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Original Article

Early Intestinal Ultrasound Predicts Intravenous Corticosteroid Response in Hospitalised Patients With Severe Ulcerative Colitis

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Abstract

Background and Aims: Our aim was to determine if transabdominal intestinal ultrasound changes after 48 ± 24 h of intravenous corticosteroids can predict treatment outcomes in hospitalised patients with severe ulcerative colitis.

Methods: We performed a blinded observational multicentre study. Ultrasound parameters were assessed before treatment initiation, after 48 ± 24 h, and 6 ± 1 days. Treatment response was determined within 7 days by two outcome measures: 1] partial Mayo score reduction; 2] no administration of rescue therapy.

Results: Out of 69 recruited patients, 56 were included in the final analysis, with 37 responders. The colon segment with the highest baseline bowel wall thickness was analysed, being the sigmoid in all patients. There was no difference in baseline bowel wall thickness between responders and non-responders in the partial Mayo score outcome. At 48 ± 24 h, a significant difference between responders and non-responders was identified in both absolute bowel wall thickness [median 3.1 mm vs 4.9 mm; p <0.0001], absolute reduction [-1.9 mm vs -0.2 mm; p <0.001], and relative reduction [-35.9% vs -4.1%; p <0.0001]. A ≤20% reduction had a sensitivity of 84.2% (95% confidence interval [CI] 60.4, 96.6%) and a specificity of 78.4% [61.8, 90.2%] for determining non-response [area under the curve 0.85]. In the multivariable analysis, a >20% reduction had the highest odds ratio (22.6 [4.2, 201.2]; p = 0.001) for determining response. Similar results were seen for the rescue therapy outcome.

Conclusions: Changes in bowel wall thickness, after 48 ± 24 h following intravenous corticosteroid treatment in hospitalised patients with severe ulcerative colitis, identify responders with high accuracy and might be used as an early marker to guide accelerated rescue therapy.

Key Words: Inflammatory bowel disease; bowel wall thickness; rescue therapy; acute severe ulcerative colitis; transmural healing

1. Introduction

Around 25% of all patients with ulcerative colitis [UC] will suffer from acute severe ulcerative colitis [ASUC] at least once in their lives. This condition requires hospitalisation, intensive monitoring, and treatment with intravenous [i.v.] corticosteroids.[1] The European Crohn's and Colitis Organisation [ECCO] and the American Gastroenterological Association [AGA] guidelines recommend an objective response assessment after 3–5 days of treatment. If primary treatment response is insufficient, a treatment change to rescue therapy [RT] with infliximab [IFX] or ciclosporin is warranted.[2,3] The medical therapy aims to avoid an emergent colectomy, which holds a pooled mortality rate of 5.3% compared with 0.7% for elective colectomies.[4]

Despite tight monitoring and advances in medical therapy, ASUC still carries a 25–30% short-term colectomy rate.[5] An accelerated IFX treatment regimen has been suggested to reduce the risk of emergent colectomy.[6,7] Outcome data vary, potentially due to problems with the treatment efficacy assessment and thereby problems with choosing the suitable patients for RT.[8] A reliable early paraclinical marker for objective response assessment could identify patients needing early RT, thus accelerating RT regimens while preventing over-treatment and reducing potential side effects. Current paraclinical markers are insufficient or based on data from the pre-biologic era.[9]

The diagnostic accuracy in detecting active UC by transabdominal intestinal ultrasonography [IUS] is well described.[10,11] However, the value of repeated IUS measurements in a tight monitoring scheme during treatment remains to be established.[12] Our primary aim was to prospectively investigate if repeated IUS measurements at baseline and 48 ± 24 h following i.v. corticosteroid treatment could predict treatment outcome.

2. Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Scientific Ethics Committee of the Capital Region Denmark, journal number H-18031264. The data underlying this article will be shared on reasonable request to the corresponding author.

2.1. Study population

Hospitalised patients with severe active UC were prospectively recruited before treatment initiation with i.v. corticosteroids [60–80 mg/day] at three Danish university hospitals between February 2019 and March 2021. Inclusion criteria were hospitalisation with a full Mayo score [fMayo] ≥8,[13] age 18 to 70, and eligible for i.v. corticosteroid treatment with detectable intestinal inflammation by IUS at admission, defined as sigmoid bowel wall thickness [BWT] ≥3 mm.[14] Patients with gastrointestinal infections, Crohn's disease [CD], isolated ultrasonographic inflammation in the terminal ileum, known malignant disease, pregnancy, contraindication for IFX, and concurrent immunomodulating therapy apart from local or oral corticosteroids, mesalazine, or azathioprine at admission were excluded.

2.2. Disease parameters, time points of assessment, and blinding

Before treatment, at 48 ± 24 h, and 6 ± 1 days after i.v. corticosteroid treatment initiation, partial Mayo score [pMayo],[13] C-reactive protein [CRP], albumin, haemoglobin, and IUS parameters were registered. The endoscopic Montreal classification for disease extension,[15] fMayo score, endoscopic Mayo score,[13] faecal calprotectin, and the Truelove–Witts criteria for ASUC[16,17] were also registered at baseline. The recruiting or treating physicians assessed the activity scores and were blinded to all IUS results throughout the study period. At baseline, the IUS examiners knew that the patient was admitted to the hospital ward with severe UC but were blinded to the non-IUS disease parameters and treatment decisions during the study period. All seven IUS examiners were international bowel ultrasound [IBUS] group-certified or had at least equal IUS experience. Before study initiation, all IUS examiners were trained in the detailed IUS protocol at each site. Different IUS examiners could perform the follow-up examinations.

2.3 . Intestinal ultrasound parameters

Bowel wall thickness [BWT] was calculated as the mean of two longitudinal and two cross-sectional measures in the thickest part of each colonic segment [sigmoid, descending, transverse and ascending colon, and caecum] with a linear probe.[14] Four different ultrasound machines were used at the study sites: GE Logiq S8, E9, E10 [GE Healthcare, Chicago, IL], and Siemens Sequoia [Siemens Healthineers, Issaquah, WA]. BWT ≥3mm was regarded as pathological.[12] Measures from the sigmoid colon were always registered. These measurements were also registered if a proximal segment had a thicker bowel wall than the sigmoid. For segments with increased BWT, colour Doppler signals [CDS] were assessed using a modified Limberg score defined as 'no pixels', 'minimal pixels', 'increased pixels limited to the wall', and 'increased pixels in the wall and mesentery'. Likewise, bowel wall stratification [BWS] was assessed as either 'normal', 'uncertain', 'focal disruption <3 cm', or 'focal disruption >3 cm'. Inflammatory mesenteric fat [i-fat][18] and haustration[19] were assessed as either 'absent', 'uncertain', or 'present' for each of these segments. All IUS images and cine loops were recorded and saved in DICOM format.

2.4 . Outcome measures

Patients were categorised as either i.v. corticosteroid responders or non-responders within 7 days of treatment, based on two different outcome measures. Outcome measure I, pMayo score responders: patients reducing their pMayo score by ≥30% and ≥3 points, including a rectal bleeding subscore of 1 or 0, or a decrease in rectal bleeding subscore ≥1 point.[20] If RT were administered before Day 6 ± 1, response assessment at Day 3 was used to avoid the effect of RT on pMayo. Outcome measure II, RT administration: all patients avoiding RT or surgery within the first 7 days of treatment were also categorised as responders.

2.5. Statistical analysis

The sample size was calculated to detect a 0.7-fold decrease in BWT with a common standard deviation [sigma] of 30% and a desired power of 80% to determine a statistically significant difference [$\alpha = 0.05$, two-sided test]. The estimated sample size was 17 subjects in each group [responders/non-responders]. Data were analysed using R Studio version 4.1.0. Categorical variables were described with frequency and percentages. Non-parametric statistics were used with non-normally distributed continuous variables described with median, interquartile ranges [IQRs], or minimum and maximum range. Statistical differences between responders and non-responders were calculated using Wilcoxon rank sum tests for continuous variables and Fisher's exact test for categorical variables. For repeated measurements, p-values were then corrected using Bonferroni correction [$p < 0.05$ = significant]. Categorical IUS variables were dichotomised. Response was defined as 'no pixels' for CDS, 'normal' for BWS, 'present' for haustration, and 'absent' for i-fat. 'Uncertain' categories were included in the non-response group. BWT at 48 ± 24 h and 6 ± 1 days were reported as both absolute, absolute reduction, and relative reduction [%] compared with baseline. By using the area under receiver operating curve [ROC], we determined the best cut-off values for BWT non-response at 48 ± 24 h. Using responders as the dependent variable, a binary generalised linear model analysis was performed for all registered parameters that could influence disease outcome. Variables achieving $p < 0.05$ in the univariable analysis were included in a multivariable analysis. If two variables were deemed nearly identical, e.g., different forms of IUS reporting, the one with the highest odds ratio [OR] was included in the multivariable analysis. All parameters achieving a $p < 0.1$ were reported. Spearman ρ for nominal and continuous data were used to explore if BWT correlated with other disease parameters. The IBUS group recently published a consensus article based on a systematic review recommending response to be defined as a BWT reduction of >25%, >2 mm or [>1 mm + 1 CDS reduction], and transmural remission [TR] to be defined as [BWT ≤3 mm + CDS 0].[12] The performance of these recommendations was only tested in the univariable analysis.

3. RESULTS

Of 69 recruited patients 56 were included in the final analysis. Reasons for exclusion were inflammation limited to the

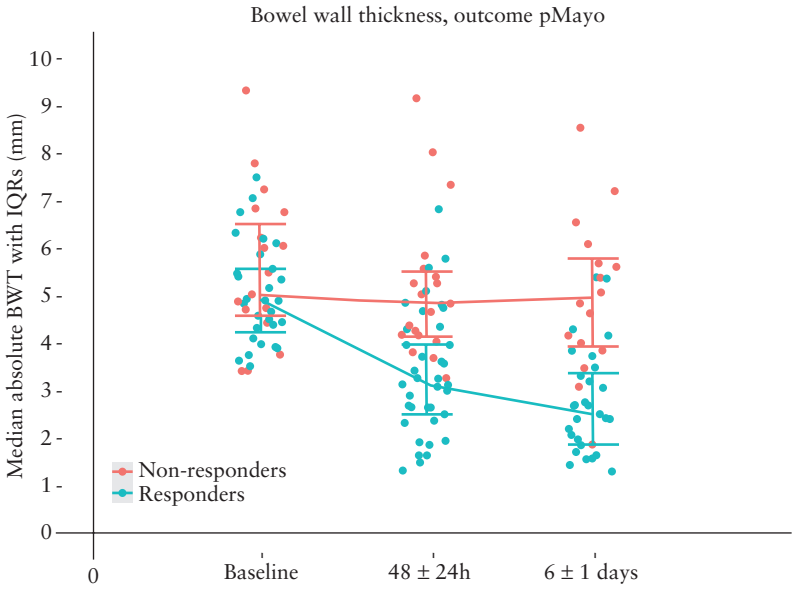
Table 1. Baseline characteristics.

Total, *n* [%]	56 [81]
Women, *n* [%]	27 [48]
Age, *n* [%]	
18–30 years	21 [38]
31–40 years	12 [21]
41–60 years	14 [25]
>60 years	9 [16]
Median years [range]	35.5 [18–70]
Disease duration, *n* [%]	
<1 year	27 [48]
1–5 years	13 [23]
6–10 years	8 [14]
>10 years	8 [14]
Median years [range]	1.0 [0–33]
pMayo score, median [range]	7 [6–9]
fMayo score, median [range]	10 [8–12]
ASUC, Truelove and Witts criteria, *n* [%]	37 [66]
Endoscopic Mayo score, *n* [%]	
Mild 1	3 [5][a]
Moderate 2	22 [39]
Severe 3	31 [56]
Median [range]	3 [1-3]
Location, *n* [%]	
Proctitis	0 [0]
Left sided colitis	9 [16]
Extensive colitis	47 [84]
Bowel wall thickness mm, median [range]	4.9 [3.4–9.3]
Colour Doppler Signal, *n* [%]	
No signal	21 [37]
Minimal pixels	10 [18]
Increased colour signal limited to the wall	16 [29]
Signal significant in the wall and mesentery	9 [16]
Bowel wall stratification, *n* [%]	
Normal/[reserved	43 [77]
Uncertain	0 [0]
Focal disruption <3.0 cm	8 [14]
Extensive disruption ≥3.0 cm	5 [9]
Inflammatory fat, *n* [%]	
Absent	22 [39]
Uncertain	6 [11]
Present	28 [50]
Haustration, *n* [%]	
Normal/preserved	30 [54]
Uncertain	3 [5]
Absent	23 [41]
Faecal calprotectin, median [range][b]	1800[372–>3000]
Biochemistry, median [range]	
CRP [mg/L]	30.0 [2.6–182]
Albumin [g/L]	33 [22-45]
Haemoglobin [mmol/L]	7.8 [4.8–10.3]
Medication at inclusion, *n* [%]	
None	23 [41]
Oral steroids	7 [12]
Local steroids	2 [3]
Oral 5-ASA	29 [52]
Local 5-ASA	8 [14]
AZA/MP6	2 [3]
Previous medication, *n* [%][c]	
No previous medication	22 [39]
Intravenous corticosteroids	11 [20]
Oral corticosteroids	18 [32]
Local corticosteroids	3 [5]
Oral 5-ASA	27 [48]
Local 5-ASA	25 [44]
AZA/MP6	3 [5]
Infliximab	3 [5]
Vedolizumab	2 [3]
Ustekinumab	0 [0]
Adalimumab	0 [0]
Golimumab	1 [2]

5-ASA, 5-aminosalicylic acid; ASUC, acute severe ulcerative colitis; AZA, azathioprine; CRP, C-reactive protein; fMayo, pMayo including endoscopic Mayo score; MP6, 6-mercaptopurine; pMayo score, including stool frequency, rectal bleeding, and Physician's global assessment.
[a]Endoscopy performed 3 to 5 days after treatment initiation.
[b]Based on measurements from 35 [63%] available results.
[c]Medication prior to admission and not related to the current disease flare, meaning that no patient was treated with biologics at the time point of inclusion.

rectum on endoscopy with a simultaneous BWT <3 mm in the sigmoid colon [*n* = 2], later diagnosed as CD [3], campylobacter infection at baseline [1], missing baseline endoscopy [1], withdrawal of consent [3], missing baseline IUS scan [1], and missing 48 ± 24 h follow-up scan [2]. All screened patients with the Montreal classification E2 and E3 disease extension on endoscopy, including all ASUC patients, had a sigmoid colon BWT ≥3 mm. Baseline characteristics for the 56 patients in the final analysis are reported in Table 1.

Nineteen patients were non-responders based on both outcome measures [see Figures 1 and 2]. However, 8 patients changed their responder status using the opposite outcome measure: four patients did not receive RT within 7 days, despite pMayo score non-response. Four patients with a significantly



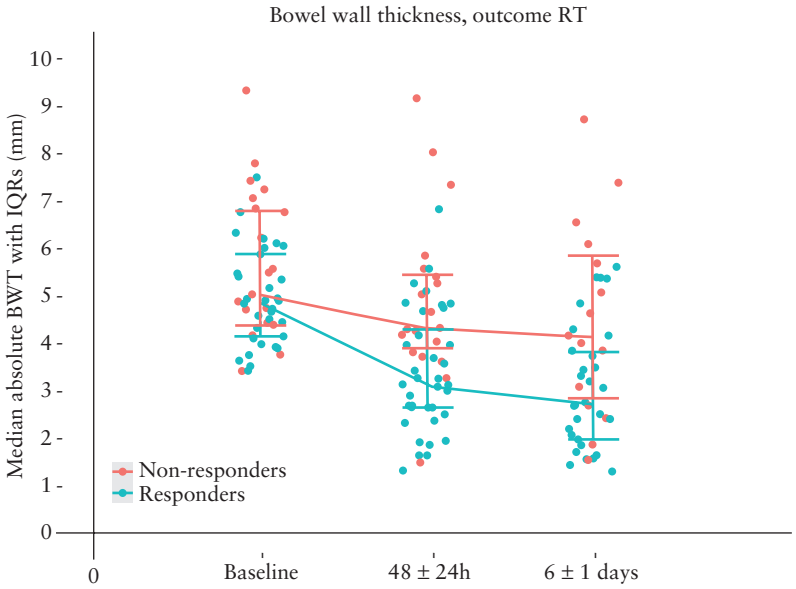
Outcome pMayo	Responders (n=37)					non-Responders (n=19)					
Bowel wall thickness	Min.	1st IQR.	Median	3rd. IQR.	Max.	Min.	1st IQR.	Median	3rd. IQR.	Max.	Bonferroni adjusted p values
Baseline											
Absolute (mm)	3.4	4.2	4.9	5.6	7.5	3.4	4.6	5.0	6.5	9.3	0.85
48 ± 24 h											
Absolute (mm)	1.3	2.5	3.1	4.0	6.8	3.3	4.2	4.9	5.5	9.2	0.000016
Absolute reduction (mm)	-4.4	-2.5	-1.9	-1.1	2.2	-2.3	-0.8	-0.2	0.4	0.8	0.00016
Relative reduction (%)	-65.6	-51.5	-35.9	-22.1	46.2	-38.5	-13.9	-4.1	8.7	22.1	0.000018
6 ± 1 days*											
Absolute (mm)	1.3	1.9	2.5	3.4	5.4	1.9	3.9	4.9	5.8	8.5	0.000018
Absolute reduction (mm)	-4.7	-3.6	-2.4	-1.6	0.7	-4.9	-0.8	-0.4	0.1	1.7	0.00046
Relative reduction (%)	-73.5	-61.3	-54.9	-31.5	15.1	-72.5	-13.6	-8.2	3.2	33.8	0.000071

Figure 1. Bowel wall thickness, outcome partial Mayo Score. *Missing transabdominal intestinal ultrasound data: eight responders and three non-responders. BWT, bowel wall thickness; IQR, interquartile range; pMayo, including stool frequency, rectal bleeding, and physician's global assessment; pMayo response, defined as a ≥30% and ≥3 points reduction, including a rectal bleeding subscore of 1 or 0 or a decrease in rectal bleeding subscore ≥1 point.

reduced pMayo received RT within 7 days. Eleven scans were lost to follow-up on Day 6 ± 1 with eight vs seven [pMayo vs. RT] responders and three vs. four non-responders. The sigmoid colon had the thickest bowel wall in all patients, and all reported IUS measurements are therefore based on the sigmoid colon.

3.1. Outcome-based on partial Mayo score

There was no difference in BWT between responders and non-responders (4.9 mm [IQR 4.2, 5.6] vs 5.0 mm [4.6, 6.5]; $p = 0.85$) at baseline [see Figure 1]. The same was true for CDS, BWS, i-fat, and haustration [see Supplementary Table 1]. After 48 ± 24 h of i.v. corticosteroid treatment, responders achieved a lower absolute BWT (median 3.1 mm [2.5, 4.0] vs 4.9 mm [4.2, 5.5]; $p < 0.0001$), absolute reduction in BWT (median -1.9 mm [-2.5, -1.1] vs -0.2 mm [-0.8, 0.4]; $p < 0.001$), and relative reduction (median -35.9% [-51.5, -22.1] vs -4.1% [-13.9, 8.7]; $p < 0.0001$) than non-responders [see Figure 1]. The presence of haustration [$p < 0.01$] and normal BWS [$p = 0.01$] and the absence of i-fat [$p = 0.003$] were all more prevalent in the response group [see Supplementary Table 1]. BWT remained lower for responders than non-responders at Day 6 ± 1 [$p < 0.001$]; however, the difference in BWS and



Outcome RT	Responders (n=37)					non-Responders (n=19)					
Bowel wall thickness	Min.	1st IQR.	Median	3rd. IQR.	Max.	Min.	1st IQR.	Median	3rd. IQR.	Max.	Bonferroni adjusted p values
Baseline											
Absolute (mm)	3.4	4.2	4.9	5.9	7.5	3.4	4.4	5.0	6.8	9.3	0.66
48 ± 24 h											
Absolute (mm)	1.3	2.7	3.1	4.3	6.8	1.5	3.9	4.4	5.5	9.2	0.0023
Absolute reduction (mm)	-4.4	-2.4	-1.8	-1.0	2.2	-3.4	-1.1	-0.5	0.0	0.8	0.019
Relative reduction (%)	-65.6	-50.9	-34.0	-19.8	46.2	-64.5	-19.9	-9.6	0.0	14.3	0.0060
6 ± 1 days*											
Absolute (mm)	1.3	2.0	2.7	3.8	5.6	1.6	2.9	4.2	5.9	8.5	0.057
Absolute reduction (mm)	-4.7	-2.9	-2.0	-0.7	0.7	-4.9	-2.9	-0.7	-0.2	1.7	0.35
Relative reduction (%)	-73.5	-58.5	-47.3	-15.3	15.1	-72.5	-48.6	-13.0	2.9	33.9	0.17

Figure 2. Bowel wall thickness, outcome rescue therapy. *Missing IUS data: seven responders and four non-responders. BWT, bowel wall thickness; IQR, interquartile range; non-responders definition, receiving RT within the first 7 days of corticosteroid treatment; RT, rescue therapy; IUS, intestinal ultrasound.

i-fat lost significance between the response groups [p >0.05] [see Figure 1 and Supplementary Table 1].

ROC analysis for absolute BWT at 48 ± 24 h to predict non-response showed an area under the curve of 0.85 [95% CI 0.76, 0.95]. The areas under the curve for absolute reduction and relative reduction were 0.81 [0.69, 0.93] and 0.84 [0.74, 0.95], respectively, see Figure 3. Sensitivity, specificity, and negative and positive predictive values vary depending on the suggested cut-off values and are shown in Supplementary Table 2. An absolute BWT above ≥4.0 mm, a delta reduction of ≤1 mm, or ≤20% had the best sensitivity [84.2%, 73.7%, 84.2%, respectively], specificity [75.7%, 78.4%, 78.4%], positive [64.0%, 63.6%, 66.7%], and negative predictive values [90.3%, 85.3%, 90.6%], respectively, for detecting non-response [see Figure 3 and Supplementary Table 2].

Changes in most IUS parameters at 48 ± 24 h were highly associated with pMayo response in univariate analysis [p <0.0001 to 0.02, see Table 2]. While pMayo and CRP at 48 ± 24 h and age <30 years, together with disease duration <1 year at baseline, showed significant odds ratio [OR] for detecting response in the univariable analysis, only a >20% BWT reduction, adjusted OR 22.6 [4.2, 201.2]; p = 0.001, and

a pMayo score, adjusted OR 8.4, [1.5, 78.1], $p = 0.03$, were significant in multivariate analysis. No changes in CRP after 48 ± 24 h could determine responders from non-responders, absolute reduction $p = 1.0$ and relative reduction $p = 0.72$.

3.2. Outcome based on rescue therapy administration

Generally, IUS performed similarly in the RT outcome compared with the pMayo outcome, although less efficiently. There was no difference in BWT between responders and non-responders (4.9 mm [IQR 4.2, 5.9] and 5.0 mm [4.4, 6.8]; $p = 0.66$) at baseline [see Figure 2]. Likewise, no major differences were seen in CDS, BWS, and i-fat, whereas baseline dehaustration was more frequent in the non-response group, $p = 0.014$ [see Supplementary Table 1]. Similar to the pMayo outcome, BWT showed a significant difference between responders and non-responders in both absolute BWT (median 3.1 mm [2.7, 4.3] vs 4.4 mm [3.9, 5.5]; $p = 0.002$), absolute reduction (-1.8 mm [-2.4, -1.0] vs -0.5 mm [-1.1, 0.0]; $p = 0.02$), and relative reduction (-34.0% [-50.9, -19.8] vs -9.6% [-19.9, 0.0]; $p = 0.006$) at 48 ± 24 h [see Figure 2]. In contrast to the pMayo outcome, the absence of CDS and the presence of haustration were more prevalent in the response group, $p < 0.05$, [see Supplementary Table 1]. Still, no IUS measurement could significantly determine corticosteroid responders from non-responders at Day 6 ± 1 [see Figure 2 and Supplementary Table 1].

ROC analysis for the ability of BWT at 48 ± 24 h to predict non-response showed a reduced area under the curve compared with the pMayo outcome [AUC 0.77, 0.71, 0.74] [see Figure 3]. Identical with the pMayo outcome, an absolute BWT above ≥ 4.0mm, a delta reduction of ≤1 mm, or ≤20%, had the best sensitivity [73.7%, 68.4%, 73.7%, respectively], specificity [70.3%, 75.7%, 73.0%], positive [56.0%, 59.1%, 58.3%], and negative predictive values [83.9%, 82.4%, 84.4%], respectively, for detecting non-response [see Figure 3 and Supplementary Table 2].

Like the pMayo outcome, most of the IUS parameters together with pMayo and CRP at 48 ± 24 h and age <30 at baseline had significant ORs for detecting response in the univariable analysis. A >20% mm reduction in BWT (adjusted OR 6.3 [1.4, 33.5]; $p = 0.02$) together with age <30 years (adjusted OR 6.8 [1.2, 61.2]; $p = 0.05$) appeared as the most important parameters for response prediction. CRP changes at 48 ± 24 h could not predict treatment outcome, absolute reduction $p = 1.0$ and relative reduction $p = 0.72$.

3.3. Association between bowel wall thickness and other disease activity measures

Absolute BWT was moderately associated with absolute CRP at 48 ± 24 h, $\rho = 0.47$, $p < 0.005$, but was not associated with absolute and relative reduction, both $\rho = -0.39$, $p = 0.44$. All other disease parameters had a poor association with BWT both at baseline and at 48 ± 24 h. On Day 6 ± 1, the pMayo score, CRP, and albumin showed moderate to strong associations with the concurrent BWT, Spearman $\rho = 0.61$, 0.64, and -0.49, respectively, $p \leq 0.01$ [see Supplementary Table 3].

3.4. Outcome in the acute severe ulcerative colitis population

According to the Truelove–Witt's criteria, 37 [66%] patients were classified as ASUC.[16,17] There was a significant difference in the ASUC group between responders and non-responders in BWT at 48 ± 24 h for both outcomes [pMayo $p = 0.00013$; RT $p = 0.009$] [see Supplementary Table 4].

3.5. Intestinal ultrasound response and transmural remission predictability

The only significant positive ORs for response prediction by all four IBUS definitions[12] were BWT >25% and >2 mm reductions [see Supplementary Table 5]. However, 10 patients achieved TR at 48 ± 24 h, and all were responders based on both treatment outcomes.

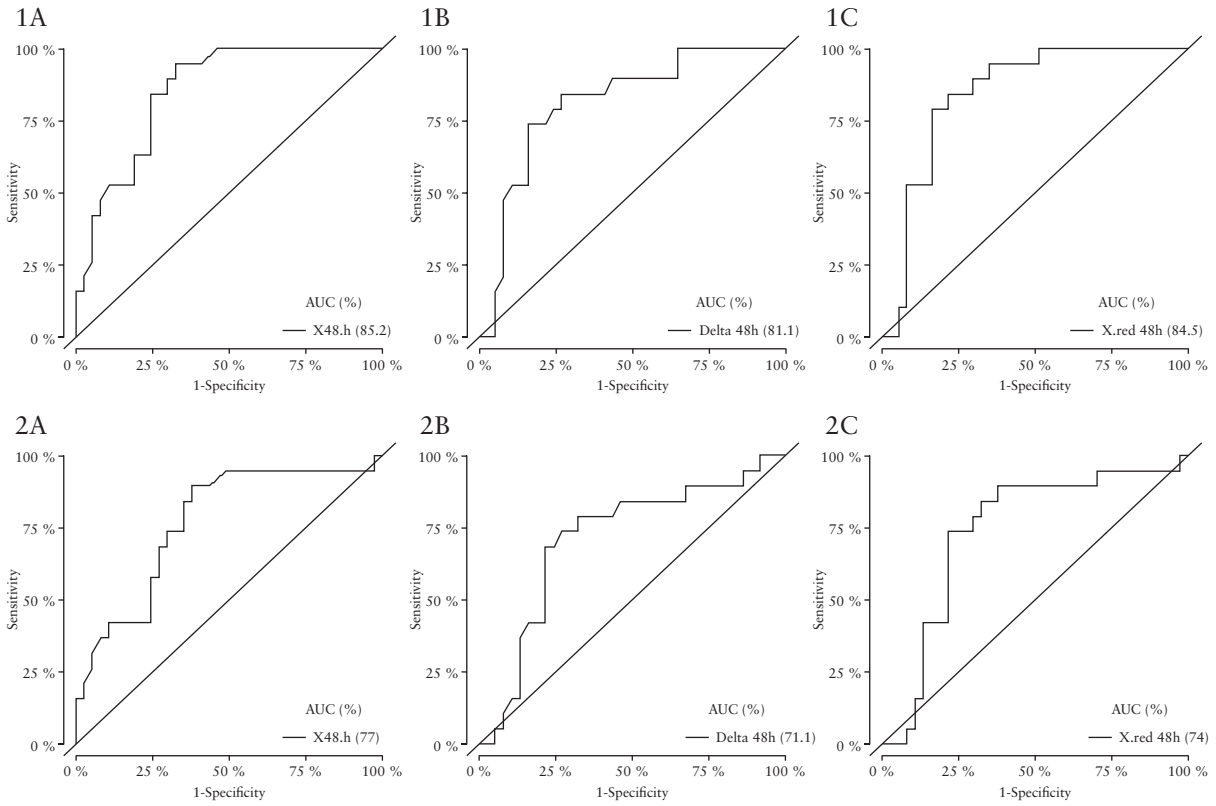
DISCUSSION

Here we present a blinded, multicenter prospective study in a hospitalised severe UC population, examining the role of repeated IUS measurements as a very early outcome predictor for i.v. corticosteroid treatment. Importantly, IUS after just 2 days of treatment was the strongest response predictor compared with other clinical and biochemical markers.

Identifying treatment failure early allows for accelerated RT and reduces unnecessary double immune suppression with the potential risk of severe side effects in this patient group.[8] Our study endorses IUS, particularly BWT, as a potent tool for objectively assessing treatment response.

In accordance with previous IUS studies, we found that BWT is the most crucial parameter for disease activity and response assessment.[10–12] Moreover, BWT and loss of haustration were the only IUS parameters predicting treatment response after 48 ± 24 h for both pMayo and RT outcomes. No baseline IUS parameter could separate responders from non-responders in both outcome measures. This highlights the need for repeated IUS assessments to predict treatment response. Receiver operating characteristic [ROC] statistics with AUCs suggest a good performance of BWT measures in the clinical setting. A BWT ≥4 mm, and a ≤1 mm reduction, or a ≤20% reduction in BWT at 48 h, showed the best sensitivity, specificity, and positive and negative predictive values for detecting non-response for both outcome measures. However, the 20% reduction cut-off for response might be the most meaningful clinical read-out, as it avoids the risk of misjudgment of insignificant changes in patients with higher BWT measures. Further, BWT showed the best predictive response capability in the multivariable generalised linear model analysis compared with both clinical and paraclinical parameters for both outcome measures. At 48 h, absolute CRP was the only parameter with a moderate correlation to absolute BWT. No correlation was seen between the absolute and relative BWT and CRP reduction. Although inferior to the predictability of the BWT measurements, absolute CRP could predict responders from non-responders at 48 h, whereas the absolute and relative CRP reduction could not. This further substantiates the potential use and importance of BWT as a predictive marker of corticosteroid response or non-response.

The power of IUS to predict outcome was better for the pMayo-based outcome than for the RT-based outcome. This is expected, since other factors might affect the physician's decision to start RT than corticosteroid response, e.g., known previous corticosteroid-dependent disease course. Further, the pMayo response is precisely defined, therefore less influenced by the treating physician or local variations in UC management within and between hospitals. Since discharged patients were not allowed to revisit the hospital for research purposes



Outcome non-response, pMayo	**AUC** (95% CI)	**Youden's index**	**Sensitivity** (95% CI)	**Specificity** (95% CI)	**NPV** (95% CI)	**PPV** (95% CI)
1a - Absolute BWT	0.85 (0.76 - 0.95)	≥4.0mm	84.2 (60.4 - 96.6)	75.7 (58.8 - 88.2)	90.3 (74.2 - 98.0)	64.0 (42.5 - 82.0)
1b - Absolute BWT reduction	0.81 (0.69 - 0.93)	≤1.0mm	73.7 (48.8 - 90.9)	78.4 (61.8 - 90.2)	85.3 (68.9 - 95.0)	63.6 (40.7 - 82.8)
1c - Relative BWT reduction	0.85 (0.74 - 0.95)	≤20%	84.2 (60.4 - 96.6)	78.4 (61.8 - 90.2)	90.6 (75.0 - 98.0)	66.7 (44.7 - 84.4)
Outcome non-response, RT	**AUC** (95% CI)	**Youden's index**	**Sensitivity** (95% CI)	**Specificity** (95% CI)	**NPV** (95% CI)	**PPV** (95% CI)
2a - Absolute BWT	0.77 (0.64 - 0.90)	≥4.0mm	73.7 (48.8 - 90.9)	70.3 (53.0 - 84.1)	83.9 (66.3 - 94.5)	56.0 (34.9 - 75.6)
2b - Absolute BWT reduction	0.71 (0.56 - 0.86)	≤1.0mm	68.4 (43.4 - 87.7)	75.7 (58.8 - 88.2)	82.4 (65.5 - 93.2)	59.1 (36.4 - 79.3)
2c - Relative BWT reduction	0.74 (0.60 - 0.88)	≤20%	73.7 (48.8 - 90.9)	73.0 (55.9 - 86.2)	84.4 (67.2 - 94.7)	58.3 (36.6 - 77.9)

Figure 3. Receiver operating curve, bowel wall thickness at 48 ± 24 h, outcome non-response. AUC, area under receiver operating curve; BWT, bowel wall thickness; Delta48h, code for absolute BWT reduction [mm] in data ark; NPV, negative predictive value; pMayo, including stool frequency, rectal bleeding, and physician's global assessment; PPV, positive predictive value; RT, rescue therapy; X48.h, code for absolute BWT [mm] in data ark; X.red48h, code for relative BWT reduction [%] in data ark.

during peak Covid-19 pandemic periods, 11 patients were lost to follow-up on Day 6 ± 1. Further, 11 patients received RT on Day 3 or 4, potentially influencing clinical, biochemical, and IUS measurements. Our Day 6 ± 1 IUS data should therefore be interpreted with caution.

Our BWT results are similar to other published corticosteroid studies with a longer follow-up time: a ≥2.5 mm reduction after 2–3 weeks[21] and a 2.3 mm reduction after 2 months.[22] Further, two cross-sectional ASUC studies have recently been published.[23,24] BWT could in both studies predict the need for RT within 48–72 h following admission. However, no study has used repeated measurements as early as ours, the earliest being 10 days.[25] As our univariable analysis shows, a relative reduction of >20% compared with baseline has the best OR for detecting response, indicating that repeated measurements are superior to single measurements in response assessment.

Almost half of our population are newly diagnosed patients [disease duration <1 year], reflected by the high number of non-medically treated patients at admission. One might speculate that the high proportion of newly diagnosed patients might correlate with a young age; no such correlation

Table 2. Predictors of response.

	Response based on pMayo						Response based on RT					
	Univariable analysis			Multivariable analysis			Univariable analysis			Multivariable analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Baseline												
Sex	0.9	0.3–2.9	0.93				1.3	0.4–4.0	0.64			
Age <30 years[a]	**5.0**	**1.4–24.4**	**0.023**				**8.9**	**2.1–61.8**	**0.0072**	**6.8**	**1.2 – 61.2**	**0.05**
BMI <25	2.1	0.6–6.4	0.21				2.0	0.6–6.4	0.21			
Disease duration < 1 year[a]	**4.0**	**1.2–13.8**	**0.021**				2.0	0.6–6.4	0.22			
Disease duration >1 year	0.4	0.1–1.1	0.08				0.5	0.2–1.5	0.23			
Faecal calprotectin	1.0	1.0–1.0	0.39				1.0	1.0–1.0	0.36			
No previous used medication	3.5	1.1–14.3	0.052				3.5	1.1–14.3	0.052			
No current oral corticosteroids	0.3	0.1–1.6	0.18				0.3	0.1–1.7	0.18			
No previous oral corticosteroids	0.5	0.1–1.6	0.26				0.7	0.2–2.4	0.59			
No previous I.v. corticosteroids	0.9	0.2–3.8	0.85				0.8	0.2–3.8	0.85			
No previous biologics	1.0	0.1–23.0	0.98				0.2	0.0–2.6	0.25			
48 ± 24 h												
Haustration present	**6.7**	**2.1–24.5**	**0.0023**				**6.7**	**2.1–24.5**	**0.0023**			
CDS absent	3.3	1.0–11.9	0.053				**4.9**	**1.4–19.9**	**0.015**			
BWS present	**8.1**	**1.6–60.2**	**0.017**				4.0	0.9–21.9	0.079			
I-fat absent	**7.8**	**2.4–29.2**	**0.0012**				2.6	0.8–8.4	0.098			
BWT <4 mm	**16.6**	**4.4–84.3**	**0.00014**				**6.6**	**2.0–24.9**	**0.0028**			
BWT >1 mm reduction	**10.1**	**2.9–40.2**	**0.00042**				**6.7**	**2.1–24.5**	**0.0023**			
BWT >20% reduction[a]	**19.4**	**5.2–89.8**	**0.000037**	**22.6**	**4.2 – 201.2**	**0.001**	**12.0**	**3.4–48.9**	**0.0002**	**6.3**	**1.4 – 33.5**	**0.02**
pMayo ≥30% reduction[a,b]	**6.3**	**1.7–30.4**	**0.0097**	**8.4**	**1.5 – 78.1**	**0.03**	**4.0**	**1.2–16.0**	**0.035**	**4.2**	**0.9 – 25.2**	**0.09**
CRP ≤20 mg/L[a]	**7.1**	**2.1–26.8**	**0.0023**				**7.1**	**2.1–26.8**	**0.0023**			
Albumin ≥36 g/L	4.1	0.9–28.4	0.089				4.1	0.9–28.4	0.089			
Haemoglobin ≥7.3 mmol/L	0.9	0.3–3.1	0.95				0.9	0.3–3.1	0.95			

BMI, body mass index; BWS, bowel wall stratification; BWT, bowel wall thickness; CDS, colour Doppler signals; CI, confidence interval; CRP, C.-reactive protein; i-fat, inflammatory fat; iv., intravenous; OR, odds ratio; pMayo, including stool frequency, rectal bleeding, and physician's global assessment; RT, rescue therapy.
Bold indicates significant values.
[a]Included in the multivariable analysis.
[b]Defined as a ≥30% and ≥3 points reduction, including a rectal bleeding subscore of 1 or 0 or a decrease in rectal bleeding subscore ≥1 point.

was however seen. Previous studies have shown that young age [<40 years], predicts a more aggressive disease course.[2] Our results did not support this finding, with young age being a predictor of response. However, we only focused on a 7-day window for outcome measures, not long-term outcomes.

Previous IUS studies on UC have not examined differences in IUS results between biologic-treated and biologic-naïve patients regarding i.v. corticosteroid response.[12] Since one of our two primary outcomes was need for RT, no patient receiving biologics at admission were included in the study. Only three patients had previously received biologic treatment in our population. We were therefore unable to investigate the role of both previous and present exposure to biologics for the outcome measures. The study design necessitated high flexibility among IUS examiners. Likewise, several IUS examiners and centres were needed to ensure recruitment. Consequently, various IUS machines were used in our study, and patients were not always re-examined by the same IUS examiner. During the Day 6 ± 1 follow-up, no endoscopy was performed to confirm the IUS findings, and hence no correlation with an endoscopic disease marker was available. Other potential limitations are the lack of central reading and inter-reader variability analysis regarding IUS results. Previous studies have shown high inter-rater reliability among IUS experts on BWT [0.92–0.96], but lower reliability for CDS [0.6–0.79], i-fat [0.36], and BWS [0.24].[14,19] Despite the variance in IUS machines and IUS examiners, as seen in real-world studies, IUS performance was superior to the clinical and paraclinical markers in measuring response and predicting outcome. This holds promise for using IUS in real-world settings.

All included patients were hospitalised to receive i.v. corticosteroids, although not all suffered from ASUC.[16,17] However, our sub-analysis showed that differences in absolute BWT measurements between responders and non-responders were significant in the ASUC cohort as well. We also conducted a sub-analysis regarding the previously published recommendations for response and TR assessments by the IBUS group.[12] These response recommendations can be applied in our population at 48 h, with slightly less accuracy in determining treatment outcomes. These recommendations are based on a much later assessment and general assumptions for various treatments. Therefore, our data are still in line with these recommendations but indicate that we may need individual response recommendations for hospitalised patients with severe UC receiving i.v. corticosteroids. Encouragingly, all who achieved TR at 48 h were responders.

Both AGA and ECCO recommend Day 3 for clinical response assessment.[2,3] We suggest that IUS, when available, could take part in the early assessment of treatment response in hospitalised patients with severe UC. However, this needs confirmation in prospective interventional trials.

In conclusion, IUS can assess and predict treatment response vs non-response to i.v. corticosteroids after 48 h in hospitalised patients with severe UC. BWT is the essential IUS parameter for response assessment and is superior to clinical scores and biochemical markers in predicting corticosteroid response. IUS might be used as an early corticosteroid non-response marker to guide accelerated RT regimens.

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Conflict of Interest

JFKFI has received research grants from Takeda, Janssen, Abbvie, ParaTech, the Danish Research Council, and the Capital Region of Denmark. RW has received grants/personal fees from Janssen, Takeda, Pfizer, Abbvie, Alimentiv. AD has received personal fees from Jansen, Pfizer, and Tillots Pharma. JB has participated in educational or advisory board activities at Takeda, Janssen, Bristol Meyers Squibb, Pfizer, and Gilead. JBS has received research grants from Takeda, Janssen, the Danish Research Council, the Capital Region of Denmark, and is the national coordinator of studies for AbbVie, Arena Pharmaceuticals, Ely Lilly, and Boehringer Ingelheim.

Author Contributions

JFKFI: Concept, methodology, validation, formal analysis, investigation, data curation, writing original draft, writing review, editing, visualisation, project administration, funding acquisition. RW: concept, methodology, investigation, writing review, editing, visualisation, project administration, supervision. PT: concept, methodology, investigation, writing review, editing, visualisation, supervision. AD: investigation, writing review, editing, visualisation, project administration. TB: investigation, writing review, editing, visualisation, project administration. JB: writing review, editing, visualisation, funding acquisition, supervision. JTB: concept, methodology, investigation, writing review, editing, visualization, project administration, supervision. JBS: concept, methodology, investigation, writing review, editing, visualisation, project administration, funding acquisition, main supervision. Conference presentation: part of the work has been presented at the 17th Congress of European Crohn's and Colitis Organisation, Vienna 2022.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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