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# Ultrasound Elasticity Imaging Predicts Therapeutic Outcomes of Patients With Crohn's Disease Treated With Anti-Tumour Necrosis Factor Antibodies

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## Abstract

**Background and Aims:** Ultrasound elasticity imaging is a non-invasive technique developed to evaluate fibrosis. Measuring tissue strain by ultrasound elasticity imaging can reliably detect severe ileal fibrosis in patients with Crohn's disease [CD]. We have hypothesised that a more severe range of fibrosis might influence the therapeutic response to anti-tumour necrosis factor [TNF] treatment. The aim of this study was to assess the ability of ultrasound elasticity imaging to predict the therapeutic outcome for CD patients.

**Methods:** Consecutive patients with ileal/ileocolonic CD, starting anti-TNF treatment, were enrolled for the study. These patients underwent bowel ultrasound and ultrasound elasticity imaging at baseline and at 14 and 52 weeks after anti-TNF treatment. Bowel wall stiffness was quantified by calculating the strain ratio between the mesenteric tissue and the bowel wall. Strain ratio ≥ 2 was used to identify severe ileal fibrosis. Transmural healing at 14 and 52 weeks was defined as bowel wall thickness ≤ 3 mm.

**Results:** Thirty patients with CD were enrolled. Five patients underwent surgery for bowel obstruction. The frequency of surgeries was significantly greater in patients with a strain ratio ≥ 2 at baseline [$p = 0.003$]. A significant reduction of the bowel thickness was observed after 14 and 52 weeks of anti-TNF treatment [$p < 0.005$]. A significant inverse correlation was observed between the strain ratio values at baseline and the thickness variations following anti-TNF therapy [$p = 0.007$]; 27% of patients achieved transmural healing at 14 weeks. The baseline strain ratio was significantly lower in patients with transmural healing [$p < 0.05$].

**Conclusions:** This study shows that ultrasound elasticity imaging predicts therapeutic outcomes for CD patients treated with anti-TNF.

**Key Words:** Ultrasound; elastography; elasticity; strain; Crohn's disease; fibrosis

## 1. Introduction

Intestinal fibrosis represents one of the main sources of morbidity for patients with Crohn's disease [CD], as its onset is associated with the development of CD-related complications, including strictures and internal fistulas, which increase the likelihood of hospitalisation and surgery.[1] Even if the true prevalence of fibrosis in CD is still unknown, population-based studies have reported that up to 30% of patients develop fibrostenotic complications within 10 years of diagnosis.[2] These studies have also contributed to unveiling the progressive behaviour of CD by showing that most CD patients present with an inflammatory phenotype early in the disease course, and then progress to more complicated phenotypes as the result of poorly controlled bowel inflammation and subsequent inflammation-driven fibrogenesis.[2]

The development of intestinal fibrosis in CD has relevant implications for therapy, as predominantly fibrotic lesions are less likely to respond to anti-inflammatory therapies, including biologics, and are best treated by surgical intervention or endoscopic dilation.[2] The understanding of the composition of CD lesions, in terms of relative proportions of inflammation and fibrosis, can therefore be useful in driving therapeutic management and to optimise resource allocation.[2]

In the past few years several cross-sectional techniques, including computed tomography and contrast-enhanced magnetic resonance imaging [MRI], have been proposed to detect fibrosis in CD.[3–7] We have recently reported that ultrasound elasticity imaging [UEI], an ultrasound-based technique, can also reliably and reproducibly detect severe intestinal fibrosis in patients with ileal CD, independently of the presence of intestinal inflammation.[8] Thus, the aim of the present explorative study was to investigate whether the severity of intestinal fibrosis, as evaluated by UEI, would predict the therapeutic outcome for CD patients undergoing treatment with anti-tumour necrosis factor [TNF] antibodies. The relationship between intestinal fibrosis and anti-TNF induced transmural healing was also assessed as a secondary outcome.

## 2. Materials and Methods

### 2.1. Patients

Consecutive CD patients initiating therapy with anti-TNF were prospectively enrolled in the study. Patients were eligible if they were 18 years or older, had an established diagnosis of ileal and/or ileocolonic CD with at least 6 months' follow-up, and a clinical indication for anti-TNF treatment according to ECCO guidelines.[9] The exclusion criteria included: pregnancy, contraindications to anti-TNF treatment, previous treatment by biological therapy, ileal stoma, or an isolated colonic, perianal, or upper gastrointestinal tract involvement. Patients were excluded if an abdominal abscess or a bowel stenosis was detected at baseline bowel ultrasound, the latter being defined by a localised, persistent intestinal narrowing, associated with pre-stenotic dilation > 2.5 cm.[9,10] At enrolment, the patients were categorised according to the Montreal classification.[11] The protocol was approved by the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan. All the patients gave their written informed consent to participating in this study.

### 2.2. Study protocol

All the patients underwent bowel ultrasound and UEI at enrolment, at 14 and 52 weeks after anti-TNF treatment initiation with infliximab or adalimumab. Infliximab was administered intravenously at the dose of 5 mg/kg intravenously [IV] at Weeks 0, 2, 6, and every 8 weeks thereafter. Adalimumab was administered subcutaneously at the initial dose of 160 mg at Week 0, followed by 80 mg at Week 2 and 40 mg every other week thereafter. Patients were clinically assessed every 2 months. If necessary, unscheduled visits were carried out as triggered by patient requests or particular medical conditions. During follow-up, all CD-related surgeries or hospitalisations due to bowel obstruction were recorded.

### 2.3. Bowel ultrasonography

All the patients underwent bowel ultrasonography [US] after overnight fasting by means of a Philips iU22 apparatus [Philips Ultrasound; Philips Healthcare, Bothell, WA] with a multi-frequency convex [C5-2, 5–2 MHz] and a linear array transducer [L12-5, 12–5 MHz]. Bowel US was performed by an expert operator, blinded to clinical findings. The ileal wall thickness, stratification pattern, and vascularisation were evaluated according to established criteria.[12–15] Ileal wall thickness was measured in both the transverse and the longitudinal sections with the linear-array transducer: it was considered normal when both measures were ≤ 3 mm. In particular, ileal thickness was calculated as the mean of three measurements of the involved ileal tract. Bowel wall stratification pattern was defined as normal in presence of a regular multi-layered pattern, or altered in presence of a prevalently hypo-echogenic pattern with disruption of the multi-layered feature. Vascularisation pattern of the bowel wall was evaluated by Power Doppler using a modified Limberg's classification.[14] In detail, the vascularisation was described as not increased, slightly increased, or substantially increased; the three vascular features corresponding respectively to grade 1, 2, and 3–4 of the semiquantitative score of vascularisation of the Limberg classification.[14,15] We decided to consider together grades 3 and 4, to reduce the numbers of categories. In particular, grade 1 corresponds to absence of Power Doppler signal, grade 2 to short stretches of vascularity [spots], grade 3 to longer stretches of vascularity, and grade 4 to vascularisation signal that extends into the surrounding mesentery.[15] Any pathological bowel dilation [as defined by a lumen diameter > 2.5 cm] and penetrating complication [fistula or abscess] were also recorded as additional parameters. The same ileal tract was analysed at baseline and at 14 and 52 weeks after anti-TNF treatment initiation. In order to analyse exactly the same tract, all the examinations were video-recorded and the landmarks precisely marked. Transmural healing at 14 and 52 weeks was defined as the normalisation [≤ 3 mm] of the ileal wall thickness.[16]

### 2.4. Ultrasound elasticity imaging

After US evaluation, ultrasound elasticity imaging [UEI] was performed on the same ileal segment. UEI technique and analysis were performed as previously described.[8] Bowel wall stiffness was estimated by calculating the strain ratio, ie the ratio between the strain of the mesenteric tissue selected as reference and the bowel wall strain. Stiffer bowel walls express lower strain and therefore show higher strain ratio values. All the UEI analyses were performed with the software provided by the manufacturer [QLab; Philips Healthcare]. A strain ratio ≥ 2 was used as the cut-off to identify patients with severe ileal fibrosis as previously reported.[8]

### 2.5. Statistical analysis

All the data are given as mean ± standard deviation [SD], unless specified otherwise. Statistical analysis was performed using t-test, one-way analysis of variance [ANOVA], or Mann-Whitney test to compare continuous variables.

Univariate and multivariate linear regression analysis[17] was carried out to estimate the relationship between baseline strain ratio values, and clinical parameters, including age at diagnosis, disease duration, smoking status, disease location, disease behaviour, concomitant therapy, anti-TNF therapy, and previous surgery. Kaplan-Meier analysis was used to estimate the incidence of surgery for bowel obstructions in patients with or without severe ileal fibrosis at baseline, in the time-to-event curve from the initiation of anti-TNF therapy. The incidence curves were compared with the Gehan-Breslow-Wilcoxon test. Receiver operating characteristic curve [ROC] analysis was used to verify whether the strain ratio cut-off ≥ 2, previously established to identify severe ileal fibrosis, might represent the best cut-off to predict CD-related surgery; *p*-values lower than 0.05 were considered statistically significant.

All the statistical analyses were performed using GraphPad Prism software for Windows [release 6.0; GraphPad Software Inc., La Jolla, CA, USA] and SAS statistical software [release 9.4; SAS Institute Inc., Cary, NC, USA].

## 3. Results

### 3.1. Patient population

Thirty patients with active ileal or ileocolonic Crohn's disease were prospectively enrolled in the study between January 2014 and June 2016. The baseline clinical characteristics of CD patients are detailed in Table 1. At enrolment, no patient showed any evidence of stenosis, but 12 patients were classified as having a stricturing behaviour as they had undergone previous surgery for stricture resection.

All the patients completed the induction phase with anti-TNF and underwent scheduled maintenance treatment. The patients were followed up for a median time of 20 months [range 10–38]. During the follow-up, five patients [16.6%] underwent CD-related surgery due to small bowel obstruction. The median time to surgery from anti-TNF treatment initiation was 15 months [range 8–26]. All enrolled patients underwent bowel US and UEI at baseline and at 14 weeks after therapy initiation. A further US evaluation at 52 weeks was available in 26 patients [four patients underwent surgery before 52 weeks].

### 3.2. Bowel ultrasound and UEI parameters at baseline

The bowel ultrasound and UEI images of a representative CD patient with a thickened terminal ileum are shown in Figure 1. The terminal ileum was thickened [> 3.0 mm] in all the enrolled patients at baseline. Most CD patients [70%] showed a normal bowel wall stratification pattern at baseline, whereas increased bowel wall vascularisation was observed in 57% of patients [43% slightly increased and 14% substantially increased]. The mean thickness of the terminal ileum before the start of the anti-TNF therapy was 5.8 ± 1.5 mm. At baseline, the mean strain ratio [SR] of the terminal ileum was 1.56 ± 0.74. A strain ratio ≥ 2, indicating severe bowel fibrosis, was found in seven out of 30 patients [23.3%]. The clinical characteristics of the patients subdivided into those with or without severe bowel fibrosis [SR < or ≥ 2] are reported in Table 1. At linear regression analysis, active smoking and short Crohn's disease duration were independently associated with higher baseline strain ratio values [Table 2].

### 3.3. The UEI strain ratio predicts the therapeutic outcome of anti-TNF treated CD patients

The patients undergoing CD-related surgery during follow-up were characterised by a significantly higher baseline strain ratio value

**Table 1**. Baseline clinical characteristics of the enrolled patients with Crohn's disease.

| Clinical parameter | | Strain ratio | |
|---|---|---|---|
| | | < 2 | ≥ 2 |
| Male/female, *n* | 20/10 | 15/8 | 5/2 |
| Age at diagnosis, mean ± SD [years] | 29.5 [± 10.4] | 29.7 [± 10.4] | 28 [± 10.6] |
| Age at enrolment, mean ± SD [years] | 38.8 [± 14.5] | 39.4 [± 15] | 36.7 [± 14] |
| Disease duration, mean ± SD [years] | 9.8 [± 7.7] | 11.2 [± 8.2] | 5[± 2.8] |
| Smoking status, yes/no/ex | 14/9/7 | 9/8/6 | 5/1/1 |
| Disease location, *n*[a] | | | |
| L1 [ileal] | 12 | 8 | 4 |
| L2 [colonic] | 0 | 0 | 0 |
| L3 [ileocolonic] | 18 | 15 | 3 |
| L4 [upper disease] | 0 | 0 | 0 |
| Disease behaviour, *n*[a] | | | |
| B1 [non-stricturing, non-penetrating] | 16 | 11 | 5 |
| B2 [stricturing] | 12 | 10 | 2 |
| B3 [penetrating] | 2 | 2 | 0 |
| Concomitant therapy at enrolment | | | |
| mesalamine, *n* | 3 | 3 | 0 |
| thiopurines, *n* | 5 | 3 | 2 |
| corticosteroids, *n* | 3 | 2 | 1 |
| Anti-TNF therapy | | | |
| infliximab, *n* | 16 | 11 | 5 |
| adalimumab, *n* | 14 | 12 | 2 |
| Previous surgery, *n* | 12 | 11 | 1 |
| ileal or ileocolonic resection, *n* | 10 | 9 | 1 |
| colonic resection, *n* | 2 | 2 | 0 |

SD, standard deviation; TNF, tumour necrosis factor.
[a]According to the Montreal classification.[11]

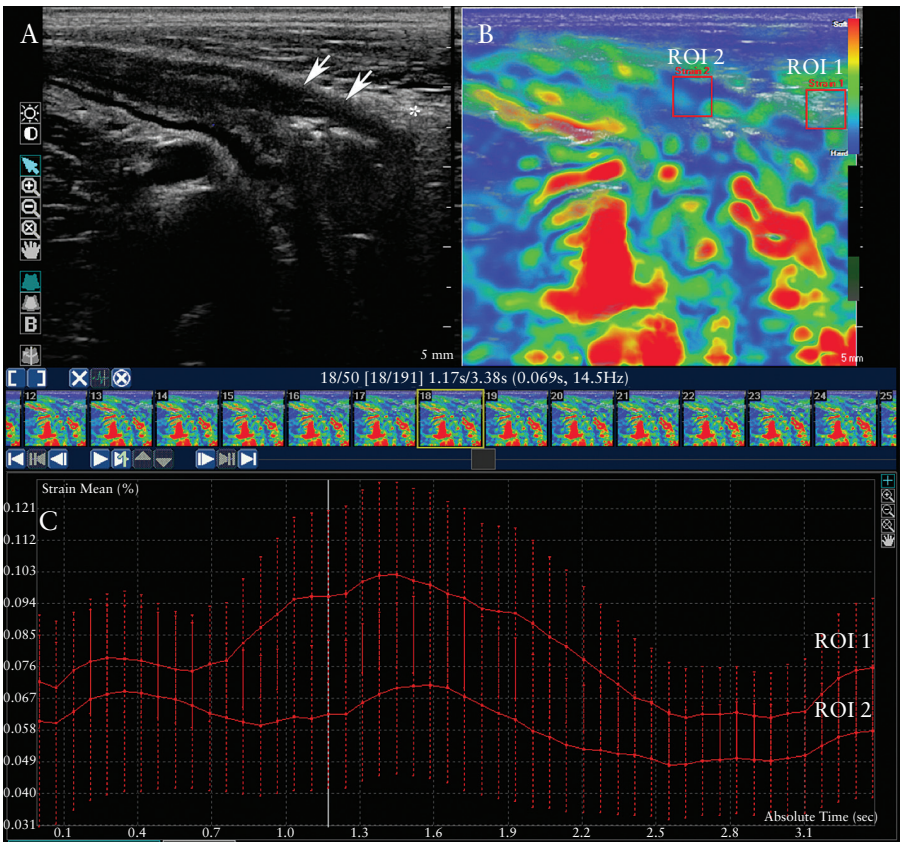


**Figure 1.** Bowel ultrasound [US] and ultrasound elasticity imaging [UEI] of a representative patient with ileal Crohn's disease before anti-tumour necrosis factor treatment. Panel A. US image showing the ileal wall [white arrows] and the surrounding mesenteric tissue [white asterisk]. Panel B. UEI colour scale imaging with the selection of regions of interest in the mesenteric tissue [ROI 1] and in the bowel wall [ROI 2] to calculate tissue strains. Panel C. Quantitative strain values of ROI 1 [mesenteric tissue] and ROI 2 [ileal wall] plotted over time.

**Table 2.** Linear regression analysis: influence of clinical parameters on strain ratio values.

| Clinical parameter | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Estimate [95% CI] | *p* | Estimate [95% CI] | *p* |
| Age at diagnosis | 0.001 [-0.026–0.028] | 0.93 | | |
| Disease duration | -0.042 [-0.075–-0.009] | 0.01 | -0.040 [-0.075–0.005] | 0.026 |
| Smoking status | | 0.03 | | 0.049 |
| Yes vs no | 0.796 [0.208–1.384] | | 0.666 [0.107–1.219] | |
| Ex vs no | 0.358 [-0.336–1.052] | | 0.604 [-0.073–1.281] | |
| Disease location[a] | | | | |
| L1 vs L3 | 0.212 [-0.353–0.778] | 0.45 | | |
| Disease behaviour[a] | | | | |
| B1 vs B3 | 0.402 [-0.753–1.558] | 0.66 | | |
| B2 vs B3 | 0.197 [-0.980–1.373] | | | |
| Concomitant therapy | | | | |
| No vs steroids | -0.704 [-1.633–0.226] | | | |
| Mesalamine vs steroids | -1.100 [-2.322–0.122] | 0.32 | | |
| Thiopurine vs steroids | -0.696 [-1.789–0.397] | | | |
| Anti-TNF therapy | | | | |
| Infliximab vs adalimumab | -0.329 [-0.876–0.219] | 0.23 | | |
| Previous surgery | | | | |
| No vs yes | 0.211 [-0.354–0.777] | 0.45 | | |

CI, confidence interval; TNF, tumour necrosis factor.
[a]According to the Montreal classification.[11]

as compared with non-operated patients [2.22 vs 1.48, $p$ = 0.009] [Figure 2A]. In contrast, neither operated and nor non-operated patients differed significantly in terms of baseline bowel thickness (0.70 ± 0.12 vs 0.54 ± 0.15, $p$ = non-significant [ns]) [Figure 2B], bowel wall stratification pattern, or bowel vascularisation.

The surgery-free survival was significantly reduced for the patients with strain ratio ≥ 2 as compared with the patients with strain ratio < 2 [$p$ = 0.003] [Figure 2C]. The accuracy of UEI in predicting CD-related surgery was confirmed by ROC curve analysis, documenting an area under the ROC of 0.86 (95% confidence inyterval [CI] 0.70–1.02). ROC curve analysis confirmed a strain ratio cut-off value of 2 [indicating severe fibrosis] as being able to predict CD-related surgery following anti-TNF treatment with a sensitivity of 88% and specificity of 80%.

### 3.4. The UEI strain ratio predicts thickness variations and transmural healing in CD patients following anti-TNF treatment

A significant reduction of the bowel wall thickness was observed after 14 weeks of anti-TNF treatment [from 5.8 ± 1.5 mm to 5.1 ± 1.7 mm, $p$ = 0.002] [Figure 3A]. The absolute and relative variations of bowel thickness after anti-TNF were -0.74 ± 1.2 mm and -12.5 ± 19.5%, respectively. No significant difference in thickness variation was documented between patients treated either with infliximab or adalimumab [data not shown].

No significant variations of the strain ratio values were observed following anti-TNF treatment either at Week 14 [1.56 vs 1.42, $p$ = ns] [Figure 3B] or at Week 52 [1.56 vs 1.36, $p$ = ns]. A significant inverse linear correlation was observed between baseline strain ratio values and both relative and absolute bowel thickness variations after 14 weeks of anti-TNF therapy [$R^2$ = 0.24, $p$ = 0.006, and $R^2$ = 0.24, $p$ = 0.02, respectively] [Figure 3C], whereas the wall thickness at baseline did not correlate with anti-TNF induced thickness variations [Figure 3D]. A further reduction of bowel wall thickness from baseline was observed at Week 52 [5.8 ± 1.5 mm vs 4.4 ± 2.1 mm, $p$ = 0.002], even if the difference between Week 14 and Week 52 thickness was not statistically significant [Figure 3E]. Noteworthy, unaltered bowel wall thickness was observed at Week 52 in two out of three patients with baseline SR > 2 and not undergoing surgical intervention.

Overall, eight out of 30 patients [27%] achieved transmural healing at 14 weeks [as defined by a bowel wall thickness ≤ 3.0 mm], and one further patient achieved transmural healing at 52 weeks. The baseline strain ratio was significantly lower for those patients achieving transmural healing 14 weeks following anti-TNF therapy initiation compared with patients not achieving this endpoint [1.06 vs 1.58, $p$ = 0.03] [Figure 3F]. In contrast, the wall thickness variations and transmural healing were not influenced by the degree of bowel vascularisation at Doppler analysis or the bowel wall stratification pattern [$p$ = 0.37 and $p$ = 0.31, respectively].

## 4. Discussion

The results of this explorative study show that the quantification by UEI of ileal fibrosis in CD patients might predict relevant outcomes from the anti-TNF treatment, including CD-related surgeries and transmural healing of the bowel wall.

It is well known that a significant proportion of patients with CD develop ileal fibrosis over time, and that the development of ileal fibrosis is associated with an increased risk of hospitalisation, abdominal surgery, and complicated course.[18,19] Preventing abdominal surgery and surgery-related bowel damage is currently regarded as one of the most relevant therapeutic outcomes for CD patients,[20] and it has led to considering the early administration of immunosuppressants to patients at increased risk for complicated course.[21] Several factors have been identified which are associated to a favourable outcome for CD patients undergoing anti-TNF treatment. These include: the early normalisation of inflammation markers, including C-reactive protein [CRP] and faecal calprotectin; the early achievement of mucosal healing; and elevated anti-TNF trough levels.[22,23] These observations have led to the elaboration of treat-to-target treatment strategies in IBD, ie a continuous re-evaluation of the above-mentioned markers, and a consequent adaptation of the treatment when objective goals are not [yet] reached.[24] Conversely, a few baseline variables have been prospectively validated to predict the therapeutic outcome of anti-TNF treatment, including isolated colitis, concomitant immunosuppressive therapy, young age, and genetic factors.[25,26]

In our study, the presence of severe ileal fibrosis at baseline has been found to predict CD-related surgery for patients undergoing anti-TNF treatment, in line with results of a retrospective series in which pre-existing small bowel stenosis or penetrating complications at MRI have been associated with the increasing likelihood of surgery following anti-TNF treatment.[27]

Active smoking and shorter disease duration were independently associated with severe ileal fibrosis. The effect of smoking is

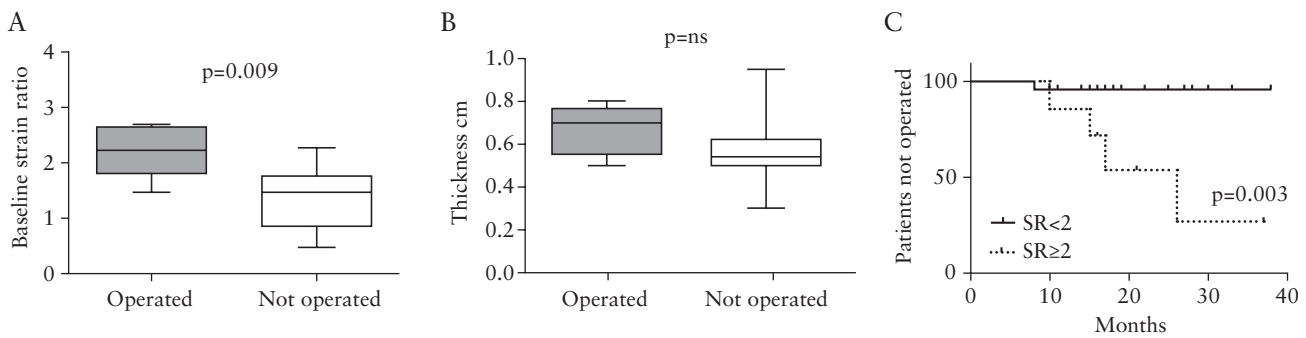


**Figure 2.** Ultrasound elasticity imaging [UEI] predicts the therapeutic outcome for Crohn's disease patients treated with anti-tumour necrosis factor [TNF] agents. Panel A. Baseline strain ratio [SR] values of Crohn's disease patients treated with anti-TNF therapy and either operated or not operated during follow-up. Panel B. Baseline bowel wall thickness of Crohn's disease patients treated with anti-TNF therapy and either operated or not operated during follow-up. Panel C. Kaplan–Meier curve showing the estimates [proportion] of patients requiring surgery with time, comparing patients with SR ≥ 2 [severe fibrosis] [dashed] and patients with SR < 2 [bold] at baseline.

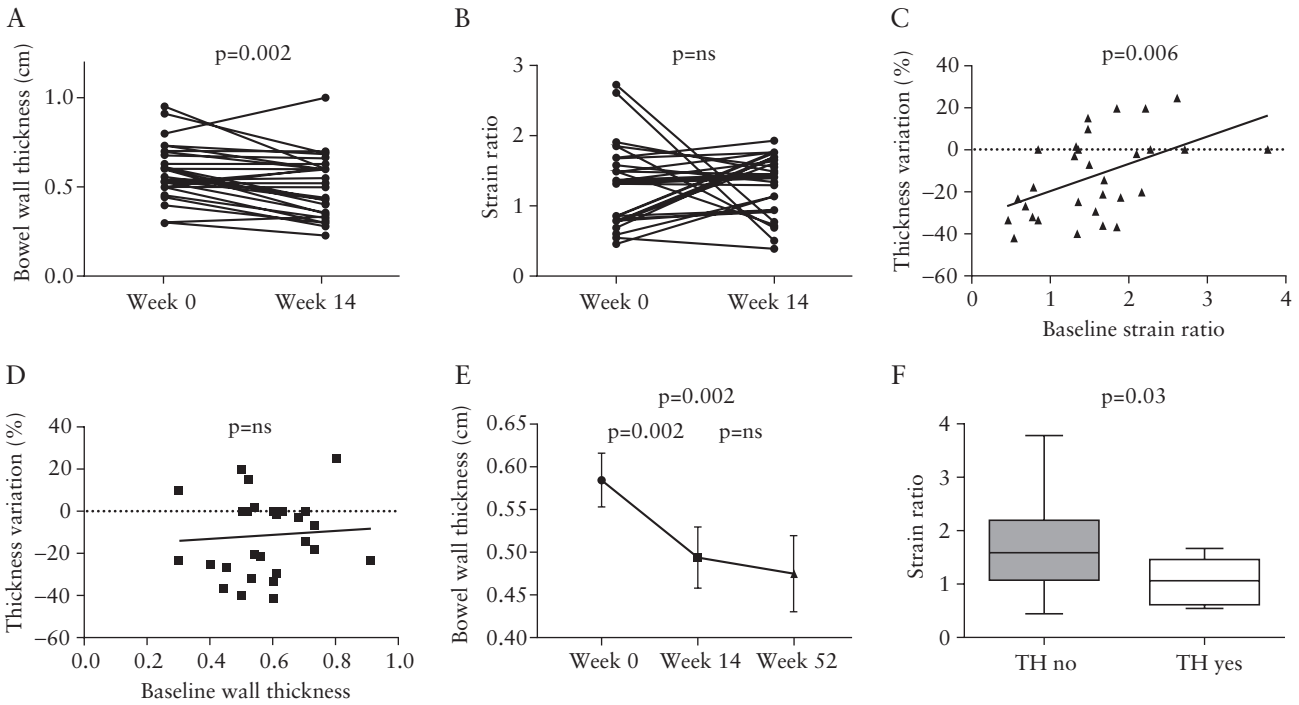


**Figure 3.** Ultrasound elasticity imaging [UEI] predicts the transmural healing [TH] of Crohn's disease-related lesions following anti-tumour necrosis factor [TNF] agents. Panel A. Bowel wall thickness [BWT] values of patients with Crohn's disease at baseline and after 14 weeks following anti-TNF therapy initation. Panel B. Strain ratio [SR] values of patients with Crohn's disease at baseline and after 14 weeks following anti-TNF therapy initation. Panel C. Correlation between SR values at baseline and BWT variations [%] after 14 weeks following anti-TNF therapy initation. Panel D. Correlation between BWT at baseline and BWT variations [%] after 14 weeks following anti-TNF therapy initation. Panel E. Mean BWT of patients with Crohn's disease at baseline, after 14 and 52 weeks following anti-TNF therapy initation. Panel F. Baseline SR values of Crohn's disease patients achieving or not transmural healing [TH] after 14 weeks following anti-TNF therapy initation.

consistent with several studies supporting the concept that smoking has a detrimental effect on the prognosis of Crohn's disease: the risk of early surgery[28] and of recurrence of the disease after surgical resection[29] have been found to be increased; and the increased need for therapy escalation, the progression to complicated disease behaviour, and the need for surgery were more frequent in smokers than in non-smokers.[30]

The interpretation of the effect of a shorter disease duration on severe ileal fibrosis is less straightforward and in apparent contrast with the hypothesis that ileal fibrosis develops over time.[18,19] However, population-based studies have demonstrated that Crohn's disease tends to follow a more aggressive course in the first years following disease onset,[31] thus leading to a maximal need for surgery within 5 years from the diagnosis.[32] In addition, a high rate of early surgery in the first 6 months[28] and a shorter interval between first symptom and diagnosis[33] were observed in retrospective studies in patients with Crohn's disease undergoing the first surgical intervention. All these data suggest the concept that among the heterogeneous population of patients with Crohn's disease, a non-negligible sub-group rapidly develops ileal fibrosis and the need for surgery within the first years after disease onset; whereas in the remaining patients, ileal fibrosis develops more slowly over time. In this context, the results of our study show that severe ileal fibrosis can be quantified by UEI early in the course of the disease, and suggest that ad hoc studies should be planned to investigate new therapeutic strategies able to modify the rapid evolution of the disease early after diagnosis. Regarding anti-TNF treatment, recent cohort studies have documented a progressive reduction in CD-related abdominal surgery and hospitalisation, which paralleled an increasing likelihood to receive anti-TNF treatment early during the disease course.[19] However, it is still matter of debate whether the early introduction of anti-TNF treatment also reduces the risk of progression towards complicated phenotypes.[19]

In contrast with previous reports,[34–36] we could not confirm the association between baseline bowel wall thickness at US and therapeutic outcomes. On the other hand, our data have demonstrated an inverse association between the degree of bowel wall fibrosis, as predicted by UEI, and the variations of bowel wall thickness following anti-TNF treatment. Additionally, the patients achieving transmural healing [ie normalisation of bowel wall thickness] upon anti-TNF were characterised by a significantly lower UEI strain ratio. Taken together, these data support for the first time the notion that the transmural restitution of CD-related lesions following biological therapy is preferably achieved in absence of significant bowel fibrosis, and that anti-TNF treatment primarily acts on inflammatory lesions. The latter concept is further corroborated by the stability of strain ratio values following anti-TNF treatment, despite variations in bowel wall thickness. This, in turn, provides additional support to the independence of UEI strain ratio values from the presence of intestinal inflammation, as already reported.[8]

The baseline strain ratio was able to predict ultrasound-assessed transmural healing following anti-TNF therapy. The possibility to achieve transmural healing with anti-TNF in CD patients has been previously documented by both MRI,[37–39] and bowel ultrasound[16,40]: it has been shown to correlate with reduced surgery and hospitalisation for patients with small bowel CD undergoing immunosuppressive treatment.[41] According to these data, ultrasound-assessed transmural healing seems to show a representative surrogate outcome of the risk of surgery for CD patients undergoing anti-TNF

therapy, in line with the conclusions of the recent STRIDE Consensus, which included cross-sectional imaging as a therapeutic target of CD, especially for patients who cannot be adequately assessed with ileocolonoscopy.[24]

Our study has some limitations. A small number of patients were enrolled, this preventing the validation of the UEI strain ratio as an independent risk factor for surgical intervention in a multivariable analysis. On the other hand, the patients were selected excluding stenotic complications at enrolment. Moreover, no data are available on mucosal healing and anti-TNF trough levels or the systematic assessment of inflammatory markers, such as CRP and faecal calprotectin. However, this exploratory proof-of-concept study was conceived to explore the prognostic role of a new variable for patients with CD undergoing anti-TNF treatment: further studies will [hopefully] confirm our results in a larger cohort of patients and the relationship of ileal fibrosis with other prognostic variables. Finally, our results were obtained in a single centre with expertise in inflammatory bowel disease [IBD] ultrasound. Further studies in other centres are needed to establish the performance of UEI in patients with CD, in order to assess how our results can be generalised.

In conclusion, our data suggest that UEI can be useful to identify within an apparently homogeneous group of CD patients with an inflammatory phenotype those patients with an early fibrotic disease at increased risk of surgery.

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## Conflict of Interest

All authors declare no conflict of interest concerning the publication of this paper.

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## Author Contributions

SO, MF, and FB designed the study, acquired data, and wrote the manuscript; MC collected and analysed clinical data; AM, SM, and CBC helped with data collection and analysis; DC and GB performed the critical revision of the manuscript for important intellectual content; FC designed and supervised the study, analysed data, and wrote the manuscript.

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