Role of Ultrasound Elastography in the Detection of Fibrotic Bowel Strictures in Patients with Crohn's Disease: Systematic Review and Meta-Analysis

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Role of Ultrasound Elastography in the Detection of Fibrotic Bowel Strictures in Patients with Crohn's Disease: Systematic Review and Meta-Analysis

Rolle der Ultraschall-Elastografie bei der Erkennung von fibrotischen Darmstrikturen bei Patienten mit Morbus Crohn: Systematischer Review und Metaanalyse

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Key words

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ABSTRACT

Purpose To perform a systematic review with meta-analysis to assess whether ultrasound elastography can have a diagnostic role in detecting fibrotic bowel strictures in patients with Crohn's disease.

Materials and Methods MEDLINE via the PubMed, Ovid Embase, Scopus and Cochrane Library databases, and abstracts of international conference proceedings were searched up to March 31, 2018. Studies were included if they assessed the performance of abdominal ultrasound elastography in detecting fibrotic bowel strictures in patients with Crohn's disease using histology or the need for surgery after medical treatment as a reference standard. The quality of the studies was assessed using Quality Assessment of Diagnostic Accuracy Studies.

Results 6 studies including a total of 217 patients with Crohn's disease and 231 bowel segments, of which 76 were bowel segments with fibrotic stricture, were selected. Three studies used strain ratio and three studies used strain value as parameters of bowel stiffness. Both the pooled standardized mean strain ratio and the pooled standardized mean strain value were higher in bowel segments with fibrotic strictures than in those without fibrotic strictures with a standardized mean difference of 0.85 (95 % confidence level [CI]: 0 to 1.71; p = 0.05) and 1.0 (95 % CI: −0.11 to 2.10; p = 0.08), respectively. There was a high heterogeneity between studies. All studies were at "high risk" or "unclear risk" of bias.

Conclusion Ultrasound elastography could be able to detect fibrotic bowel strictures in patients with Crohn's disease. Well-designed high quality diagnostic studies with a large sample size are needed.

ZUSAMMENFASSUNG

Ziel Durchführung eines systematischen Reviews mit Meta-Analyse, um zu beurteilen, ob Ultraschall-Elastografie eine diagnostische Rolle beim Erkennen fibrotischer Darmstrikturen bei Patienten mit Morbus Crohn spielen kann.

Material und Methoden Es wurden MEDLINE über die Datenbanken PubMed, Ovid Embase, Scopus und Cochrane Library sowie die Abstracts aus den Tagungsbänden internationaler Konferenzen bis zum 31. März 2018 durchsucht. Aufgenommen wurden Studien, wenn sie die Leistung der abdominalen Ultraschall-Elastografie bezüglich der Erkennung fibrotischer Darmstrikturen bei Patienten mit Morbus Crohn bewerteten und wenn als Referenzstandard eine histologische Untersuchung oder eine notwendige Operation im Anschluss an medizinische Behandlung durchgeführt wurde. Die Qualitätsbeurteilung der Studien erfolgte mittels QUADAS („Quality Assessment of Diagnostic Accuracy Studies").

Ergebnisse 6 Studien wurden ausgewählt, die insgesamt 217 Patienten mit Morbus Crohn und 231 Darmsegmente, darun-

ter 76 Darmsegmente mit fibrotischer Striktur, einschlossen. 3 Studien verwendeten die Strain-Ratio und die 3 anderen den Strain-Value als Parameter für die Darmsteifigkeit. Sowohl die gepoolte standardisierte mittlere Strain-Ratio als auch der gepoolte standardisierte mittlere Strain-Value waren in Darmsegmenten mit fibrotischen Strikturen höher als in solchen ohne fibrotische Strikturen. Die standardisierte Mittelwertdifferenz betrug mit fibrotischen Strikturen 0,85 (95 % Konfidenzniveau [CI]: 0 bis 1,71; p = 0,05) und ohne Strikturen 1,0 (95 % CI: −0,11 bis 2,10; p = 0,08). Es gab eine große Heterogenität zwischen den Studien. Alle Studien hatten ein „hohes" oder „nicht eindeutiges Risiko" für Bias.

Schlussfolgerung Die Ultraschall-Elastografie könnte fibrotische Darmstrikturen bei Patienten mit Morbus Crohn nachweisen. Erforderlich sind gut konzipierte, qualitativ hochwertige Diagnosestudien mit ausreichender Stichprobengröße.

Introduction

Crohn's disease (CD) is a chronic condition characterized by intestinal inflammation involving various sites of the gastrointestinal tract associated with progressive bowel damage [1]. Patients with CD may develop ileal and/or colonic strictures which are characterized by inflammation, fibrosis and/or muscular hypertrophy [2, 3]. Bowel fibrotic strictures represent one of the main sources of morbidity in patients with CD and are associated with high rates of hospitalization and surgery [4]. The pathogenetic mechanisms which induce intestinal fibrosis have not yet been fully elucidated but seem to be similar to those inducing fibrogenesis in other organs [5]. It is widely accepted that bowel wall fibrosis develops as a consequence of chronic inflammation and is characterized by excessive extracellular matrix protein deposition which, along with disorganized smooth muscle proliferation, contributes to modifying the mechanical properties of fibrostenotic intestinal damage [6, 7]. The assessment of the inflammatory and fibrotic components of bowel strictures represents a major step towards noninvasive evaluation of CD [8]. In fact, the presence of fibrosis negatively affects the response to medical treatment, often leading to an endoscopic or surgical approach [1].

Over the last decade, bowel ultrasound (US) has been recognized as a useful tool for detecting stenosis in CD [9] and, more recently, US elastography has been proposed as a promising tool for differentiating fibrosis from inflammation in the bowel wall of CD strictures [10, 11].

Ultrasound elastography is able to estimate tissue elasticity by means of a US force which propagates a wave into the tissue. Since the wave velocity depends on tissue elasticity, it has been postulated that this method is able to detect the presence of fibrosis in the bowel wall [12]. Preliminary animal and human studies have confirmed this hypothesis [13, 14].

Ultrasound elastography has many advantages in comparison to magnetic resonance imaging and computed tomography, such as easy handling, no radiation and low cost, thus making it the optimal modality for detecting fibrosis in the bowel wall of patients with CD [8].

Clarifying the role of US elastography in the diagnosis of fibrotic bowel strictures is essential for introducing it in the management of patients with CD. In particular, this test could be very useful for choosing the most appropriate treatment and for the follow-up of patients with CD strictures.

The aim of this study was to carry out a systematic review and meta-analysis to assess whether abdominal US elastography may have a diagnostic role in detecting fibrotic bowel strictures in patients with CD.

Methods

A systematic review and meta-analysis was carried out following the recommendations of the Cochrane Collaboration Diagnostic Test Group [15].

Search strategy and study selection

The following databases were searched up to March 31, 2018: MEDLINE via the PubMed, Ovid Embase, Scopus and the Cochrane Library databases. The electronic search of the literature was carried out using the following keywords: "elastography", "intestinal fibrosis", "Crohn's disease", "inflammatory bowel disease", "fibrotic strictures" and "stenosis". The search strategies are reported in Supplementary 1. The first study regarding the diagnostic role of ultrasound elastography in Crohn's disease patients was published in 2011 [14]. In order to report on earlier studies, the search period was extended back to January 2005. In addition, the abstracts of the conference proceedings of Digestive Diseases Week, United European Gastroenterology Week, European Crohn's and Colitis Organization Congress, Asia Pacific Digestive Week for the same period were searched electronically and by hand. The references lists of the studies and relevant published reviews were searched. There were no restrictions on language or publication status.

Two authors (GM and AV) carried out the initial selection on the basis of titles and abstracts. A detailed full text assessment of potentially relevant publications was independently carried out by the two reviewers, with any discrepancies being resolved by means of discussion or arbitration by a third reviewer (RMZ). Studies were selected for inclusion in the review if they met the following pre-specified criteria: studies evaluating the performance of abdominal US elastography in detecting fibrotic bowel strictures in patients with CD using histology or the need for surgical resection after medical treatment as reference standards. Even though histology is the "gold standard" for diagnosing fibrosis, the indication for surgery after failure of medical treatment can be reasonably used as an indirect marker of fibrotic bowel strictures in patients with CD [1, 16].

Studies which did not report US elastography values as strain ratio (SR) or strain value (SV) expressed as meter per second, i. e. studies which used other semi-quantitative scales, color scales or kiloPascal, were excluded. We excluded studies that reported results in kiloPascal as it is an indirect measurement of shear weave speed [17]. Studies which did not meet the inclusion criteria or in which essential information was missing and could not be obtained from the authors were also excluded.

Data extraction and quality assessment

Two authors (GM and AV) independently extracted the relevant data regarding the publication, study methods and results using a standardized data extraction form. The following items were extracted from each study: year of publication, country, inclusion and exclusion criteria, total number including age and gender of the participants, total number of participants with and without fibrotic bowel stricture, total number and site of bowel segments with and without fibrotic strictures, reference standard, type of ultrasound elastography technique, equipment, parameters and values of tissue elasticity assessment. When multiple publications for a single study were found, the latest publication was considered and supplemented, if necessary, with data from the previous publications.

Two authors (GM and AV) independently assessed the methodological quality of the studies included using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool (Supplementary 2) [18]. Any disagreements were resolved by means of discussion and, if necessary, arbitration by a third reviewer (RMZ).

Statistical analysis

Data from studies which used strain ratio and strain value separately were pooled. Mean differences with 95 % confidence intervals (CIs) of strain ratio and strain value were pooled using standardized mean difference (SMD) and a random-effect model [19]. Heterogeneity across the studies was assessed using the I^2 statistic and the Q test. As part of the sensitivity analysis, sub-group analyses were designed to explore the following sources of heterogeneity: index test, target condition, setting, study design, country, type of publication and methodological quality of the studies included. Publication bias was investigated using the Egger test. A p-value of less than 0.05 was considered statistically significant. All analyses were carried out using STATA statistical software (Stata Corp., College Station, TX, USA).

Results

The electronic search identified 382 records. After duplicates were removed, 31 studies (26 full text articles [8, 11 – 14, 16, 20 – 39] and 5 abstracts [40 – 44] were assessed for eligibility. Of the 31 records selected, 2 [20, 29] were excluded because they used other semi-quantitative or color scales as a parameter of bowel stiffness, 1 reported the results in kPa [44], 11 [8, 11, 12, 16, 23, 24, 27, 28, 31, 33, 34] were review articles, 3 [21, 22, 32] were excluded as they used magnetic resonance as a reference standard, and 8 [13, 30, 35 – 38, 40, 43] for other reasons (▶ **Fig. 1**). Eventually, a total of 6 studies consisting of 4 full text articles [14, 25, 26, 39] and 2 abstracts [41, 42] met the eligibility criteria and were included in the meta-analysis.

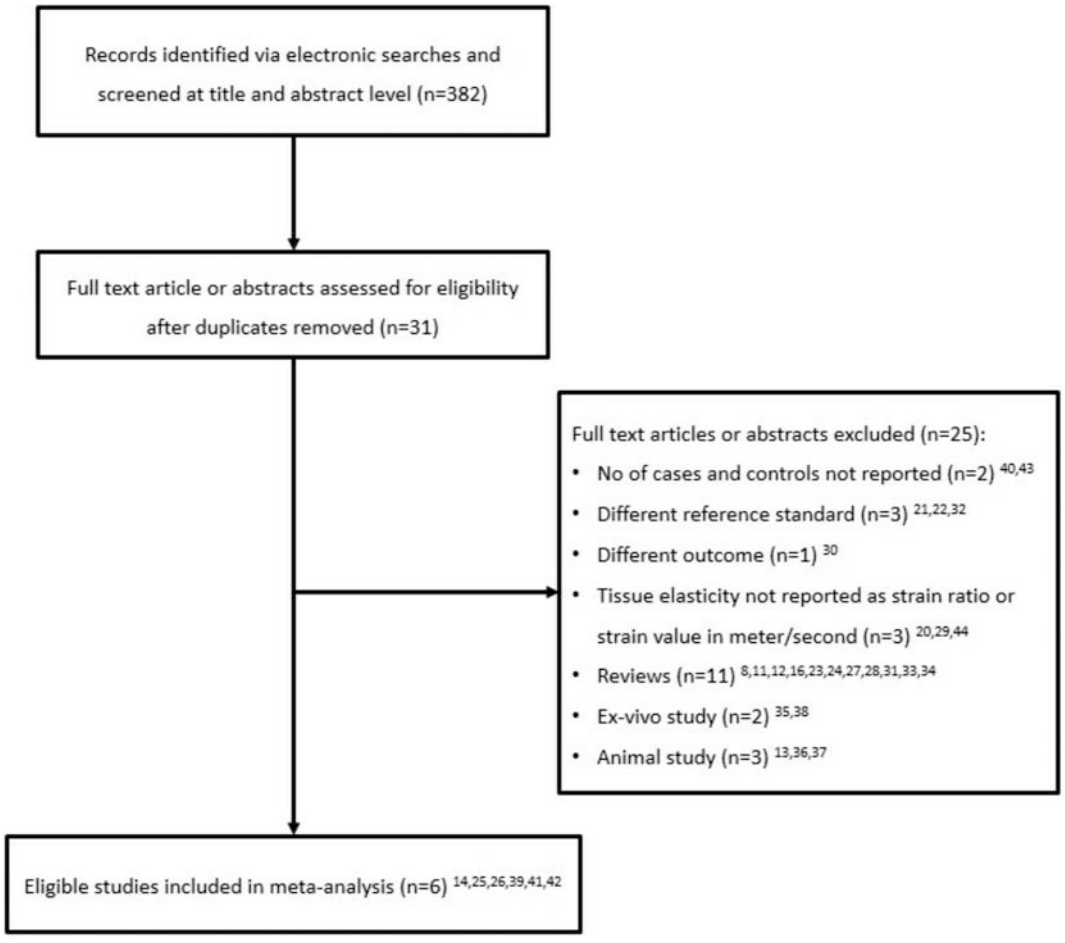
Study characteristics

The 6 included studies involved a total of 217 patients with CD and 231 bowel segments, of which 71 were bowel segments with fibrotic stricture. ▶ **Table 1** shows the characteristics of the included studies. Only three studies reported the mean age of the participants and the proportion of men [25, 26, 39]: the mean age ranged from 35.5 years [25] to 46.1 years [26] and the proportion of men from 33.3 % [26] to 61.5 % [25]. One study included both humans and animals, but only the data regarding humans were considered [14]. Two studies were carried out in Italy [25, 39], two in the USA [14, 41], one in Russia [42] and one in China [26]. All of the studies were carried out in a single center. Four studies [25, 26, 41, 42] had a cohort design while two [14, 39] were case-control studies.

Three studies [14, 25, 42] used the histological examination of surgical specimens as a reference standard. Two studies [26, 39] used histological examination for the diagnosis of fibrotic bowel strictures (cases) and the lack of indication for surgery after medical treatment (controls), while one study [41] used the indication for surgery for both cases and controls as a reference standard. The histological assessment of fibrosis was carried out using different classification systems. Two studies [14, 42] used the Likert-like scoring system (score 0 – 3) and a fibrosis score of ≥ 2 (moderate/severe fibrosis) for defining a bowel stricture as fibrotic, one study [25] used a modified Chiorean scoring system (score 0 – 4) with a fibrosis score of ≥ 3 (moderate-severe fibrosis), one study [26] used a different modified Chiorean scoring system (score 0 – 3) with a fibrosis score of ≥ 1 (any grade of fibrosis) and one study [39] used the Chiorean scoring system (score 0 – 2) with a fibrosis score of ≥ 1 (any grade of fibrosis) for defining a bowel stricture as fibrotic.

As the control group for the fibrotic bowel stricture, one study [14] used the adjacent normal bowel loop, one study [39] used non-stricturing CD bowel segments, three studies [25, 41, 42] used stricturing CD bowel segments and one study [26] used both stricturing and non-stricturing CD bowel segments. Three studies [14, 26, 41] included patients with ileal CD, two studies [25, 39] included patients with ileal and ileo-colonic CD and one study [42] included patients with ileal and colonic disease.

All of the studies used axial strain elastography, except for two [26, 41] which used shear wave elastography. As regards the equipment, two studies performed US elastography using the ElastPQ iU22 (Philips, USA) [25, 39], one using the virtual touch quantification (VTQ) Acuson S3000 (Siemens, USA) [41], one using the Hi Vision 900 (Hitachi, Japan) [42], one using the Z-1 (Zonare, USA) [14] and one using either the ElastPQ Epiq 5 (Philips, USA) or the VTQ Acuson S3000 [26]. Three studies measured the tissue elasticity of the bowel wall using strain ratio [25, 39, 42] and three studies using strain value [14, 26, 41]. In all of the studies, the strain ratio was calculated using two regions of interest (ROIs), one placed on the affected bowel wall and one on the



▶ **Fig. 1** Flowchart of the systematic literature search and studies included in the meta-analysis.

adjacent mesenteric tissue, except for one study [25] which used the upper part of the cross-sectioned bowel wall.

▶ **Supplementary Table 1** and ▶ **Table 2** show the results of the evaluation of the methodological quality of the studies included. All of the studies were at "high risk" or "unclear risk" in one or more domains concerning bias or applicability to the review question (▶ **Table 2**). Approximately half of the studies were at high risk of bias in the selection of patients as they did not enroll a consecutive or random sample of subjects. The majority of studies did not include all patients in the analysis or did not report the time interval between US elastography and histological examination or surgical resection of the bowel segment.

Strain ratio and fibrotic bowel stricture

Using data from three studies including a total of 94 bowel segments of which 45 were bowel segments with fibrotic stricture, the standardized pooled mean strain ratio was higher in the bowel segments with fibrotic stricture (case) than in those without fibrotic stricture or without stricture (control). The pooled standardized mean difference of the strain ratio was 0.85 (95 % CI: 0 to 1.71) (▶ **Fig. 2**). The statistical significance was borderline ($p = 0.05$). There was substantial heterogeneity between the studies ($I^2 = 73.2\,\%$). No publication bias was found ($p = 0.458$).

Strain value and fibrotic bowel stricture

Pooling data from three studies including a total of 137 bowel segments of which 31 were bowel segments with fibrotic stricture, the pooled standardized mean difference of the strain value was 1.0 (95 % CI: −0.11 to 2.10) (▶ **Fig. 3**). Thus, the pooled mean strain value, similarly to the pooled strain ratio, was higher in fibrotic bowel strictures than in controls with a borderline statistical significance ($p = 0.08$). There was notable heterogeneity between studies ($I^2 = 78.9\,\%$). No publication bias was found ($p = 0.391$).

Discussion

This systematic review with meta-analysis included six studies assessing the ability of abdominal US elastography to detect fibrotic bowel strictures in patients with CD. Three studies measured the tissue elasticity of the bowel wall using strain ratio while three studies used strain value. Pooling data from these studies yielded a higher value of the mean strain ratio (SMD: 0.85, 95 % CI: 0 to

▶ **Table 1** Characteristics of the studies included in the meta-analysis.

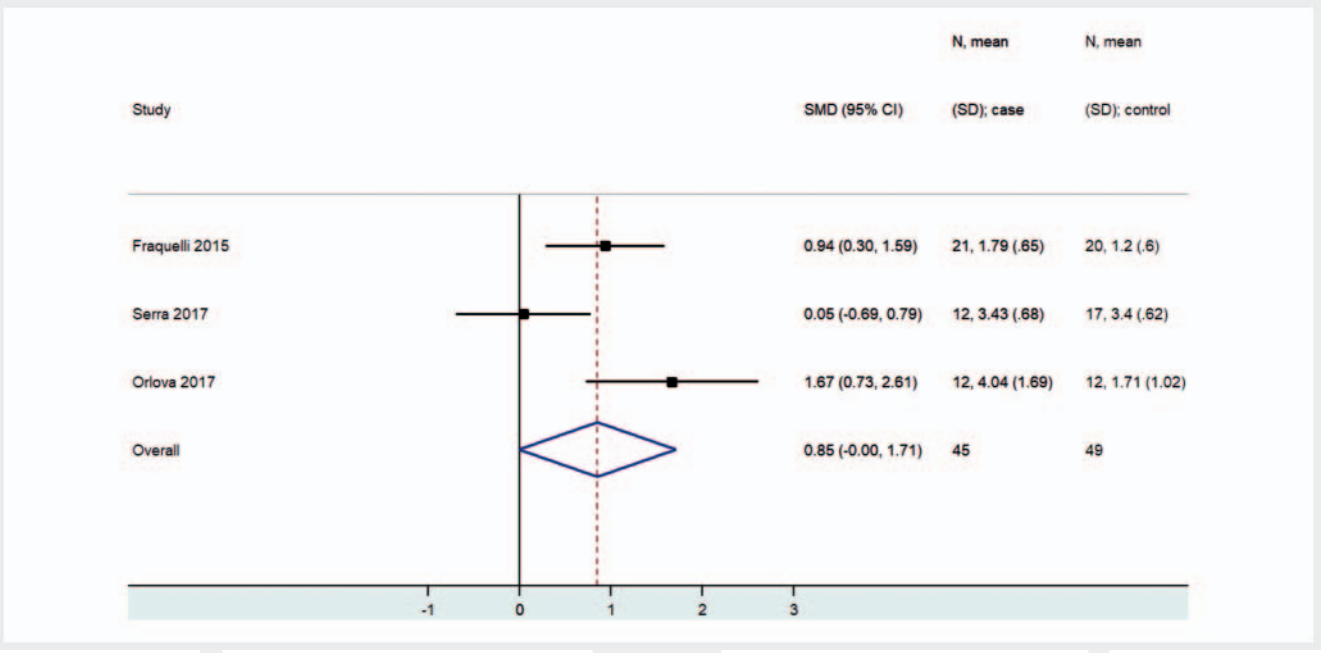
author, year	country	total subjects included n.	age, mean (range or SD)	gender, male n (%)	total bowel segments n.	reference standard	histological scoring system for fibrosis (score)	ultrasound elastography technique	ultrasound elastography equipment	Tissue elasticity assessment
Stidham 2011 [14]	USA	7	n/a	N/a	14	histology	Likert-like (0 – 3) fibrosis score: ≥ 2	strain elastography	Z-1 (Zonare, USA)	strain value
Fraquelli 2015 [39]	Italy	21	40 (12)	10 (43.5)	21	histology for cases/no need for surgery in controls	Chiorean (0 – 2) fibrosis score: ≥ 1	strain elastography	iU22 (Philips, USA)	strain ratio
Stidham 2016 [41]	USA	28	n/a	n/a	28	surgery	–	shear wave elastography	Acuson S3000 (Siemens, USA)	strain value
Serra 2017 [25]	Italy	26	35.5 (11)	16 (61.5)	29	histology	modified Chiorean (0 – 4) fibrosis score: ≥ 3	strain elastography	iU22 (Philips, USA)	strain ratio
Lu 2017 [26]	China	95	cases, 41 (14.4); controls 46.1 (16.5)	5 (33.3)	95	histology for cases/no need for surgery in controls	modified Chiorean (0 – 3) fibrosis score: ≥ 1	shear wave elastography	Epiq 5 (Philips, USA); Acuson S3000 (Siemens, USA)	strain value
Orlova 2017 [42]	Russia	20	N/A (18 – 43)	NA	24	histology	Likert-like (0 – 3) fibrosis score: ≥ 2	strain elastography	Hi Vision 900 (Hitachi, Japan)	strain ratio

N/A: not available; Case: bowel segment with fibrotic stricture in patients with Crohn's disease; Control: bowel segment without fibrotic stricture or without stricture in patients with Crohn's disease.

▶ **Table 2** Risk of bias and applicability concerns of the studies included in the meta-analysis.

study	patient selection		index test		reference standard		flow and timing
	risk of bias	concerns about applicability	risk of bias	concerns about applicability	risk of bias	concerns about applicability	risk of bias
Stidham 2011	H	L	L	L	L	L	L
Fraquelli 2015	H	L	L	L	L	L	H
Stidham 2016	U	L	L	H	L	H	U
Serra 2017	H	L	L	L	L	H	U
Lu 2017	L	L	L	H	L	H	H
Orlova 2017	H	L	U	L	U	L	U

L, low; H, high; U, unclear.

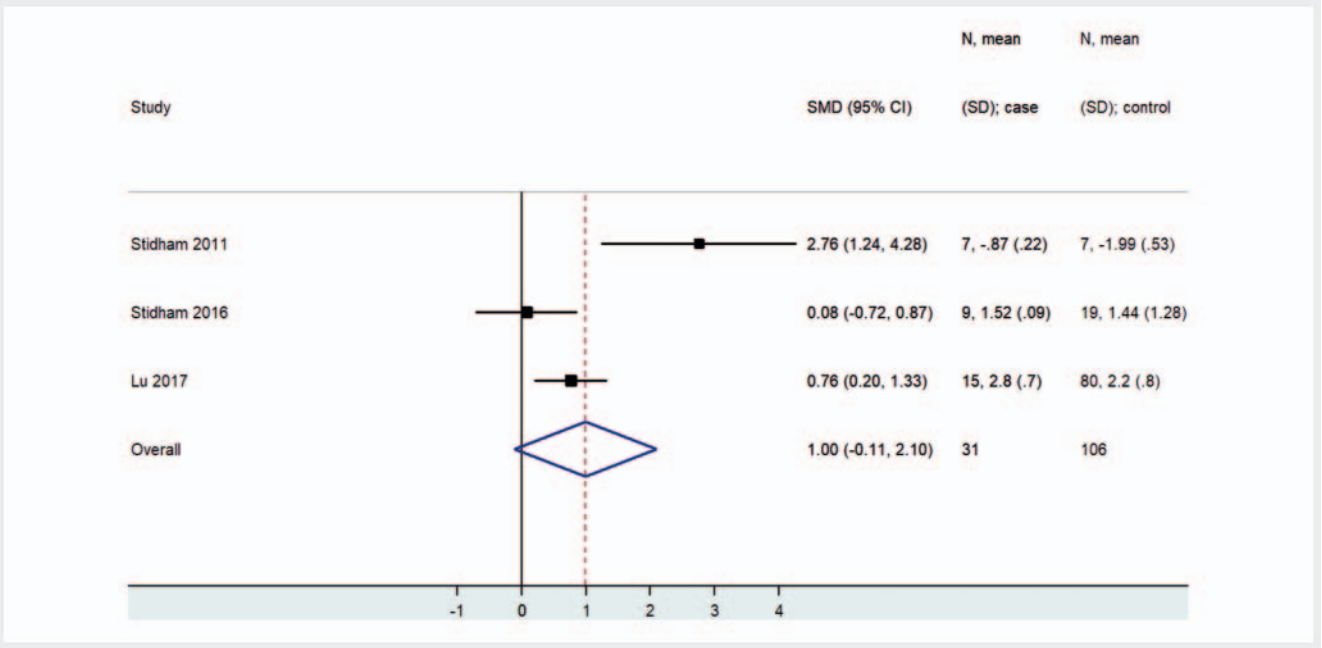


▶ **Fig. 2** Forest plot of the pooled standardized mean difference of the strain ratio on ultrasound elastography. SMD: standard mean difference; CI: confidence interval; N: number of bowel segments; Mean: mean strain ratio; SD: standard deviation; Case: bowel segment with fibrotic stricture in patients with Crohn's disease; Control: bowel segment without fibrotic stricture or without stricture in patients with Crohn's disease.

1.71, p = 0.05) and mean strain value (SMD: 1.0, 95 % CI: –0.11 to 2.10, p = 0.08) in fibrotic bowel strictures than in the controls, although the statistical significance was borderline. Thus, the value of US elastography, which measures the tissue elasticity of the bowel wall, was higher in the presence of a fibrotic bowel stricture.

To our knowledge, this is the first meta-analysis assessing the diagnostic value of abdominal US elastography for detecting fibrotic bowel strictures in patients with Crohn's disease, using an appropriate tool for the evaluation of the methodological quality of the included studies.

A recent systematic review of the literature up to December 2016 was not able to carry out a meta-analysis due to the lack of studies with standardized parameters for the evaluation of tissue elasticity, i. e., the included studies used different color or semi-quantitative scales for bowel strain assessment [11]. In recent years, some studies using standardized parameters were published, and this allowed us to carry out a meta-analysis obtaining pooled estimates of their results. The previous systematic reviews did not assess the quality of the studies which is essential for assessing the strength of their results. In contrast, we carried out an appropriate assessment of the methodological quality of the studies using the QUADAS-2 tool [18].



▶ **Fig. 3** Forest plot of the pooled standardized mean difference of the strain value on ultrasound elastography. SMD: standard mean difference; CI: confidence interval; N: number of bowel segments; Mean: mean strain value; SD: standard deviation; Case: bowel segment with fibrotic stricture in patients with Crohn's disease; Control: bowel segment without fibrotic stricture or without stricture in patients with Crohn's disease.

In comparison with the systematic review by Pescatori [11], the present meta-analysis provides additional evidence that US elastography could be a promising tool for detecting bowel fibrotic strictures in patients with CD, although the pooled estimates were not robust.

One strength of this systematic review is the comprehensive literature search which minimized the risk of missing studies. When data were missing, an attempt was made to contact authors for additional data in order to improve on the data extraction and the evaluation of the methodological quality of the study.

The present meta-analysis has several limitations. The main limitation is the paucity of included studies and the very small sample size. In particular, the small sample size could have potentially led to an underestimation of the diagnostic value of US elastography. Another weakness of the findings in the present study is the notable heterogeneity between the studies. The small number of studies did not allow exploration of the main cause of the heterogeneity. The studies differed based on several factors, such as the index test and reference standard. As regards the index test, different ultrasound techniques (strain or share wave elastography) and equipment (i. e., ElastPQ, VTQ, etc.) were used. It is well known that there could be substantial variability between the various types of elastography equipment [45]. Furthermore, US elastography is an operator-dependent technique and just one of the included studies evaluated inter-operator variability [39]. With respect to the reference standard, different histological classification systems with different scores for defining the presence of fibrotic stricture were used and, in addition, some studies used the surgical resection of bowel strictures after medical treatment as a reference standard. This may have introduced a misclassification bias, in particular for the definition of the absence of fibrotic strictures. Another weakness of the present meta-analysis is the low methodological quality of the included studies. Approximately half of the studies did not enroll a consecutive or random sample of subjects, and this could have introduced selection bias. The majority of studies did not report the time interval between US elastography and bowel histological examination or surgical resection, and whether these patients had any treatment in the meantime which would potentially change the prevalence of fibrosis in the bowel wall of the strictures, or did not include all patients in the analysis, thus introducing a bias in the pooled estimates. However, we believe that the present meta-analysis is still valuable as it provides pooled estimates of the results of studies assessing the role of US elastography in the diagnosis of fibrotic bowel strictures in patients with Crohn's disease for the first time.

In conclusion, our findings provide additional evidence that abdominal US elastography could have a diagnostic value in detecting fibrotic bowel strictures in patients with Crohn's disease. Ultrasound elastography could play a relevant role in the management of patients with stricturing Crohn's disease. Ultrasound elastography is a noninvasive, real-time, well-tolerated and low-cost technique. In fact, this technique is ideal for the noninvasive assessment and the post-treatment follow-up of bowel strictures, in particular in young patients with CD. It may help in differentiating fibrotic from inflammatory strictures and, thus, help clinicians select medical or endoscopic/surgical treatment. As two studies were conducted in Europe, two in the U.S.A., one in Russia and one in China, we think that our findings are applicable to patients with Crohn's disease worldwide.

Well-designed high-quality studies with a large sample size are needed to assess the performance of US elastography in the diagnosis of fibrotic bowel strictures in patients with Crohn's disease.

Conflict of Interest

Giovanni Maconi has served as a speaker, a consultant and an advisory board member for Abbvie, Allergan, Alfa-Sigma, Janssen-Cilag, Novartis, Takeda. Franco Bazzoli has served as a speaker, a consultant and an advisory board member for Allergan and as a speaker for Malesci. Rocco Maurizio Zagari has served as a speaker, a consultant and an advisory board member for Allergan, and as a speaker for Malesci and Takeda. The remaining authors disclosure no conflicts.

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