Comparison of Contrast-enhanced *versus* Non-enhanced Helical Computed Tomography in the Diagnosis of Acute Appendicitis: A Meta-analysis

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ABSTRACT

The aim of this review was to compare the performance of contrast-enhanced versus non-contrast-enhanced helical computed tomography (CT) for acute appendicitis as reported. A systematic search of PubMed and Embase was conducted. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the summary receiver operating characteristic curves (AUC) were evaluated using Meta-DiSc. Quality was assessed using QUADAS 2. Eight articles with 1602 patients were included. For contrast-enhanced CT, the pooled sensitivity was 0.95 (95% CI: 0.93-0.96) with a specificity of 0.94 (95%CI: 0.93-0.96). The PLR, NLR, and DOR were 14.74 (95%CI: 9.06-23.97), 0.06 (95%CI: 0.03-0.11), and 305.31 (95%CI: 107.14-870.08), respectively. For non-contrast-enhanced CT, the pooled sensitivity was 0.85 (95% CI: 0.82-0.87) with a specificity of 0.93 (95%CI: 0.92-0.95). The PLR, NLR, and DOR were 12.22 (95% CI: 9.52-15.69), 0.15 (95%CI: 0.09-0.25), 80.98 (95%CI: 41.65-157.45), respectively. The AUC was not statistically different (Z=0.737, p=0.461). This data suggest that the contrast-enhanced CT has better diagnostic performance for acute appendicitis than non-contrast CT.

Key Words: *Acute appendicitis, Contrast-enhanced computed tomography' scan, Non-contrast-enhanced computed tomography' scan, Meta-analysis.*

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INTRODUCTION

Appendicitis has been recognised as one of the most common causes of acute abdominal pain in adults and children. The lifetime risk of the disease reached 8.6% in males and 6.7% in females.[1] There are many ways to diagnose appendicitis. White blood cell count, C-reactive protein, and other biomarkers can be used to supplement the clinical examination of patients. However, these biomarkers have no external validity and cannot be used in clinical practice.[2] Secondly, there are systematic reviews on methods similar to Alvarado scores for the diagnosis of appendicitis, but they are generally less specific.[3] Traditionally, formal ultrasonography was recommended as the preferred diagnostic tool for patients with appendicitis.

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For better visualisation of the appendix, phlegmon, and abscess in complicated appendicitis (perforated or gangrenous appendicitis), abdominal computed tomography (CT), especially contrast-enhanced CT, has been widely applied in many institutions.

The role of CT in the routine diagnosis of acute appendicitis has been widely demonstrated.[4] However, as for contrast-enhanced CT, the side effects of contrast media and ionising radiation exposure should be considered, especially in children.[5] In addition, standard oral contrast agents will cause emergency patients to spend more time in the emergency department and delay treatment. Furthermore, oral contrast agents can hinder the induction of general anaesthesia during surgery.[6] Kim *et al*. identified CT features with high specificity for differentiating complicated appendicitis in patients.[7] Some researchers recommended low-dose CT as the better choice for acute appendicitis because of reduced exposure with similar diagnostic performance.[8,9] However, peritoneal fat acts as inherent contrast on a non-enhanced CT and less amount of body fat makes the scan interpretation difficult.[10]

Therefore, a comprehensive evaluation of the existing literature will allow a better comparison of the overall diagnostic ability of contrast-enhanced and non-contrast-enhanced CT for acute appendicitis. In this study, we conducted a meta-analysis that included the head-to-head comparison of unenhanced CT versus enhanced CT in the diagnosis of appendicitis.

METHODOLOGY

This meta-analysis was performed following the guidelines of the PRISMA-DTA (Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies) statement.[11]

Two individuals (Chen and Cong) independently performed the literature search in PubMed and Embase. English articles published up to 26 August 2021 with the following keywords would be enrolled: “appendicitis”, “computed tomography”, “CT”, “non-enhanced”, “noncontrast”, “non-contrast”, “nonenhanced”, “Diagnostic”, “sensitivity”, “specificity”, “Diagnosis”, and “ROC”.

The inclusion criteria for the literature search are (1) adults (age $\geq$18 years) and children (age <18 years) being investigated for acute appendicitis; (2) literature that compared the value of contrast-enhanced CT and non-contrast-enhanced CT in the diagnosis of acute appendicitis in the same study; and (3) the data on true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) were provided in the study, or these factors could be obtained based on the relevant known indicators.

Relevant publications would be excluded if the data in the article were incomplete. Moreover, letters, comments, and reviews were excluded during the screening process. If the same subjects were included in several articles, the newest or most informative literature would be included.

Chen and Cong conducted the literature search, screening, and data extraction independently. The third investigator (Yang) would be included in the discussion on data extraction if disagreements occurred. The extracted data included the following information: first author, publication year, the conducted country, the age composition of the included study, the number of appendicitis, non-appendicitis, TP, FP, FN, and TN of contrast-enhanced and non-contrast-enhanced scan CT. The quality of included studies was assessed by the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.[12] Specifically, QUADAS-2 utilise an overall judgement of “low”, “high”, or “unclear” risk. For judging the “risk of bias”, Cong and Chen analysed all articles by answering each signalling question with a “yes,” “no,” or “unclear” independently. For the overall judgement of “low risk of bias” or “low concern regarding applicability,” a study must be ranked “low” on all relevant domains. If a study receives a “high” or “unclear” rating in one or more domains, it may be judged as “at risk of bias” or having “concerns regarding applicability.”[13]

Meta-DiSc was used to perform the meta-analyses (version 1.4). The factors associated with diagnostic accuracy, including sensitivity, specificity, PLR, NLR, DOR, forest plots, and summary receiver operating characteristic (SROC) curves, were analysed in the meta-analysis. Cochran’s I^2 test was used to identify heterogeneity among individual studies, and the authors defined that significant heterogeneity occurred when $p < 0.05$ and $I^2 > 50\%$.[14] If significant heterogeneity was observed among individual studies, the random-effects model would be used to estimate the pooled effect of outcomes. The fixed effect model would be used if no obvious heterogeneity was observed.[15] The difference in diagnostic indicators between contrast-enhanced and non-contrast-enhanced CT were analysed by the Z test. Finally, publication bias was assessed by Egger’s test using Stata software.

RESULTS

The detailed selection progress is shown in Figure 1. Initially, 1628 articles were retrieved, including 607 articles from PubMed, 785 articles from Embase, and 236 articles from Web of Science. Then, 511 duplicated documents were excluded. After reviewing the abstracts of the remaining 1117 articles, 1083 articles that did not conform to the topic were excluded. Twenty-six of the remaining 34 articles were excluded after reading the full text, including four articles with the same data, nine articles that did not compare contrast-enhanced CT and non-contrast-enhanced CT, and 13 articles that failed to obtain data. Finally, eight articles were included in this study.[16-23]

As shown in Table I, the overall baseline characteristics of the included studies were collected. A total of 1602 subjects were included, containing 695 patients with acute appendicitis and 907 patients without appendicitis. The published year of the selected articles ranged from 2002 to 2020. These studies were conducted between 1997 and 2017, and the participants included 777 males and 825 females. The study of Yun (2016) divided the CT examination time of the research subjects into two stages (2011.9-2012.5 and 2012.5-2013.2), so there were nine sets of research data.

In the Chiu study, two experienced radiologists viewed the CT images, one of whom was responsible for viewing contrast-enhanced CT images, and the other was responsible for viewing non-contrast-enhanced CT images. In the study of Eurboonyanun (2020) and Platon (2008), the CT images were also reviewed by two radiologists, but the two agreed on the diagnosis results. In the remaining studies, independent diagnoses of multiple radiologists were reported, and their average value was used for meta-analysis.

As shown in supplementary Table I and supplementary Figure 1, the quality of individual studies was relatively high for the meta--analysis.

The threshold effect was determined by the Spearman correlation coefficient of the logarithm of sensitivity and 1-specificity. For contrast-enhanced CT and non-contrast-enhanced CT, the Spearman correlation coefficients were -0.653 and -0.433, and the p-values were 0.057 and 0.244, respectively. The results indicated no threshold effect, and other statistics could be combined.

Table I: The baseline characteristics of included articles.

Study	Location	Study year	Gold criterion	N/n*	Age (years)	Males / Females	Group	TP	FP	FN	TN
Chang CC, 2016	Taiwan	2008.12- 2009.12	Surgical and pathological	48/53	38.9±12.6	44/57	NE	40	6	8	47
			findings				CE	43	5	5	48
Chiu YH, 2013	China	2008.7- 2009.2	Surgery, radiological findings,	42/58	16-90	55/45	NE	38	0	4	58
			clinical course				CE	42	3	0	55
Eurboonyanun, K 2020	Thailand	2016.6- 2017.11	Radiological findings or	57/83	15-86	48/92	NE	46	11	11	72
			clinical follow-up data				CE	49	15	8	68
Jacobs JE, 2001	USA	1997.8- 1999.4	Surgical findings or clinical	51/159	32 (13-87)	131/79	NE	38	9	13	150
			follow-up data				CE	47	8	4	151
Kaiser S, 2004	Sweden	2002.2- 2002.10	Surgery, Histopathologic	129/177	10.6(2-15)	154/152	NE	85	8	44	169
			examination				CE	116	11	13	166
Platon A, 2008	Switzerland	NA	Surgical findings and / or the	37/49	18-96	41/45	NE	35	2	2	47
			final discharge report				CE	37	2	0	47
Seo H, 2009	Korea	2007.2- 2007.3	Surgical and pathologic	78/129	38.6±15.2	86/121	NE	78	5	0	124
			findings				CE	78	6	0	123
Yun SJ1, 2016	China	2011.9- 2012.5	Surgery, pathologic reports,	112/70	38.8±14.2	95/87	NE	103	5	9	65
			medical records				CE	108	3	4	67
Yun SJ2, 2016	China	2012.5- 2013.2	Surgery, pathologic reports,	141/129	38.9±12.6	123/147	NE	125	13	16	116
			medical records				CE	139	4	2	125

*1: Scan 1; 2: Scan 2; *: Appendicitis/Control;TP: true positives; TN: true negatives; FP: false positives; FN: false negatives; NE: non-enhanced CT; CE: contrast-enhanced CT.*

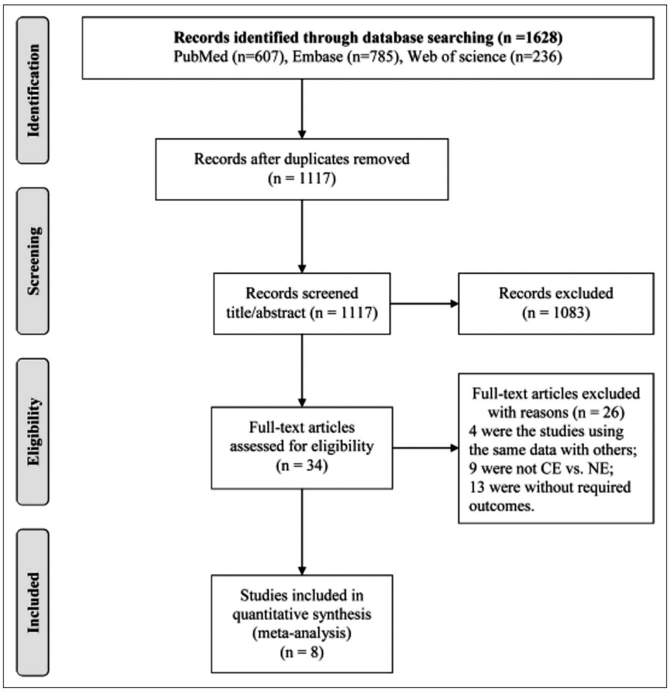


Figure 1: The detailed flow chart of the meta-analysis for research selection.

The diagnostic performance of contrast-enhanced CT is shown in Figure 2. The sensitivity for enhanced CT diagnosis was 0.95 (95%CI: 0.93-0.96), which was pooled by the random-effects model (heterogeneity test, $p<0.001$, $I^2=78.4\%$). The pooled specificity was 0.94 (95%CI: 0.92-0.95) using the random-effects model (heterogeneity test, $p=0.0143$, $I^2=58.1\%$). The PLR was 14.74 (95%CI: 9.06-23.97) based on pooled data using the random-effects model (heterogeneity test, $p<0.001$, $I^2=71.2\%$). The NLR (0.06, 95%CI: 0.03-0.11) was obtained based on the random-effects model (heterogeneity test, $p<0.001$, $I^2=70.8\%$). The heterogeneity for the individual data for calculating DOR was not significant (heterogeneity test, $p<0.0001$, $I^2=77.1\%$), and the DOR was 305.31 (95%CI: 107.14-870.08) as calculated by the fixed effect model. The AUC of the SROC curve was 0.983±0.009.

As shown in Figure 3, the sensitivity for non-contrast-enhanced CT was 0.85 (95%CI: 0.82-0.87), which was pooled by the random-effects model (heterogeneity test, $p<0.001$, $I^2=88.6\%$). The pooled specificity was 0.93 (95%CI: 0.92-0.95) using the random-effects model (heterogeneity test, $p= 0.008$, $I^2=60.9\%$). The PLR was 12.22 (95%CI: 9.52-15.69) based on data pooled using the fixed effects model (heterogeneity test, $p=0.0584$, $I^2=46.8\%$). The NLR (0.15, 95%CI: 0.09-0.25) was obtained based on the random-effects model (heterogeneity test, $p<0.001$, $I^2=85.2\%$). The heterogeneity for the individual data for calculating DOR was significant (heterogeneity test, $p=0.004$, $I^2=64.2\%$), and the DOR was 80.98 (95%CI: 41.65-157.45) as calculated by the random effect model. The AUC of the SROC curve was 0.96±0.01.

Given all the results of the diagnostic analysis (supplementary Table II), the effect of contrast-enhanced CT was better than that of non-contrast-enhanced CT. Similar performances were found on the specificity, PLR, and diagnostic ratio of the two CT administrations in the diagnosis of acute appendicitis. There was a difference in sensitivity between the two groups, and contrast-enhanced CT had better sensitivity than non-contrast-enhanced CT ($Z=6.723$, $p<0.001$). There was a significant difference in NLR between the two CT administrations in the diagnosis of acute appendicitis ($Z=1.972$, $p=0.049$). However, the difference between AUC was not statistically different in the diagnosis of acute appendicitis ($Z=0.737$, $p=0.461$), indicating that the effect of contrast-enhanced CT was not better than non-enhanced CT.

Egger's test showed no significant publication bias between non-enhanced CT and contrast-enhanced CT ($t=0.58$, $p=0.579$; $t=0.30$, and $p=0.774$).

DISCUSSION

Currently, abdominal CT has been widely used in detecting acute appendicitis. Various CT protocols have been put forward, including non-enhanced CT and contrast-enhanced CT in various manners such as intravenous, oral, or rectal perfusion. However, the better choice for acute appendicitis remains controversial among institutions.

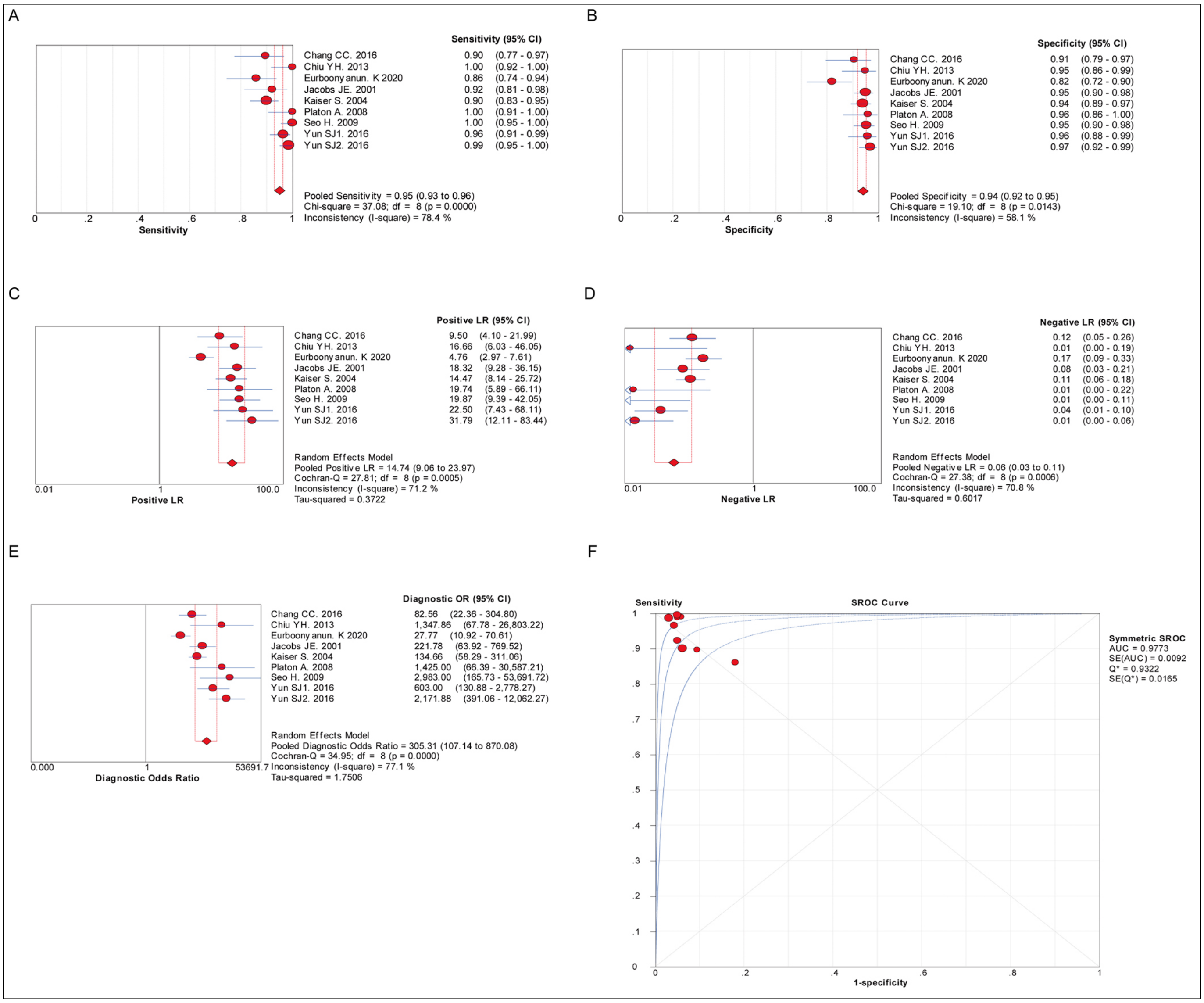


Figure 2: Forest plots of the indicators of diagnostic ability of contrast-enhanced computed tomography for detection of acute appendicitis. (A) sensitivity; (B) specificity; (C) positive likelihood ratio; (D) negative likelihood ratio; (E) diagnostic odds ratio; (F) area under the summary receiver operating characteristic curves.

MRI as a method of diagnosing appendicitis may eliminate the radiation produced by CT diagnosis. However, there are few studies on using MRI for the diagnosis of appendicitis, and its accuracy is no better than that of CT in identifying perforated appendicitis.[24] This data showed that contrast-enhanced CT had a higher sensitivity than non-contrast-enhanced CT in the diagnosis of acute appendicitis, but there was no statistical difference in specificity. The study by Rud *et al*. also showed that in the diagnosis of adult appendicitis, the sensitivity of non-contrast-enhanced CT is lower than that of contrast-enhanced CT, but the specificity is similar.[25] Moreover, the dosage of contrast medium is also worth discussing. A study demonstrated an increase in standardised uptake value in normal and pathologic regions of high concentration when IV contrast-enhanced CT is used for attenuation.[26] Another study has shown that the use of intravenous contrast agents significantly improved the diagnostic accuracy compared to oral contrast agents.[27] Acute appendicitis is diagnosed with a 90-99% accuracy with the use of contrast media.[28] There is also a need to study the optimal dose of contrast medium in a larger patient population. However, neither study considered the body mass index (BMI) of the included patients. The amount of visceral fat may affect the accuracy of the diagnostic test. Because the appendix is easier to identify in the presence of high amounts of abdominal fat, changes in inflammation around the appendix are easier to assess.[29] Moreover, many physicians in the emergency department are not particularly familiar with interpreting non-enhanced images. Thus, contrast-enhanced CT can be widely used in the emergency department.

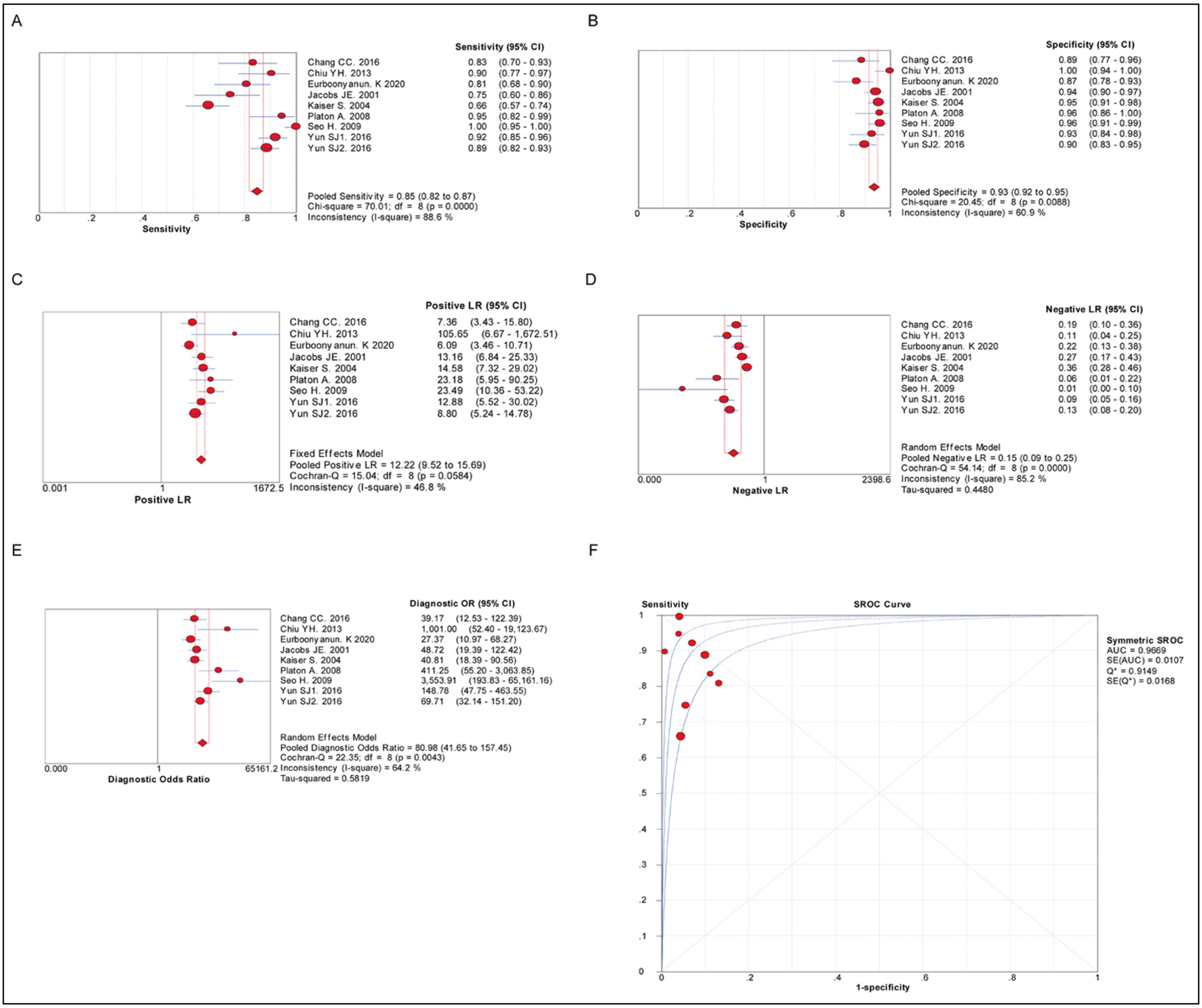


Figure 3: Forest plots of the indicators of diagnostic ability of non-enhanced computed tomography for detection of acute appendicitis. (A) sensitivity; (B) specificity; (C) positive likelihood ratio; (D) negative likelihood ratio; (E) diagnostic odds ratio; (F) area under the summary receiver operating characteristic curves.

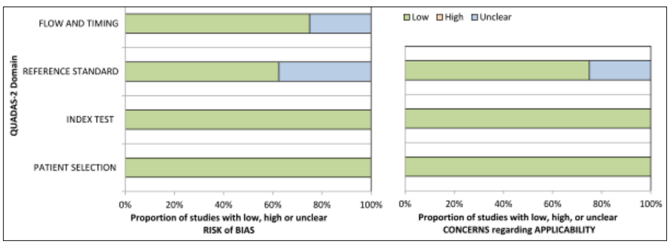
Supplementary Table I: The quality evaluation of enrolled studies.

Study	Risk of BIAS				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Chang CC, 2016	☺	☺	☺	☺	☺	☺	☺
Chiu YH, 2013	☺	☺	☺	?	☺	☺	☺
Eurboonyanun, K 2020	☺	☺	?	☺	☺	☺	☺
Jacobs JE, 2001	☺	☺	☺	☺	☺	☺	☺
Kaiser S, 2004	☺	☺	☺	?	☺	☺	☺
Platon A, 2008	☺	☺	?	☺	☺	☺	?
Seo H, 2009	☺	☺	☺	☺	☺	☺	☺
Yun SJ, 2016	☺	☺	?	☹	☺	☺	?

☺ Low Risk *☹ High Risk* *? Unclear Risk*

Supplementary Table II: The results of a meta-analysis on the diagnostic performance of contrast-enhanced versus non-enhanced helical computed tomography (CT) scans in the diagnosis of acute appendicitis.

Indexes	Contrast-enhanced CT (95%CI)	Non-enhanced CT (95%CI)	Z	P
Sensitivity	0.95 (0.93-0.96)	0.85 (0.82-0.87)	6.723	<0.001
Specificity	0.94 (0.92-0.95)	0.93 (0.92-0.95)	0.924	0.356
Positive likelihood ratio	14.74 (9.06-23.97)	12.22 (9.52-15.69)	0.612	0.540
Negative likelihood ratio	0.06 (0.03-0.11)	0.15 (0.09-0.25)	1.972	0.049
Diagnostic odds ratio	305.31 (107.14-870.08)	80.98 (41.65-157.45)	1.140	0.254
AUC	0.9773 (0.9593, 0.9953)	0.9669 (0.9459, 0.9879)	0.737	0.461



Supplementary Figure 1: Proportion of studies with low, high, or unclear risk of bias (left), and proportion of studies with low, high, or unclear concerns regarding applicability.

Our study has several limitations. First, our data were all designed as retrospective data. Second, patient selection bias might be present. Previous data have demonstrated that patients with atypical appendicitis positions such as retrocecal, pericolic gutter, retroileal, or retroperitoneal appendicitis may have different performance characteristics. In addition, the experience and interpretation differences among physicians may also affect the results. Although the present study suggested the better diagnostic ability of contrast-enhanced CT on acute appendicitis diagnosis, further study on the side effect and clinical characteristics should be considered. However, this meta-analysis included only studies comparing unenhanced *vs*. enhanced CT in a head-to-head manner in diagnosing appendicitis, which makes the study prominent compared to pre-existing meta-analysis.

CONCLUSION

Compared with non-contract-enhanced CT, contrast-enhanced CT showed better overall diagnosis performance. However, future studies including more eligible articles are needed to determine the most suitable diagnostic method for acute abdominal appendicitis.

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COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
BH: Conception and design of the research acquisition of data.
MW, JZ: Analysis and interpretation of data.
JX, RC, JY: Statistical analysis.
JX, JY: Obtaining funding.
BH, JY: Drafting the manuscript.
YC, RC: Revision of manuscript for important intellectual content.
BH, YH: All authors read and approved the final manuscript.

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