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Original Research

Bedside ultrasonography for acute appendicitis: An updated diagnostic meta-analysis

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ABSTRACT

Background: Bedside ultrasonography is a promising tool for identification of acute appendicitis. We assessed the accuracy and clinical value of bedside ultrasonography for diagnosis of acute appendicitis in the emergency department.

Methods: Pubmed, Embase and Cochrane Library were searched from inception to November 2018. The diagnostic accuracy of bedside ultrasonography was compared with that of surgery and/or CT scan, which was used as reference standard. Pooled summary estimates of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) from each included study were estimated using bivariate logistic regression model. Inter-study heterogeneity was examined using I^2 statistic. Meta-regression was performed to further investigate the source of heterogeneity. Deeks's funnel plot was used to test publication bias.

Results: Our search yielded 5394 citations, of which 27 satisfied the inclusion criteria. Bivariate analysis yielded a mean sensitivity of 90% (95% CI 82%–0.95%) and specificity of 95% (95% CI 89%–98%). The area under the receiver operating characteristic curve was 0.97 (95% CI 0.95–0.98). There was significant inter-study heterogeneity (I^2 = 96%, 95% CI 94%–99%). Meta-regression analysis suggested that study region and patient sample size could attribute to the heterogeneity. Deeks's funnel plot did not indicate the existence of publication bias (P = 0.15).

Conclusion: Bedside ultrasonography, a radiation-free and noninvasive modality, provides superior diagnostic performance in the diagnosis of acute appendicitis, but its value in different abdominal emergencies warrants further development and research.

1. Introduction

Acute appendicitis is known as one of the most common abdominal emergencies in the world. In general, the estimates for lifetime acute appendicitis prevalence range from 1.8% to 16% throughout the world [1]. It also accounts for the most common abdominal surgical emergency in the pediatric population, which occurs in nearly 1%–8% of children with acute abdominal pain [2]. The diagnosis of this emergency can be challenging due to atypical symptoms, variable clinical presentation and shared clinical features with other disease status [3].

Recently, modern diagnostic imaging techniques, such as CT scan and ultrasonography are regarded as pivotal diagnostic approaches in acute appendicitis which are shown to improve diagnostic accuracy and patient prognosis [4–7]. Since the application of those imaging

Abbreviations: CIs, Confidence intervals; DOR, Diagnostic odds ratio; EP, Emergency physicians; FN, False negative; FP, False positive; Mesh, Medical Subject Heading; QUADAS-2, Quality Assessment of Diagnostic Accuracy-2 Studies; SROC, Summary receiver operating characteristic; TN, True negative; TP, True positive

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modalities, the rate of negative appendectomy and other complications such as appendiceal perforation has considerably decreased. The surgical removal of the appendix or tonsils at an earlier age has been proposed as a risk factor leading to increased risk of comorbidities like acute myocardial infarction [8]. CT scan has been considered as a preferred imaging technique with higher sensitivity (72%–97%) and specificity (92%–98%) in the diagnosis of acute appendicitis than ultrasonography [9]. However, due to ionizing radiation exposure and higher cost, CT scans are not recommended for young adults, pediatric or pregnant patients [10–13]. Moreover, as a noninvasive and reproducible diagnostic modality, ultrasonography does not require any contrast agent but still with relatively high sensitivity (76%–90%) and specificity (86%–95%) in the diagnosis of acute appendicitis [9,14].

Bedside ultrasonography, known as a convenient tool of patient condition with real-time ultrasound images, can help emergency physicians (EPs) make a rapid decision on diagnosis or treatment in emergency situations [15–18], especially acute abdomen like acute appendicitis and acute cholecystitis. Bedside ultrasonography has now been applied as one of the frequently used diagnostic approaches in various medical areas such as abdominal trauma and pain, eye trauma, obstetrics and orthopedic emergencies [19–23]. To date, several studies have documented the diagnostic accuracy of bedside ultrasonography [24–32]. However, the results are not conclusive. Therefore, in this study we aimed to update the evidence and assess the accuracy and clinical value of bedside ultrasonography for diagnosis of acute appendicitis in the emergency department.

2. Materials and methods

This study was conducted and reported based on PRISMA-DTA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines.

2.1. Search strategy and selection criteria

We systematically searched three major databases including Pubmed, Embase and the Cochrane Library for studies that assessed the performance of bedside ultrasonography for the diagnosis of acute appendicitis.

The searched Medical Subject Heading (Mesh) terms for Pubmed, EMTREE terms for Embase and text words for others included the following: (Appendicitis OR Appendectomy) AND (Ultrasonography OR echography OR “echotomograph*” OR sonograph*) AND (“Sensitivity and Specificity” OR “Predictive Value of Tests” OR “negative predictive value” OR “positive predictive value” OR diagnosis OR “false positive” OR “false positive”). Detailed search strategies were presented in **Supplementary Materials**. We searched the databases from inception through November 2018. Additional searches were likewise performed by reading the reference list of each primary study and systematic review.

Studies were judged to be eligible for inclusion if they satisfied all of the following criteria: (1) involved adult or pediatric patients who underwent bedside ultrasonography for known or suspected acute appendicitis, (2) included reference standards based on surgery or CT scan results, and (3) results that could obtain from original studies with detailed data to construct 2 × 2 contingency tables for determination of the diagnostic performance of bedside ultrasonography to detect acute appendicitis. Two authors independently screened and selected the citations. Any disagreements were resolved by discussion until consensus was reached.

2.2. Exclusion criteria

Studies were excluded if they satisfied any of following criteria: (1) case reports or case series with low methodological quality; (2) letters, editorials, comments, abstracts, meta-analyses, reviews or guidelines without original data for analysis; (3) studies regarding topics other than the application of bedside ultrasonography to diagnose acute appendicitis; (4) studies having the same or overlapping individuals; and (5) studies with other modalities as reference standards.

2.3. Data extraction and quality assessment

Two authors independently abstracted data from each study using a predesigned standardized data sheet including first author, year of publication, country, study design, patient age, male percentage, sonographer experience, reference standards, sample size, results of true-positive (TP), false-positive (FP) false-negative (FN) and true-negative (TN), disease prevalence, initial sonographer performer, follow-up period and enrollment criteria.

The methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2), a validated commonly used tool for the quality assessment of diagnostic accuracy studies [33]. Four domains including patient selection, index test, reference standard, as well as flow and timing were evaluated. Quality assessment was performed independently by two authors.

2.4. Statistical analysis

The primary outcome measures were sensitivity and specificity. We defined bedside ultrasonography sensitivity as the proportion of patients with a positive surgery or CT scan result that was also positive for bedside ultrasonography. We defined bedside ultrasonography specificity as the proportion of patients with a negative surgery or CT scan result that was also negative for bedside ultrasonography. The bivariate logistic regression model was used for the meta-analysis of diagnostic test accuracy and forest plots were created [34]. We preferred a bivariate random-effects model as heterogeneity was expected in meta-analysis of diagnostic accuracy studies [35–39]. I^2 statistic was used to assess the inter-study heterogeneity, with an I^2 value ranging from 0% to 25%, 25%–50%, and 50%–75% considering as low, moderate and high heterogeneity, respectively [40]. Data for the number of TP, FP, TN, and FN findings were used to calculate a pooled sensitivity and specificity along with 95% confidence intervals (CIs) for bedside ultrasonography. Meta-regression analysis was further performed to examine the effects of the following confounding factors on pooled sensitivity and specificity including study region (USA vs. Europe vs. Asia), study design (prospective vs. retrospective), study hospital (single hospital vs. multiple hospitals), patient age (less than 18 years vs. more than 18 years), gender (male vs. female), sample size (more than 200 vs. less than 200) and initial ultrasound performer (resident EPs vs. attending EPs). Hierarchical summary receiver operating characteristic meta-analysis methods were used to generate summary receiver operating characteristic curves along with corresponding 95% confidence regions and prediction regions. To assess for the possibility of publication bias, funnel plots were constructed and Deeks' funnel plot asymmetry test was performed, with a P value less than 0.1 indicating existence of publication bias [41]. We also drew a Fagan's nomogram, in which the left axis indicated the pre-test probability, middle axis represented the likelihood ratio and right axis signified the post-test probability [42]. All analyses were conducted using STATA statistical software (version 15.0, Stata Corp LP, College Station, TX, USA).

3. Results

3.1. Literature search

Our database search yielded 5394 citations. After removing all duplicates, reviewing the titles and abstracts, we excluded 5340 irrelevant citations. We excluded another 27 articles after full-text viewing,

Table 1
Baseline features of included studies.

Author	Year	Country	Design	Mean/median age, years	Male %	Sonographer Experience	Reference Standards	Sample size	TP	FN	TN	FP	Prevalence (%)
Doniger	2018	USA	Prospectively	10.7	20.8	EP, a 30-min appendicitis ultrasound tutorial	Surgery, CT	40	15	1	21	3	40
Karimi	2017	Iran	Prospectively	23.91	61.1	NR	Surgery, CT	108	27	10	59	12	34.26
Gungor	2017	Turkey	Prospectively	30	57.2	EP, 1-h theoretical lecture	Surgery, CT	264	156	13	91	4	64
Ünlüer	2016	Turkey	Prospectively	33.58	43	EP, one-day introductory course and 6-h appendicitis assessment as a core course given by an experienced radiologist	Surgery, CT	100	34	12	36	18	45
Topin	2016	Djibouti	Prospectively	33.2	54	EP, with 2-year postgraduate US diploma	Surgery, CT	100	22	3	72	3	24
Fathi	2015	Iran	Prospectively	34.4	57.7	EP, resident/attending with 4-h course	Surgery	97	19	24	46	8	44.3
Hasani	2015	Iran	Prospectively	47.44	56	EP, 1 year of other US experience and 2-day abdominal US course	Surgery, CT	150	9	18	123	0	17.9
Kim	2015	Korea	Retrospectively	10.6	56.6	EP, one with 4-year experience and one with > 7 years	Surgery, CT	166	40	0	126	0	24.3
Mallin	2015	USA	Prospectively	28	NR	EP, all with 30-min didactic	Surgery, CT	97	23	11	62	1	35.1
Elikashvili	2014	USA	Prospectively	12	44	EP, with 1-h course	Surgery	150	30	20	95	5	33.3
Lam	2014	USA	Prospectively	20.2	51	EP, minimum 1-h didactic on appendicitis US	Surgery	52	33	0	6	13	63.8
Sivitz	2014	USA	Prospectively	10.2	53	EP, one attending with 4 year, 12 fellows with 45-min didactic and five supervised scans	Surgery	264	72	13	166	13	32.2
Lin	2013	China	Retrospectively	6	61.7	Pediatric EP, unclear	Surgery, CT	287	108	4	165	10	0.39
Burford	2011	USA	Retrospectively	8.8	52	Surgeons, resident with 3-day abdominal US course	Surgery	54	27	2	21	4	53.7
Lin	2009	China	Retrospectively	11	46	Pediatric GI, unclear	Surgery, CT	64	35	2	12	15	57.8
Fox	2008	USA	Prospectively	NR	50.8	EP, resident/attending with 57–607 US scans	Surgery, CT	126	37	20	62	7	45.2
Siu	2007	Hong Kong	Prospectively	31.6	NR	EP, unclear	Surgery	85	18	11	47	9	34.1
Summa	2007	Italy	Retrospectively	35	47	Surgeons, “specific expertise”	Surgery	1455	361	8	1079	7	25.4
Fox	2007	USA	Retrospectively	NR	54.8	EP, 3 were RDMS; 7 had > 300 ultrasound examinations of all types	Surgery, CT	155	27	42	77	9	45
Kaneko	2004	Japan	Prospectively	10.6	47.9	Surgeons, “experienced”	Surgery	126	54	2	70	0	44.3
Tarantino	2003	Italy	Prospectively	31	56.7	ID/hepatology, unclear	Surgery, CT	180	11	0	169	0	6.4
Zielke	2001	Germany	Prospectively	24.8	42.7	Surgeons, minimum 3-mo rotation on surgical US	Surgery	2209	403	137	1616	53	24.4
Chen	2000	China	Prospectively	37.1	55.8	EP, with > 12 months experience	Surgery	147	106	4	25	12	74.8
Fujii	2000	Japan	Retrospectively	NR	51	GI, two with < 5-year experience and four with > 5 years	Surgery	200	54	3	143	0	28.4
Allemann	1999	Switzerland	Prospectively	45	47.2	Surgeons	Surgery	496	89	6	399	2	19.2
Chen	1998	China	Prospectively	39.4	59.7	Surgeons, with > 200 appendicitis scans	Surgery	191	143	1	32	15	75.4
Rossi	1996	Italy	Prospectively	19	67.5	Unclear	Surgery	40	19	0	19	2	48

Author	Year	Initial US performer	Follow-up period	Enrollment Criteria
Doniger	2018	Attending EP	2 weeks to 12 months	Convenience sampling of patients aged 2–18 years presenting with abdominal pain to a pediatric emergency department.
Karimi	2017	Attending EP	48-h	Convenience sample of patients of any age with suspected acute appendicitis
Gungor	2017	Resident/attending EP	NR	Patients over the age of 18 years who presented to the ED with abdominal pain and underwent diagnostic evaluation for AA
Ünlüer	2016	Attending EP	1 month	Adult patients with acute abdominal pain referred to the ED
Topin	2016	Attending EP	3 months	Consecutive patients referred to the ED
Fathi	2015	Resident/attending EP	NR	Convenience sample of patients of any age with suspected appendicitis (80.8%)
Hasani	2015	Attending EP	2 weeks	All patients requiring workup for acute nontraumatic abdominal pain (71.1%)
Kim	2015	Resident with supervision	6 months	Chart review of pediatric patients with suspected appendicitis
Mallin	2015	Resident with supervision	5 months	All cases of suspected appendicitis which had US performed
Elikashvili	2014	Trained pediatric EPs	3-week phone follow-up	A convenience sample of patients presenting with suspected appendicitis requiring laboratory or radiographic evaluation
Lam	2014	Trained EPs	1 month	Patients 4 y of age and older with suspected appendicitis
Sivitz	2014	Resident/attending EP	6 months	Children requiring surgical or radiologic consultation for suspected acute appendicitis (90.9%)
Lin	2013	EP who was board certified in pediatric gastroenterology.	NR	Chart review of children < 18 years old who presented with acute abdominal pain and had US performed
Burford	2011	Resident EPs	NR	All patients evaluated for possible appendicitis (98.2%)
Lin	2009	Resident/attending EP	1 week	Chart review of children < 18 years old who presented with RLQ pain
Fox	2008	Resident/attending EP	3 months	Convenience sample of patients of any age with suspected acute appendicitis
Siu	2007	Attending EPs	NR	Convenience sample of patients with RLQ pain and at least one other sign/symptom of appendicitis
Summa	2007	NR	Until the symptoms disappeared	Patients with suspected appendicitis who underwent US
Fox	2007	Resident/attending EP	2 weeks	Consecutive patients of all ages and genders who had right lower quadrant scans
Kaneko	2004	NR	36 months	All children with acute abdominal pain and tenderness suspected of having appendicitis (100%)
Tarantino	2003	Physician specialist	6 months	Consecutive patients admitted for suspected infectious enteritis or typhoid fever

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Initial US performer	Follow-up period	Enrollment Criteria
Zielke	2001	Sonographically trained surgeons	NR	Consecutive and unselected sample of all patients admitted for suspected acute appendicitis
Chen	2000	Staff members or senior EPs	2 weeks	All patients with right lower abdominal pain
Fujii	2000	Attending EP	7.6 days	Consecutive patients with suspected acute appendicitis
Allemann	1999	Resident EP	12 months	Consecutive adult patients with acute abdominal pain
Chen	1998	Resident EP	1 month	Patients admitted with clinically diagnosed or suspected appendicitis
Rossi	1996	Attending EP	3 month	Review of US performed on patients admitted with a diagnosis of acute appendicitis

Abbreviations: AA = acute appendicitis; ED = emergency department; EP = emergency physician; FN = false-negatives; FP = false-positives; GI = gastroenterology; ID = infectious disease; NR = not reported; POCUS = point-of-care ultrasonography; RLQ = right lower quadrant; TN = true-negatives; TP = true-positives; US = ultrasonography.

leaving 27 studies for inclusion [16,24–30,43–61]. The literature selection process is presented in Supplementary Fig. 1. We did not find any additional articles through search of the reference lists of identified articles and previous systematic reviews [31,32].

Table 1 shows the detailed patient characteristics of each included study. In summary, 27 studies published between 1996 and 2018 with 7403 suspected acute appendicitis patients were involved in the analysis, of which 8 from USA (30%), 7 from Europe (26%), 11 from Asia (41%) and one from Africa (3%). Twenty of the included studies were prospective in study design, and the remaining 7 studies were retrospective ones. The population size for the included studies ranged from 40 to 2209 and the patient mean or median age ranged from 6 to 47.4 years. Fourteen studies used surgical findings as the reference standard for acute appendicitis and 13 studies used both surgical and CT scan findings as the reference standard. Initial ultrasound performers were attending EPs or physician specialists in 24 studies and resident EPs in three studies.

3.2. Quality assessment

Two authors independently assessed the quality of each study according to the QUADAS-2 items. The quality assessment of the included studies was summarized in Supplementary Fig. 2. The majority of the included studies were at low risk for two categories with respect to applicability, including the reference standard and index test. The patient selection scored an average rating of 18.5% for low risk, 66.7% for unclear and 14.8% for high risk. The index test scored an average rating of 51.9% for low risk, 48.1% for high risk. The reference standard scored an average rating of 29.6% for low risk and 70.4% for high risk. Overall, 18 of the 27 eligible studies were rated with an average acceptable applicability in terms of index test and reference standard, while the others were unclear or poor quality (high risk). However, 5 of the 27 eligible studies were rated with an average acceptable applicability in terms of patient selection.

3.3. Diagnostic performance of bedside ultrasonography for diagnosis of acute appendicitis

The primary analysis revealed that the pooled sensitivity and specificity of all included studies were 90% (95% CI, 82%–95%) and 95% (95% CI, 89%–98%), respectively (Fig. 1). The Q test revealed significant inter-study heterogeneity ($P < 0.001$). I^2 statistic demonstrated substantial heterogeneity in terms of both sensitivity ($I^2 = 94.8\%$) and specificity ($I^2 = 96.8\%$). The forest plot for sensitivity and specificity indicated the lack of a threshold effect, with the Spearman correlation coefficient between the sensitivity and false-positive rate being 0.003, which further indicating the lack of a threshold effect. The pooled positive likelihood ratio (PLR) was 17.7 (95% CI, 8.3–37.7) and the pooled negative likelihood ratio (NLR) was 0.11 (95% CI, 0.06–0.19). The area under the receiver operating characteristic (ROC) curve was 0.97 (95% CI, 0.95–0.98) (Fig. 2) and the diagnostic odd ratio (DOR) was 167 (95% CI, 58–475), indicating a high diagnostic accuracy. We also used a Fagan nomogram to illustrate the relations between pre-test and post-test probabilities and likelihood ratio (Fig. 3).

3.4. Subgroup analysis

Subgroup analyses were conducted to assess various clinical settings, the results of which were summarized in Table 2. We pooled results from 8 studies conducted in the USA, with the pooled characteristic estimates for diagnosing acute appendicitis of 83% (95% CI, 59%–95%) for sensitivity and 89% (95% CI, 77%–95%) for specificity; seven studies conducted in Europe, with pooled characteristic estimates of 93% (95% CI, 83%–97%) for sensitivity and 98% (95% CI, 92%–99%) for specificity; and 11 studies conducted in Asia, with

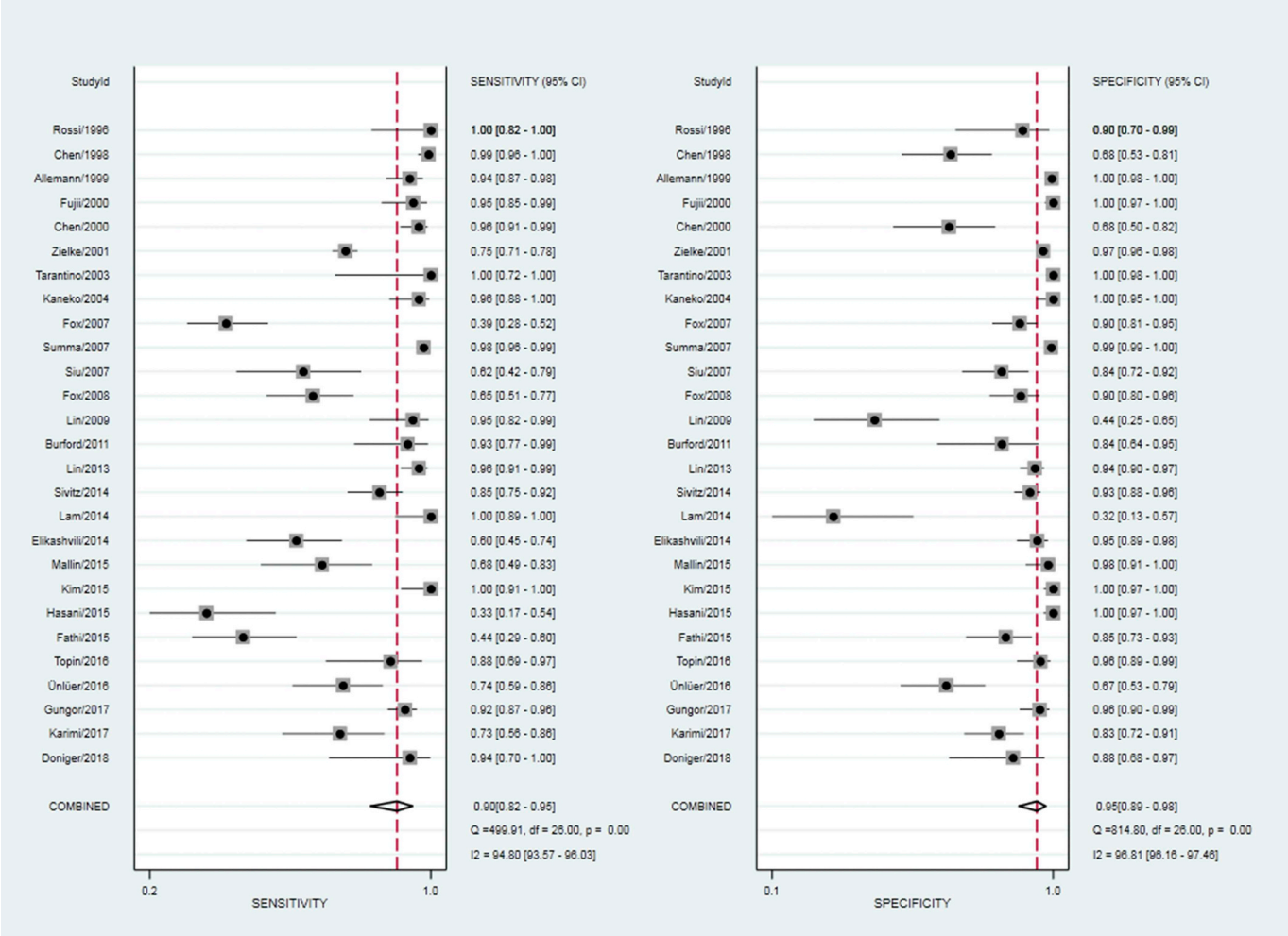

Fig. 1. Sensitivity and specificity of bedside ultrasonography for diagnosis of acute appendicitis.

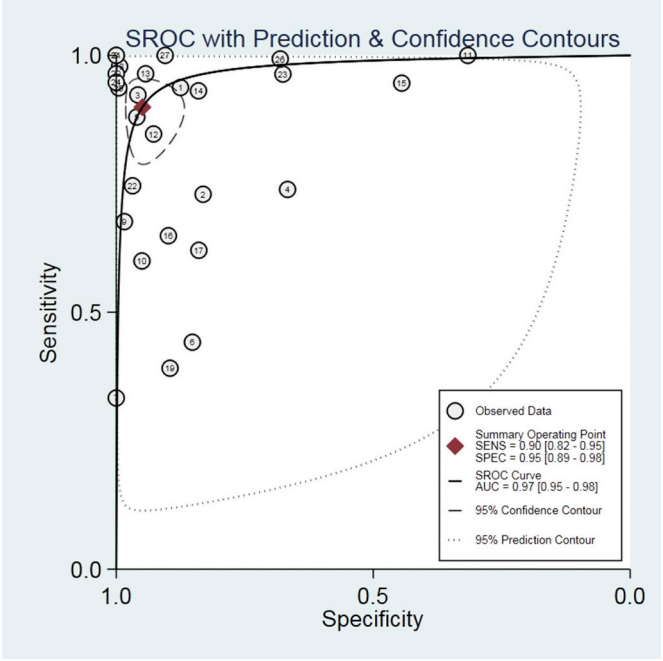

Fig. 2. Summary receiver operating characteristic curve with 95% confidence contour and 95% prediction contour.

pooled characteristic estimates of 92% (95% CI, 77%–97%) for sensitivity and 96% (95% CI, 80%–99%) for specificity.

We also conducted a subgroup analysis including data from prospective and retrospective studies, respectively. We pooled results from 20 prospective studies with the pooled characteristic estimates for diagnosing acute appendicitis of 87% (95% CI, 79%–95%) for sensitivity and 94% (95% CI, 89%–99%) for specificity; and 7 retrospective studies with pooled characteristic estimates of 95% (95% CI, 88%–100%) for sensitivity and 97% (95% CI, 92%–100%) for specificity.

Moreover, a subgroup analysis was also conducted including data from single-center studies and multiple-center studies, respectively. We pooled results from 25 single-center studies with the pooled characteristic estimates for diagnosing acute appendicitis of 91% (95% CI, 86%–96%) for sensitivity and 95% (95% CI, 92%–99%) for specificity; and 2 multiple-center studies with pooled characteristic estimates of 60% (95% CI, 9%–100%) for sensitivity and 85% (95% CI, 50%–100%) for specificity.

Additionally, we calculated the pooled estimates including data from pediatric patients and adult patients, respectively. We pooled results from 9 studies including only pediatric patients with the pooled characteristic estimates for diagnosing acute appendicitis of 95% (95% CI, 90%–100%) for sensitivity and 95% (95% CI, 88%–100%) for specificity; and 18 studies including only adult patients with the pooled characteristic estimates of 86% (95% CI, 77%–95%) for sensitivity and 95% (95% CI, 91%–100%) for specificity.

Also, we explored the robustness of our results in a subgroup analysis according to male patient percent. We pooled results from 9

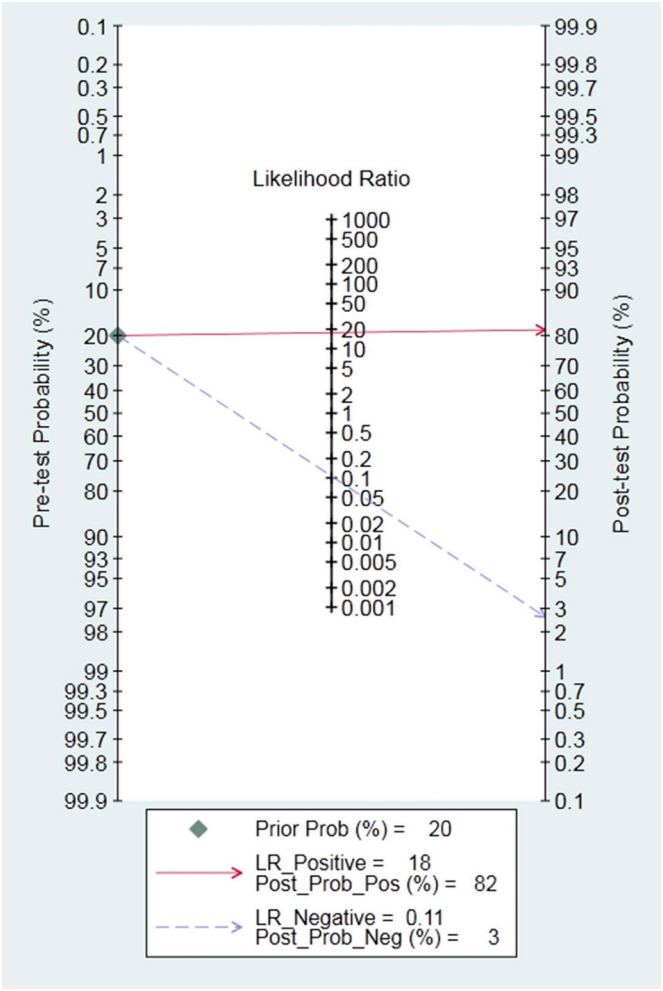

Fig. 3. Fagan's nomogram for bedside ultrasonography illustrating post-test probability with a fixed pre-test probability of 20% for acute appendicitis.

studies of male patient percent < 50% with the pooled characteristic estimates for diagnosing acute appendicitis of 89% (95% CI, 78%–100%) for sensitivity and 95% (95% CI,89%–100%) for specificity; and 18 studies of male patient percent ≥ 50% with the pooled characteristic estimates of 91% (95% CI, 83%–98%) for sensitivity and 95% (95% CI, 90%–100%) for specificity.

Furthermore, we calculated the pooled estimates in a subgroup analysis based on study sample size. We pooled results from 20 studies of sample size < 200 with the pooled characteristic estimates for diagnosing acute appendicitis of 88% (95% CI, 80%–96%) for sensitivity and 92% (95% CI,86%–98%) for specificity; and 7 studies of male patient percent ≥ 200 with the pooled characteristic estimates of 93% (95% CI, 86%–100%) for sensitivity and 98% (95% CI, 96%–100%) for specificity.

Finally, we also conducted a subgroup analysis according to initial ultrasound performer. When pooling results from 24 studies in which the initial ultrasound performers were attending EPs, we found the pooled characteristic estimates for diagnosing acute appendicitis were 88% (95% CI, 81%–95%) for sensitivity and 95% (95% CI, 91%–99%) for specificity; and 3 studies in which the initial ultrasound performers were resident EPs, we found the pooled characteristic estimates were 97% (95% CI, 92%–100%) for sensitivity and 93% (95% CI, 79%–100%) for specificity.

3.5. Meta-regression

Supplementary Fig. 3 shows meta-regression results. Among the investigated potential covariates, study design, the number of hospital, patient type, male patient percent, and initial ultrasound performer failed to show any statistically significant effects on sensitivity or specificity (P > 0.05). For study region among the USA, Europe and Asia, an effect was noted on sensitivity (P = 0.04); for the patient sample size, an effect was also noted on specificity (P = 0.01).

Deeks' funnel plot asymmetry test indicated no potential publication bias (P = 0.15) (Fig. 4).

4. Discussion

This meta-analysis confirms that the diagnostic performance of bedside ultrasonography in determination of acute appendicitis was clinically acceptable, yielding a combined sensitivity of 90% (95% CI, 82%–95%), summary specificity of 95% (95% CI, 82%–98%), and area under the SROC curve of 0.97 (95% CI, 0.95–0.98). The DOR was 167 (95% CI, 58 to 475), indicating a high diagnostic accuracy. There was significant heterogeneity across the studies. Study region and patient sample size were statistically significant and clinically meaningful causes of heterogeneity in meta-regression analysis for sensitivity or specificity, respectively. In terms of these findings, bedside ultrasonography, a noninvasive radiation-free modality, demonstrates high diagnostic performance in the diagnosis of acute appendicitis in both pediatric patients and adult ones.

The noninvasiveness and high accuracy are two significant requirements for imaging studies in the diagnosis and monitoring of

Table 2
Results of meta-regression of bedside ultrasonography for diagnosis of acute appendicitis.

Covariates	Subgroup	n	Sensitivity, % (95% CI)	P value	Specificity, % (95% CI)	P value
Study region	USA	8	83 [59–95]	0.04	89 [77–95]	0.08
	Europe	7	93 [83–97]		98 [92–99]	
	Asia	11	92 [77–97]		96 [80–99]	
Study design	Prospective	20	87 [79–95]	0.05	94 [89–99]	0.34
	Retrospective	7	95 [88 – 100]	.	97 [92 – 100]	.
No. of hospital	Single	25	91 [86–96]	0.05	95 [92–99]	0.07
	Multiple	2	60 [9–100]	.	85 [50 – 100]	.
Patient type	Children	9	95 [90 – 100]	0.75	95 [88 – 100]	0.54
	Adults	18	86 [77–95]	.	95 [91 – 100]	.
Male %	< 50%	9	89 [78 – 100]	0.24	95 [89 – 100]	0.59
	≥50%	18	91 [83–98]	.	95 [90 – 100]	.
Sample size	< 200	20	88 [80–96]	0.09	92 [86–98]	0.01
	≥200	7	93 [86 – 100]	.	98 [96 – 100]	.
Initial US performer	Attending EPs	24	88 [81–95]	0.14	95 [91–99]	0.39
	Resident EPs	3	97 [92 – 100]	.	93 [79 – 100]	.

Abbreviations: CI, confidence interval; EPs = emergency physicians; No. = number; US = ultrasound.

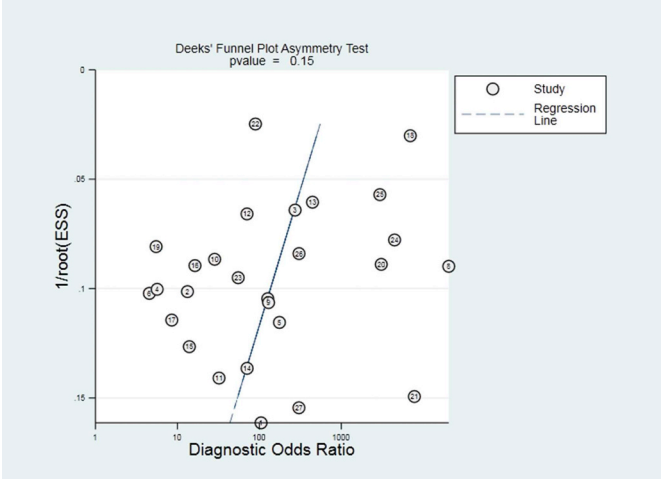

Fig. 4. Deeks' funnel plot asymmetry test for publication bias.

patients with lower abdominal pain suspected of acute appendicitis [62–64]. As the patients may experience several imaging studies during their lifetime, we consider radiation-free is more important. Therefore, bedside ultrasonography is undoubtedly such a noninvasive technique without radiation. Based on the findings of this study, we obtained solid evidence for the superior diagnostic performance of bedside ultrasonography. The summary sensitivity and specificity that we noted were 90% (95% CI, 82%–95%) and 95% (95% CI, 82%–98%), respectively. Previous studies regarding the diagnostic performance of bedside ultrasonography for acute appendicitis demonstrated a summary sensitivity of 84%–91% and a summary specificity of 91%–97%, which were consistent with those of our study [31,32]. Significant inter-study heterogeneity was noted in terms of sensitivity (I^2 = 94.8%) and specificity (I^2 = 96.8%). In the meta-regression analysis for exploring the sources of the heterogeneity, study region and patient sample size were clinical meaningful variables influencing study heterogeneity for our study. However, this meta-analysis is also limited by some other unmeasured causes of heterogeneity. Patient factors such as body habitus and clinician factors such as experience performing bedside ultrasonography could also affect the result. In our study, though we did not find significantly different effects between attending EPs and resident EPs, this factor should not be neglected due to the study of ultrasonography is usually operator-dependent. Quality control and risk of bias were conducted among included studies using the QUADAS-2 tool and meta-regression. Nevertheless, the results should also be interpreted with caution.

To the best of our knowledge, this is the largest and most comprehensive systematic review and meta-analysis evaluating the diagnostic accuracy of bedside ultrasonography in individuals suspected of acute appendicitis. The findings of our study were in line with the previous systematic reviews [65–68]. Furthermore, we strictly adhered to the PRISMA-DTA statement in order to improve the internal validity of our findings [69] and make the process of the systematic review more transparent and objective. Multiple major electronic databases were comprehensively searched without applying language or publication type restrictions. At least two authors conducted data extraction and quality assessment and cross checked the abstracted data. QUADAS-2 was used to assess study quality and a more conservative method, random-effect model was applied to synthesize existing data.

This study suggests that given bedside ultrasonography safety, simplicity, high efficiency, low cost, and non-invasiveness, it could be served as an acceptable alternative for fast screening of individuals suspected of acute appendicitis for both novices and experts. Although our results further ascertain the diagnostic accuracy of bedside ultrasonography in individuals suspected of acute appendicitis, 74% (20/27) of the included studies had less than 200 patients for analysis. The studies with a relatively small sample size were limited to further subgroup analyses. Thus future studies should be better to include a larger population with more homogeneous characteristics, though it could be prone to selection bias [70]. We also consider it important to establish similar ultrasonography parameters, levels of methodological quality, the reference standards, and the experience of ultrasound performers in future studies [71,72].

We should also acknowledge the limitations of the review itself. Though we applied exhaustive and meticulous search strategies for all the electronic databases, we still could not identify all the studies meeting the inclusion criteria in that we did not include unpublished grey literature, abstract meeting conferences or ongoing trials, which might resulted in publication bias. Moreover, the result of study quality assessment showed that some of these studies were at high or unclear risk of bias in several different domains such as patient selection, index test and reference standard along with their application. In addition, most studies (20/27) had a small sample size (< 200), limiting the precision of pooled effect estimates. Moreover, heterogeneity could not be thoroughly explained, because the majority of studies did not address sufficient information for all of the study characteristics. Consequently, we could not conduct more detailed subgroup analyses, thus raising concerns about the reliability of our findings. However, the robustness of the findings was verified in numerous subgroup analyses.

5. Conclusions

Bedside ultrasonography has high overall diagnostic accuracy for individuals with suspected acute appendicitis. However, the accuracy for studies conducted in the USA and studies with small sample size is moderate, and further well-designed studies with homogenous characteristics are warranted. Inter-study heterogeneity as well as small sample size could undermine the quality and validity of the findings. Moreover, further larger prospective studies and even randomized controlled trials are advocated to verify the comprehensive effectiveness of bedside ultrasonography as a noninvasive means for detecting patients with suspected acute appendicitis.

Ethical approval

Not applicable.

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Conflicts of interest

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Author contribution

Study concept and design (FF MM ZM);
Acquisition of data (GS ZM);
Analysis and interpretation of data (GS JW ZM);
Drafting of the manuscript (FF MM ZM);
Critical revision of the manuscript for important intellectual content (all authors);
Study supervision (FF MM ZM).

Guarantor

Zubing Mei.

Contributions

Dr. Guixin Shen and Dr. Jing Wang contributed equally to this work as co-first author.

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The authors declare that they have no conflict of interest.

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Data statement

This is a summary design study. Data used for meta-analysis was extracted from previously published papers.

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Appendix A. Supplementary data

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