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Contrast-enhanced ultrasound and contrast-enhanced computed tomography for differentiating mass-forming pancreatitis from pancreatic ductal adenocarcinoma: a meta-analysis

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Abstract

Background: Patients with mass-forming pancreatitis (MFP) or pancreatic ductal adenocarcinoma (PDAC) presented similar clinical symptoms, but required different treatment approaches and had different survival outcomes. This meta-analysis aimed to compare the diagnostic performance of contrast-enhanced ultrasound (CEUS) and contrast-enhanced computed tomography (CECT) in differentiating MFP from PDAC.

Methods: A literature search was performed in the PubMed, EMBASE (Ovid), Cochrane Library (CENTRAL), China National Knowledge Infrastructure (CNKI), Weipu (VIP), and WanFang databases to identify original studies published from inception to August 20, 2021. Studies reporting the diagnostic performances of CEUS and CECT for differentiating MFP from PDAC were included. The meta-analysis was performed with Stata 15.0 software. The outcomes included the pooled sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (−LR), diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) curves of CEUS and CECT. Meta-regression was conducted to investigate heterogeneity. Bayesian network meta-analysis was conducted to indirectly compare the overall diagnostic performance.

Results: Twenty-six studies with 2115 pancreatic masses were included. The pooled sensitivity and specificity of CEUS for MFP were 82% (95% confidence interval [CI], 73%–88%; $I^2 = 0.00\%$) and 95% (95% CI, 90%–97%; $I^2 = 63.44\%$), respectively; the overall +LR, −LR, and DOR values were 15.12 (95% CI, 7.61–30.01), 0.19 (95% CI, 0.13–0.29), and 78.91 (95% CI, 30.94–201.27), respectively; and the area under the SROC curve (AUC) was 0.90 (95% CI, 0.87–92). However, the overall sensitivity and specificity of CECT were 81% (95% CI, 75–85%; $I^2 = 66.37\%$) and 94% (95% CI, 90–96%; $I^2 = 74.87\%$); the overall +LR, −LR, and DOR values were 12.91 (95% CI, 7.86–21.20), 0.21 (95% CI, 0.16–0.27), and 62.53 (95% CI, 34.45–113.51), respectively; and, the SROC AUC was 0.92 (95% CI, 0.90–0.94). The overall diagnostic accuracy of CEUS was comparable to that of CECT for the differential diagnosis of MFP and PDAC (relative DOR 1.26, 95% CI [0.42–3.83], $P > 0.05$).

Conclusions: CEUS and CECT have comparable diagnostic performance for differentiating MFP from PDAC, and should be considered as mutually complementary diagnostic tools for suspected focal pancreatic lesions.

Keywords: Pancreatitis; Pancreatic neoplasms; Ultrasonography; Tomography, X-ray computed; Meta-analysis

Introduction

Mass-forming pancreatitis (MFP) is a specific type of chronic pancreatitis associated with autoimmune responses, alcohol consumption, tobacco use, and a history of biliary tract disease.[1,2] It is challenging to differentiate MFP from pancreatic ductal adenocarcinoma (PDAC) because both conditions may present with clinically recurrent abdominal pain, weight loss, exocrine and endocrine pancreatic insufficiency, and a pancreatic mass on imaging. In some patients, PDAC may develop from chronic pancreatitis or may be accompanied by chronic pancreatitis.[2,3] Considering the different treatment strategies, management strategies, and prognoses for MFP and PDAC, accurate differential diagnosis of MFP and PDAC is of paramount importance to prevent unnecessary surgical resection in patients suffering solely from MFP.

Contrast-enhanced ultrasound (CEUS) is a suitable imaging method for the delineation of the intra-pancreatic

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macro- and microvasculature, and has been recommended by the guidelines for the characterization of solid pancreatic lesions.[4,5] MFP may display an enhancement pattern on CEUS that is similar to that of normal pancreatic parenchyma.[6] Several studies have also reported the diagnostic performance of CEUS for benign pancreatic lesions and have described substantial variability, i.e., a sensitivity of 67.0% to 94.0% and specificity of 30.0% to 100%.[6-13] Contrast-enhanced computed tomography (CECT) and magnetic resonance imaging have been widely used for the preoperative evaluation and post-operative follow-up of pancreatic masses, especially malignant pancreatic tumors; however, limited information regarding the significance of CEUS for patients with PDAC has been reported.[4,5,14,15] One meta-analysis described the overall diagnostic accuracy of CEUS for differentiating PDAC from other pancreatic lesions.[16] Two studies compared the performance of CEUS and CECT for the differential diagnosis of MFP and PDAC; however, these studies were published before 2015 and included $\leq$120 samples in total;[7,8] thus, the optimal imaging method in differentiating MFP from PDAC could not be determined. Therefore, in this study, we investigated whether the ability of CEUS to diagnose PDAC was comparable to that of CECT. Considering that PDAC always showed poor perfusion in contrast-enhanced examination due to its strong intralesional desmoplastic reaction, we hypothesized that the diagnostic performance of CEUS might be comparable to that of CECT in the differential diagnosis of PDAC and MFP. Since previous studies did not reach reliable conclusions, we performed this meta-analysis to compare the diagnostic performance of CEUS and CECT for differentiating MFP from PDAC, and to compare the two imaging modalities.

Methods

Literature search strategy

The PubMed, EMBASE, The Cochrane Library (CENTRAL), China National Knowledge Infrastructure (CNKI), Weipu (VIP), and WanFang databases or other sources were searched to identify articles reporting the performance of CEUS and CECT in the differential diagnosis of MFP and PDAC in humans. The search time was from inception until August 20, 2021. The query terms included "pancreatitis," "pancreatic neoplasm," "CECT," "CEUS," "diagnosis," and "differential." The detailed search terms are listed in Supplementary Table 1, http://links.lww.com/CM9/B302. The studies were limited to English and Chinese. The study was reported according to the Meta-analysis of Observational Studies in Epidemiology guidelines [Supplemental Table 1, http://links.lww.com/CM9/B302].[17]

Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) patients with MFP or PDAC; (b) index test: CEUS; (c) comparison test: CECT; (d) outcomes: diagnostic accuracy for differentiating MFP from PDAC; (e) study design: clinical diagnoses; and (f) reference standard: both histological and clinical diagnoses. The exclusion criteria were as follows: (a) studies with duplicated patients or data; (b) studies that lacked sufficient information to create a 2×2 diagnostic table or to explain the diagnostic criteria; (c) case reports, reviews, editorials, letters, and conference abstracts; (d) studies not within the field of interest; and (e) studies without human subjects. Two reviewers (Huang J.Y. and Yang J., with 10 and 5 years of experience in abdominal ultrasonic radiology) screened the abstracts and titles of the selected studies and reread the full texts of potentially eligible studies. Both review sessions were completed independently, and studies with definite ineligibility were excluded. Studies about which the reviewers disagreed were discussed, and disagreements were resolved by consensus.

Data extraction

Two reviewers independently extracted the data from the included studies. The following data were extracted from the eligible studies: (a) study characteristics (the first author, year of publication, country in which the articles were published, and study design [retrospective or prospective]); (b) lesion characteristics {numbers of MFPs and PDACs, and pancreatitis subtype (chronic mass-form pancreatitis [CMFP] or autoimmune pancreatitis [AIP])}; (d) CECT techniques (multiphase enhanced images, slice thickness, and number of channels); (e) the number of raters; and (f) the reference criteria for pancreatitis and PDAC (histopathological or clinical criteria).

To determine the diagnostic accuracy, the numbers of true positives, false positives, false negatives, and true negatives were extracted. Since individual characteristics were used in the case of multiple sets of results, the highest Youden index value was considered for further analyses. The two reviewers independently extracted the data, and all disagreements were reassessed in a consensus meeting.

The quality of the reviewed studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) criteria.[18] Two reviewers independently carried out the data analysis, evaluated the quality assessment of the studies, and reached a consensus by discussion.

Data synthesis and statistical analysis

To examine the effect of each imaging test on diagnostic accuracy, the results of all the studies were separated and evaluated as separate studies according to the type of modality (CECT *vs.* CEUS). Statistical analysis was performed on a per-lesion basis. The sensitivity and specificity of the differential diagnosis of MFP and PDAC, and their 95% confidence intervals (CIs), were calculated using the relevant data extracted from each individual study. The sensitivity was defined as the number of patients diagnosed with MFPs on imaging divided by all patients with MFPs, while the specificity was defined as the number of patients presenting PDACs on imaging divided by all patients with PDAC. The diagnostic ability of CEUS and CECT for differentiating MFP from PDAC was compared by Bayesian network meta-analysis.

The threshold effect between the sensitivity and false positive rate was evaluated by Spearman correlation analysis. A correlation coefficient >0.6 was considered to indicate a considerable threshold effect. Cochran's *Q* test and Higgins' I^2 statistic were used to determine the heterogeneity, and *P* value <0.1 or an I^2 statistic >50% was considered to indicate significant heterogeneity.[19,20] If there was no threshold effect present, a random effects model was used to obtain pooled estimates of the sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (−LR), and diagnostic odds ratio (DOR). Bivariate and hierarchical summary receiver operating characteristic models were used to provide equivalent summary estimates for sensitivity and specificity. We performed a Bayesian network meta-analysis to indirectly compare the overall diagnostic performance.[21,22]

If significant heterogeneity presented, a meta-regression analysis was conducted to investigate the cause of heterogeneity. The following covariates were used in the meta-regression: (a) patient numbers (patients ≤50 *vs*. patients >50); (b) publication year (before 2015 *vs*. after 2015); (c) subtype of pancreatitis (CMFP *vs*. AIP); (d) CT slice thickness (≤3 mm *vs*. >3 mm); (e) the use of multiphase enhanced CT (multiphase *vs*. single-phase); (f) the use of multiple CT channels (≥64 *vs*. <64 or unclear); (g) image reviewer (single or unclear *vs*. multiple raters); (h) reference standard for MFP and PDAC, respectively (unique *vs*. not unique); (i) country of publication (Asia or non-Asian country); and (j) blinded review (clear or unclear). Publication bias was determined by visual assessment of Deeks' funnel plot, and statistical significance was evaluated by Deeks' asymmetry test. All statistical analyses were performed using Stata version 15.0 (College Station, USA) software, and $P < 0.05$ was considered statistically significant.

Results

Literature search

The study selection process is shown in [Figure 1]. A total of 1558 studies were identified after searching the databases. After screening the studies, 26 studies with 2115 pancreatic masses were included.[6-13,23-40] Of the 26 included studies, 18 used only CECT for diagnosis,[23-40] seven used only CEUS for diagnosis,[6,8-13] and only one cohort study simultaneously compared the differential diagnosis between CEUS and CECT.[7] Fan *et al*[8] did not report the diagnostic standard of CECT for pancreatic lesions; thus, the CECT data were not included for data analysis. The characteristics of the included articles are summarized in [Table 1]. Regarding the subtype of MFP, 11 studies included AIP, and 15 studies included CMFP [seven studies were conducted with CEUS[6-10,12,13] and eight were conducted with CECT.[23,31,33,34,36-40] Of the 19 articles that evaluated CECT, 15 used multiphase contrast-enhanced images,[23,25-37,39,40] three used single/two-phase contrast-enhanced images, and one study did not report the phase. Twelve studies used thin slices (≤3 mm),[7,23,25-28,31-35,40] whereas the others used a slice thickness >3 mm

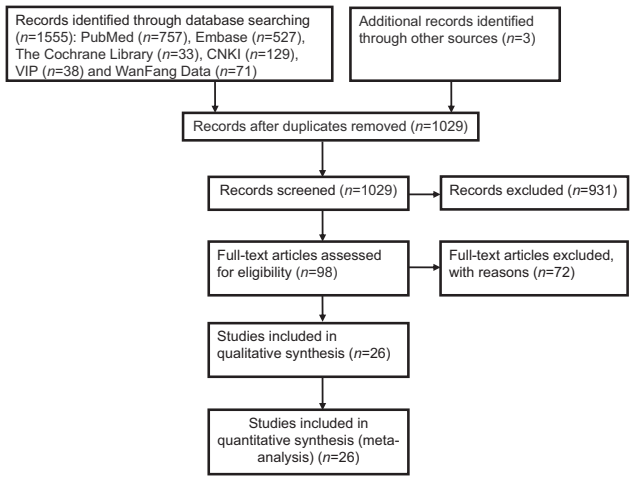

Figure 1: Flowchart of the studies' selection.

or did not report the slice thickness. Of the 26 studies, 20 studies involved multiple image raters (>2 raters),[8,9,24-29,31,33-35] and the remaining studies involved only one or an unclear number of image raters.

For the reference diagnosis of MFP, ten studies used only histopathology,[6,7,11,23,31,34,36,38-40] and the others used only clinical criteria or both histopathology and clinical criteria. For the reference diagnosis of PDAC, 18 studies used only histopathology,[6,7,9,23-29,31,32,34,35] and eight studies employed both clinical follow-up and histopathology. The detailed imaging criteria for differentiating MFP from PDAC in the 26 included studies are shown in [Supplementary Table 2, http://links.lww.com/CM9/B302].

Study quality of included studies

Based on the results of QUADAS-2, the quality assessment of the 26 included studies was considered good. The domain of flows and timing was the main quality issue because the patients included in 14 of the 26 studies were compared with more than one reference standard. Patient selection and reference standards were pivotal areas of quality concern, which performed well in the current study. Twenty-four studies included consecutive patients, while two studies included random or matched patients.[31,34] The other five studies did not clearly describe the patient selection process.[8,24,28-30] Eight studies reported patients with PDAC confirmed by histopathology or clinical follow-up results, while the other studies diagnosed MFP by various criteria. Thus, the reference standard bias of the included studies was unclear. A composed reference, to some extent, could avoid inappropriate exclusions but also cause a risk of bias in the reference standard. In addition, when we assessed the section of the index test, 11 studies were unclear about the information of the blinded review,[6,7,11,12,23,30,36-40] but had acceptable quality. The detailed assessed results are shown in [Figure 2A and 2B and Supplementary Tables 3A and 3B, http://links.lww.com/CM9/B302].

Table 1: Characteristics of the 26 eligible included articles.

Study	Country	Study design	No. analysed*	Sub-type of pancreatitis	Reference standard		Image test	Reviewer	CECT		
					MFP	PDAC			Phase	Slice	Channel
D'Onofrio *et al*[6]	Italy	Retros-	35/138	CMFP	His-	His-	CEUS	NA	–	–	–
Fan *et al*[8]	China	Retros-	28/36	CMFP	His-/clinical	His-/clinical	CEUS	Three	–	–	–
Wang *et al*[9]	China	Retros-	25/86	CMFP	His-/clinical	His-	CEUS	Two	–	–	–
Xie *et al*[10]	China	Retros-	8/42	CMFP	His-/clinical	His-/clinical	CEUS	Two	–	–	–
Xu and Feng[12]	China	Retros-	5/34	CMFP	His-/clinical	His-/clinical	CEUS	Two	–	–	–
Li *et al*[13]	China	Retros-	9/39	CMFP	His-/clinical	His-/clinical	CEUS	Three	–	–	–
Yuan *et al*[11]	China	Retros-	2/26	AIP	His-	His-	CEUS	Two	–	–	–
Grossjohann *et al*[7]	Denmark	Retros-	5/44	CMFP	His-	His-	CEUS/CECT	NA	Single	≤3	64
Chari *et al*[24]	USA	Retros-	48/100	AIP	HISORt	His-/clinical	CECT	Single	Single	>3	NA
Yamada *et al*[33]	Japan	Retros-	18/34	CMFP	His-/clinical	His-/clinical	CECT	Two	Three	≤3	NA
Brimiene *et al*[23]	USA	Pros-	58/88	CMFP	His-	His-	CECT	NA	Multiple	≤3	64
Kawai *et al*[27]	Japan	Retros-	55/50	AIP	HISORt/ JPC/ KDC	His-	CECT	Two	Multiple	≤3	≥64
Muhi *et al*[29]	Japan	Retros-	11/70	AIP	JPC	His-	CECT	Three	Multiple	5	16
Naitoh *et al*[30]	Japan	Retros-	36/60	AIP	JPC/rHISORt	His-/clinical	CECT	Single	Multiple	NA	NA
Sun *et al*[32]	China	Retros-	19/30	AIP	ADCA	His-	CECT	Three	Multiple	≤3	≤64
Zaheer *et al*[35]	USA	Retros-	32/32	AIP	His-/ICDC	His-	CECT	Three	Multiple	<3	128
Furuhashi *et al*[26]	Japan	Retros-	23/61	AIP	ICDC/JPC	His-	CECT	Two	Multiple	≤2	64
Yin *et al*[34]	China	Retros-	15/20	CMFP	His-	His-	CECT	Three	Two	2.5	64
Lee *et al*[28]	Korea	Retros-	61/122	AIP	HISORt/ICDC	His-	CECT	Two	Multiple	<3	≥64
Ren *et al*[31]	China	Retros-	21/47	CMFP	His-	His-	CECT	Two	Multiple	<3	≥64
Linning *et al*[25]	China	Retros-	45/51	AIP	His-/ICDC	His-	CECT	Two	Multiple	≤3	256
Luo *et al*[37]	China	Retros-	25/31	CMFP	His-/clinical	His-/clinical	CECT	Two	Multiple	6	16
Lv *et al*[38]	China	Retros-	42/59	CMFP	His-	His-	CECT	Two	Multiple	5	320
Wang *et al*[39]	China	Retros-	32/36	CMFP	His-	His-	CECT	NA	NA	6	64
Zhu and Lu[40]	China	Retros-	21/21	AIP	His-	His-	CECT	Two	Multiple	1	320
Guo[36]	China	Retros-	45/45	CMFP	His-	His-	CECT	Three	Multiple	5	32

*Numbers of MFP/ADCA lesions. ADCA: The Asian Diagnostic Criteria for Autoimmune Pancreatitis; AIP: Autoimmune pancreatitis; Clinical: Clinical diagnosis; CMFP: Chronic mass-form pancreatitis; CECT: Contrast-enhanced computed tomography; CEUS: Contrast-enhanced ultrasound; His-: Histological diagnosis; HISORt: Histology, imaging, serology, other organ involvement, and response to steroid therapy; ICDC: International Consensus Diagnostic Criteria; JPC: Japanese diagnostic criteria; KDC: Korean diagnostic criteria; MFP: Mass-forming pancreatitis; NA: Not available; Pros-: Prospective; PDAC: Pancreatic ductal adenocarcinoma; Retros-: Retrospective study; rHISORt: Revised histology, imaging, serology, other organ involvement, and response to steroid therapy.

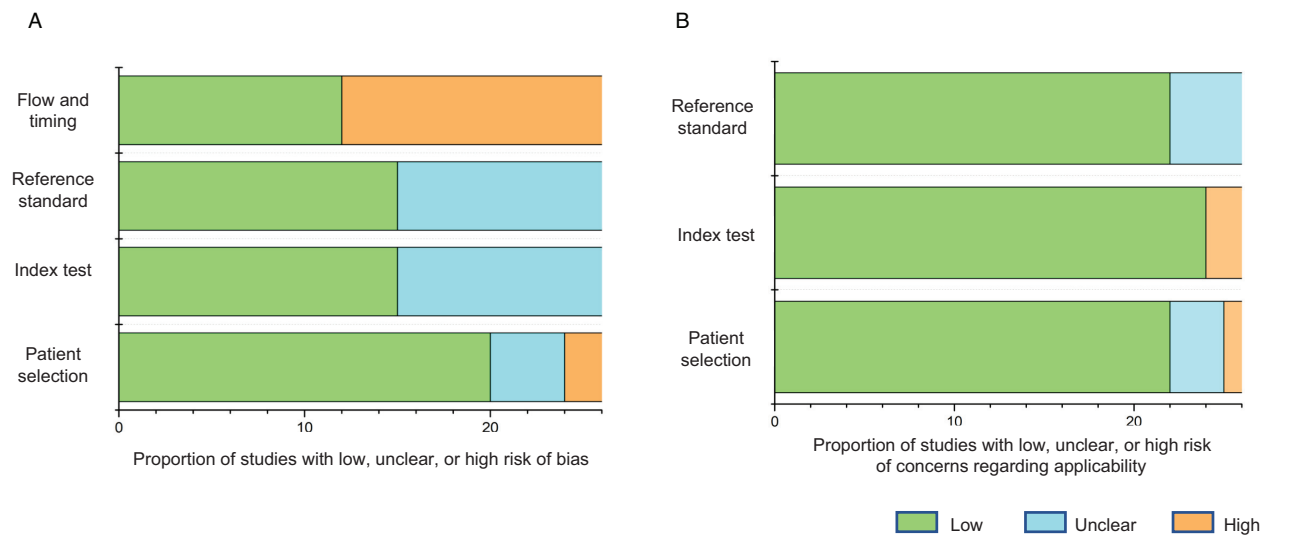

Figure 2: Quality assessment of the studies according to QUADAS-2 criteria. (A) The methodological quality of the articles is presented as the proportion of 26 articles with low (ie, high quality), or high risk of bias; and (B) the proportion of articles with low, or high unclear concerns regarding the applicability of each domain. The *X* axis presents the numbers of the included 26 articles. QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies 2.

Diagnostic performance of CEUS and CECT for differentiating MFP from PDAC

There was no significant threshold effect among the eight studies (562 lesions) that used CEUS (Spearman correlation coefficient = 0.270, $P = 0.518$). The sensitivities (72%–100%) and specificities (86%–100%) of CEUS and the 95% CI of each study are presented in [Figure 3A]. The pooled sensitivity and specificity values for CEUS were 82% (95% CI, 73%–88%; $I^2 = 0.00\%$) and 95% (95% CI, 90%–97%; $I^2 = 63.44\%$), respectively. The pooled +LR, −LR, and DOR values were 15.12 (95% CI, 7.61–30.01), 0.19 (95% CI, 0.13–0.29), and 78.91 (95% CI, 30.94–201.27), respectively [Supplementary Figure 1A,B, http://links.lww.com/CM9/B303], and the SROC value was high (AUC = 0.90; 95% CI, 0.87–0.92; Figure 4A).

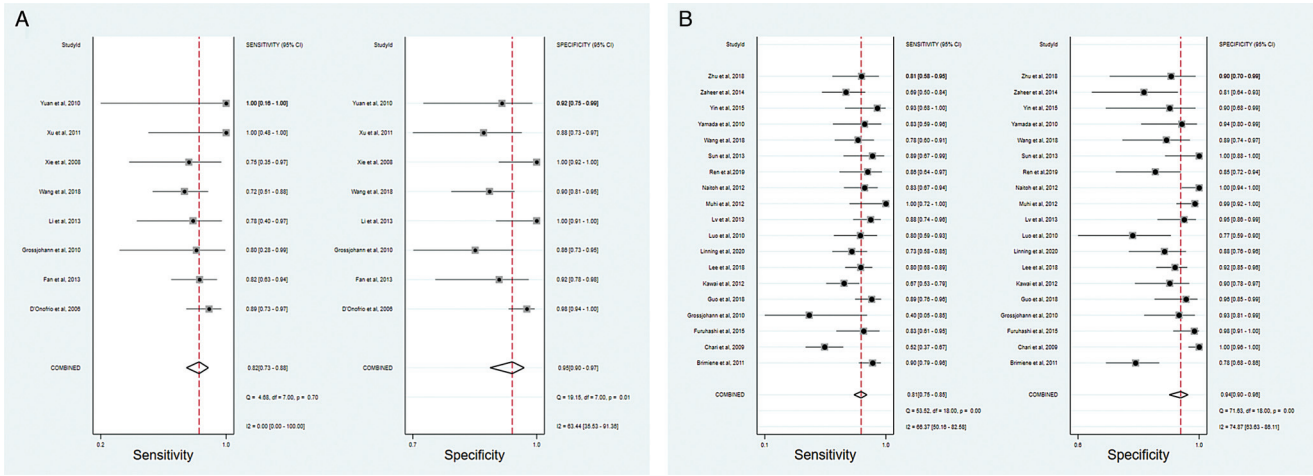

Figure 3: Coupled forest plots of the sensitivity and specificity for the differential diagnosis of MFP from PDAC on CEUS (A) and CECT (B). CECT: Contrast-enhanced computed tomography; CEUS: Contrast-enhanced ultrasound; MFP: Mass-forming pancreatitis; PDAC: Pancreatic ductal adenocarcinoma.

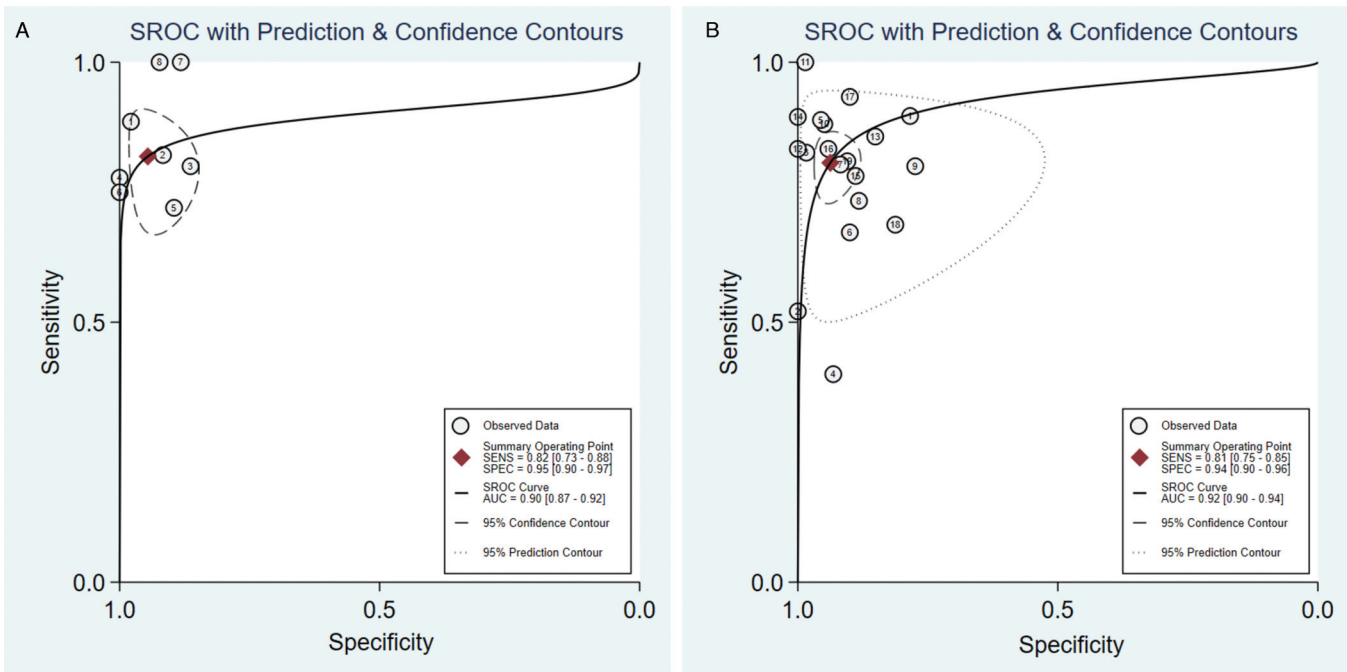

Figure 4: SROC of the sensitivity and specificity for the differential diagnosis of MFP from PDAC on CEUS (A) and CECT (B). CECT: Contrast-enhanced computed tomography; CEUS: Contrast-enhanced ultrasound; SROC: Summary receiver operating characteristic; MFP: Mass-forming pancreatitis; PDAC: Pancreatic ductal adenocarcinoma.

For the 19 CECT studies, no significant threshold effect was found (Spearman correlation coefficient = 0.007, $P = 0.076$). The pooled sensitivity and specificity for MFP and the 95% CI of each study are shown in Figure 3B. The pooled sensitivity and specificity were 81% (95% CI, 75–85%; $I^2 = 66.37\%$) and 94% (95% CI, 90–96%; $I^2 = 74.87\%$), respectively. The pooled +LR, −LR, and DOR values were 12.91 (95% CI, 7.86–21.20), 0.21 (95% CI, 0.16–0.27), and 62.53 (95% CI, 34.45–113.51), respectively [Supplementary Figure 1C,D, http://links.lww.com/CM9/B303], and the SROC AUC was 0.92 (95% CI, 0.90–0.94; Figure 4B). A summary of the data about the two modalities reported in the 26 studies is shown in [Table 2].

Based on the result of adjusted indirect comparison, the results showed that CEUS and CECT had comparable overall diagnostic accuracy for the differentiation of MFP from PDAC (relative DOR [RDOR] = 1.26, 95% CI [0.42–3.83], $P > 0.05$; Figure 5).

Meta-regression analysis

The heterogeneity of pooled sensitivity on CEUS for MFP was acceptable; however, moderate heterogeneity ($I^2 = 63.44\%$) in the pooled specificity of CEUS was observed. The meta-regression analysis results are shown in [Supplementary Table 4, http://links.lww.com/CM9/B302]. The results indicated that all factors were not

Table 2: The diagnostic performance of CEUS and CECT for differentiating MFP from PDAC.

Study	No. of patients	Number of patients				Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
		TP	FP	FN	TN		
CEUS							
D'Onofrio *et al*[6]	173	31	3	4	135	89 (73–97)	98 (94–100)
Grossjohann *et al*[7]	49	4	6	1	38	80 (28–99)	86 (73–95)
Fan *et al*[8]	64	23	3	5	33	82 (63–94)	92 (78–98)
Wang *et al*[9]	111	18	9	7	77	72 (51–88)	90 (81–95)
Xu and Feng [12]	39	5	4	0	30	100 (48–100)	88 (73–97)
Yuan *et al*[11]	28	2	2	0	24	100 (16–100)	92 (75–99)
Li *et al*[13]	48	7	0	2	39	78 (40–97)	100 (91–100)
Xie *et al*[10]	50	6	0	2	42	75 (35–97)	100 (92–100)
Higgins I^2 for heterogeneity*						0.00	63.44
Meta-analytic summary estimate using the bivariate model						82 (73–88)	95 (90–97)
CECT							
Chari *et al*[24]	148	25	0	23	100	52 (37–67)	100 (96–100)
Grossjohann *et al*[7]	49	2	3	3	41	40 (5–85)	93 (81–99)
Yamada *et al*[33]	52	15	2	3	32	83 (59–96)	94 (80–99)
Brimiene *et al*[23]	146	52	19	6	69	90 (79–96)	78 (68–86)
Muhi *et al*[29]	81	11	1	0	69	100 (72–100)	99 (92–100)
Kawai *et al*[27]	105	37	5	18	45	67 (53–79)	90 (78–97)
Naitoh *et al*[30]	96	30	0	6	60	83 (67–94)	100 (94–100)
Sun *et al*[32]	49	17	0	2	30	89 (48–84)	97 (85–100)
Zaheer *et al*[35]	64	22	6	10	26	69 (50–84)	81 (64–93)
Furuhashi *et al*[26]	84	19	1	4	60	83 (61–95)	98 (91–100)
Yin *et al*[34]	35	14	2	1	18	93 (68–100)	90 (68–99)
Lee *et al*[28]	183	49	10	12	112	80 (68–89)	92 (85–96)
Ren *et al*[31]	68	18	7	3	40	86 (64–97)	85 (72–94)
Linning *et al*[25]	96	33	6	12	45	73 (58–85)	88 (76–96)
Wang *et al*[39]	68	25	4	7	32	78 (60–91)	89 (74–97)
Zhu *and Lu*[40]	42	17	2	4	19	81 (58–95)	90 (70–99)
Luo *et al*[37]	56	20	7	5	24	80 (59–93)	77 (59–90)
Guo[36]	90	40	2	5	43	89 (76–96)	96 (85–99)
Lv *et al*[38]	101	37	3	5	56	88 (74–96)	95 (86–99)
Higgins I^2 for heterogeneity						66.37	74.87
Meta-analytic summary estimate using the bivariate model						81 (75–85)	94 (90–96)

* The value of I^2: 0% to 25%, heterogeneity might not be important; 25% to 50%, may represent low heterogeneity; 50% to 75%, may represent moderate heterogeneity; 75% to 100%, high heterogeneity. CI: Confidence index; CECT: Contrast-enhanced computed tomography; CEUS: Contrast-enhanced ultrasound; FP: False positive; FN: False negative; MFP: Mass-form pancreatitis; PDAC: Pancreatic ductal adenocarcinoma; TP: True positive; TN: True negative.

strongly associated with the specificity of CEUS for differentiating MFP from PDAC (all $P \geq 0.05$). Furthermore, no publication bias was found for the CEUS studies ($t = -0.55$, $P > |t| = 0.60$; Supplementary Figure 2A, http://links.lww.com/CM9/B303).

The results of the meta-regression analysis of CECT are summarized in [Table 3]. The publication year, subtype of pancreatitis, CT slice thickness (meets the $\leq$3 mm), CT channels, blinded review, and single reference criteria for MFP were significant factors associated with the study heterogeneity of the sensitivity on CECT (all $P \leq 0.02$). In addition, CT slice thickness ($\leq$3 mm), CT channels, the presence of more than two reviewers, and the use of a single reference criteria for PDAC were significantly associated with the study heterogeneity for the specificity of CECT (all $P \leq 0.02$). No remarkable publication bias was found in the CECT studies ($t = 0.12$, $P > |t| = 0.91$; Supplementary Figure 2B, http://links.lww.com/CM9/B303).

Discussion

Patients with MFP or PDAC present similar clinical symptoms but require different treatment approaches, and have different survival outcomes. Therefore, it is necessary for clinicians to differentiate between MFP and PDAC. The current systematic review found that the summary diagnostic accuracy of CEUS was comparable to that of CECT for the differentiation of MFP from PDAC (RDOR = 1.26, 95% CI [0.42–3.83], $P > 0.05$).

The diagnostic sensitivity of CEUS for MFP was consistent with two recent studies that reported that CEUS had a

higher sensitivity than CECT (80% *vs*. 40%, $P = 0.003$; and 82% *vs*. 68%, $P = 0.253$, respectively).[7,8] Due to its ability to provide real-time continuous visualization of the blood perfusion of the pancreas and its masses, CEUS has been increasingly used for the diagnosis of pancreatic lesions.[4,5,14] Based on this unique imaging characteristic, MFP on CEUS showed slight iso/hyperenhancement of contrast compared to the adjacent normal pancreatic parenchyma.[5,8,9] In contrast to CEUS, CECT could not be used to visualize transient enhancement features due to the fixed time point and the fixed slice thickness.

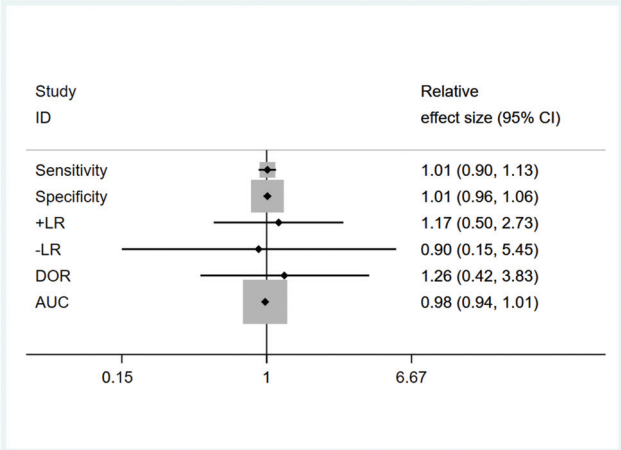

Figure 5: The overall diagnostic performance of contrast-enhanced ultrasound and contrast-enhanced computed tomography for differentiating mass-forming pancreatitis from pancreatic ductal adenocarcinoma by using network meta-regression analysis. AUC: Area under the SROC curve; DOR: Diagnostic odds ratio; LR: likelihood ratio.

Furthermore, it is not recommended that patients with chronic pancreatitis repeatedly undergo CT examination within a short period of time. Of note, CEUS showed the specific enhancement characteristics of MFPs in patients with the disease. Therefore, CEUS could play a key role in evaluating treatment efficiency.

D'Onofrion *et al*[5,41] reported that for PDAC, the diagnostic sensitivity of CEUS was comparable to that of CECT (86.47% *vs*. 83.58%). Therefore, if conventional ultrasound detects a suspected pancreatic mass, CEUS might be recommended to identify the characteristics of PDAC. This meta-analysis also found that CEUS had a slightly higher overall sensitivity than CECT for differentiating PDAC from MFP (95% *vs*. 94%), which was inconsistent with the results of the most recent studies.[7,8] The various definitions of PDAC in CECT image features might explain the low summary sensitivity in CECT reports.[24,25,35,37] On the other hand, PDAC showed hypoenhancement in all phases on CEUS due to its abundant fibrosis and desmoplasia.[5] The results of the meta-analysis suggest that the imaging characteristics of PDAC on CECT require a relatively unified standard and that CEUS and CECT are mutually complementary for suspected focal pancreatic malignant lesions.

Of the 19 CT reviewed studies, Chari *et al*[24] reported high specificity (100%) but low sensitivity (52%) for CECT when differentiating MFP from PDAC. The imaging criteria of AIP were diffuse pancreatic enlargement without a low-density mass, pancreatic duct cutoff, or distal pancreatic atrophy, which were inconsistent with the typical imaging features of pancreatitis.[2]

Table 3: Results of the meta-regression analysis on the CECT studies.

Covariate	Subgroup	Sensitivity (%, 95% CI)	*P* values	Specificity (%, 95% CI)	*P* values
Country of publication	Asia ($n = 15$)	83 (78–88)	0.43	94 (91–97)	0.18
	Non-Asia ($n = 4$)	70 (56–83)	–	92 (85–100)	–
Patients' numbers	$\leq$ 50 ($n = 4$)	83 (71–95)	0.17	95 (89–100)	0.35
	> 50 ($n = 15$)	80 (75–84)	–	92 (89–96)	–
Publication year	Before 2015 ($n = 13$)	80 (75–86)	<0.01	93 (90–97)	0.17
	Year 2015 and after ($n = 6$)	82 (74–90)	–	91 (84–98)	–
Sub-type of pancreatitis	CMFP ($n = 9$)	85 (80–91)	<0.01	90 (84–96)	0.16
	AIP ($n = 10$)	76 (69–83)	–	96 (93–99)	–
CT slice thickness	$\leq$3 mm ($n = 12$)	80 (74–86)	<0.01	92 (92–92)	<0.01
	>3 mm ($n = 7$)	81 (74–89)	–	96 (93–99)	–
CT multi-phase	Yes ($n = 16$)	83 (78–87)	0.76	93 (90–97)	0.05
	No ($n = 3$)	61 (46–77)	–	96 (92–100)	–
Multiple CT channel	Yes ($n = 13$)	81 (75–87)	0.01	91 (87–96)	<0.01
	No ($n = 6$)	81 (72–90)	–	97 (94–100)	–
Image reviewer	Single reviewer ($n = 5$)	75 (64–86)	0.12	95 (92–98)	0.02
	Multiple reviewers ($n = 14$)	83 (77–88)	–	93 (89–97)	–
Blinded to read	Clear ($n = 11$)	77 (70–84)	<0.01	95 (91–98)	0.06
	Unclear ($n = 8$)	84 (78–90)	–	92 (87–98)	–
Reference criteria for MFP	Single criteria ($n = 11$)	83 (77–89)	0.02	95 (91–98)	0.05
	Combine $\geq$2 criteria ($n = 8$)	77 (70–85)	–	93 (88–98)	–
Reference criteria for PDAC	Histologic criteria ($n = 15$)	82 (77–87)	0.18	93 (89–96)	0.02
	Histologic and clinical criteria ($n = 4$)	74 (62–86)	–	97 (93–100)	–

AIP: Autoimmune pancreatitis; CMFP: Chronic mass-form pancreatitis; CI: Confidence index; CECT: Contrast-enhanced computed tomography; MFP: Mass-form pancreatitis; PDAC: Pancreatic ductal adenocarcinoma.

Grossiohann *et al*[7] reported a low sensitivity of CECT (40%) and a high sensitivity of CEUS (80%) based on the characteristics of CMFP with isoechogenic lesions in 49 patients; these results were consistent with the current study and indicated that CEUS was a useful tool for differentiating pancreatitis from PDAC.[4] Both studies reported the diagnostic performance of each CECT feature; however, the evaluated data varied according to the feature analyzed. Therefore, further studies combining multiple imaging features should be conducted to further elucidate the diagnostic performance of these imaging tests.

The meta-regression analysis failed to elucidate the factors that caused the moderate heterogeneity in overall specificity among the CEUS studies (all $P > 0.05$). To examine the cause of the considerable heterogeneity in the CECT studies, meta-regression was performed, and the results indicated that certain CT parameters (thin-slice and multiple CT channels) affected the heterogeneity in both the sensitivity and specificity of CECT ($P \leq 0.01$). Overall, the use of advanced equipment for CECT could yield more information about pancreatic lesions, which might also explain why the studies published after 2015 showed higher overall sensitivity than those published before 2015 (82% *vs*. 80%, $P < 0.01$). Although the diagnosis of CMFP had higher sensitivity than that of AIP by CECT, the combination of imaging features and IgG4 serum levels might improve the diagnostic accuracy.[42] Interestingly, we found that a single rater had higher specificity than multiple raters and that blinded reviews showed lower sensitivity than those with unclear information (all $P < 0.05$). Some CECT-related studies did not provide detailed information about the radiological image analyses, which might have influenced the diagnostic results.[7,23,30,36,38-40] Therefore, it was suggested that in later related studies, the standards for analyses should be included. The included articles had various reference standards for the target patients. Interestingly, the meta-regression results showed that a single reference standard for MFP or PDAC had significantly higher diagnostic performance (all $P = 0.020$). These results suggested that using a single gold standard for the included patients was beneficial for improving the diagnostic heterogeneity.

This study has some limitations. First, most of the original studies were originally designed to examine the performance of only one of the two modalities, and thus, the effect of the characteristics of different patients could not be avoided. Although we performed a Bayesian network meta-analysis to indirectly compare the overall diagnostic performance of the two modalities, more original studies should be designed to directly compare the two diagnostic tests. Second, substantial study heterogeneity was found in terms of both the overall sensitivity and specificity of CECT/CEUS. Therefore, we used a meta-regression analysis to explore the reason for this study heterogeneity, and the results suggested that advanced imaging modality and a standardized imaging analysis and reporting system would help to improve the diagnostic heterogeneity. Third, AIP was a unique type of chronic pancreatitis related to an autoimmune mechanism,[43] and the meta-analysis failed to compare the performance of CEUS and CECT in the differential diagnosis of AIP and PDAC because of the limited number of studies.[11] Additional studies are needed to evaluate the diagnostic accuracy of CEUS in the differentiation of AIP from PDAC. Finally, the study excluded certain types of literature, such as letters, conference abstracts, and unpublished data, which might raise concerns over publication bias. However, the data from these trials could not be accurately extracted for further meta-analysis.

In conclusion, both CEUS and CECT have outstanding sensitivity for the diagnosis of PDAC; however, they have suboptimal sensitivity for the diagnosis of MFP. This results of this work indicated that the overall diagnostic performance of CEUS for pancreatic tumors is similar to that of CECT. Taking into account the characteristics of the two imaging modalities and the patient's condition, CEUS and CECT should be considered mutually complementary diagnostic tools for suspected focal pancreatic lesions.

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Conflicts of interest

None.

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