SUPPLEMENT

METHODS

The following syntax was applied for the literature search:

**MEDLINE (Ovid, 1946-Jan 31, 2019)**

1. exp crohn disease/
2. (cross-section* OR cross section* OR ultrasonograph* OR sonograph* OR ultrasound* OR sonoelastograph* OR elastograph* OR tomograph* OR MRI OR magnetic resonance OR magnetiz* OR contrast enhancement OR enteroclysis OR MR-enteroclysis OR enterograph*).m_titl.

**EMBASE (Ovid, 1947-Jan 31 2019)**

3. exp crohn disease/
4. (cross-section* OR cross section* OR ultrasonograph* OR sonograph* OR ultrasound* OR sonoelastograph* OR elastograph* OR tomograph* OR MRI OR magnetic resonance OR magnetiz* OR contrast enhancement OR enteroclysis OR MR-enteroclysis OR enterograph).m_titl.

Additionally, references of cited original articles and reviews were considered for identification of additional relevant publications. After removing the duplicates from our search, all identified abstracts as well as full text publications of potentially eligible studies were dually assessed by D. B. and F. R. Disagreement regarding inclusion/exclusion or extraction were resolved by V. J. The following criteria were applied: Exclusion criteria: studies enrolling patients younger than 18 years of age, studies only available in abstract
form, non-English language publications, studies containing less than 3 patients, stricture in non-small bowel location, animal studies, no evaluation of stricturing Crohn’s disease, ileal pouch anal anastomosis related strictures, missing evaluation of modality of interest, reviews and non-human subjects. Full text articles were excluded due to missing evaluation of modality of interest, ex vivo studies, no evaluation of stricturing Crohn’s disease. All studies that did not use full thickness histopathology as the gold standard for all patients included in the respective manuscript were excluded from further analysis. Furthermore, studies that neither provided accuracy measures for diagnosis of a stricture nor discriminatory and separate evaluation for inflammation and fibrosis were not considered for analysis. The search included studies from the inception to January 31st, 2019. Variables pertaining to radiologic definitions of strictures, diagnosis and differentiation of fibrosis and inflammation were retrieved independently by D. B. and F. R. A PRISMA diagram can be found in Supplemental Figure 1.
RESULTS

Definitions of CD-associated strictures on cross sectional imaging

Of the 9 US studies identified, 1 study employed conventional transabdominal ultrasound (TUS) and 3 studies used TUS with oral contrast application (SICUS). Three additional studies applied contrast intravenously (contrast-enhanced ultrasound; CEUS) and 2 evaluated TUS with US elasticity imaging.

Definitions used in ultrasound to diagnose CD-associated strictures

Only 2/9 studies assessed all three components luminal narrowing, wall thickening and prestenotic dilation. In addition, 1/9 studies solely examined luminal narrowing and three studies evaluated only wall thickening for stricture detection. One of 28 studies evaluated prestenotic dilation and luminal narrowing while another study assessed prestenotic dilation and wall thickening.

Notably, specific definitions for the three components varied substantially between studies or are not provided. More specifically, of those 4 studies that assessed prestenotic dilation, two studies indicate a cut-off value for prestenotic dilation and both studies chose a luminal diameter of more than 25 mm to be an accurate definition. The two other investigators did not provide a specific definition of prestenotic dilation. The selection of the cutoff value is likely to affect the test operating properties including sensitivity and specificity for stricture detection.

In 4 of the 9 studies that assessed luminal narrowing, 2 investigators suggested a luminal diameter of less than 10 mm to be indicative of a stenosis while one study did not provide a definition and one study specified “a markedly narrowed lumen” without defining a cut-off.
value.\(^1\) Wall thickening as an indicator for intestinal stenosis was determined by \(7/10\) studies.\(^1\) \(2,5,7,9\) One study defined a pathological thickness of \(>3\text{mm},\) \(9\) while 2 other studies used \(>4\text{mm}\) \(^1,7\) as cut-off level for pathological wall thickening. \(3\) authors did not provide an exact definition for thickened bowel wall.\(^2,5,6\)

Interestingly; the number of items required for diagnosis of a stricture varies between different studies and investigators. In \(2/9\) studies all three components are required for stricture diagnosis.\(^5,7\) In \(2/9\) studies, the investigators defined a stricture by the presence of luminal narrowing irrespective of any other parameters.\(^3,4\) while in \(1/9\) studies, only the item wall thickening was necessary to define a stricture.\(^2\) Lastly, in \(4\) studies the authors did not provide a specific definition for stricture diagnosis.\(^5,6,8,9\)

Although the choice of a “gold standard” reference comparator for use in these studies is problematic, quantitative assessment of fibrosis on resection specimens is accepted as being the most valid reference. However, it should be noted that there are several other published studies on US that did not use histopathological analysis as a reference standard.\(^10-26\) These studies were not included into the analysis.

**Definitions used in computed tomography to diagnose CD-associated strictures**

Similar to the US studies, not all studies investigating CT assessed all of these items. More specifically, only \(3\) of \(4\) studies assessed all three items\(^25-29\) while \(1\) of \(4\) studies solely assessed wall thickening.\(^30\)

Of \(3\) studies that investigated prestenotic dilation as a diagnostic criterion, one study defined this item as a bowel diameter of more than \(30\text{mm}\)\(^28\) while \(2\) of \(3\) studies did not provide a specific cut-off value.\(^27,29\) \(3\) studies evaluated luminal narrowing as a feature of stricture diagnosis.

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diagnosis, however, heterogeneous definitions were used: one study less than <10 mm,\textsuperscript{28} one study by reduction of luminal narrowing of 50% or more\textsuperscript{27} and one study did not provide a specific definition for luminal narrowing.\textsuperscript{29}

All 4 studies determined wall thickening as a diagnostic criterion. Of these, one study used the cut-off of 3 mm;\textsuperscript{29} one study of more than 3 mm\textsuperscript{30} and another study used more than 5 mm.\textsuperscript{28} The other study did not provide further information regarding the definition of wall thickening.\textsuperscript{27}

With respect to items required for stricture diagnosis, 1 of 4 studies required the evidence of luminal narrowing alone\textsuperscript{27} while another study defined stricture presence based on luminal narrowing and wall thickening.\textsuperscript{28} Finally, 2 out of 4 studies did not provide an exact definition for stricture diagnosis.\textsuperscript{29,30}

There are several studies on CT available that did not use full-thickness histopathology in all patients as a reference standard.\textsuperscript{31-45}

Definitions used in magnetic resonance imaging to diagnose CD-associated strictures

We next evaluated the use of the above-mentioned three components (prestenotic dilation, luminal narrowing and wall thickening) for stricture detection in available MRI studies.

Of the 12 identified studies, only one study evaluated all three items: prestenotic dilation, luminal narrowing and wall thickening.\textsuperscript{\textit{a}} 3 studies assessed prestenotic dilation and wall thickening.\textsuperscript{2,47,48} and 6 studies solely evaluated wall thickening.\textsuperscript{5,30,49-52} Finally, 2 studies did not provide information on which item they assessed for stricture detection.\textsuperscript{53,54} Of those 4 that evaluated prestenotic dilation, one study defined a prestenotic dilation by an 1.5 times
increase compared to normal loop diameter\textsuperscript{48}. While \textit{3} studies did not provide a specific definition for this item\textsuperscript{2,46,47} Luminal narrowing was \textit{solely} assessed by \textit{1} study that used a criterion of a reduction of lumen diameter of \textit{50}\% or less compared to the prestenotic loop\textsuperscript{46}. The item wall thickening was used as a diagnostic criterion by \textit{10} studies. \textit{2} of \textit{10} studies defined wall thickening by a diameter of \textit{3 mm}\textsuperscript{30,50} while \textit{8} of \textit{10} studies did not state an exact definition of wall thickening\textsuperscript{2,5, 46-49, 51, 52}.

With regard to stricture diagnosis, \textit{in 1 of 12 studies} required a luminal narrowing of \textit{50}\% or more and prestenotic dilation\textsuperscript{46}, while \textit{11} of \textit{12} studies did not provide an exact definition for stricture diagnosis.\textsuperscript{2,5, 30, 47,54} As mentioned in the context of US and CT studies, several MRI studies are available that did not use histopathology as a reference standard in all patients.\textsuperscript{17, 24, 25, 32, 33} Again, these studies were not included into the analysis.
REFERENCES


