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Superb Microvascular Imaging Is Superior to Doppler Imaging in Ruling Out Ulcerative Colitis Disease Activity

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Background: There is an unmet medical need for noninvasive techniques to determine disease activity in inflammatory bowel disease (IBD) and intestinal ultrasound (IUS) has shown promising performance in this regard. In addition to parameters such as bowel wall thickness, stratification, and mesenteric fat, color Doppler signals are used to determine inflammatory activity in the gut. However, whether superb microvascular imaging (SMI), a microvascular flow imaging technique, improves the diagnostic accuracy is currently unclear.

Methods: We performed a prospective single-center cross-sectional cohort study including 62 patients with ulcerative colitis (UC). IUS was performed on the sigmoid colon within 30 days of colonoscopy and the International Bowel Ultrasound (IBUS) group Segmental Activity Score (SAS) as well as SMI signals were determined and correlated to established endoscopic, clinical, and biochemical read-outs of disease activity.

Results: Semiquantitative scoring of SMI signals had a substantial interobserver agreement between 2 blinded and expert central readers. It showed excellent correlation to endoscopic, clinical, and biochemical disease activity. While SMI did not improve the overall diagnostic performance of the IBUS-SAS to predict endoscopic disease activity, SMI alone was highly precise and superior to Doppler imaging in predicting endoscopic remission.

Conclusions: IUS is a highly precise noninvasive diagnostic tool to monitor disease activity in UC, in particular for predicting endoscopic remission. Assessing the SMI signals in the bowel wall of patients with IBD seems a promising tool to simplify IUS diagnostics in IBD that warrants further research.

Lay Summary

Intestinal ultrasound holds promise in noninvasively monitoring disease activity in inflammatory bowel disease. We show that in the hands of experienced investigators, superb microvascular imaging shows an improved correlation to disease activity in ulcerative colitis compared to Doppler imaging.

Key Words: intestinal ultrasound, IBUS-SAS, inflammatory bowel disease, superb microvascular imaging

Introduction

Despite an increasing number of available treatment options, inflammatory bowel diseases (IBDs) such as Crohn's disease (CD) and ulcerative colitis (UC) continue to pose a substantial therapeutic challenge.[1,2] Due to primary nonresponse or secondary loss of response, long-term remission is not achieved in the majority of patients, when treated with a conventional drug, a biological, or a small molecule.[3] At the same time, numerous studies have shown that deep remission, that is, achieving mucosal healing on endoscopy and/or histological remission, clearly improves the outcomes of IBD patients with regard to flares, hospitalizations, or surgery during the follow-up.[4–6]

Thus, it is consensus, that a treat-to-target strategy should be followed in IBD, which regularly monitors disease activity to ensure that insufficient response to treatment is noted in time and therapy can be adjusted, if necessary.[7] Since it has also been shown that assessing mucosal inflammation by more objective measures such as endoscopy and histology is superior to assessing clinical symptoms by patient-reported outcomes to predict long-term remission,[8,9] this strategy also requires repeat follow-up endoscopy.

Although being the gold standard and providing the opportunity to obtain tissue samples for histology,[10] endoscopy requires potentially burdensome bowel cleanse and comes with low, but measurable risks such as perforation, bleeding, and sedation complications.[11,12] Together, these aspects limit the acceptance and rate of endoscopic examinations and underscore that there is an unmet need for easy and noninvasive techniques for objective judgment on disease activity.

Intestinal ultrasound (IUS) has previously been suggested as a noninvasive method to quantify transmural inflammation in

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Key Messages

What is already known?

- Intestinal ultrasound (IUS) can help to noninvasively monitor disease activity in inflammatory bowel disease.

What is new here?

- Superb microvascular imaging (SMI) shows an improved correlation to ulcerative colitis disease activity compared to Doppler imaging.

How can this study help patient care?

- Using IUS complemented with SMI might help identify patients in deep remission, in which colonoscopy intervals can be prolonged.

CD[10,13–15] and various scoring systems such as the International Bowel Ultrasound (IBUS) group Segmental Activity Score (SAS) have been suggested[16] and validated.[17] To the contrary, the use of IUS in UC has only rarely been investigated until it has recently been shown that determining the IBUS-SAS clearly correlates with endoscopic disease activity.[18]

One important item to assess intestinal inflammation with IUS is hypervascularization of the bowel wall as determined by Doppler imaging (Duplex mode).[19] Modern ultrasound devices offer even more sensitive techniques to determine vascularization such as the superb microvascular imaging (SMI) tool provided by Canon.[20] SMI and other microvascular flow imaging techniques are able to visualize low-velocity blood flow in small diameter vessels by using a clutter suppression algorithm to differentiate these flow signals from background noise.[20]

Here, we hypothesized that using SMI to assess bowel wall vascularization might be superior to conventional Doppler imaging in quantifying mucosal inflammation in UC and addressed this question in a prospective mono-centric cohort study.

Materials and Methods

Patients and Procedures

Patients with an established diagnosis of UC that presented to the IBD Outpatient Clinic of the Department of Medicine 1 of the University Hospital Erlangen for regular treatment and had received or were scheduled for regular follow-up colonoscopy due to clinical indication within 30 days prior to or after the visit, respectively, were eligible for the study. After obtaining informed consent, IUS was performed on a Canon Aplio 900 machine by a team of 9 physicians with extensive training in IUS according to a standardized protocol on the sigmoid colon: B mode images in longitudinal and cross-sectional orientation were obtained. Moreover, images and videos with Color Doppler and SMI duplex mode were acquired in inspiration with the gain adjusted to slightly below artifact level. Patients with isolated proctitis (Montreal classification E1) were not included in the study.

The following items were determined and documented by 2 central readers with extensive experience in IUS using the full set of images and videos available per patient: Skin-to-bowel wall distance, bowel wall thickness (2 measurements in longitudinal orientation in at least 1 cm distance, 2 measurements in cross-sectional orientation with at least 90° angle), bowel wall stratification, mesenteric fat, and color Doppler imaging score. The latter 3 parameters were semiquantitatively scored as suggested by the IBUS-SAS (Table 1). In addition, SMI signals arising from hyperemic microvessels in the bowel wall were semiquantitatively scored according to the same criteria as Doppler imaging (SMI score; Table 2; Figure 1). To avoid bias arising from unfavorable ultrasound conditions, patients with a skin-to-bowel wall distance of more than 30 mm were excluded from the study.

The following additional data were collected: Baseline demographic data, disease characteristics (eg, disease duration, disease extent, concomitant treatment), endoscopic disease activity in the sigmoid colon within 30 days of IUS (endoscopic Mayo score [eMS], Ulcerative Colitis Endoscopic Index of Severity [UCEIS]), biochemical disease activity (C-reactive protein [CRP], fecal calprotectin [fCP]), clinical disease activity (partial Mayo score [PMS]).

The study was approved by the Ethics Committee of the Friedrich-Alexander-Universität Erlangen-Nürnberg (22-389-B).

Statistical Analysis

Statistical analyses were performed with GraphPad Prism v10 (GraphPad Software). In descriptive statistics, categorial data

Table 1. Calculation and items of the IBUS-SAS.[16]

	Calculation	Bowel wall thickness (BWT)	Bowel wall stratification (BWS)	Color Doppler signals (CDS)	Inflammatory signals at mesentery (i-fat)
IBUS-SAS	IBUS-SAS [0–100] = 4·BWT [mm] + 15·i-fat + 7·CDS + 4·BWS	Mean of 4 two-dimensional measurements	0 = Normal 1 = Uncertain 2 = Focal ≤ 3 cm 3 = Extensive > 3 cm	0 = Absent 1 = Short signals 2 = Long signals inside bowel 3 = Long signals inside bowel and outside bowel	0 = Absent 1 = Uncertain 2 = Present

Abbreviations: IBUS-SAS, International Bowel Ultrasound group Segmental Activity Score.

Table 2. Superb microvascular imaging (SMI) score.

SMI score	0	1	2	3
SMI signals	Absent and/or BWT < 3 mm	Short signals	Long signals inside bowel	Long signals inside bowel and outside bowel

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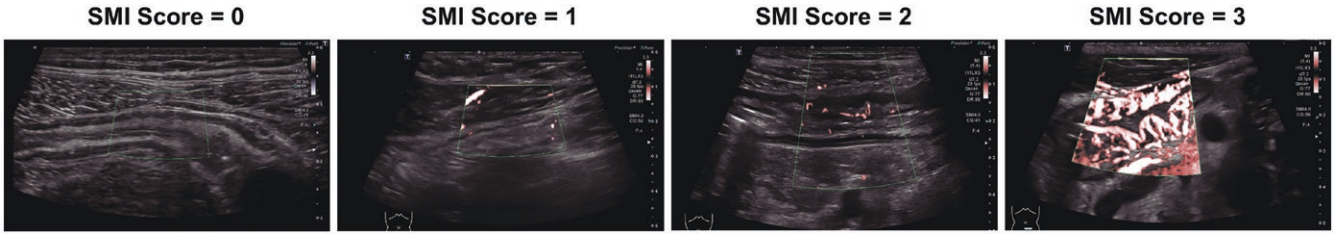


Figure 1. Examples of superb microvascular imaging (SMI) scoring.

are indicated as numbers or percentages, and continuous data are indicated as mean with standard deviation or range.

In correlative analyses, Person's or Spearman's correlation coefficients were calculated depending on data distribution. For diagnostic accuracy analyses, receiver-operator-characteristic (ROC) analyses were performed. *P*-values <.05 were considered statistically significant. Asterisks indicate the significance levels as follows: $*P < .05$; $**P < .01$; $***P < .001$, $****P < .0001$.

Results

Patient Cohort

A total of 62 patients were recruited for the study. Table 3 summarizes their baseline characteristics.

Superior Correlation of the SMI Score than the Doppler Imaging Score With Disease Activity

We initially explored the interobserver agreement for the SMI score compared with the Doppler imaging score. The interobserver agreement of both central readers was high both for Doppler imaging (weighted $\kappa = 0.773$) and for SMI ($\kappa = 0.826$).

In the next step, we correlated Doppler imaging and SMI scores with established read-outs of disease activity. We found a clearly significant correlation of Doppler imaging with endoscopic and clinical disease activity as well as biochemical disease activity. This correlation was similar when considering the scores of central reader 1 (Figures 2A and S1A) and when considering the scores of central reader 2 (Figure S1B). Similarly, SMI scores were significantly correlated with endoscopic, clinical, and biochemical disease activity. However, correlation coefficients were substantially higher than for Doppler imaging scores for both central readers (Figures 2B and S2A).

Thus, these data highlighted the superior potential of SMI scoring for the detection of disease activity compared with Doppler imaging scores.

Similar Performance of IBUS-SAS Using SMI and Doppler Imaging

Since vascularization is only one aspect reflecting intestinal inflammation on IUS, we further aimed to explore, how far the SMI score might improve the diagnostic performance of the compound IBUS-SAS (Table 1). To this end, we additionally calculated an "SMI-IBUS-SAS," in which the Doppler imaging score was replaced by the SMI score. When correlating the IBUS-SAS with disease activity, we observed a substantial correlation with endoscopic, clinical, and biochemical disease activity for central reader 1 (Figure 3A, central reader 2 not further shown from this point on due to almost identical results). Similarly, the SMI-IBUS-SAS correlated with these read-outs of disease activity (Figure 3B) and the correlation coefficients were overall slightly, albeit not relevantly, better than with the IBUS-SAS.

In the next step, since it has recently been shown that the IBUS-SAS correlates with endoscopic disease activity, we sought to explore whether the SMI-IBUS-SAS might further increase the diagnostic accuracy. To that end, we performed ROC analyses using IBUS-SAS and SMI-IBUS-SAS. As expected, the IBUS-SAS had a high accuracy to predict endoscopic disease activity (UCEIS > 1) with an area under the ROC (AUROC) of 0.99. Indeed, a cutoff of 21.26 points had 95.9% sensitivity and 92.3% specificity (Figure 4A, Table 4). These measures were slightly worse when using the IBUS-SAS to predict moderate or severe disease activity (UCEIS > 4) or severe disease activity (UCEIS > 6). Similarly, the accuracy of

Table 3. Baseline characteristics.

Patients (*n*)		62
Age (years): mean (range)		40 (18-79)
Gender		Female: 43.5% Male: 56.5%
Montreal classification		E2 = 40.3% E3 = 59.7%
Medication		None = 8.1% Mesalamine = 11.3% Steroids = 21.0% Infliximab = 14.5% Adalimumab = 4.8% Vedolizumab = 12.9% Ustekinumab = 8.1% Mirikizumab = 4.8% Upadacitinib = 4.8% Filgotinib = 3.2% Tofacitinib = 3.2% Trial medication = 3.2%
Duration of illness (years): mean		9
Body mass index (kg/m²): mean (range)		24.7 (17.8-30.4)
Disease activity: mean (range)	Endoscopic Mayo score (eMS)	2.1 (0-3)
	Ulcerative colitis endoscopic index of severity (UCEIS)	4.2 (0-8)
	Partial Mayo score (pMS)	4.2 (0-9)
	Fecal calprotectin (fCP) [µg/g]	2277 (33.2-19 005)
	C-reactive protein (CRP) [mg/l]	15.5 (0.2-171)

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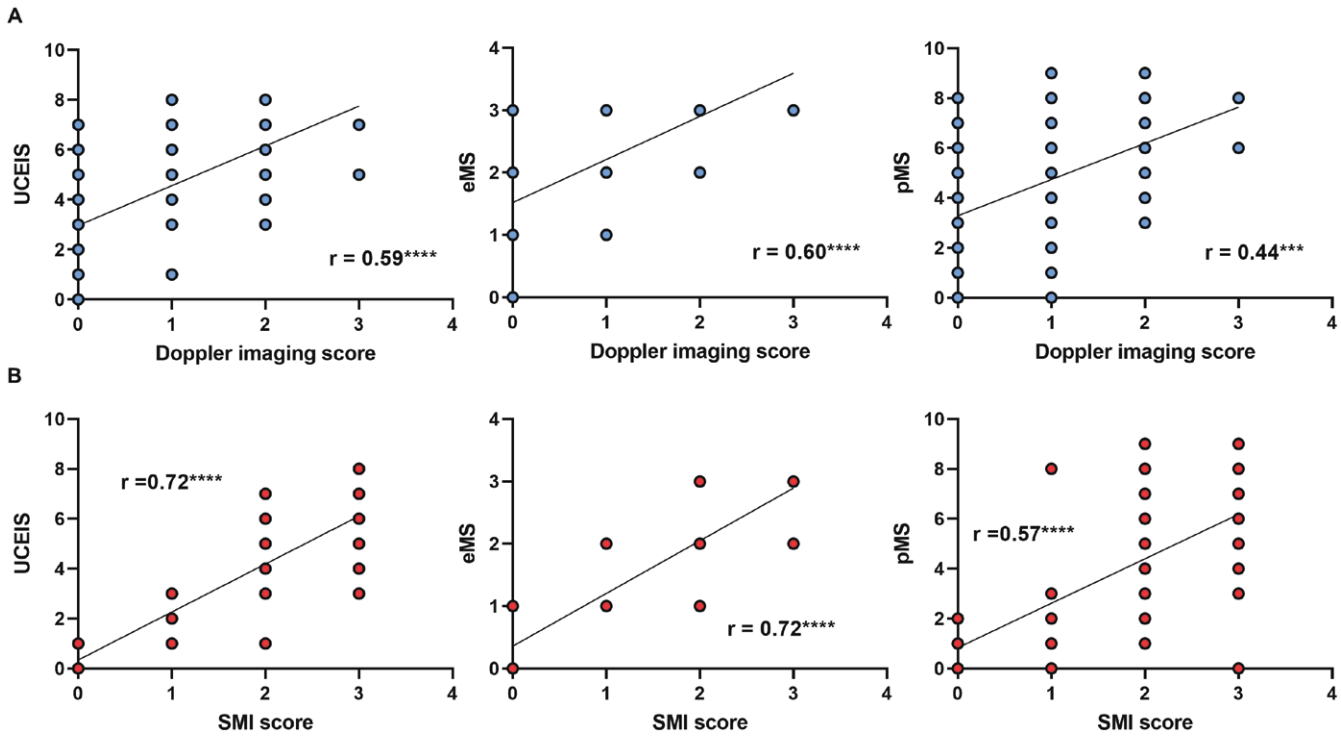


Figure 2. Correlation of the first central reader's Doppler imaging score (A) and SMI score (B) with endoscopic and clinical disease activity. Spearman's correlation co-efficient (r) and significance levels are indicated. UCEIS, ulcerative colitis endoscopic index of severity; eMS, endoscopic Mayo score; pMS, partial Mayo score.

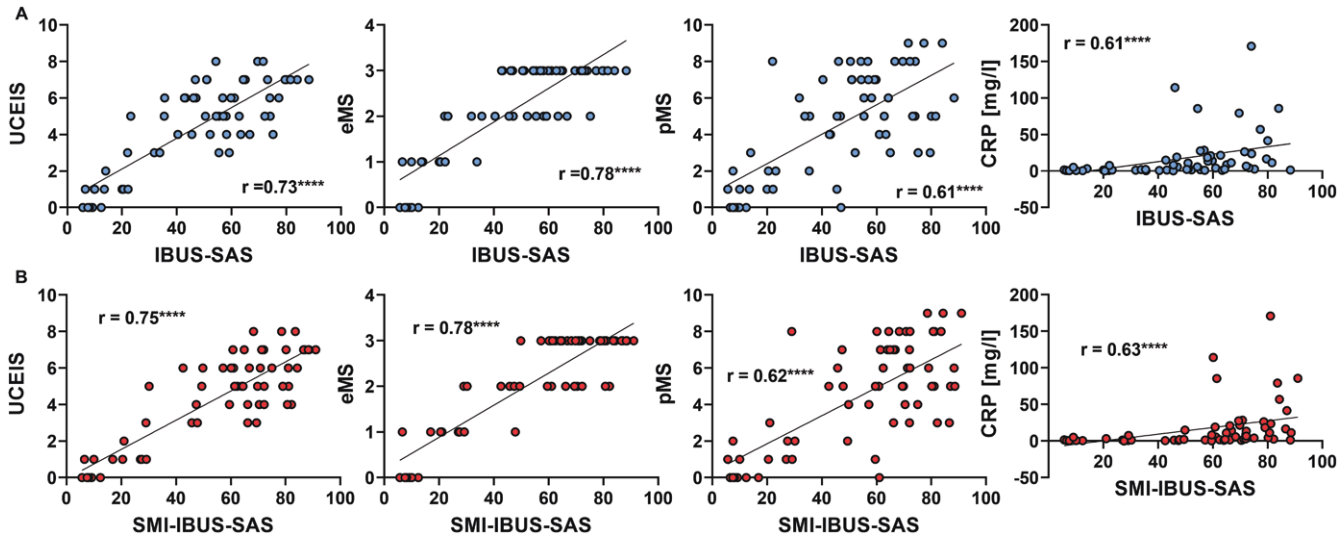


Figure 3. Correlation of the first central reader's IBUS-SAS (A) and SMI-IBUS-SAS (B) with endoscopic, clinical and biochemical disease activity. Spearman's correlation co-efficient (r) and significance levels are indicated. UCEIS, Ulcerative colitis endoscopic index of severity; eMS, endoscopic Mayo score; pMS, partial Mayo score; CRP, C-reactive protein.

the SMI-IBUS-SAS for these predictions was high. However, it was not superior to the IBUS-SAS. For the prediction of endoscopic disease activity (UCEIS > 1), it reached an identical AUROC of 0.99 associated with a sensitivity of 97.9% and a specificity of 92.3% for a cutoff of 28.26 points (Figure 4B). Again, these numbers were slightly worse, but comparable to IBUS-SAS, for the prediction of moderate and severe and severe endoscopic disease activity.

SMI Is Highly Precise to Assess Deep Remission

Finally, we wondered whether the SMI score might be useful to rule out endoscopic disease activity as a standalone parameter. Indeed, on ROC analysis, the AUC was 0.98 and a cutoff of 1.5 reached 95.8% sensitivity, 92.3% specificity, 97.9% positive predictive value (PPV), and 85.7% negative predictive value (NPV) (Figure 5A). Of note, this was almost similar to the performance of the IBUS-SAS for this prediction and

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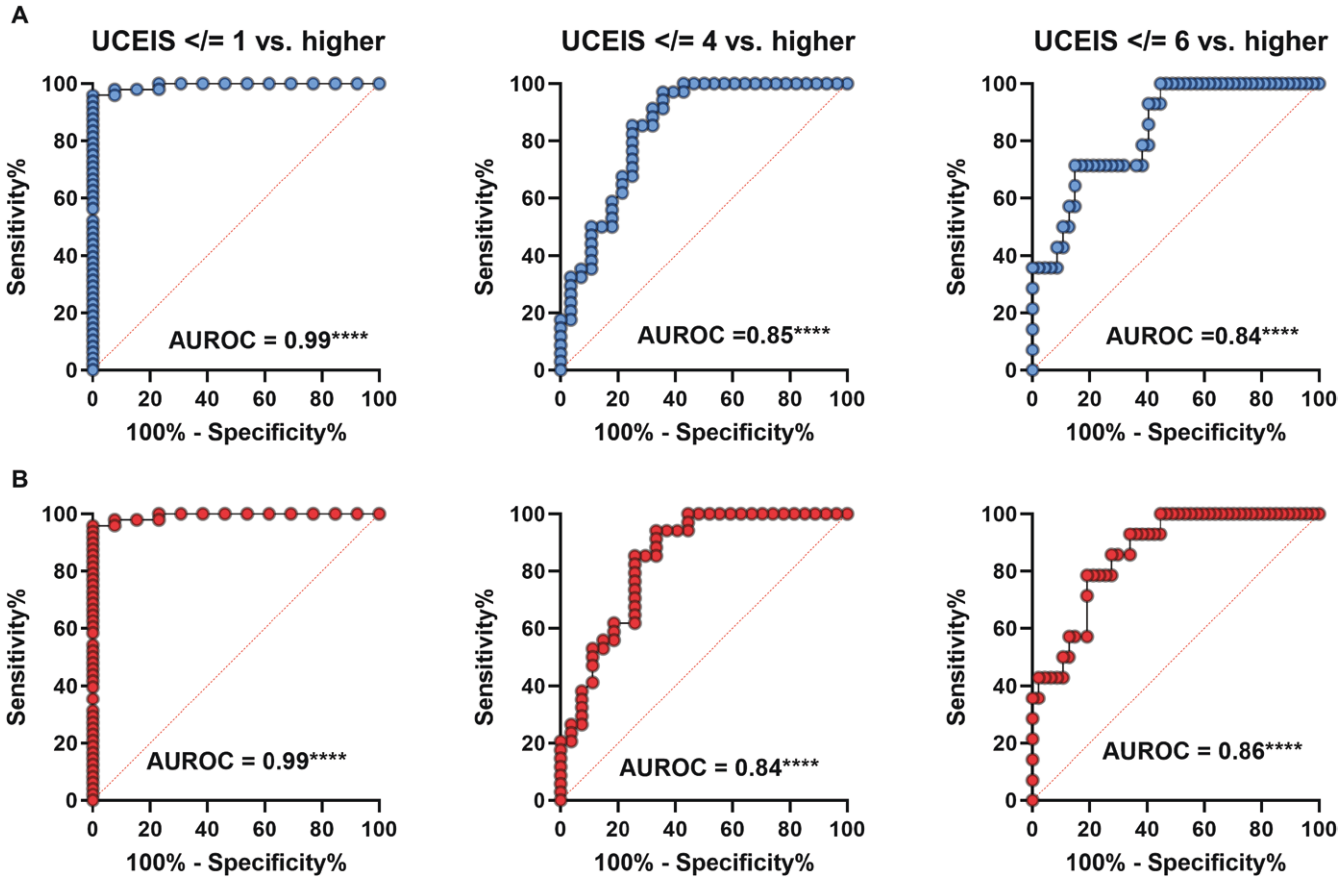


Figure 4. Receiver-operator characteristics (ROC) of the first central reader's IBUS-SAS (A) and the SMI-IBUS-SAS (B) for predicting various levels of endoscopic disease activity as indicated. The area under the ROC (AUROC) and significance levels are indicated. UCEIS, Ulcerative colitis endoscopic index of severity.

Table 4. Fourfold table statistics for ROC analyses.

Prediction	Cutoff	Sensitivity	Specificity	PPV	NPV
IBUS-SAS for UCEIS > 1	21.26	97.9%	92.3%	97.9%	92.3%
SMI-IBUS-SAS for UCEIS > 1	28.26	97.9%	92.3%	97.9%	92.3%
IBUS-SAS for UCEIS > 4	45.86	85.3%	75.0%	80.6%	80.0%
SMI-IBUS-SAS for UCEIS > 4	59.86	85.3%	74.1%	80.6%	80.0%
IBUS-SAS for UCEIS > 6	63.55	71.4%	85.1%	58.8%	90.9%
SMI-IBUS-SAS for UCEIS > 6	71.05	78.6%	80.9%	55.0%	92.7%

Abbreviations: IBUS-SAS, International Bowel Ultrasound group Segmental Activity Score; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver-operator characteristic; SMI, superb microvascular imaging; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

was clearly better than when using the Doppler imaging score for the same purpose (Figure 5B), which reached 72.9% sensitivity and 92.3% specificity (PPV 97.2%, NPV 52.0%) for a cutoff of 0.5.

To exclude that this performance of the SMI score was biased by a higher number of patients with high endoscopic disease activity, we additionally tested, how well the SMI score can distinguish between endoscopic remission and low endoscopic disease activity. ROC analyses for UCEIS 0/1 versus UCEIS 2/3 and for eMS 0 versus eMS1 showed AUROCs of 0.91 and 0.94, respectively, whereas the AUROCs for Doppler imaging scores were 0.63 and 0.56, respectively (Figure 5C and D). Accordingly, for UCEIS, a cutoff of 0.5 provided 100% sensitivity, 61.5% specificity, 54.5% PPV, and 100% NPV; a cutoff of 1.5 provided 66.7% sensitivity, 92.3% specificity, 80% PPV, and 85.7% NPV; and for eMS, a cutoff of 0.5 provided 87.5% sensitivity, 100% specificity, 100% PPV, and 87.5% NPV to predict mild versus absent endoscopic disease activity. Collectively, these data showed that SMI is highly precise to evaluate deep remission.

Discussion

The potential of IUS to noninvasively fill the gap between assessing disease activity based on patient-reported outcomes and based on endoscopy or histology is increasingly

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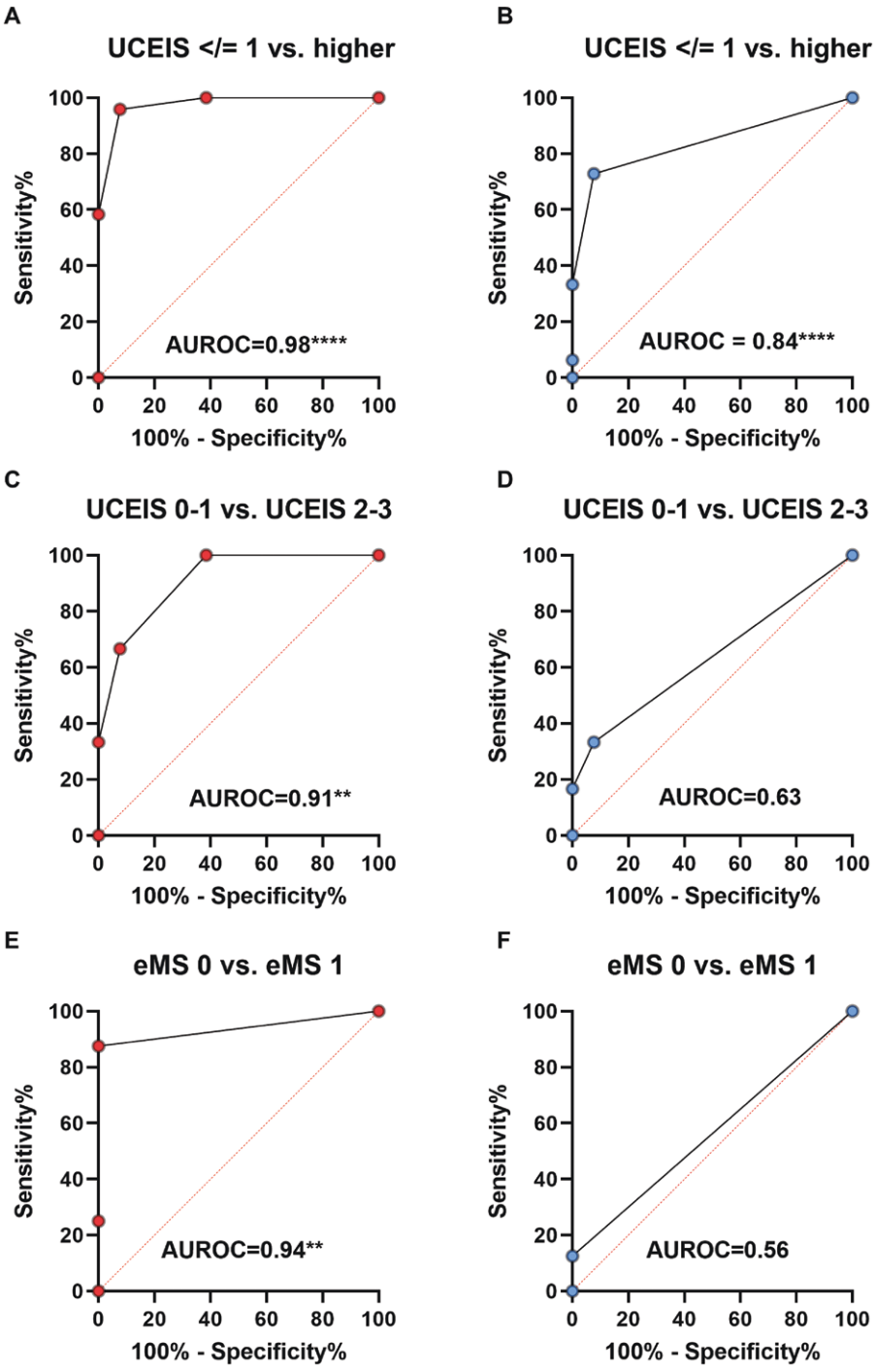


Figure 5. Receiver-operator characteristics (ROC) of the first central reader's SMI score (A) and the Doppler imaging score (B) for predicting endoscopic disease activity vs. endoscopic remission. (C-F) ROC of the first central reader's SMI score (C, E) and the Doppler imaging score (D, F) for discriminating endoscopic remission from low endoscopic disease activity as determined by the UCEIS (C, D) and the eMS (E, F). The area under the ROC (AUROC) and significance levels are indicated. UCEIS, Ulcerative colitis endoscopic index of severity; eMS, endoscopic Mayo score.

acknowledged.[21,22] So far, it has predominantly been advocated in CD and has recently also been introduced as an endpoint in clinical trials.[14,23] Here, we observed that semiquantitative SMI scores correlated clearly better with established read-outs of UC disease activity than conventional Doppler imaging scores. Moreover, although using SMI instead of Doppler in complex compound scores did not increase their high diagnostic accuracy, SMI alone almost reached the diagnostic accuracy of the IBUS-SAS. Thus, this study underscores the potential of IUS to serve as a noninvasive tool to determine disease activity in UC and highlights SMI as a promising tool for further improvements and/or simplifications of IUS techniques and scores.

In particular, our present study conveys 2 important messages. First, it clearly highlights the great and still unleveraged potential of IUS to objectively quantify disease

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activity in UC. Well consistent with a recent report,[18] IBUS-SAS as well as SMI-IBUS-SAS were highly precise in predicting endoscopic disease activity. This was particularly true for the clinically relevant question of endoscopic remission. The main reason for advocating IUS mainly for CD in the past has been the transmural nature of the disease,[24,25] which might be well accessible with IUS. However, it has been shown that several IUS parameters are also indicative of intestinal inflammation in UC[21,26] and our study confirms that these features can accurately be summarized by the compound score IBUS-SAS. In fact, IUS in UC as a continuously extending disease has the advantage that, in contrast to CD, a dedicated quantitative assessment of the sigmoid colon might be sufficient to judge overall disease activity in patients that are systemically treated and in which the disease extends beyond the rectum.[27] This might also be one reason, why the sensitivities and specificities reported here are somewhat better than in previous studies in CD. For example, in a study with 115 patients with CD, the sensitivity and specificity for the prediction of endoscopic disease activity with the IBUS-SAS (cutoff: 46.7) were 73.7% and 93.7%, respectively.[17] In further cohorts, 85.4% sensitivity and 82.4% specificity for a cutoff value of 48.7 and a cutoff of 25.2 associated with 82.2% sensitivity and 100% specificity were reported.[28,29] In conclusion, it seems time for IUS in UC to step out of the shadow and to explore its broad applicability as a read-out of disease activity in further studies as well as to consider it as an endpoint in clinical trials.

Second, our data show that SMI scoring correlates better with disease activity than conventional Doppler imaging scores and is superior to Doppler imaging for ruling out endoscopic disease activity. SMI has previously been used to explore microvascular flow in liver tumors, thyroid nodules, cystic and solid renal lesions, breast lesions, skeletal muscle, and carotic plaques.[30–33] Due to the superior detection of low flow velocities in small vessels, it seems clear that it holds potential also for IUS. For example, it might be a more convenient alternative to contrast-enhanced ultrasound[34] to detect early changes in bowel wall vascularization during therapy and thereby predict the outcomes. Inter-rater reliability for SMI was high and in the range reported in other settings.[16] However, despite a better correlation to disease activity than Doppler imaging, SMI did not improve the diagnostic performance of the IBUS-SAS regarding the prediction of endoscopic disease activity. This seems contradictory at first view, but can easily be explained by the already very good diagnostic performance of the IBUS-SAS, which is difficult to outperform, and the substantial contribution of the further parameters of bowel wall thickness, bowel wall stratification, and mesenteric fat,[16] which "dilute" the impact of the Doppler or SMI score. Thus, based on our cross-sectional validation study, SMI-IBUS-SAS does currently not provide added value and can therefore not replace the IBUS-SAS for the purpose of monitoring disease activity in its current form. However, it seems that the SMI score as a standalone parameter might be very helpful to predict whether a patient has endoscopically active versus inactive disease. In fact, when we observed no or only spots of vascularization with SMI (scores 0 and 1), the probability of endoscopic remission was very high. In this regard, the simple visual SMI score alone performed almost as good as the complex IBUS-SAS, which requires further calculations, and is clearly better than Doppler imaging. Thus, determining bowel wall vascularization with the SMI might be a helpful add-on to identify patients in deep remission, in which the intervals of follow-up colonoscopy can be prolonged.

Given the potential of SMI to analyze the microvasculature in detail, further studies should be performed to correlate SMI scores with histological grading of disease activity in IBD, but also to evaluate its potential in the diagnosis and assessment of other inflammatory and neoplastic conditions along the GI tract.

Collectively, our data nominate IUS as a highly promising future noninvasive diagnostic tool in UC and highlight the potential of SMI to improve current IUS read-outs, which warrants further prospective and multicenter trials.

Supplementary data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Funding

None declared.

Conflicts of Interest

None declared.

Ethical Considerations

The study was approved by the Ethics Committee of the Friedrich-Alexander-Universität Erlangen-Nürnberg (22-389-B).

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