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WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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ORIGINAL ARTICLE

Prospective Study

Limited validity of Mayo endoscopic subscore in ulcerative colitis with concomitant primary sclerosing cholangitis

Pavel Wohl, Alzbeta Krausova, Petr Wohl, Ondrej Fabian, Lukas Bajer, Jan Brezina, Pavel Drastich, Mojmir Hlavaty, Petra Novotna, Michal Kahle, Julius Spicak, Martin Gregor

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Abstract

BACKGROUND

Ulcerative colitis (UC) with concomitant primary sclerosing cholangitis (PSC) represents a distinct disease entity (PSC-UC). Mayo endoscopic subscore (MES) is a standard tool for assessing disease activity in UC but its relevance in PSC-UC remains unclear.

AIM

To assess the accuracy of MES in UC and PSC-UC patients, we performed histological scoring using Nancy histological index (NHI).

METHODS

MES was assessed in 30 PSC-UC and 29 UC adult patients during endoscopy. NHI and inflammation were evaluated in biopsies from the cecum, rectum, and terminal ileum. In addition, perinuclear anti-neutrophil cytoplasmic antibodies,

fecal calprotectin, body mass index, and other relevant clinical characteristics were collected.

RESULTS

The median MES and NHI were similar for UC patients (MES grade 2 and NHI grade 2 in the rectum) but were different for PSC-UC patients (MES grade 0 and NHI grade 2 in the cecum). There was a correlation between MES and NHI for UC patients (Spearman's r = 0.40, P = 0.029) but not for PSC-UC patients. Histopathological examination revealed persistent microscopic inflammation in 88% of PSC-UC patients with MES grade 0 (46% of all PSC-UC patients). Moreover, MES overestimated the severity of active inflammation in an additional 11% of PSC-UC patients.

CONCLUSION

MES insufficiently identifies microscopic inflammation in PSC-UC. This indicates that histological evaluation should become a routine procedure of the diagnostic and grading system in both PSC-UC and PSC.

Key Words: Primary sclerosing cholangitis; Ulcerative colitis; Diagnosis; Nancy histological index; Mayo endoscopic subscore

Core Tip: Ulcerative colitis (UC) with concomitant primary sclerosing cholangitis (PSC) represents a distinct disease entity (PSC-UC). Our results highlight the limitations of endoscopic examination in uncovering microscopic inflammatory lesions, resulting in the erroneous classification of PSC-UC patients as healthy. To mitigate the risk of underdiagnosis, histopathological examination should therefore be an essential component of the diagnostic approach for UC in PSC patients.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive inflammation, fibrosis, and diffuse multiple stricturing of the intrahepatic and extrahepatic bile ducts[1]. In up to 80% of patients, PSC is closely associated with inflammatory bowel disease (IBD) prevalently with a unique type of ulcerative colitis (UC) known as PSC-UC[2,3].

As a distinct clinical phenotype, PSC-UC manifests with colonoscopic features that differ from those of typical UC without hepatobiliary disease. Interestingly, PSC-UC may not develop clinically apparent gastrointestinal symptoms[4,5]. Multiple studies[2,6,7] have shown that the colonic inflammation in PSC-UC is typically more pronounced in the right-sided colon with often minimal to normal mucosal findings in the rectum. Furthermore, PSC-UC is characterized by a lower incidence of inflammatory polyps[4,8] and a higher incidence of backwash ileitis[9] when compared to UC. In up to 94% of PSC-UC cases, the phenotype is reported as pancolitis with rectal sparing. Although colitis in PSC tends to follow a quiescent course, PSC-UC is associated with a high incidence of malignancies represented mainly by colitis-associated carcinoma (CAC)[10-13]. The risk of CAC is higher in PSC-UC than in UC alone[14], which is why accurate diagnosis is important for all PSC-UC patients.

IBD diagnosis is largely based on clinical symptoms, endoscopy, and histopathology[15] with endoscopic assessment being the most feasible and reliable approach[16] in routine clinical practice. Among many different endoscopic scores for UC[17], the Mayo endoscopic subscore (MES)[18,19], a component of the Mayo Clinic Score, is recommended to assess disease activity and remains the most frequently used score in both clinical practice and clinical trials[18]. Surprisingly, despite accumulating evidence for the limited diagnostic accuracy of endoscopic techniques[20-24], namely in the context of mild mucosal inflammation, neither MES nor any of the other endoscopic scores have been validated for PSC-UC.

Endoscopy-based approaches are not sufficiently reliable for PSC-UC patients. This can lead to poor therapeutic decisions and misguided treatment. Histopathological evaluation can remedy this by detecting potential microscopic disease activity, despite the absence of clinical or endoscopic signs of disease common in PSC-UC patients[20-24]. Out of the more than 30 described UC histological scores[25], the newly established Nancy histological index (NHI)[25-27] has quickly become one of the most popular histological scoring systems of inflammatory activity in UC. In 2020, the European Crohn's and Colitis Organization recommended NHI for daily clinical practice[28].

Given the challenges of endoscopy for PSC-UC, the diagnostic relevance of MES for PSC-UC is unclear despite MES being a standard tool for assessing inflammation in UC. The overall objective of this study was: (1) To compare the reliability of MES as a diagnostic tool between UC and PSC-UC patient cohorts; and (2) To assess the accuracy of MES in PSC-UC patients using histological disease activity scoring (NHI).

MATERIALS AND METHODS

Patients

This was a prospective longitudinal study performed at the Institute for Clinical and Experimental Medicine (Prague, Czech Republic), a tertiary health care center. We included 59 Caucasian adult patients diagnosed with UC (n = 29) and PSC-UC (n = 30) according to conventional diagnostic criteria, who were admitted to the Hepatogastroenterology Department for a colonoscopy from July 2016 to March 2021. As portal hypertension with portal colopathy in liver cirrhosis are common endoscopic features that may mimic some inflammatory changes typical for PSC-UC, patients with advanced liver cirrhosis with portal hypertension were excluded. Other exclusion criteria were colitis-associated cancer and colonic dysplasia. The study cohort consisted of 20 females and 39 males (sex). This study was approved by the Ethics Committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital with Multi-Center Competence (G16-06-25) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects before the study. All patients have been characterized as summarized in Table 1.

Endoscopic and histological evaluations

All UC and PSC-UC patients were subjected to a colonoscopy with a standard white light endoscope. During the colonoscopy, two or three biopsies from the terminal ileum, cecum, and rectum of endoscopically most severely inflamed mucosa were collected. Endoscopic disease activity was assessed using MES[18]. Histological inflammation in the colon biopsies (cecum and rectum) was assessed by NHI as published previously for UC[26]. In addition, histological inflammation in biopsies from the terminal ileum was determined by a four-grade scoring system (0-3), where 0 corresponds to normal and 3 to severe inflammation. Blinded histopathological evaluation of paraffin-embedded sections stained with hematoxylin-eosin was performed by a trained pathologist (Ondrej Fabian).

PSC

PSC was defined by the presence of intra- and/or extra-hepatic bile duct abnormalities in the form of beading, duct ectasia, and stricturing of the intra- or extra-hepatic bile ducts documented in the medical record from endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography, and/or liver biopsy. Small duct PSC was defined when there were histological features consistent with PSC on liver biopsy in the absence of characteristic radiological features. The diagnosis of PSC was also confirmed by laboratory tests (see below).

Laboratory and biochemical parameters

Blood analysis was performed on the day of the colonoscopy, including the determination of hemoglobin, leukocytes, platelets, and albumin (not shown). A stool sample that was obtained immediately before bowel preparation was provided by each patient for the analysis of fecal calprotectin (FC). FC level was measured by ELISA EliA kit (Phadia AB, Uppsala, Sweden). Detection of anti-neutrophil cytoplasmic antibody and IgG4 was performed using kits from Inova Diagnostics Inc. (San Diego, CA, United States).

Statistical analyses

All ordinal variables are presented as medians with 95%CI; continuous variables are expressed as means ± standard errors. All differences between independent ordinal variables were tested by Mann-Whitney U test, differences in paired measurements were assessed by Wilcoxon signed-rank test and differences in proportions were tested by Fisher exact test. Correlations are expressed as Spearman's rank correlation coefficient (r). For comparison of MES with NHI, only the most severely affected lesion with the highest NHI grade was considered for each patient. All data were analyzed using the Python ecosystem. Statistical significance was accepted at $P \leq 0.05$. The statistical methods of this study were reviewed by Michal Kahle from Department of Data Analysis, Statistics, and AI, Institute for Clinical and Experimental Medicine, Prague, Czech Republic.

RESULTS

MES and NHI scoring

The severity of UC was assessed both endoscopically and histologically in PSC-UC (Figure 1, upper panels) and UC (Figure 1, lower panels) patients. Endoscopy and histopathology involved examination of samples from the cecum, rectum and ileum. Among UC patients, only two individuals (7%) showed normal endoscopic findings (MES grade 0); the majority exhibited mild to moderate mucosal inflammation and damage (MES grades 1 and 2; median MES grade 2; Table 2). Similarly, histopathological examination revealed that most UC patients (90%) showed normal findings or mild inflammation with median NHI grade 1 in the cecum (Table 2). However, in the rectum, 30% of UC patients exhibited a shift towards moderate to severe active inflammation (median NHI grade 2; Table 2), which aligned with the MES findings. When considering the most severely inflamed biopsy for each patient (Figure 1, "cecum and rectum" panel), a significant correlation between MES and NHI was observed in UC patients (Spearman's r = 0.40, P = 0.029).

In contrast to only two UC patients, MES identified 16 (53%) PSC-UC patients with normal endoscopic appearance (MES grade 0; median MES grade 0; Table 2). In the rectum, a similar distribution was observed with a majority (57%) of PSC-UC patients without histologically active disease (median NHI grade 0, Table 2). However, in the cecum, a more pronounced inflammatory pattern emerged, with 80% of PSC-UC patients displaying NHI grades ranging from 1 to 4

Table 1 Characterization of patients

Characteristic	UC	PSC-UC	*P* value
Patients	29	30	
Male sex	16 (55)	23 (77)	0.10
Age in years	43.2 ± 12.5	37.2 ± 2.9	0.07
Duration of disease in years	12.9 ± 10.6	10.6 ± 6.9	0.62
pANCA positive	14 (48)	16 (53)	0.8
Portal hypertension	0	0	
Cholecystectomy	1 (3)	1 (3)	
BMI in a.u.	25.1 ± 4.1	23.5 ± 4.2	0.1
Corticosteroids	10 (34)	10 (33)	
Mesalamine	12 (41)	20 (66)	
Mesalamine and immunomodulators	12 (41)	9 (30)	
Biological treatment	5 (17)	0	
Ursodeoxycholic acid	0	30 (100)	
Fecal calprotectin in µg/g, median (95%CI)	478 (263–917)	96 (60-231)	< 0.001

Data are expressed as *n* (%) or mean ± standard deviation, unless otherwise indicated. a.u.: Arbitrary units; BMI: Body mass index; CI: Confidence interval; pANCA: Perinuclear anti-neutrophil cytoplasm autoantibodies; PSC-UC: Primary sclerosing cholangitis with concomitant ulcerative colitis; UC: Ulcerative colitis.

Table 2 Calculated Mayo endoscopic subscore and Nancy histological index

Parameter	PSC-UC	UC	*P* value
MES	0 (0-1)	2 (1-2)	< 0.001
Inflammation (ileum)	0 (0-0)	0 (0-0)	
NHI (cecum)	2 (1-2)	1 (0-2)	0.048
NHI (rectum)	0 (0-1)	2 (0-3)	0.002

Data are expressed as median (95%CI). CI: Confidence interval; MES: Mayo endoscopic subscore; NHI: Nancy histological index; PSC-UC: Primary sclerosing cholangitis with concomitant ulcerative colitis; UC: Ulcerative colitis.

(median NHI grade 2; Table 2). This highlights a significant discrepancy between MES and NHI in PSC-UC patients, which is further corroborated by the lack of correlation between the two measures (Spearman's r = 0.27, P = 0.14). Notably, for the correlation analysis, only the grades corresponding to the most affected lesions were considered, effectively approximating the situation in the cecum (Figure 1, "cecum and rectum").

MES and NHI in PSC-UC

To understand the discrepancy between MES and NHI in PSC-UC patients, the NHI values of 16 PSC-UC patients with MES grade 0 were analyzed (Figure 2, upper panels). Surprisingly, this analysis revealed that 13 of these patients (81%) had NHI grades between 1 and 4 in the cecum (Figure 3A and B) and 9 (56%) had NHI grades between 1 and 4 in the rectum. When considering both the cecum and rectum for each patient, only two individuals (12.5%) had NHI grades of 0 in both segments (Figure 2, "cecum and rectum" panel). Hence, MES failed to detect active UC in 14 (88%) of the PSC-UC patients with MES grade 0, which corresponds to 46% of all PSC-UC patients.

Further analysis of the NHI scores revealed that among the eight PSC-UC patients with MES grade 1, three patients showed no signs of inflammation (NHI grade 0) while three exhibited active inflammation with NHI grades ranging from 2 to 4 (Figure 2, middle panels; Figure 3C). Similarly, among the five patients with MES grade 2, two individuals displayed active inflammation with NHI grade 3 (Figure 2, lower panels; Figure 3D). This suggests that MES incorrectly diagnosed three PSC-UC patients. Taken together, these results clearly indicate that MES insufficiently identified ongoing microscopic inflammation in 17 (57%) of PSC-UC patients, which would negatively affect therapeutic decisions.

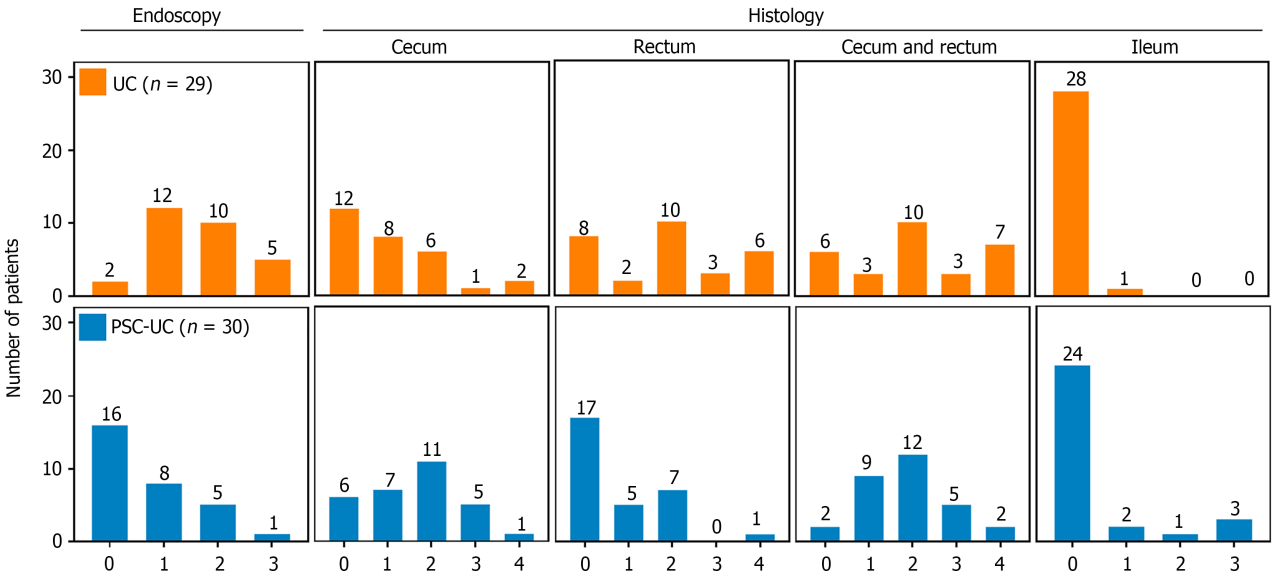

Figure 1 Mayo endoscopic subscore, Nancy histological index and inflammation grade of primary sclerosing cholangitis-ulcerative colitis and ulcerative colitis patients in the cecum, rectum and ileum. 'Cecum and rectum' panels represent only the most severely affected lesions for each patient. The numbers of patients per grade are indicated in the graph. PSC-UC: Primary sclerosing cholangitis-ulcerative colitis.

Backwash ileitis and rectal sparing in PSC-UC patients

All patients were characterized as summarized in Table 1. Of note, fecal calprotectin (FC) levels in UC patients were significantly elevated, with a median of 478 μg/g (95%CI: 263–917), compared to the widely accepted upper limit of 100 μg/g[29]. In contrast, FC levels in PSC-UC patients were within the normal range, with a median of 96 μg/g (95%CI: 60-231). This suggests that PSC-UC patients have nearly absent or very mild UC manifestation, compared to the severe manifestation in UC patients.

Histopathological examination consistently supported the notion of a more severe inflammatory pattern in the rectum of UC patients, as evidenced by the highest NHI grades (Figure 1, Table 2). In contrast, PSC-UC patients predominantly exhibited inflammatory changes in the cecum (median NHI grade 2 *vs* 0 in rectum; $P < 0.01$; Figure 1; Table 2), suggesting complete or partial rectal sparing. Indeed, 60% of PSC-UC patients had spared rectal mucosa compared to just 10% of UC patients ($P < 0.001$).

In addition, inflammation scoring in the ileum exhibited similar median values in both UC and PSC-UC patients (median NHI grade 0; Figure 1, Table 2). Nevertheless, 6 PSC-UC patients (20%) exhibited mild to severe inflammation (NHI grades 1-3) compared to only one patient in the UC group (3%; $P = 0.047$; Figure 1), thus suggesting higher incidence of backwash ileitis in PSC-UC patients. These findings collectively underscore the variability of inflammation intensity across different segments of the intestine in both PSC-UC and UC.

DISCUSSION

To date, almost 30 scoring systems have been introduced to accurately assess colitis disease severity in IBD. However, despite extensive validations, none of these systems have been universally recognized as versatile[30]. In this study, we aimed to validate the commonly used MES system for evaluating UC in PSC-UC patients and compare the results with histopathological observations expressed through the NHI. Our findings demonstrate a correlation between MES and NHI in UC patients, but a lack of correlation in PSC-UC patients (as indicated by Spearman's *r*). MES fails to identify ongoing histological inflammation (NHI grade 1-4, Figure 2 and Figure 3) in more than 46% of PSC-UC patients who were assigned MES grade 0. This significant discrepancy highlights a major limitation of endoscopic assessment, which could potentially lead to an underestimation of PSC-UC severity. Therefore, we recommend the routine use of histological scoring in clinical practice to overcome this limitation.

It has been reported that UC in PSC manifests mildly or even completely without symptoms compared to typical UC[5,31]. Additionally, Murasugi *et al*[5] documented no correlation between the severity of liver disease and colonic inflammation expressed by MES. They concluded that it is important for colonoscopy to be routinely performed immediately following a diagnosis of PSC. However, our observations show that histopathological evaluation should always accompany colonoscopy to avoid underdiagnosis.

In our current study, NHI revealed more severe colitis in the cecum of PSC-UC patients, along with an increased occurrence of backwash ileitis and rectal sparing. These findings are consistent with previous studies that have reported a high prevalence of pancolitis in PSC-UC patients ranging from 80% to 95% with varying degrees of severity and pronounced localization in the right-sided colon[4,5,7,31]. Therefore, it is crucial to inspect all colonic segments (ileum, cecum, rectum, sigmoid, descending, transverse and ascending colon) using both colonoscopy and histopathology to

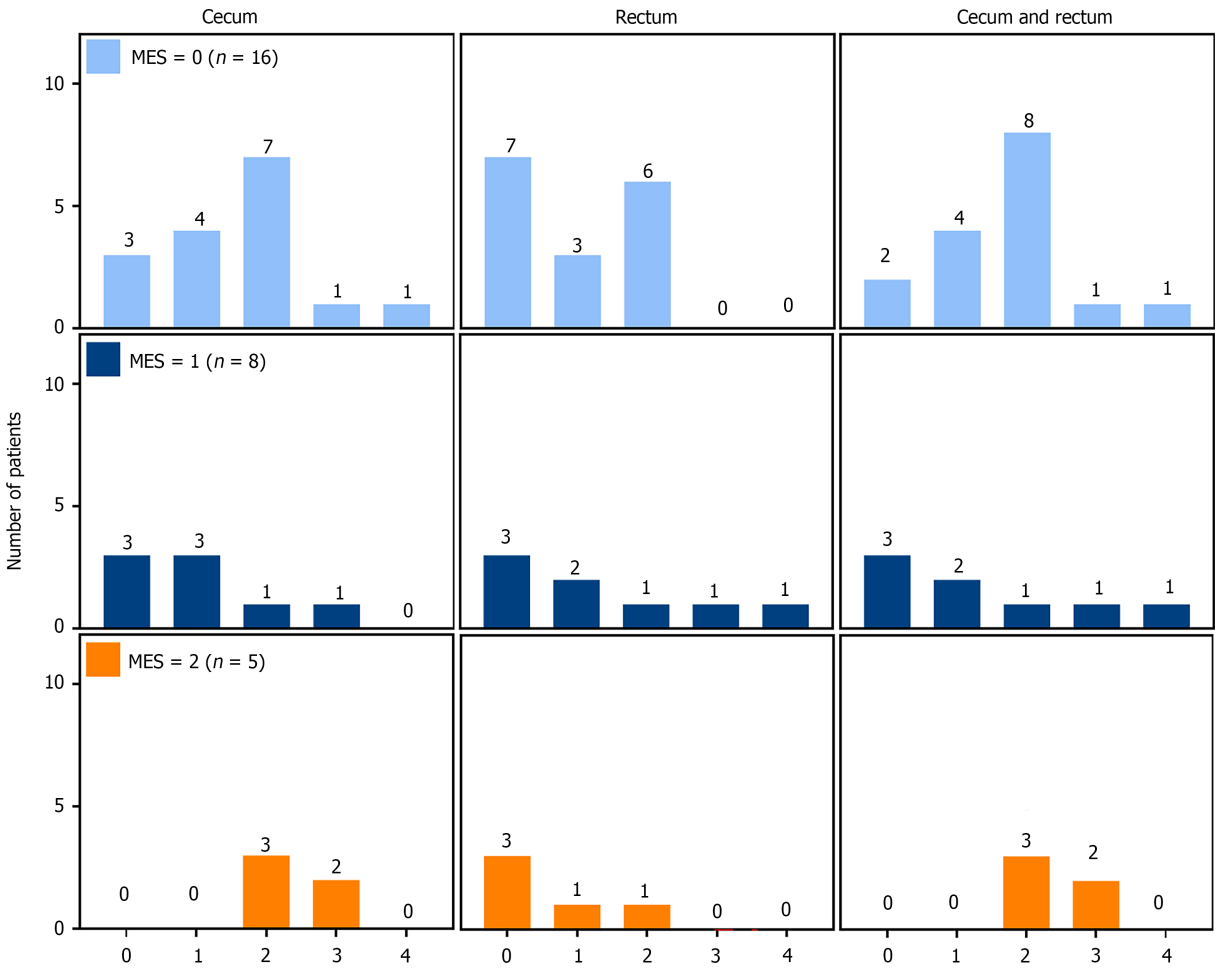

Figure 2 Nancy histological index scores of primary sclerosing cholangitis-ulcerative colitis patients with Mayo endoscopic subscore grade 0 (top panels), Mayo endoscopic subscore grade 1 (middle panels) and Mayo endoscopic subscore grade 2 in the cecum and rectum. 'Cecum and rectum' panels represent only the most severely affected lesions for each patient. The numbers of patients per grade are indicated in the graph. MES: Mayo endoscopic subscore.

obtain a comprehensive understanding of the disease presentation in PSC-UC patients.

Lobatón *et al*[32] previously introduced two scoring systems for assessing UC activity: the modified score (MS) and the extended modified score (EMS). The MS summarizes MES from all colonic segments, while the EMS multiplies the MS by the disease extent in centimeters. These scores are both comprehensive and valuable, particularly in comparing clinical outcomes and assessing treatment effects over time, including mucosal healing. However, they do not fully address the challenge of underestimating UC severity in PSC or PSC-UC patients, especially in those with minimal endoscopic lesions or mild disease activity. This limitation highlights the need for complementary diagnostic tools beyond endoscopy in this patient population.

Although NHI has not been previously validated for PSC-UC, it has been validated for UC[27]. Furthermore, it has shown a good correlation with other established indices such as the Geboes score and Global visual analog scale[25]. Given this correlation, we have successfully employed NHI to evaluate the microscopic disease activity in PSC-UC. Importantly, interpretation must be cautiously exercised especially in treated patients, as NHI grade 0 is assigned to both normal histological observation and mild chronic inflammation without activity.

Our study highlights the critical importance of incorporating histological evaluation into the diagnostic and grading framework for PSC and PSC-UC. Although our cohort was small (59 patients from a single center), similar findings were reported in a larger study involving 131 UC patients, which compared the MES with various histologic scores[22]. Interestingly, while a strong correlation between MES and histologic scores was found in cases of inactive or severe UC, histology proved essential for accurate assessment in patients with mild disease. MES tends to underestimate mild progression, potentially leading to suboptimal patient management.

We propose that routine endoscopy followed by histological evaluation of biopsy samples should be standard practice for all PSC patients, particularly those without UC symptoms or visible endoscopic inflammation (MES grade 0). This approach ensures more accurate follow-up and monitoring, especially regarding the risk of malignant complications. PSC-UC carries a higher oncologic risk than UC alone, making vigilant surveillance essential[14]. While endoscopy and MES scoring remain valuable tools, they lack the resolution to capture microscopic changes critical to patient care.

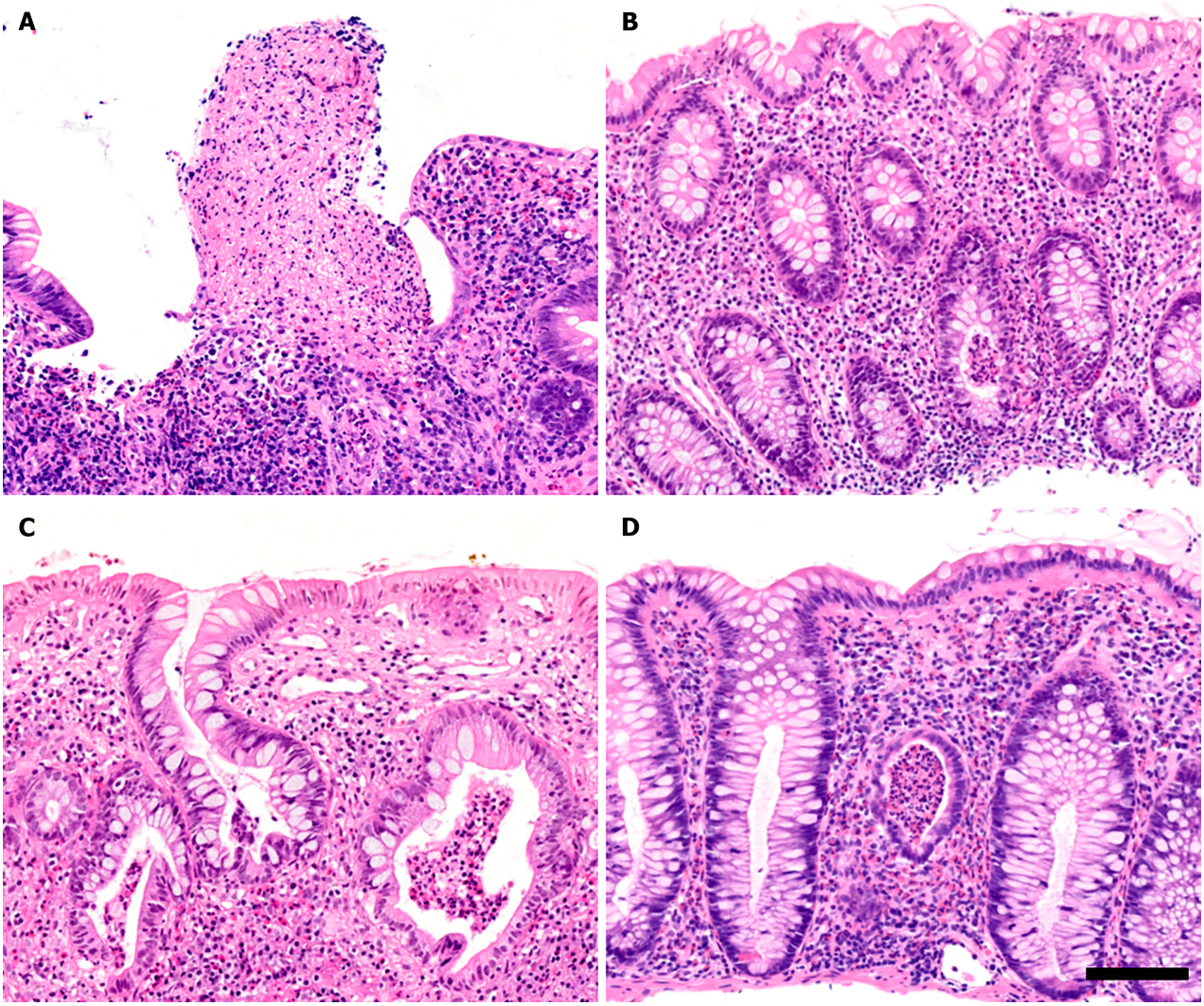

Figure 3 Hematoxylin-eosin stained cecal biopsies from primary sclerosing cholangitis-ulcerative colitis patients with Mayo endoscopic subscore grade 0, Mayo endoscopic subscore grade 1, and Mayo endoscopic subscore grade 2. A-D: All samples show an active colitic pattern with numerous neutrophils infiltrated into lamina propria and epithelium accompanied by ulceration (A) and crypt abscesses (B-D). Samples were thus assigned Nancy histological index grades 4 (A) and 3 (B-D). Scale bar, 100 mm. A and B: Mayo endoscopic subscore (MES) grade 0; C: MES grade 1; D: MES grade 2.

In recent years, artificial intelligence (AI) has made significant strides in the field of gastroenterology, particularly in the detection and classification of colorectal polyps[33]. AI has also shown high accuracy, reaching up to 93% in distinguishing between adenomatous and hyperplastic lesions[34,35]. This technology holds promise for accurately diagnosing UC in patients with PSC, especially if deep learning models are trained on images displaying characteristic PSC-UC lesions. However, because clear endoscopic lesions are frequently absent in PSC-UC patients, the applicability of AI may be limited in these cases. As a result, histopathological evaluation will remain crucial for diagnosis and management when endoscopic findings are inconclusive.

CONCLUSION

Our study highlights that the standard MES scoring system has limited capacity to assess UC activity in the context of PSC-UC. Our results prove that histological evaluation must be incorporated into the diagnostic and grading system for PSC and PSC-UC to improve clinical management of patients, particularly in terms of monitoring malignant complications and determining the need for orthotopic liver transplantation.

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FOOTNOTES

Author contributions: Wohl Pa designed the study; Wohl Pe, Bajer L, Brezina J, Drastich P and Hlavaty M recruited and treated the patients and collected and analyzed the data; Fabian O performed the histological evaluations; Novotna P analyzed the data; Kahle M performed the statistical analyses; Wohl Pa, Krausova A and Gregor M wrote the manuscript; All authors have read and approve the final manuscript.

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Clinical trial registration statement: Our study does not fulfill the criteria for a clinical trial according to the legislation of the Czech Republic and implemented EU laws. To conduct our prospective study, only ethical approval was required from the Czech Grant Agency and the Department of Gastroenterology at the Institute for Clinical and Experimental Medicine, where the study was conducted.

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