance between the histopathological and endoscopic activity indices was poor. The low endoscopic activity scores predicted inactive histopathological disease with a low sensitivity.

Simsek/Basyigit/Aktas/Simsek/Vargol/
Kucukazman/Nazlıgul

There was a poor agreement between the Rachmilewitz EAI and Harpaz HSS. Although it may be expected that pathological findings would correlate with the endoscopic and clinical findings, disparities among the clinical, endoscopic and pathological data were revealed [10]. While endoscopic studies can appear to be normal, histopathological activity can be high (fig. 3). Additionally, when an endoscopic approach is indicative of severe disease, the histopathological findings can be normal (fig. 4). In their research, Truelove and Richards [15] showed that although endoscopic findings were normal after successful induction therapy, there were frequent histological findings of active inflammation. Similarly, in clinically and endoscopically inactive UC cases, pathological signs of inflammation have been shown to increase the likelihood of a relapse occurring [16, 17]. Our study is similar to previous studies in UC patients conducted with other scoring systems [16, 17]. The poor concordance between the endoscopic and histopathological scoring systems could be due to the result of a delayed reflection of mucosal changes in the macroscopic appearance. Although endoscopic findings indicate normal mucosa, microscopic inflammatory processes may occur. Furthermore, in experimental animal models, Bou-Fersen et al. [18] reported that ultrastructural changes occur in the Golgi apparatus, mitochondria and endoplasmic reticulum in the mucosal and muscle layers of both the inflamed colon and uninflamed ileum of colitis.

Another plausible explanation for the poor concordance might be an endoscopist's preference for selecting a mucosal area for biopsy during endoscopy. Whereas some endoscopists prefer not to take biopsies from intensely active areas because of the risk of complications, such as perforation, others may prefer to take biopsies in more active areas to determine the highest disease activity. Therefore, it is of critical importance to evaluate multiple biopsies during diagnosis and follow-up [19]. For cases in routine daily practice, it is necessary to rule out more severe inflammation with serial biopsy sections.

Regardless of the reason for the poor concordance, this study indicates that evaluating both endoscopic and pathological findings could provide the most benefit to the patient. Lemmens et al. [1] reported a significant correlation between an endoscopic Mayo score and Geboes histological score for UC patients, but they suggested that for clinical follow-up and treatment decisions, histological scores along with an endoscopic examination should also be used. Furthermore, they suggested that a microscopic examination would be better than an endoscopic evaluation, especially to identify severe disease. The nature of mucosal inflammation and its degree is important in UC follow-up and treatment. Especially when there is no distinctive endoscopic mucosal disease, the existence of histopathologically active disease can guide clinicians to properly treat the disease [20].

Conclusion

In this study, the concordance between histopathological and endoscopic activity indices was poor. Because neither the histopathological nor endoscopic score was a better technique for evaluating disease activity, we recommend that the follow-up of patients with UC and determination of a treatment plan be decided multidimensionally by considering both histopathological and endoscopic results.

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