Value of Abdominal Radiography, Colonic Transit Time, and Rectal Ultrasound Scanning in the Diagnosis of Idiopathic Constipation in Children: A Systematic Review

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Objective To perform a systematic review evaluating the value of abdominal radiography, colonic transit time (CTT), and rectal ultrasound scanning in the diagnosis of idiopathic constipation in children.

Study design Eligible studies were those assessing diagnostic accuracy of abdominal radiography, CTT, or rectal ultrasound scanning in children suspected for idiopathic constipation. Methodological quality of the included studies was assessed with the Quality Assessment of studies of Diagnostic Accuracy included in Systematic reviews checklist.

Results One systematic review summarized 6 studies on abdominal radiography until 2004. The additional 9 studies evaluated abdominal radiography (n = 2), CTT (n = 3), and ultrasound scanning (n = 4). All studies except two used a case-control study design, which will lead to overestimation of test accuracy. Furthermore, none of the studies interpreted the results of the abdominal radiography, ultrasound scanning, or CTT without knowledge of the clinical diagnosis of constipation. The sensitivity of abdominal radiography, as studied in 6 studies, ranged from 80% (95% CI, 65-90) to 60% (95% CI, 46-72), and its specificity ranged from 99% (95% CI, 95-100) to 43% (95% CI, 18-71). Only one study presented test characteristics of CTT, and two studies presented test characteristics of ultrasonography. **Conclusion** We found insufficient evidence for a diagnostic association between clinical symptoms of constipation and fecal loading on abdominal radiographs, CTT, and rectal diameter on ultrasound scanning in children. (*J Pediatr 2012;161:44-50*).

n children, constipation and fecal incontinence can lead to social withdrawal, low self-esteem, and even depression.¹ Early diagnosis and treatment of idiopathic constipation may prevent a chronic course with continuation of infrequent painful defecation, psychosocial problems, and the need for long-lasting laxative therapy.

History taking and physical examination constitute the most important steps in the diagnosis of idiopathic constipation. However, there is debate which aspects of history and physical examination are most important in discriminating between constipation and no constipation. The current best "gold standard" are the ROME III criteria, on the basis of the presence of two or more of a number of well-defined clinical symptoms.^{2,3} However, a diagnosis might be doubtful when insufficient key symptoms of constipation are present or when a rectal examination is not feasible. Several relatively safe and easy to perform tests are used in daily practice to distinguish between constipation or no constipation.

Assuming that fecal retention is one of the main features of constipation, Barr et al introduced a score to appraise fecal retention on a single radiograph of the abdomen.⁴ Since then, different scoring systems have been developed to assess fecal loading on an abdominal radiograph.^{5,6} On the basis of the same assumption, assessment of stool retention and size of rectum and colon are measured with rectal ultrasound scanning.

One of the underlying mechanisms of idiopathic constipation is thought to be a disturbance of intestinal motility. Consequently, colonic transit time (CTT) is assumed to be decreased in children with idiopathic constipation in comparison with healthy children. On the basis of this assumption, transit time is measured with radiopaque markers and abdominal radiography.

We carried out a systematic literature review to evaluate the value of abdominal radiography, CTT, and rectal ultrasound scanning in the diagnosis of idiopathic constipation in children.

Methods

Eligible studies were those that assessed the diagnostic accuracy of abdominal radiography, CTT, or rectal ultrasound scanning in children aged 0 to 18 years,

AUC	Area under the curve	L
CTT	Colonic transit time	L
QUADAS	Quality Assessment of studies of Diagnostic Accuracy included in Systematic reviews	

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with idiopathic constipation suspected on clinical grounds and as defined by the authors. Data collection had to include a (well-defined) verification of the diagnosis (reference standard).

Identification of Studies

A clinical librarian searched for diagnostic studies published in the Medline and Embase databases from inception to January 2010 (Appendix; available at www.jpeds.com). Keywords used were: "constipation," "obstipation," "fecal incontinence," "coprostasis," "encopresis," and "soiling." These words were combined with keywords referring to the diagnostic tests that were investigated in this review. All terms were included as Medical Subject Heading heading and as text word. The results of this search were combined with the search strategy for identifying diagnostic studies, as described by Haynes and Wilczynski.⁷ Additional strategies for identifying trials included searching the reference lists of review articles and included studies. When a systematic review was found, additional searches started from the date the systematic review stopped searching. We applied no language restrictions. The full search strategy is available from the authors.

Study Selection and Data Extraction

The selection was carried out independently by two reviewers (M.B. and M.K.) on the basis of title and abstract. Specific criteria were used: (1) the study population consisted of children aged 0 to 18 years, or when adults were also included, the study had to report separately on children; (2) constipation had to be defined; and (3) one of the aims of the study was to evaluate the diagnostic value of abdominal radiography, rectal ultrasound scanning (measuring rectal diameter), or CTT (involving radio-opaque markers with serial radiographs) for functional constipation. All potentially relevant studies and the studies for which the abstracts did not provide sufficient information for inclusion or exclusion were retrieved as full papers. Systematic reviews with the Quality Assessment of studies of Diagnostic Accuracy included in Systematic reviews (QUADAS) for quality assessment and individual studies were eligible.⁸ Excluded were papers about children with organic causes of constipation and children with exclusively functional nonretentive fecal incontinence. Two reviewers independently assessed eligible studies for inclusion. Disagreement was resolved with discussion. For data extraction, a structured form was used. One reviewer extracted the data; a second reviewer controlled data extraction. These characteristics were extracted from each selected study: age range, inclusion and exclusion criteria, prevalence of constipation in the study population, description of the index test used, description of reference test, and data for construction of a two-by-two table.

Assessment of Methodological Quality

From the QUADAS checklist, we choose 6 of the best differentiating items (**Table I**; available at www.jpeds.com). Each item is scored as "yes," "no," or "unclear." We did not calculate summary scores because their interpretation is potentially misleading. One reviewer assessed methodological quality (M.B.).

Data Analysis

Whenever possible, we calculated sensitivities and specificities with a 95% CI for each study. In case of clinical heterogeneity (patient population, definition of reference and index test, or both are not considered to be sufficiently similar), the results were not pooled.

Results

The search identified 767 papers, 23 of which were retrieved for full-text review. Ten diagnostic accuracy studies could be included in the analysis (**Figure**; available at www.jpeds. com).⁹⁻²² Study characteristics of 6 studies reporting data on sensitivity and specificity of radiography are presented in **Table II**, and study characteristics of studies on CTT and ultrasound scanning are presented in **Table III**. Test characteristics are presented in **Table IV**.

Only 3 studies^{24,31,32} of all included selected consecutive children with gastrointestinal symptoms related to constipation. All other studies selected cases and controls. Constipation was excluded in the controls.

Differential verification bias occurs when the performance of the diagnostic test is verified with a different reference standard. All studies, except 3,^{5,26,32} used comparable definitions for constipation, including at least weekly frequency of defecation, hard stools, and difficulty in evacuating. Gutiérrez,²⁶ Beckmann,³² and Leech⁵ did not specify their diagnosis of constipation.

None of the studies interpreted the results of radiography, ultrasound scanning, or CTT without knowledge of the clinical diagnosis constipation.

In most studies, the selection procedure was not clearly described. Only 3 studies^{26,28,29} described the reason and number of children who did not undergo the diagnostic test.

Abdominal Radiography

We identified one robust systematic review, 4 included studies that reported data that enabled calculation of sensitivity and specificity,^{4,5,32,33} and two more recent studies (**Table IV**).^{24,25} All studies except one²⁴ were performed in referred children. The 6 included studies were heterogeneous for study design, the definition of constipation, and the methods used to evaluate the abdominal radiography (**Table II**). In the systematic review, conflicting evidence was found for a diagnostic association between clinical symptoms of constipation and fecal loading in abdominal radiographs in children.

In an receiver operating characteristic analysis, De Lorijn et al^{23} found an area under the curve (AUC) of 0.68 (95% CI, 0.58-0.80), indicating poor diagnostic accuracy.

Colonic Transit Time

The 3 included studies were heterogeneous for study design, for the definition of constipation, and the methods used to evaluate CTT. In the study of De Lorijn et al, the optimal CTT to define constipation was found to be 54 hours, leading to a sensitivity rate of 79% and a specificity rate of 92%.²⁵ The

Table II. Study characteristics of two recent studies evaluating the diagnostic value of abdominal radiography and of 4 studies included in an earlier review on diagnosis of idiopathic constipation

Study	Patients included in analysis, n	Age range, years	Index test	Cases (reference standard)	Controls
Radiography Çayan 2001 ²⁴	125	5-19	Fecal loading on abdominal radiography according to Blethyn ⁴	<3 bowel movements per week for a period of at least 6 months	Children with primary nocturnal enuresis selected at day care centers and schools, without clinical constipation
Lorijn 2006 ²⁵	89	Median 9.8	Fecal loading on abdominal radiograph according to Leech et al resulting in a score of 0 to maximum of 15 Total score >9 considered as constipation	At least two of the following: defecation frequency <3 times per week; 2 or more episodes of fecal incontinence per week; production of large amounts of stool once in a period of 7-30 days; the presence of a palpable abdominal or rectal mass ($n = 52$)	Solitary encopresis and/or solitary encopresis and/or solitary encopresis and/or solitary encompation Functional abdominal pain ($n = 37$)
Beckmann 2001 ³²	251	2-12	Fecal loading on abdominal radiograph according to Blethyn et al Radiographically proven constipation defined as grade 1-3	Clinical constipation (not further defined)	Children presenting at emergency department with gastrointestinal symptoms
Leech 1999 ⁵	100	1 month-14 years	Abdominal radiograph divided in 3 segments, each segment given a score 0-5, giving a total score of 0-15 Total score 8-15 indicates significant constipation.	Children with a clinical diagnosis of constipation (intractable idiopathic constipation), $n = 33$	Children who underwent IVP for suspected renal tract disorder, $n = 67$
Benninga 1995 ³³	101	5-14	Abdominal radiography scored according to Barr: total score, 0-25; score >10 indicates fecal retention	At least 2 of the following 4 criteria: stool frequency <3 times per week; >2; soiling/encopresis episodes per week; periodic passage of very large amounts of stools once every 7-30 days; a palpable abdominal or rectal mass ($n = 57$)	Solitary encopresis and/or soiling without any of the other criteria of constipation ($n = 30$) Recurrent abdominal pain severe enough to interfere with day-to-day activities in at least a 3-month period without any of the other symptoms of constipation ($n = 14$)
Barr 1979 ⁴	42	3-7	Abdominal radiograph scored according to Barr: total score: 0-25; a score >10 indicated fecal retention	Symptomatic stool retention based on evidence of "pellet" stools, straining, having a bowel movement no more often than every 3 days, blood streaking on stools, very large stools, history of soiling, positive rectal examination results, or colonic stool palpated on abdominal examination; patients with a present history of soiling were excluded; $n = 30$	Children who had abdominal radiography for lead ingestion and who did not present with either abdominal pain or constipation and who had blood lead levels >50 μ g/dL (2.41 μ mol/L); n = 12

IVP, intravenous pyelogram.

Table III.	Study characte	ristics of st	udies evaluating the diagnostic value of CTT	and rectal ultrasound scanning in the diagn	osis of idiopathic constipation
Patients included Age range, Study in analysis, n years			Index test Cases (reference standard)		Controls
CTT De Lorijn ²⁵	89	Median 9.8	CTT according to Bouchacha ³⁴ ; the radiography on day 7 was used to count the number of markers visible in the colon; cutoff value for constipation is CTT >62 hours	At least two of the following: defecation frequency <3 times per week; 2 or more episodes of fecal incontinence per week; production of large amounts of stool once in a period of 7-30 days; the presence of a palpable abdominal or rectal mass (n = 52)	Solitary encopresis and/or soiling without any of the other criteria of constipation; functional abdominal pain ($n = 37$)
Gutiérrez ²⁶	60	2-14	CTT according to Bouchacha ³⁴ ; the radiography on day 7 was used to count the number of markers visible in the colon; no cutoff value for constipation defined	Chronic idiopathic constipation for >6 months, with or without secondary encopresis (n = 30)	Normal bowel habits (between 3 defecations daily and 3 defecations weekly, without straining at stool, and feces of normal consistency) for at least 12 month before the study
Zaslavsky ²⁷ Ultrasound sca	26	12-18	CTT according to Metcalf et al ³⁵ ; the radiography on day 7 was used to count the number of markers visible in the colon; no cutoff value for constipation defined	Hard stools, difficulty in evacuating, <3 bowel movements a week, no evidence of palpable rectal mass, and a history of constipation of at least 1 year's duration	No digestive complaints and more than 3 bowel movements per week
Klijn ²⁹	49	5-13	Transverse rectal diameter behind the bladder at ultrasound scanning: participants had a partly full bladder at examination	At least 2 of the following: 2 or fewer bowel movements weekly without laxative treatment; 2 or more episodes of fecal soiling weekly; periodic passage of a large amount of stool once every 7-30 days; a palpable abdominal or rectal mass ($n = 23$)	Urological patients without lower tract dysfunction and a normal defecation pattern ($n = 26$)
Joensson ²⁸	51	4-12	Transverse rectal diameter behind the bladder at ultrasound scanning as described by Klijn et al ²⁹ ; participants had a partly full bladder at examination	Rome III criteria of constipation ($n = 27$)	Healthy controls (n = 24)
Singh ³⁰	177	0.3-16.4	Transverse rectal crescent behind the bladder at ultrasound scanning; participants had a partly full bladder at examination	2 or more of the following: less than 3 bowel movements per week; periodic passage of a large stool with discomfort or pain; a palpable abdominal fecal mass; fecal soiling in the presence of any of the aforementioned ($n = 95$)	Children with no bowel problems or history of constipation (n = 82)
Bijos ³¹	120	Not described	A rectopelvic ratio was calculated by dividing the transverse diameter of the rectal ampulla by the transverse diameter of the pelvis		Children with a normal defecation pattern in whom various symptoms were diagnosed and treated (chronic abdominal pain, food allergies; $n = 105$)

Table III. Study characteristics of studies evaluating the diagnostic value of CTT and rectal ultrasound scanning in the diagnostic of idionathic constinution

	Number of patients with clinical constipation/number of patients		
Source	without clinical constipation	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Radiography			
Beckmann 2001 ³²	180/71	61 (53-68)	55 (43-67)
Leech 1999 ⁵	33/67	76 (58-89)	75 (63-85)
Benninga 1995 ³³	57/44	60 (46-72)	43 (18-71)
Barr 1979 ⁴	30/12	80 (65-90)	90 (74-98)
De Lorijn 2006 ²⁵	52/37	75 (61-86)	59 (42-75)
Çayan 2001 ²⁴ CTT	10/115	70 (35-93)	99 (95-100)
De Lorijn 2006 ²⁵	52/37	71 (57-83)	95 (82-99)
Ultrasound scanning		()	
Klijn 1986 ²⁹	23/26	100 (85-100)	89 (70-98)
Joensson 1997 ²⁸	27/22	56 (35-75)	96 (77-99)

most frequently used cutoff value for CTT in the literature is 62 hours, leading to a sensitivity rate of 71% and a specificity rate of 95% (**Table IV**). The AUC for CTT was 0.90 (95% CI, 0.83-0.96), indicating good diagnostic accuracy. Gutiérrez et al found that in constipated children the mean CTT was significantly prolonged compared with that of the control group (mean \pm SD 49.57 \pm 25.38 hours compared with 29.08 \pm 8.3 hours)²⁶; CTT was inversely related to the number of defecations per week. Zaslavsky et al found that in children with constipation, the mean CTT was significantly different from that in the control group (58.25 \pm 17.46 hours compared with 30.18 \pm 13.15 hours).²⁷ No further test characteristics could be calculated in the latter two studies.

Rectal Ultrasound Scanning

The 4 included studies were heterogeneous for study design, the definition of constipation, and the methods used to evaluate rectal ultrasound scanning. Test characteristics could be calculated in two studies (Table IV).^{28,29} In the study of Joensson et al, it was possible to visualize the transverse diameter of the rectum at least 3 hours after the last bowel movement, in all included children.²⁸ Children with constipation had a significantly larger rectal diameter than healthy children (39.6 \pm 8.2 mm versus 21.4 \pm 6.0mm). With a cutoff value for constipation of 33.4 mm, 13 children would be misclassified. After laxative treatment, the rectal diameter of the children with constipation reduced significantly to 26.9 ± 5.6 mm. Klijn et al found a statistically significant difference in the diameter of the rectum between the constipated group and the control group.²⁹ The mean diameter in the constipated group was 4.9 cm, compared with 2.1 cm in the control group. A cutoff value of 3.3 cm was used, when >3.3 cm indicated constipation (Table IV). In the study of Singh et al, the median rectal crescent size in children with constipation was 3.4 cm (range, 2.10-7.0; IQR, 35.3), as compared with 2.4 cm (range, 1.3-4.2; IQR, 0.72) in healthy control subjects.³⁰ A receiver operating characteristic analysis found an AUC of 0.847 (95% CI, 0.790-0.904), indicating good diagnostic accuracy. Cutoff values for constipation were not presented. Bijoś et al calculated a recto-pelvic ratio by dividing the transverse diameter of the rectal ampulla by the transverse diameter of the pelvis.³¹ In children with functional constipation, the mean recto pelvic ratio was 0.22 \pm 0.05, compared with 0.15 \pm 0.04 in healthy control subjects. The difference was statistically significant in all age groups.

Discussion

In this systematic review of studies on the diagnostic value of additional tests for childhood constipation, all of the individual studies except two had a case-control design. Studies that recruited a group of healthy control subjects or control subjects in whom other gastrointestinal complaints like abdominal pain were excluded are likely to overestimate diagnostic accuracy. Therefore, the results of this review will give an overestimation of the true diagnostic accuracy of the tests evaluated. Most studies had small sample sizes. This may result in large 95% CIs. Pooling of data would have been a solution to overcome the problem of small sample size; however, we refrained from pooling because of the substantial differences in studies. All studies, however, were homogeneous in their hospital-based setting. Therefore, the results of our review cannot be generalized to general practice.

Constipation is a syndrome characterized by typical clinical symptoms. The included studies used different definitions for constipation. Therefore the reference standard varied in studies. This hampered comparison of the results. To overcome heterogeneity in diagnosis and research, a committee of clinical experts proposed to use a uniform definition for constipation, the so-called ROME III criteria.^{2,3} The consensus was that, on the basis of thorough history and rectal examination, a diagnosis of constipation can be made. It was reported, however, that 85% of primary care physicians do not perform digital rectal examination before referral for constipation,³⁸ and as far as we know, the additional diagnostic value of digital rectal examination has never been properly tested.²³ Therefore, a validated reference standard, including the evidence for additional value of rectal examination, that is acceptable for clinicians, in primary and secondary care, is urgently needed.

The conclusion of the authors of the included systematic review was that there is conflicting evidence for a diagnostic association between clinical symptoms of constipation and fecal loading in abdominal radiographs in children.²³ The two additional studies included in this review add to the evidence for no association. On the basis of this evidence, the recently published National Institute for Health and Clinical Excellence guideline concluded that abdominal radiography should not be recommended as an additional test for constipation in children.³⁶

Only one study presented test characteristics of CTT. The AUC in this study was 0.90 (95% CI, 0.83-0.96), indicating good discrimination between children with and children without constipation. Compared with abdominal radiography, the accuracy of CTT was significantly better in this study population (AUC, 0.68; 95% CI, 0.58-0.80).²⁵ A 1-year follow-up study of children treated with laxatives or biofeed-back showed results in favor of the discriminative ability of CTT.³⁷ In this study, children with a total CTT >100 hours had fewer treatment successes after 12 months than children with a shorter total CTT. Before recommending CTT as a diagnostic test for constipation, however, further studies in clinically relevant populations are needed.

Ultrasound scanning is not invasive and does not involve radiation so might be a potentially feasible test in primary and secondary care. Measuring rectal diameter was associated with the results of digital rectal examination and therefore seems to assess fecal impaction. It is suggested that ultrasound scanning might replace digital rectal examination because it will be less unpleasant.³⁷ Our results show that, for now, there is insufficient evidence that the transverse diameter can be used as a predictor of constipation and fecal impaction.

We used a sensitive search strategy without language restrictions, but might have missed eligible studies. We refrained from pooling because of large heterogeneity in studies. The use of different definitions for constipation might have caused misclassification of patients. Pooled results will then be biased, without any insight in the direction of the bias: over- or underestimation. We included studies from an earlier systematic review on diagnostic value of abdominal radiography. Because the search strategy of this review was comparable with ours and methodological quality was performed with the QUADAS, we considered the methodology used comparable and included the individual studies of this review.

A diagnosis of constipation becomes uncertain when not enough key symptoms of the Rome III criteria are present. Additional diagnostic information from rectal examination, radiography, or ultrasound scanning might be useful in such situation. Future studies should be performed in clinically relevant populations not fulfilling enough criteria for constipation. In case an adequate reference standard is lacking, follow-up studies (preferably randomized) are needed to quantify the effect of a diagnostic test on patient outcome. Because of the assumption that laxatives are effective in idiopathic childhood constipation, we propose that the diagnostic value of key symptoms should be evaluated with the effect of laxative treatment as the reference standard.³⁸ In addition, not only the accuracy of the test should be evaluated, but also the additional diagnostic value greater than clinical characteristics should be addressed. By improving the quality

of research methods, the quality of care will improve with an earlier and better recognition of constipation and improved diagnostic and therapeutic strategies.

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Value of Abdominal Radiography, Colonic Transit Time, and Rectal Ultrasound Scanning in the Diagnosis of Idiopathic 49 Constipation in Children: A Systematic Review

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Appendix

Search Strategy Medline (Adapted for Embase)

((((((((("sensitivity and specificity" [All Fields] OR "sensitivity and specificity/standards"[All Fields]) OR "specificity"[All Fields] OR "screening"[All Fields] OR "false positive" [All Fields]) OR "false negative" [All Fields]) OR "accuracy"[All Fields]) OR ((((("predictive value"[All Fields] OR "predictive value of tests" [All Fields]) OR "predictive value of tests/standards" [All Fields]) OR "predictive values"[All Fields]) OR "predictive values of tests" [All Fields])) OR (("reference value" [All Fields] OR "reference values" [All Fields]) OR "reference values/standards"[All Fields])) OR (((((((("roc"[All Fields] OR "roc analyses"[All Fields]) OR "roc analysis" [All Fields]) OR "roc and" [All Fields]) OR "roc area" [All Fields]) OR "roc auc" [All Fields]) OR "roc characteristics" [All Fields]) OR "roc curve" [All Fields]) OR "roc curve method" [All Fields]) OR "roc curves" [All Fields]) OR "roc estimated" [All Fields]) OR "roc evaluation"[All Fields])) OR "likelihood ratio"[All Fields]) AND "human" [MeSH Terms])

Disease

((("constipation"[MeSH Terms] OR constipation[Text Word]) OR ("fecal impaction"[MeSH Terms] OR coprostasis[Text Word])) OR obstipation[All Fields])

"Fecal-Incontinence"/all subheadings "Fecal-Incontinence"/all subheadings "Defecation"/all subheadings "Abdominal-Pain"/all subheadings

Test

("radiography, abdominal" [MeSH Terms] OR abdominal radiography [Text Word])

((("diagnosis"[MeSH Subheading] OR "diagnosis"[MeSH Terms]) OR signs[Text Word]) OR (("diagnosis"[MeSH Subheading] OR "diagnosis"[MeSH Terms]) OR symptoms[Text Word]))

(((solid[All Fields] AND ("biological markers"[MeSH Terms] OR marker[Text Word])) AND transit[All Fields]) AND studies[All Fields])

(((solid[All Fields] AND ("biological markers"[MeSH Terms] OR marker[Text Word])) AND transit[All Fields]) AND study[All Fields])

"Ultrasonics"/all subheadings

"Ultrasonography"/all subheadings

Papers identified through searches of Medline and Embase (n=767)						
	Excluded on basis of title and abstract (n=744)					
Full text papers (n=23)						
	No diagnostic accuracy study (n=8;CTT;X-ray) ^{9.16} No children included (n=1;ultrasound) ¹⁷ No control group (n=1;CTT) ¹⁸ No reference standard defined (n=2;ultrasound;X-ray) ^{19,20} Patients with severe comorbidity (n=1;CTT) ²¹ Systematic review, no QUADAS (n=1;CTT) ²²					
ncluded papers (n=10)						
•	Systematic review including 6 studies on abdominal radiography (n=1) ²³ → Diagnostic value of abdominal radiography (n=2) ^{24,25} Diagnostic value of CTT (n=3) ^{25,27} Diagnostic value of Ultrasonography (n=4) ^{25,31}					

Figure. Flowchart describing study selection (numbers refer to references).

	Abdominal radiography		Ultrasound scanning			CTT		
QUADAS items	Çayan 2001	De Lorijn 2006	Klijn 1986	Joensson 1997	Singh 2005	Bijos 2007	Zaslavsky 1998	Gutiérrez 2002
Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	No	No	No	No	Yes	No	No
Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	No	No	No	No	No	No	No
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were withdrawals from the study explained?	No	No	Yes	Yes	No	No	No	Yes

Table I. Summary of methodological quality of included studies on basis of 6 items from QUADAS checklist for each