Systematic Review and Meta-Analysis

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Value of contrast-enhanced ultrasound in differential diagnosis of solid lesions of pancreas (SLP)

A systematic review and a meta-analysis

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Abstract

Background: Contrast-enhanced ultrasound (CEUS) is considered a novel method for diagnosing pancreatic cancer, but currently, there is no conclusive evidence of its accuracy. Using CEUS in discriminating between pancreatic carcinoma and other pancreatic lesions, we aimed to evaluate the diagnostic accuracy of CEUS in predicting pancreatic tumours.

Methods: Relevant studies were selected from the PubMed, Cochrane Library, Elsevier, CNKI, VIP, and WANFANG databases dating from January 2006 to May 2017. The following terms were used as keywords: "pancreatic cancer" OR "pancreatic carcinoma," "contrast-enhanced ultrasonography" OR "contrast-enhanced ultrasound" OR "CEUS," and "diagnosis." The selection criteria are as follows: pancreatic carcinomas diagnosed by CEUS while the main reference standard was surgical pathology or biopsy (if it involved a clinical diagnosis, particular criteria emphasized); SonoVue or Levovist was the contrast agent; true positive, false positive, false negative, and true negative rates were obtained or calculated to construct the 2×2 contingency table; English or Chinese articles; at least 20 patients were enrolled in each group. The Quality Assessment for Studies of Diagnostic Accuracy was employed to evaluate the quality of articles. Pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, summary receiver-operating characteristic curves, and the area under curve were evaluated to estimate the overall diagnostic efficiency. Pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio with 95% confidence intervals (CIs) were calculated with fixed-effect models.

Results: Eight of 184 records were eligible for a meta-analysis after independent scrutinization by 2 reviewers. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratios were 0.86 (95% CI 0.81–0.90), 0.75 (95% CI 0.68–0.82), 3.56 (95% CI 2.64–4.78), 0.19 (95% CI 0.13–0.27), and 22.260 (95% CI 8.980–55.177), respectively. The area under the SROC curve was 0.9088.

Conclusion: CEUS has a satisfying pooled sensitivity and specificity for discriminating pancreatic cancer from other pancreatic lesions.

Abbreviations: AUC = the area under the curve, CEUS = contrast-enhanced ultrasound, CI = confidence interval, CT = computed tomography, DOR = diagnostic odds ratio, FN = false negative, FP = false positive, MRI = magnetic resonance imaging, PDAC = pancreatic ductal adenocarcinoma, PET-CT = positron emission tomography-computed tomography, QUADAS = Quality Assessment of Diagnostic Studies, SROC = summary receiver-operating characteristic, TN = true negative, TP = true positive, US = ultrasound.

Keywords: contrast-enhanced ultrasound, diagnosis, meta-analysis, pancreatic carcinoma

1. Introduction

Owing to its high morbidity and mortality, cancer has been a major public health concern worldwide. A total of 1,658,370 new cancer cases and 589,430 cancer deaths were projected to occur in the United States in 2015.[1] A similar situation has occurred in developing countries, such as China. Approximately 2,814,000 Chinese were estimated to die from cancer in 2015, corresponding to over 7500 cancer deaths on average per day.[2] Currently, an

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L.R. and W.Z. contributed equally to this study.

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increasing number of people have focused attention on pancreatic cancer owing to its rapidly increasing incidence. Pancreatic carcinoma is a malignant tumor of the digestive system, and 85% to 90% pancreatic carcinoma cases are of pancreatic ductal adenocarcinoma (PDAC).[3] An almost universally lethal disease, pancreatic cancer has an incidence that is 13th among malignant tumors worldwide, but its mortality is fourth.[4] According to the latest representative statistics from the National Central Cancer Registry of China,[2] the incidence rate of new cancer cases in 2015 was 90.1 per 100,000 (incidence rate in males was higher than in females, 52.2 vs 37.9 per 100,000), and the mortality rate was 79.4 per 100,000 (mortality rate in males was higher than in females, 45.6 vs 33.8 per 100,000). It should be noted that in the USA, pancreatic cancer is suggested to surpass breast cancer, which currently is 1 of the top 2 cancers, to become the second leading cause of cancer-related death by 2030.[5]

To date, radical resection surgery remains the first choice of treatment for pancreatic cancer because there is no effective chemical drug or physiotherapy, but the prognosis, unfortunately, is poor. The 5-year survival rate is only approximately 6%.[1] More surveillance is needed, as recommended by the new version of guidelines for pancreatic cancer published by the National Comprehensive Cancer Network in 2016, in which the frequency of surveillance after 2 years has been changed from "annually" to every "6 to 12 months."[6] Thus, early detection, specific diagnosis, effective and timely surgical treatment, and close monitoring of the pancreas are of vital significance.

Owing to the lack of typical clinical symptoms in the early stage, it is crucial to seek a method with excellent performance in diagnosing pancreatic cancer. Compared with the gold standard—surgical pathology or biopsy—medical imaging technology undoubtedly has the advantage of being relatively easy and noninvasive; therefore, ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography-computed tomography (PET-CT) have been widely applied in the initial detection and diagnosis with pancreatic cancer or not. It has been reported that owing to its convenience and low price, US is a first choice in pancreatic adenocarcinoma, yielding a sensitivity of 76%.[7] CT yields a higher sensitivity of 91%, whereas MRI yields a sensitivity of 84%.[7] Characteristics of the pancreas, surrounding vessels, and abnormal lymph nodes can be detected using CT; thus, there is a possibility of detecting pancreatic cancer with a high sensitivity. However, CT is not suitable for some groups of people, especially those with low incomes or living in areas that lack sufficient medical treatment and public health. The high prices of CT and MRI, which are much higher than that of US, will increase the burden in the initial stage of the diagnosis and treatment. Such high costs are a concern for PET-CT use also; additionally, residual radioisotopes in the body make it difficult for this procedure to gain acceptance by the public because it might be harmful to some degree.

Contrast-enhanced ultrasound (CEUS) can overcome the disadvantages above. It uses SonoVue (sulphur hexafluoride microbubbles) as the contrast agent, which is injected intravenously into the systematic circulation. It is able to differentiate malignant lesions from benign tumors by providing real-time imaging of vascular flow.[8] SonoVue is the most popular new contrast agent in clinical application and has superior safety and a long duration in imaging. Furthermore, CEUS is much cheaper, with a price that is at least 50% lower than that of CT or MRI. In recent years, CEUS has been applied mainly for breast, ovarian, and liver tumors, and its application has been validated.

2. Methods

2.1. Article search strategy

All published articles from January 2006 to May 2017 and relevant to CEUS and pancreatic cancer were searched on the PubMed, Cochrane Library, Elsevier, CNKI, VIP, and WANFANG databases by 2 independent reviewers. The following terms were used as keywords: "pancreatic cancer" OR "pancreatic carcinoma," "contrast-enhanced ultrasonography" OR "contrast-enhanced ultrasound" OR "CEUS," and "diagnosis." Records were retrieved and scrutinized independently by 2 partners. For disagreements (any additional article had been left out), the search strategy was checked and redone, and if necessary, a decision was made by another researcher.

2.2. Study eligibility and quality assessment

The inclusion criteria were as follows: pancreatic carcinomas diagnosed by CEUS while the main reference standard was surgical pathology or biopsy (if it involved a clinical diagnosis, particular criteria emphasized); SonoVue or Levovist was the contrast agent; true positive (TP), false positive (FP), false negative (FN), and true negative (TN) rates were obtained or calculated to construct the 2×2 contingency table; English or Chinese articles; at least 20 patients were enrolled in each group.

Studies were excluded if they lacked an evaluation of pancreatic malignant lesions (such as the evaluation of hepatic metastases in pancreatic cancers or the evaluation of resectability); had insufficient data to complete the 2×2 contingency table; were reviews, case reports, and other articles that did not report their own data; analyzed cases with less than 20 patients.

The Quality Assessment of Diagnostic Studies (QUADAS) was applied to assess the quality, risk of bias, and applicability of the included studies by assessing items as "yes," "no" or "unclear" by reviewers.[9]

2.3. Statistical analysis

Heterogeneity and the diagnostic accuracy of CEUS were performed with Meta-Disc version 1.4, the latter of which was calculated by pooled estimates of sensitivity, specificity, and diagnostic odds ratio (DOR) with corresponding 95% confidence intervals (CIs).

Heterogeneity was detected by Cochrane Q test and I^2 (inconsistency) statistics, with $P < .10$ or $I^2 > 50\%$, indicating a significance in heterogeneity.[10] Furthermore, if there was significant heterogeneity ($I^2 > 50\%$ or $P \leq .05$), the random-effects model (DerSimonian-Laird method) was preferred over the fixed-effects model (Mantel-Haenszel method); otherwise, the fixed-effects model was the first choice.

A pooled DOR combined the sensitivity with specificity, reflecting the connectivity to diseases. The formula for DOR is: (TP/FN)/(FP/TN). The value of the DOR ranges from 0 to infinity, and when it equals 1, the test has no ability to discriminate people with/without the disease. A higher DOR indicates a better performance in discrimination.

Summary receiver-operating characteristic (SROC) curves, which estimate the area under the curve (AUC), indicated the accuracy and validation of diagnostic tests. The closer the value of the AUC is to 1, the better the performance.[11]

3. Results

3.1. Study selection

A total of 193 systematic records were identified through the PubMed, Cochrane Library, Elsevier, CNKI, VIP, and WAN-

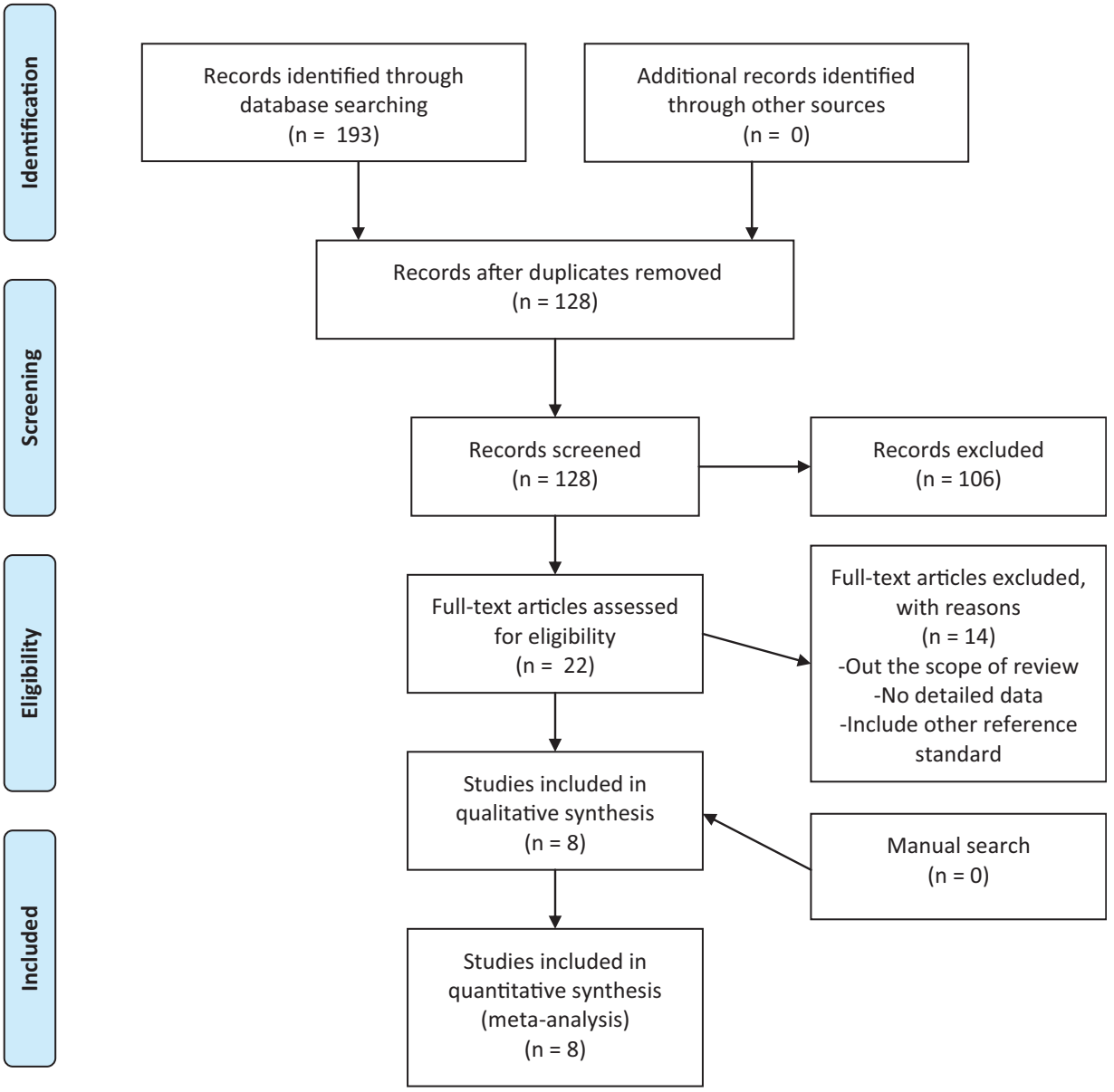

Figure 1. Study selection procedure.

FANG DATA databases, 65 of which were duplicated. Of the remaining 128 studies, 106 were generally excluded based on the titles and abstracts. Finally, after reading the full manuscripts and conducting manual search of the reference lists of primary studies, 8 articles were included in this study as they fulfilled our eligibility criteria.[12–19] The study selection procedure is outlined in Fig. 1.

3.2. Study characteristics and quality

The 8 studies (4 retrospectives,[16–19] 1 prospective,[15] and 3 not specified[12–14]) comprised 389 patients, 385 of whom were included in the analysis. Their principal characteristics are summarized in Table 1. Two articles (25%)[13,14] were in English, 1 of which was written by Chinese researchers and the other was published in Denmark. All records showed the use of SonoVue as the contrast agent, and in 6 studies (75%), a clinical diagnosis was the reference standard in addition to surgical pathology or biopsy.[12–13,15–18] The detailed risk of bias and the applicability are shown in Table 2.

3.3. Diagnostic performance

3.3.1. Heterogeneity. Moderate heterogeneity was found in the specificity (Cochrane Q test = 13.00, degrees of freedom [df] = 7, $P = .0721$, $I^2 = 46.2\%$), the positive likelihood ratio (Cochrane Q test = 15.42, df = 7, $P = .0310$, $I^2 = 54.6\%$) and the negative likelihood ratio (Cochrane Q test = 12.28, df = 7, $P = .0918$, $I^2 = 43.0\%$), whereas mild heterogeneity was found in the sensitivity (Cochrane Q test = 7.96, df = 7, $P = .3361$, $I^2 = 12.1\%$) (from Figs. 2–5).

3.3.2. Sensitivity and specificity. As is reflected in Fig. 2, the pooled sensitivity (fixed-effects model) of CEUS in discriminating pancreatic carcinoma from other pancreatic lesions was 0.86 (95% CI 0.81–0.90), and the pooled specificity (fixed-effects model) of CEUS was 0.75 (95% CI 0.68–0.82), as shown in Fig. 3.

Table 1

Characteristics of included studies.

First author	Year	Country	N enrolled	N analyzed	Reference standard	Design	TP	FP	FN	TN
Chen[12]	2010	China	21	21	Pathology Clinical diagnosis	Not specified	8	2	3	8
Fan[13]	2013	China	90	90	Surgical pathology Biopsy Clinical diagnosis	Not specified	33	12	3	42
Grossjohann[14]	2010	Denmark	49	49	Radiological image Surgical pathology	Not specified	38	1	6	4
Han[15]	2015	China	72	72	Surgical pathology Biopsy Clinical diagnosis	Prospective	27	16	9	20
Li[16]	2013	China	54	54	Surgical pathology Biopsy Clinical diagnosis	Retrospective	36	2	3	13
Wang[17]	2010	China	26	22	Pathology Clinical diagnosis	Retrospective	12	0	2	8
Xie[18]	2008	China	56	56	Surgical pathology Biopsy Clinical diagnosis	Retrospective	36	3	6	11
Yuan[19]	2009	China	21	21	Surgical pathology Biopsy	Retrospective	24	3	2	12

FN = false negative, FP = false positive, TN = true positive, TN = false negative.

3.3.3. Positive likelihood and negative likelihood ratios. Owing to the little high level of heterogeneity (Cochrane Q test = 15.42, df = 7, $P = .0310$, $I^2 = 54.6\%$), the positive likelihood ratio was analyzed with random-effects model. Figure 4 shows that the pooled positive likelihood ratio was 3.66 (95% CI 2.22–6.03), and Fig. 5 shows that the pooled negative likelihood ratio (fixed-effects model) was 0.19 (95% CI 0.13–0.27).

3.3.4. AUC and diagnostic odds ratio. The AUC was 0.9008 (Fig. 6), and the pooled DOR was 22.260 (95% CI 8.980–55.177).

3.3.5. Publication bias. Publication bias was assessed with the Deeks test ($t = -1.53$, $P = .144$), indicating that there would be no significant publication bias.

Table 2

Risk of bias of each included study with QUADAS.

	Chen[12]	Fan[13]	Grossjohann[14]	Han[15]	Li[16]	Wang[17]	Xie[18]	Yuan[19]
Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were selection criteria clearly described?	Unclear	Unclear	Yes	Yes	No	No	No	No
Is the reference standard likely to correctly classify the target condition?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Did the whole sample or a random selection of the sample, receive verification using a reference standard?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Did patients receive the same reference standard regardless of the index test result?	No	No	No	No	No	No	No	Yes
Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the execution of the reference standard described in sufficient detail to permit its replication?	No	No	No	No	No	No	No	No
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Were uninterpretable/intermediate test results reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were withdrawals from the study explained?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

QUADAS = Quality Assessment of Diagnostic Studies.

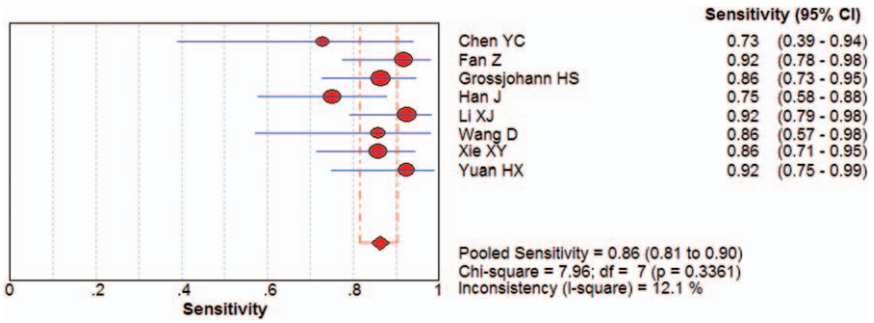

Figure 2. Forest plot of the meta-analysis of sensitivity.

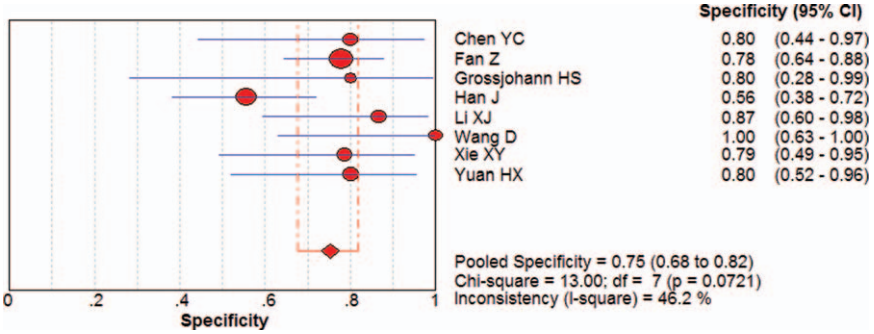

Figure 3. Forest plot of the meta-analysis of specificity.

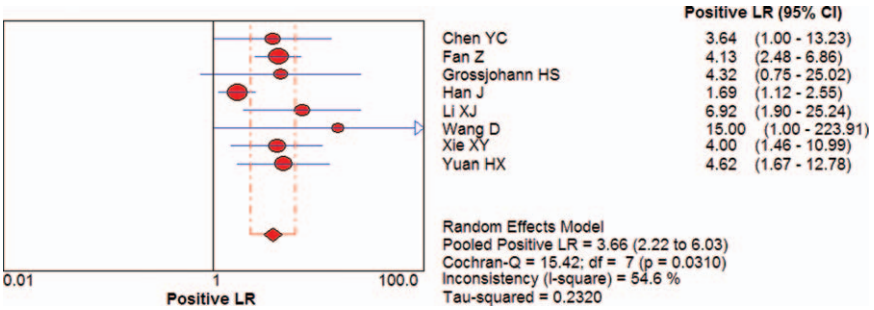

Figure 4. Forest plot of the meta-analysis of positive likelihood ratio.

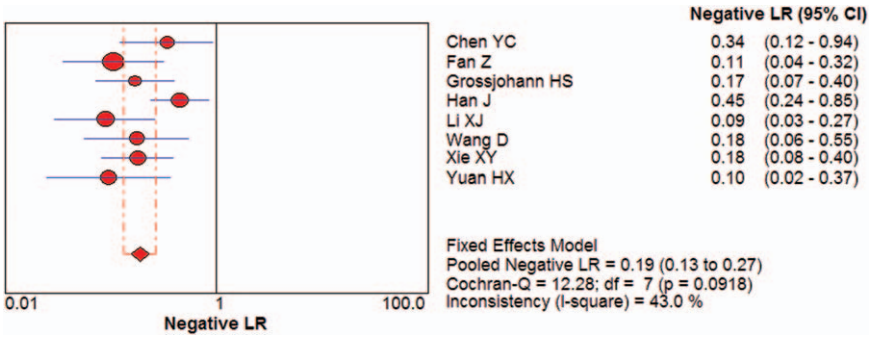

Figure 5. Forest plot of the meta-analysis of negative likelihood ratio.

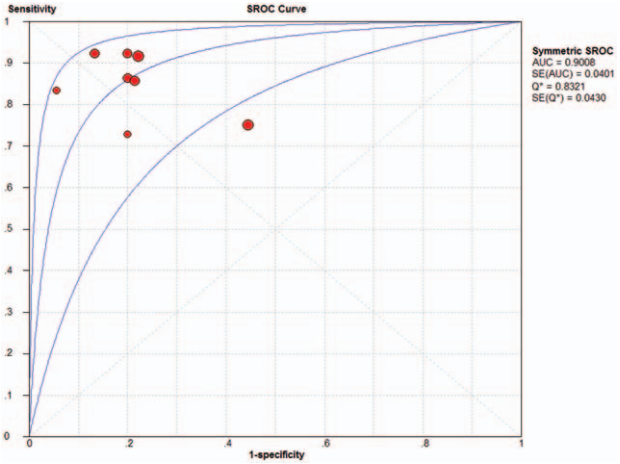

Figure 6. Summary receiver-operating characteristic (SROC) curve.

4. Discussion

With the development of CEUS, a series of well-designed prospective and retrospective studies have assessed the differentiation of malignant pancreatic tumors from nonmalignant pancreatic lesions. Our primary goal was to evaluate the accuracy of CEUS in this meta-analysis.

Moderate heterogeneity occurred in the specificity (Cochrane Q test = 13.00, df = 7, $P = .0721$, $I^2 = 46.2\%$), whereas mild heterogeneity was observed in the sensitivity (Cochrane Q test = 7.96, df = 7, $P = .3361$, $I^2 = 12.1\%$) among the 8 studies evaluated. Considering that the heterogeneity was not extremely high, a subgroup analysis was not performed. We excluded the article with the lowest specificity (Han[15]) and reperformed the analysis. The pooled specificity increased to 0.81 (95% CI 0.73–0.88) from 0.75 (95% CI 0.68–0.82), and the heterogeneity decreased (Cochrane Q test = 4.13, df = 6, $P = .6585$, $I^2 = 0.0\%$). Heterogeneity exists in Han's article, and this problem is expected to persist in future research.

Fourteen detailed items are listed in Table 2, which indicates that the quality was not as good as envisioned. The bias mainly came from too many "unclear" and "no" descriptions, such as items 4, 6, and 9. In all articles, there were no descriptions of whether the time period between the reference standard and index tests was short enough, and only in Xie et al's[18] article, patients had surgical pathology or biopsy as the same gold standard. None of the articles described how the gold standard was used to diagnose pancreatic cancer, preventing the replication of the study. In contrast, the sufficient details of the index test permitted its replication. Only in Grossjohann et al's[14] article, the diagnostic results from CEUS were obtained without knowing those of the gold standard. Consequently, there is no evidence to indicate whether the index test results were interrupted by the reference standard or whether the reference standard results were interrupted by the index test in the remaining 7 studies. Therefore, we conclude that more details concerning the patients' selection, process of interpreting the gold standard and test method, and reports of the results should be given. It is necessary to improve the written quality of diagnostic articles for the benefit of later researchers and scholars.

Based on our results, the 0.86 pooled sensitivity means there is an 86% chance that a patient will be correctly diagnosed with pancreatic cancer after positive CEUS examination, whereas there is still a 14% chance that a patient will not be correctly diagnosed. In contrast, the 0.75 pooled specificity means every 75 of 100 people will have a negative result of CEUS examination, whereas 25 people will be wrongly diagnosed with pancreatic cancer. Relatively, CEUS yields a higher sensitivity in detecting pancreatic tumors than do the most frequently used imaging technologies—US and MRI—which yield sensitivities of 76% and 84%, respectively.[7] It should be noted that there is only a slight variability in the diagnostic capabilities of CEUS and MRI. With regard to the different capabilities in image interpretation and different target users, we cannot definitely deem CEUS better than MRI in the accuracy. Given this, what is the efficacy of the combination of CEUS and other imaging technologies? As was shown in Dong and Shen's[20] study, the sensitivity of CEUS and endoscopic US in detecting pancreatic malignancies was 0.769 and 0.752, respectively. After their combination, the sensitivity increased significantly to 0.917. The same occurred in the combination with CT. As illustrated, the sensitivity after combination was 96%, whereas the sensitivity of CEUS and CT separately was 93% and 89%, respectively.[21] In addition to depending on the efficacy, the combination of imaging examinations should also depend on the patients' preferred choices, the available hospitals equipment, and even the politics and economics in different areas. To our knowledge, no cost-effectiveness analyses have been published to date in which CEUS was used as a complement to other clinical methods; we selected the costs of CT and MRI in some typical grade 3 and first-class hospitals in 7 areas in China. The statistics were from the clinical laboratories of hospitals in cities and provinces, which set their prices according to the Pricing Bureau. The average cost of CT and MRI was approximately 700 Chinese Renminbi (RMB, US $100.98) and 1200 RMB (US $173.11), respectively. Actually, patients were charged per body part 1 time, and the film fees and other fees were not included; the cost of CEUS was much cheaper, typically at least 50% lower than that of CT (350 RMB, US $50.49). Furthermore, the use of CT and MRI is greatly limited by the regional economic development or medical and health facilities, and the results of inspection are influenced by doctors' knowledge and skills. Compared with surgical pathology or biopsy as the reference standard, the strengths of CEUS are emphasized. These strengths include its ease of operation, low associated pain, low cost, clear outcomes, and noninvasive nature. Considering the above-mentioned benefits, we confidently believe that CEUS is a good and available method for some degree of early detection. There is no denying the fact that the sensitivity of CEUS is not as good as that of CT, but we still hope the statistics will be beneficial and provide a reference for later studies.

There are several limitations to our study. First, because of the strict inclusion criteria, there were a small number of eligible articles. This might have resulted in bias. Second, the diagnostic accuracy of CEUS was compared with that of the gold standard, whereas the standard was not the unique one. Therefore, it is necessary to continue this meta-analysis with more sole-criterion articles, and the results of our study should be interpreted with caution. Third, because of insufficient information, many "unclear" items from the QUADAS lowered the quality of these 8 studies. Finally, we focused on evaluating the value of CEUS in distinguishing pancreatic tumors from other malignant lesions, but failed to discuss what clinical advice should be given to maintain diagnostic precision.

5. Conclusions

Contrast-enhanced ultrasound has a satisfying pooled sensitivity and specificity for discriminating pancreatic tumors from other

pancreatic lesions. It can be applied as an effective, economical, and convenient clinical diagnostic method for diagnosis of pancreatic cancer.

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