Pediatr Radiol
DOI 10.1007/s00247-016-3775-8

ORIGINAL ARTICLE

Diagnostic utility of intravenous contrast for MR imaging in pediatric appendicitis

Gray R. Lyons [1] · Pooja Renjen [1] · Gulce Askin [2] · Ashley E. Giambrone [2] · Debra Beneck [3] · Arzu Kovanlikaya [1]

Received: 17 May 2016 / Revised: 23 October 2016 / Accepted: 23 December 2016

Abstract
Background Magnetic resonance imaging (MRI) is increasingly employed as a diagnostic modality for suspected appendicitis in children. However, there is uncertainty as to which MRI sequences are sufficient for safe, timely and accurate diagnosis. Several recent studies have described different MRI protocols, including exams both with and without the use of intravenous contrast.
Objective We hypothesized that intravenous contrast may be useful in some patients but could be safely omitted in others.
Materials and methods All MRI examinations (n=112) performed at our institution for evaluating appendicitis in children were retrospectively reevaluated. Exams were reread by pediatric radiologists under three conditions: *With* postcontrast images, *Without* postcontrast images, and *Without/With* – selective use of postcontrast sequences only when needed for diagnostic certainty. Samples were scored as positive, negative or equivocal for appendicitis. Findings were compared to pathological or clinical follow-up in the medical record.
Results *Without* the use of intravenous contrast yielded more equivocal results (12.4%) compared to *With* contrast (3.4%). By selectively using postcontrast sequences, the *Without/With* group yielded fewer equivocal results (1.1%) compared to *Without* while also reducing contrast use 79.8% compared to the *With* contrast group. No significant differences in conditional sensitivity or conditional specificity were detected among the three groups.
Conclusion MRI diagnosis of acute appendicitis can be performed without contrast for most patients; injection of contrast can be reserved for only those patients with equivocal noncontrast imaging.

Keywords Appendicitis · Children · Intravenous contrast · Magnetic resonance imaging

Introduction

Acute appendicitis is the most common indication for urgent abdominal surgery in children [1]. Diagnosis on clinical grounds can be difficult as presenting signs and symptoms can be nonspecific or atypical. Imaging is useful in providing timely, accurate diagnosis of acute appendicitis [2]. Current American College of Radiology appropriateness criteria recommend ultrasound (US) as the preferred initial modality, followed by computed tomography (CT) for cases where US is nondiagnostic [3]. The use of US and CT has reduced the number of unnecessary appendectomies [4]. However, the benefits of CT come at the cost of radiation exposure, which is concerning in children [5, 6].

In an effort to reduce the use of ionizing radiation, magnetic resonance imaging (MRI) has been increasingly employed as a modality instead of CT [7, 8]. Several recent studies have reported high sensitivity and specificity for MRI in the diagnosis of acute appendicitis; however, there is diversity in the specific MR protocol used to obtain these results [9–14]. Most groups report using fast or ultrafast spin echo sequences supplemented

✉ Arzu Kovanlikaya
ark2011@med.cornell.edu

[1] Department of Radiology, New York-Presbyterian Hospital/Weill Cornell Medicine, 525 E. 68th St., F631E, New York, NY 10065, USA

[2] Department of Biostatistics and Epidemiology, New York-Presbyterian Hospital/Weill Cornell Medicine, New York, NY, USA

[3] Department of Pathology, New York-Presbyterian Hospital/Weill Cornell Medicine, New York, NY, USA

Published online: 21 January 2017

by additional sequences such as gradient echo [15], short tau inversion recovery [16] and diffusion-weighted sequences [17].

Notably, there is diversity in the reported use of intravenous contrast for the diagnosis of acute appendicitis. Koning et al. [10] demonstrated the accuracy of contrast-enhanced MRI, which was followed by a study by Rosines et al. [13], who concluded that contrast-enhanced images, along with T2-weighted images, were most helpful in assessing for acute appendicitis. However, several other reports have demonstrated adequate diagnostic utility of MR in suspected acute appendicitis without the use of intravenous contrast [18–21]. There are many practical drawbacks to the use of intravenous contrast in pediatric imaging, including the need for intravenous access, increased scan time and accompanying patient fatigue/motion, and exposure to possible side effects of the contrast agent. Therefore, more research is warranted in determining the utility of intravenous contrast for the diagnosis of acute appendicitis in children.

At our institution, we routinely use postcontrast spoiled gradient echo imaging as part of our standard protocol in evaluating appendicitis in children. We have anecdotally noted that postcontrast imaging was useful in evaluating some cases, while others could have been read without contrast. This led us to hypothesize that intravenous contrast could be safely omitted in some patients. The purpose of this study was to investigate the utility of intravenous contrast in the diagnosis of acute appendicitis in children.

Materials and methods

Subjects

Institutional review board approval was obtained for this single-institution retrospective study. Patients ages 21 and younger were enrolled if they had undergone an MRI of the abdomen and pelvis and the clinical indication as entered by the ordering provider indicated suspicion for acute appendicitis. As is our institutional protocol, all patients had undergone US as first-line imaging; MRI was used as a second-line modality in the case of nondiagnostic US. Ultrasonography was considered nondiagnostic in cases of non-visualization of the appendix with or without suspicious secondary sonographic signs of inflammation and with persistent clinical concern for acute appendicitis based on clinical symptoms and laboratory data. Patients known to be pregnant at the time of scan were excluded from the study. Data collected included patient age and sex at the time of imaging, the clinical diagnosis, surgical notes (if applicable), the pathological diagnosis for those undergoing appendectomy, and the clinical course for those treated nonsurgically. Scan time was recorded as the time the exam was initialized by the technician to the time the scan was finalized by the technician.

Procedures

Imaging was performed on a 1.5-T scanner using an 8-channel torso array coil (Signa HDxt, GE Medical Systems, Milwaukee, WI). Our standard protocol includes T1- and T2-weighted sequences as well as diffusion-weighted images (Table 1). For all contrast-enhanced exams, gadobutrol (Gadavist) was injected intravenously using weight-based dosing as specified by the manufacturer (Bayer HealthCare, Whippany, NJ). Patients did not undergo postcontrast imaging only if the scan was ordered as a non-contrast examination by the ordering provider. Patients who did not undergo diffusion-weighted imaging for any purpose were excluded from the study.

Data collection

Images were interpreted separately by two pediatric attending radiologists (P.R. and A.K., with 5 and 22 years' post-fellowship experience, respectively). A third radiologist was selected as a tiebreaker in the case of radiologist interobserver discordance, although this did not occur in our study. The radiologists re-reviewed each case, blinded to the US data, original radiologist MRI report and the clinical outcome. The exams were reviewed under three conditions: 1) exams were read using all available sequences ("*With*" contrast group), 2) exams were read using only non-contrast sequences ("*Without*" contrast group), and 3) exams were initially read using only non-contrast sequences, however, if the radiologist was unable to report a certain diagnosis, then the postcontrast images were added and the exam was interpreted using contrast ("*Without/With*" contrast group).

Exams were scored as positive, negative or equivocal for appendicitis as previously described [22]. A diagnosis of appendicitis was made in the case of visualization of a dilated (>6 mm), fluid-filled appendix, with mural diffusion restriction and/or enhancement (if postcontrast sequences were available) were present. In cases where the appendix appeared abnormal but did not meet all of the above criteria, secondary signs of periappendiceal inflammation such as periappendiceal free fluid or peri-cecal/ileal wall thickening or abscess formation were sufficient to make the diagnosis. A negative diagnosis for appendicitis was made in cases where a healthy appendix was visualized or the appendix was not visualized and suspicious secondary signs were absent. Equivocal cases involved either an abnormal-appearing appendix not meeting all of the above appendicitis criteria and without secondary signs of appendicitis *or* non-visualization of the appendix with secondary signs of appendicitis [23].

Order was randomized and a 6- to 8-week time interval was placed between readings to minimize recall of the cases. Rereads from the three groups were compared to pathology or clinical outcome. Clinical outcome was defined as alternative diagnosis made on imaging grounds, hospital discharge

Table 1 Standard MRI acquisition protocol of the pediatric abdomen and pelvis

Sequence	Planes	TR (ms)	TE (ms)	Flip (°)	FOV (cm)	Slice (mm)	Gap (mm)	Notes
SSFSE	Ax/Cor/Sag	778	79	90	48 × 48 (all planes)	8	25	Scout
BSSGE	Ax/Cor	3.75	1.5	70	32 × 25.6 ax 38 × 38 cor	5	0	
T2 FSE	Ax/Cor	2,000	90	111	32 × 25.6 ax 44 × 44 cor	5	0	Without and with fat saturation
DWI/ADC	Ax	5,900	85	83	32 × 32 ax	8	2	B=0,500,1000 NEX=6
T1 3DSGE	Ax/Cor	4.2	2	12	32 × 25.6 ax 44 × 44 cor	4	0	Fat saturation, Postcontrast

3DSGE three-dimensional spoiled gradient echo (LAVA [liver acquisition with volume acceleration]), *ADC* apparent diffusion coefficient, *Ax* axial, *BSSGE* balanced steady-state gradient echo (FIESTA [fast imaging employing steady state acquisition]), *Cor* coronal, *DWI* diffusion-weighted imaging, *FSE* fast spin echo, *NEX* number of excitations, *Sag* sagittal, *SSFSE* half-acquisition single-shot fast spin echo, *TE* echo time, *TR* repetition time

with remote follow-up or hospital discharge of a clinically diagnosed well child without follow-up.

Statistical analysis

A six-cell matrix was used to calculate conditional sensitivity and conditional specificity as previously described [24] and detailed in Table 2. Briefly, the six-cell matrix includes test outcomes that are positive, negative or equivocal for disease compared against a gold standard for disease that is positive or negative in diagnosis. Conditional sensitivity and conditional specificity, positive yield (YD+) and negative yield (YD-) were calculated as follows: YD+ is the probability of a positive or a negative test result when the disease is present, YD- is the probability of a positive or a negative test result when disease is absent, conditional sensitivity is the ratio of conventional sensitivity/YD+, and conditional specificity is the ratio of conventional specificity/YD-. Differences in conditional sensitivity and conditional specificity between the groups were compared using a z-test for independent proportions. Differences in age and scan time between groups were compared using a two-tailed Student's *t*-test and differences in patient sex were analyzed with a Fisher exact test. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

Results

To understand the role of intravenous contrast in the MRI evaluation of appendicitis in children, we analyzed all 112 scans acquired at our institution between May 2013 and January 2015. The average age for patients included in this study was 12.7 years with standard deviation of 3.9 years and 1:1.4 male-to-female ratio. Eighty-nine of the 112 scans (79%) were performed with intravenous contrast; 23/112 (21%) were performed without. These scans were retrospectively correlated with pathological diagnosis (available in 30/112 [27%] of cases) and nonsurgical clinical outcome. In our data set, the clinical outcome was defined either as: alternative diagnosis made on imaging grounds (14/112, 13%), hospital discharge with follow-up (19/112, 17%) or hospital discharge of a clinically diagnosed well child without follow-up (49/112, 43%). All cases of MRI-diagnosed appendicitis were treated surgically; 27/112 (24%) of all cases resulted in pathologically confirmed acute appendicitis.

To investigate the utility of postcontrast imaging in the diagnosis of acute appendicitis, all contrast-enhanced scans were reread under two experimental conditions: with contrast (using all available sequences; hereafter labeled *With*) or without contrast (using all available pre-contrast sequences; hereafter labeled *Without*). We noted that without the use of contrast, more

Table 2 Conventional and conditional sensitivity and specificity calculation (adapted from Simel et al. 1987 [24])

	Contingency table		Conventional calculation		Six square calculation (Conditional)	
	Positive	Negative	Sensitivity	A/(A+C)	Positive yield	(A+C)/(A+E+C)
Positive	A	B	Specificity	D/(B+D)	Negative yield	(B+D)/(B+F+D)
Equivocal	E	F	PPV	A/(A+B)	Sensitivity'	Conventional sensitivity/Positive yield
Negative	C	D	NPV	D/(C+D)	Specificity'	Conventional specificity/Negative yield

Contingency table depicts imaging diagnosis in rows and pathological/clinical diagnosis in columns

NPV negative predictive value, *PPV* positive predictive value, *Sensitivity'* conditional sensitivity, *Specificity'* conditional specificity scans yielded equivocal results (Table 3, Fig. 1): 11/89 (12.4%) in the *Without* group compared to 3/89 (3.4%) in the *With* group (*P*=0.011). The conditional sensitivity of both groups was identical (100%, *P*=1.00), and the conditional specificity was not significantly different, measuring 96.4% *With* contrast and 90.2% *Without* contrast (*P*=0.178). The odds ratio for a *With* contrast scan yielding unequivocal, concordant results compared to a *Without* contrast scan was 2.9 (95% confidence interval [CI]: 1.1-8.8, *P*=0.045).

In clinical practice, the radiologist and clinician may be able to monitor and modify a scan in real time to increase diagnostic utility, for example, by adding contrast-enhanced sequences. Using this technique as a model, those scans originally read as *Without* contrast yielding nondiagnostic results in the previous experiment were further analyzed by the same radiologist with the addition of the contrast-enhanced sequences (hereafter labeled *Without/With*) as a third experimental condition (Table 3, Fig. 1). The number of nondiagnostic scans in the *Without/With* group, 1/89 (1.1%), was significantly lower compared to the *Without* group (11/89, 12.4%; *P*=0.004), but were not significantly different compared to the *With* contrast group (3/89, 3.4%; *P*=0.157). The conditional sensitivity of *Without/With* contrast was unchanged (100%); the conditional specificity was 93.7%, not significantly different relative to the *With* (*P*=0.451) or *Without* (*P*=0.621) contrast groups. The odds ratio for a Without/*With* contrast scan yielding unequivocal, concordant results compared to a *Without* contrast scan was 3.0 (95% CI: 1.1-9.0, *P*=0.040).

Of those cases where addition of contrast changed the diagnosis from equivocal to certain, 3/18 (16.7%) were ultimately positive for appendicitis and 15/18 (83.3%) were negative for appendicitis. No significant difference was noted in those benefitting from contrast with respect to age (mean benefitting 12.7 [95% CI: 11.2-14.2]; mean not benefitting 12.7, [95% CI: 11.8-13.7]; *P*=0.98), sex (7:13 M:F benefitting; 27:42 M:F not benefitting; *P*=0.80), or scan time (mean benefitting 62 min, [95% CI: 56–68]; mean not benefitting 64 min [95% CI: 60–68], *P*=0.66).

We note that in our three experimental conditions (*With*, *Without*, and *Without/With* contrast) the hypothetical percentages of patients who would have received intravenous contrast were 100% (89/89), 0% (0/89) and 20.2% (18/89), respectively. Therefore, *Without/With* selective use of intravenous contrast resulted in a 79.8% reduction in contrast use compared to the *With* contrast group.

Discussion

In this paper, we find that intravenous contrast is useful in the MRI diagnosis of appendicitis in children in selected cases. Although the number of equivocal scans was globally reduced when intravenous contrast was used compared to non-contrast exams, that same reduction could be obtained through the selective application of contrast to difficult cases. In our experience, only approximately one-fifth of cases required the use of postcontrast images without any commensurate decrease in diagnostic utility.

We believe these results may arbitrate the discrepancy in the literature between those groups that advocate for or against the utility of intravenous contrast [13, 21]. We find that the frequency of uncertain diagnosis is higher in non-contrast exams,

Table 3 Conventional and conditional sensitivity and specificity calculation under simulated conditions: *With* contrast, *Without* contrast, or *Without/With* contrast

	Contingency table		Conventional		Conditional	
With Contrast						
	Positive	Negative	Sensitivity	1	Positive yield	1
Positive	23	5	Specificity	0.921	Negative yield	0.955
Equivocal	0	3	PPV	0.821	Sensitivity'	1
Negative	0	58	NPV	1	Specificity'	0.964
Without Contrast						
	Positive	Negative	Sensitivity	0.870	Positive yield	0.870
Positive	20	12	Specificity	0.793	Negative yield	0.879
Equivocal	3	8	PPV	0.625	Sensitivity'	1
Negative	0	46	NPV	0.727	Specificity'	0.902
Without/With Contrast						
	Positive	Negative	Sensitivity	1	Positive yield	1
Positive	23	5	Specificity	0.923	Negative yield	0.985
Equivocal	0	1	PPV	0.821	Sensitivity'	1
Negative	0	60	NPV	1	Specificity'	0.937

Contingency table depicts imaging diagnosis in rows and pathological/clinical diagnosis in columns

NPV negative predictive value, *PPV* positive predictive value, *Sensitivity'* conditional sensitivity, *Specificity'* conditional specificity

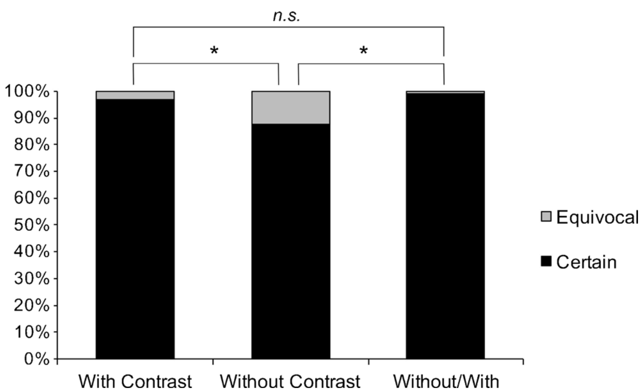

Fig. 1 Comparative diagnostic certainty of non-contrast and contrast-enhanced MRI. Percentage of MRI examinations yielding equivocal (*gray*) or certain (*black*) diagnosis under simulated conditions: *With* contrast, *Without* contrast, or *Without/With* contrast (*n.s.* not significant; * $P < 0.05$)

arguing for the use of contrast. However, two recent meta-analyses reported good sensitivity and specificity in the diagnosis of acute appendicitis without contrast [25, 26]. In our experience, only certain cases required the use of intravenous contrast for improving diagnostic performance. Our experience may be different due to factors particular to our institution, such as patients presenting early with mild disease or radiologist familiarity with contrast-enhanced scans thus influencing confidence in interpreting exams without contrast. The relative number of these types of cases at a given institution or for a given radiologist may affect the preference to use or avoid the use of intravenous contrast in diagnosing acute appendicitis.

From this study, we propose a new dynamic scanning algorithm for the MR investigation of pediatric appendicitis. We propose initiating the scan as a non-contrast study with a radiologist actively monitoring the images as acquired to determine if the non-contrast images are diagnostic. If so, the scan can be stopped, findings reported and the patient spared a contrast injection. If the non-contrast images are nondiagnostic, then the radiologist can proceed with contrast administration and postcontrast imaging.

The resultant clinical change for institutions that routinely use contrast might be to reduce the number of patients receiving contrast, which can save time, resources and patient discomfort. For institutions that routinely use non-contrast imaging, the number of nondiagnostic scans can possibly be reduced by the selective addition of contrast in select cases.

Several limitations should be considered when interpreting these results. First, we note that ordering clinicians at our institution have the latitude to choose either CT or MRI for second-line imaging, which introduces the possibility of selection bias in our patient population. This effect is likely minimized as the use of MRI has been standard in our emergency department for several years and includes the time period when most of the studies were acquired. Secondly, we recognize as a limitation of the study the fact that MRI was only employed in cases of equivocal US results, which may increase the number of equivocal cases seen on subsequent MRI. Thirdly, we acknowledge the possibility of reader order bias, which we attempted to minimize by randomizing, blinding and incorporating a washout interval to minimize recall.

Finally, we note the logistical challenges of our proposed scanning algorithm, which may be impractical for financial or operational reasons in busy practice settings. However, the increased logistical complexity may be offset by efficiency increases in fewer postcontrast sequences to acquire and interpret, decreased risk of contrast-related complications such as fluid extravasation, and potentially shorter length of stay as patients without diagnostic imaging may be held for observation.

Intravenous contrast can improve diagnostic certainty in some cases. MRI diagnosis of acute appendicitis can be performed without contrast for most patients with contrast injection reserved only for those cases with nondiagnostic non-contrast imaging. Selective administration of contrast may yield similar diagnostic quality to the routine use of contrast with a substantial reduction in the number of patients receiving contrast injection. For second-line evaluation of suspected appendicitis in children, we propose a new scanning algorithm where contrast is used in select cases. With this approach, fewer children will receive intravenous contrast without deterioration in overall diagnostic quality.

Conclusion

Most children with suspected acute appendicitis can be accurately diagnosed with non-contrast MR imaging, but intravenous contrast may improve diagnostic certainty in some cases.

Compliance with ethical standards

Conflicts of interest None

References

1. Addiss DG, Shaffer N, Fowler BS et al (1990) The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 132:910–925
2. Brown JJ (1991) Acute appendicitis: the radiologist's role. Radiology 180:13–14
3. Rosen MP, Ding A, Blake MA et al (2011) ACR Appropriateness Criteria(R) right lower quadrant pain–suspected appendicitis. J Am Coll Radiol 8:749–755
4. Bachur RG, Hennelly K, Callahan MJ et al (2012) Diagnostic imaging and negative appendectomy rates in children: effects of age and gender. Pediatrics 129:877–884
5. Brenner D, Elliston C, Hall E et al (2001) Estimated risks of radiation-induced fatal cancer from pediatric CT. AJR Am J Roentgenol 176:289–296

6. Miglioretti DL, Johnson E, Williams A et al (2013) The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr 167:700–707
7. Aspelund G, Fingeret A, Gross E et al (2014) Ultrasonography/MRI versus CT for diagnosing appendicitis. Pediatrics 133:586–593
8. Leeuwenburgh MM, Wiarda BM, Wiezer MJ et al (2013) Comparison of imaging strategies with conditional contrast-enhanced CT and unenhanced MR imaging in patients suspected of having appendicitis: a multicenter diagnostic performance study. Radiology 268:135–143
9. Johnson AK, Filippi CG, Andrews T et al (2012) Ultrafast 3-T MRI in the evaluation of children with acute lower abdominal pain for the detection of appendicitis. AJR Am J Roentgenol 198:1424–1430
10. Koning JL, Naheedy JH, Kruk PG (2014) Diagnostic performance of contrast-enhanced MR for acute appendicitis and alternative causes of abdominal pain in children. Pediatr Radiol 44:948–955
11. Kulaylat AN, Moore MM, Engbrecht BW et al (2015) An implemented MRI program to eliminate radiation from the evaluation of pediatric appendicitis. J Pediatr Surg 50:1359–1363
12. Moore MM, Gustas CN, Choudhary AK et al (2012) MRI for clinically suspected pediatric appendicitis: an implemented program. Pediatr Radiol 42:1056–1063
13. Rosines LA, Chow DS, Lampl BS et al (2014) Value of gadolinium-enhanced MRI in detection of acute appendicitis in children and adolescents. AJR Am J Roentgenol 203:W543–548
14. Thieme ME, Leeuwenburgh MM, Valdehueza ZD et al (2014) Diagnostic accuracy and patient acceptance of MRI in children with suspected appendicitis. Eur Radiol 24:630–637
15. Orth RC, Guillerman RP, Zhang W et al (2014) Prospective comparison of MR imaging and US for the diagnosis of pediatric appendicitis. Radiology 272:233–240
16. Herliczek TW, Swenson DW, Mayo-Smith WW (2013) Utility of MRI after inconclusive ultrasound in pediatric patients with suspected appendicitis: retrospective review of 60 consecutive patients. AJR Am J Roentgenol 200:969–973
17. Bayraktutan U, Oral A, Kantarci M et al (2014) Diagnostic performance of diffusion-weighted MR imaging in detecting acute appendicitis in children: comparison with conventional MRI and surgical findings. J Magn Reson Imaging 39:1518–1524
18. Cobben L, Groot I, Kingma L et al (2009) A simple MRI protocol in patients with clinically suspected appendicitis: results in 138 patients and effect on outcome of appendectomy. Eur Radiol 19: 1175–1183
19. Hormann M, Paya K, Eibenberger K et al (1998) MR imaging in children with nonperforated acute appendicitis: value of unenhanced MR imaging in sonographically selected cases. AJR Am J Roentgenol 171:467–470
20. Dillman JR, Gadepalli S, Sroufe NS et al (2015) Equivocal pediatric appendicitis: Unenhanced MR imaging protocol for nonsedated children-a clinical effectiveness study. Radiology 279:216–225
21. Petkovska I, Martin DR, Covington MF et al (2016) Accuracy of unenhanced MR imaging in the detection of acute appendicitis: single-institution clinical performance review. Radiology 279: 451–460
22. Athans BS, Depinet HE, Towbin AJ et al (2016) Use of clinical data to predict appendicitis in patients with equivocal US findings. Radiology 280:557–567
23. Kearl YL, Claudius I, Behar S et al (2016) Accuracy of magnetic resonance imaging and ultrasound for appendicitis in Ddagnostic and nondiagnostic studies. Acad Emerg Med 23:179–185
24. Simel DL, Feussner JR, DeLong ER et al (1987) Intermediate, indeterminate, and uninterpretable diagnostic test results. Med Decis Mak 7:107–114
25. Duke E, Kalb B, Arif-Tiwari H et al (2016) A systematic review and meta-analysis of diagnostic performance of MRI for evaluation of acute appendicitis. AJR Am J Roentgenol 206:508–517
26. Moore MM, Kulaylat AN, Hollenbeak CS et al (2016) Magnetic resonance imaging in pediatric appendicitis: a systematic review. Pediatr Radiol 46:928–939