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● *Review Article*

# VALUE OF LOW-MECHANICAL-INDEX CONTRAST-ENHANCED TRANSABDOMINAL ULTRASOUND FOR DIAGNOSIS OF PANCREATIC CANCER: A META-ANALYSIS

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**Abstract—The incidence and mortality rates of pancreatic cancer (PC) are increasing. It is important to discriminate PC from the other pancreatic lesions; however, differential diagnosis based on conventional transabdominal ultrasound (US) remains challenging even though US is often the first examination performed. Transabdominal contrast-enhanced ultrasound (CEUS) has high diagnostic accuracy for PC. This meta-analysis aimed to examine the utility of low-mechanical-index CEUS with enhancement for PC diagnosis. A systematic meta-analysis of all potentially relevant articles was performed. Fixed-effects or random-effects models were used to investigate pooled sensitivity, specificity, positive likelihood ratio (LR) and negative LR. The study enrolled 983 patients from nine eligible studies. The pooled estimates of sensitivity and specificity were 92% (95% confidence interval [CI]: 0.89−0.94) and 76% (95% CI: 0.71−0.81), respectively. The diagnostic odds ratio (DOR) for CEUS was high (53.62). The area under the summary receiver operating characteristic curve was 0.95. Funnel plots revealed no publication bias, and there was no significant relationship between the DORs and study characteristics, including continent, type of contrast agent, contrast agent dosage and scan phase. Only number of patients affected diagnostic ability. This meta-analysis indicates that CEUS with enhancement pattern is useful for diagnosis of PC. (E-mail: kitano@wakayama-med.ac.jp)** 

*Key Words:* **Contrast-enhanced transabdominal ultrasound, Enhancement pattern, Low mechanical index, Meta-analysis, Pancreatic cancer.**

## INTRODUCTION

Despite the rapid development of imaging modalities, the incidence and mortality rates of pancreatic cancer (PC) are rising rapidly; indeed, PC is the fourth leading cause of cancer-related death in the United States (Siegel et al. 2017). In 2017, there were 448,000 cases of PC worldwide, a figure that is 2.3 times higher than the 196,000 cases recorded in 1990 (Global Burden of Disease Study 2017 Pancreatic Cancer Collaborators 2019). Moreover, PC is still diagnosed in the advanced stage. Initial screening for PC is performed using transabdominal ultrasound (US), because it is the most convenient, simple and cost-effective diagnostic tool; also, the patient is not exposed to ionizing radiation. However, US alone has limitations with respect to differentiating PC from benign solid pancreatic lesions as most solid pancreatic lesions appear as hypo-echoic lesions (Martínez-Noguera and D'Onofrio 2007). Therefore, contrast-enhanced US (CEUS), which allows evaluation of the vascularization of pancreatic lesions, improves characterization and differentiation.

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Currently, low-mechanical-index CEUS is the most accurate technique for investigating pancreatic lesions because it allows real-time depiction of microvessels and parenchymal perfusion without Doppler-related artifacts. Indeed, many studies report the utility of CEUS for differential diagnosis of pancreatic lesions (D'Onofrio et al. 2005, 2006; Dietrich et al. 2008; Grossjohann et al. 2010; Vasile et al. 2012; Serra et al. 2013; Miwa et al. 2014; Wang et al. 2018; Tanaka et al. 2020).

Three meta-analyses have examined the use of CEUS for differential diagnosis of pancreatic lesions (Lin et al. 2016; Ran et al. 2017; Li et al. 2018); however, these reports included high- mechanical-index CEUS, cystic lesions and other diagnostic criteria for pancreatic cancer, such as the presence of vessels in the tumor, a heterogeneous enhancement pattern and quantitative analysis with time−intensity curves. Therefore, we performed a meta-analysis of the utility of CEUS for diagnosis of PC using unified criteria (*i.e.,* enhancement pattern). Moreover, we included only current state-of-the-art low-mechanical-index CEUS techniques. Finally, we analyzed differences in study characteristics (*e.g.,* continent, type of contrast agent, contrast agent dosage, scan phase and number of patients).

## RESEARCH METHODS

The PubMed, Cochrane library and Google Scholar databases were searched for relevant English-language full-text articles using the following key words: (“pancreatic cancer” OR “pancreatic mass” OR “pancreatic carcinoma” OR “pancreatic lesions”) AND (“contrast-enhanced” OR “echo enhanced” OR “contrast enhancement”) AND (“US” OR “ultrasound” OR “ultrasonography”). All pertinent articles were checked carefully to identify further relevant articles.

## INCLUSION AND EXCLUSION CRITERIA

The inclusion criteria were as follows: PC diagnosed by CEUS with a hypo-enhancement pattern; low-mechanical-index CEUS; final diagnoses determined by histopathological examination or clinical follow-up for at least 12 mo; and provision of sufficient data to allow determination of true-positive, false-positive, false-negative and true-negative rates. The “hypo-enhancement pattern” was defined as a pattern of enhancement in which vascularity was lower than that of the surrounding pancreatic tissue on CEUS during the early or late phase. When the pattern was hypo-enhancement, the CEUS diagnosis was PC (Fig. 1). All reports that used the same definition of “hypo-enhancement pattern” were included. In all reports, informed consent was obtained from each study participant, and the protocol was approved by an ethics committee or institutional review board.

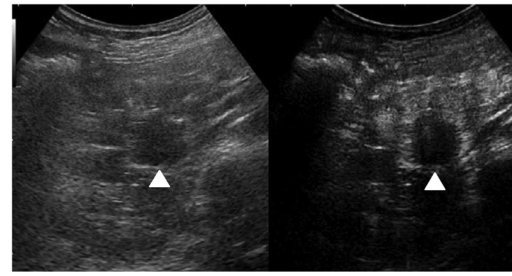

Fig. 1. Representative case of pancreatic cancer with hypo-enhancement pattern by contrast-enhanced transabdominal ultrasound. A hypo-echoic lesion 10 mm in size (*arrowheads*) was depicted in the pancreas using fundamental B-mode ultrasound observation systems (ARIETTA 850; Hitachi Aloka Medical, Ltd, Tokyo, Japan) (left). After reconstitution with 2 mL of sterile water for injection, 0.7 mL of Sonazoid (GE Healthcare, Tokyo, Japan) was administered through a peripheral vein. Contrast-enhanced transabdominal ultrasound (right) revealed that the lesion (*arrowheads*) was hypo-enhancing compared with the surrounding pancreatic tissue during the late phase.

The exclusion criteria were as follows: a cystic pancreatic lesion; lack of complete data; and conference abstracts, case reports, reviews and editorials. Cystic lesions were excluded because it is difficult to include both solid and cystic lesions in a meta-analysis because of the different classifications of contrast enhancement (D'Onofrio et al. 2012).

## STATISTICAL METHODS

The pooled estimates of sensitivity, specificity and DORs were obtained using Meta-Disc Version 1.4. Pooled results were analyzed using a fixed effect model (Mantel−Haenszel method) when no significant heterogeneity was present and using a random-effects model (DerSimonian−Laird method) when significant heterogeneity was present (Bell et al. 2019). The heterogeneity of the studies was evaluated using the Cochrane $Q$-test and the $I^2$ statistic. A summary receiver operating characteristics (SROC) curve was constructed, and the area under the SROC was calculated.

Meta-regression analysis was performed using the following data: contrast agent = SonoVue (sulfur hexafluoride microbubbles, Bracco, Italy) or Sonazoid (perfluorobutane microbubbles, GE Healthcare, Japan); continent = Europe or Asia; contrast agent dosage (continuous variable); scan phase = early or late phase; and number of patients $\leq$80 or $>$80. A funnel plot, constructed using R3.4.3, was used to investigate publication bias. A subgroup analysis was carried out after exclusion of outliers. $p$ Values $< 0.05$ were considered to indicate statistical significance. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was used to assess the quality of the selected studies.

## RESULTS

*Study selection and quality assessment*

A total of 873 articles were identified from PubMed, the Cochrane library and Google Scholar. After application of the inclusion and exclusion criteria, 9 articles (D'Onofrio et al. 2005, 2006; Dietrich et al. 2008; Grossjohann et al. 2010; Vasile et al. 2012; Serra et al. 2013; Miwa et al. 2014; Wang et al. 2018; Tanaka et al. 2020) (983 patients in total) were selected for the final analysis. Two studies were published by the same authors (D'Onofrio et al.). However, before performing the present meta-analysis, we confirmed that these studies did not overlap in any way. Figure 2 is a flowchart detailing the study selection process, and Table 1 lists the main characteristics of the studies. QUADAS-2 assessment of the included studies revealed that most had a low risk of bias (Fig. 3 and Table 2).

*Diagnostic value*

The pooled estimates of sensitivity and specificity for the diagnosis of PC were 92% (95% confidence interval [CI]: 89%−94%) and 76% (95% CI: 71%−81%), respectively (Figs. 4 and 5). The pooled positive likelihood and negative LRs were 5.21(95% CI: 2.80−9.65) and 0.12 (95% CI: 0.08−0.17), respectively (Figs. 6 and 7). CEUS was useful for the diagnosis of pancreatic cancer, with a high value for the DOR (53.62; Fig. 8). The area under the SROC was 0.95 (Fig. 9). Funnel plots did not identify publication bias (Fig. 10).

*Meta-regression*

There was no significant relationship between the DOR and the study characteristics (*e.g.,* continent [Europe vs. Asia], contrast agent [SonoVue vs. Sonazoid], contrast agent dosage [continuous variable] and scan phase [early vs. late]). Only number of patients affected diagnostic ability (Table 3). Assessment of meta-regression detected three outliers (D'Onofrio et al. 2005; Grossjohann et al. 2010; Vasile et al. 2012), and subgroup analysis consisted of the main results after exclusion of the three outliers (Table 4).

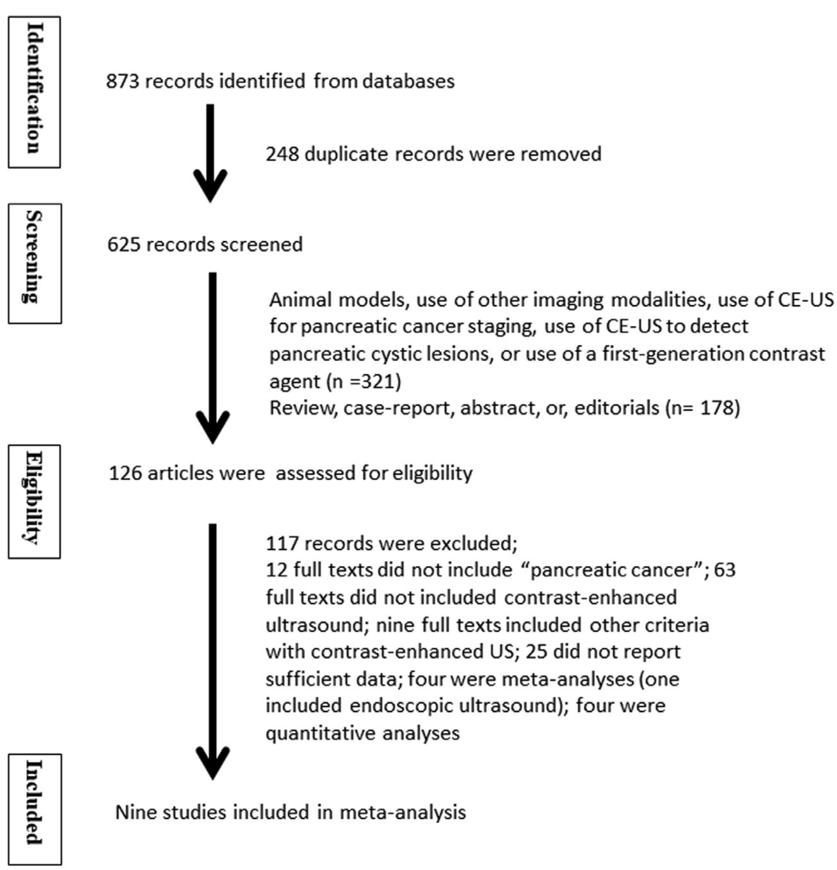


Fig. 2. Flowchart of the study selection process. A total of 873 articles were identified. After application of the inclusion and exclusion criteria, 983 patients from nine eligible studies were selected for the final analysis. CE-US = contrast-enhanced ultrasound.

Table 1. Characteristics of the selected studies

| Study | Publication | Country | No. of patients | Sex (M/F) | Age | Diagnostic standard | Contrast agent | Gold standard |
|---|---|---|---|---|---|---|---|---|
| Tanaka et al. 2020 | Full text | Japan | 200 | 108/92 | 66 | Hypo-enhancement | Sonazoid | Histology follow-up (>24 m) |
| Wang et al. 2018 | Full text | China | 136 | — | — | Hypo-enhancement | SonoVue | Histology follow-up (>12 m) |
| Miwa et al. 2014 | Full text | Japan | 85 | 47/38 | 68 | Hypo-enhancement | Sonazoid | Histology follow-up (>12 m) |
| Serra et al. 2013 | Full text | Italy | 127 | 76/68 | 67.2 | Hypo-enhancement | SonoVue | Histology |
| Vasile et al. 2012 | Full text | Romania | 59 | — | — | Hypo-enhancement | SonoVue | Histology |
| Grossjohann et al. 2010 | Full text | Denmark | 49 | 26/23 | 66 | Hypo-enhancement | SonoVue | Histology |
| Dietrich et al. 2008 | Full text | Germany | 112 | — | — | Hypo-enhancement | SonoVue | Histology |
| D'Onofrio et al. 2006 | Full text | Italy | 173 | — | — | Hypo-enhancement | SonoVue | Histology |
| D'Onofrio et al. 2005 | Full text | Italy | 42 | — | — | Hypo-enhancement | SonoVue | Histology |

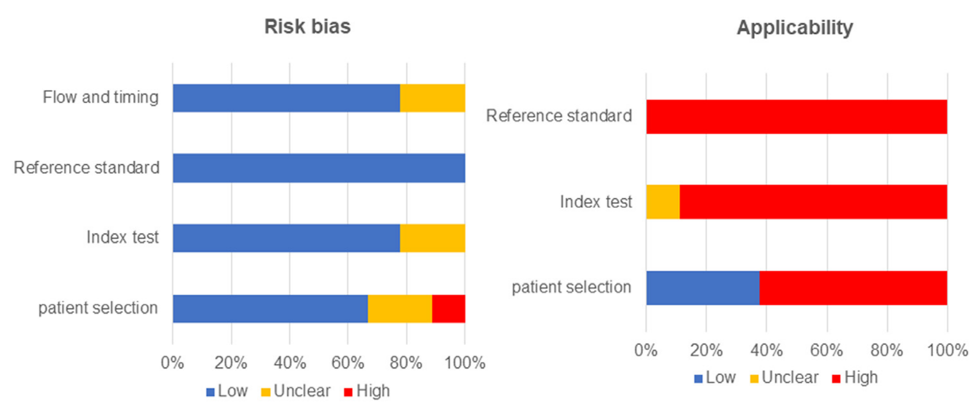


Fig. 3. Quality assessment of studies according to Quality Assessment of Diagnostic Accuracy Studies 2. Red: high risk of bias; yellow: unclear risk of bias; blue: low risk of bias. QUADAS-2 assessment of the included studies revealed that most had a low risk of bias.

Table 2. Quality assessment of studies according to QUADAS-2

| | Risk bias | | | | Applicability concerns | | |
|---|---|---|---|---|---|---|---|
| | Patient selection | Index test | Reference standard | Flow and timing | Patient selection | Index test | Reference standard |
| Tanaka et al. 2020 | Unclear | Low | Low | Low | High | High | High |
| Wang et al. 2018 | Low | Low | Low | Low | High | High | High |
| Miwa et al. 2014 | Low | Low | Low | Low | Low | High | High |
| Serra et al. 2013 | Low | Low | Low | Low | Low | High | High |
| Vasile et al. 2012 | Low | Low | Low | Low | High | High | High |
| Grossjohann et al. 2010 | Low | Low | Low | Low | Low | High | High |
| Dietrich et al. 2008 | Low | Low | Low | Unclear | Low | High | High |
| D'Onofrio et al. 2006 | High | Unclear | Low | Unclear | High | Unclear | High |
| D'Onofrio et al. 2005 | Unclear | Unclear | Low | Low | High | High | High |

QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2.
QUADAS-2 assessment of the included studies revealed that most had a low risk of bias.

## DISCUSSION

This meta-analysis on the utility of CEUS with assessment of the enhancement pattern revealed a pooled sensitivity and specificity of 92% and 76%, respectively, for diagnosis of pancreatic cancer. In this study, there was significant inconsistency ($I^2 > 50\%$ and $p < 0.05$) among parameters such as sensitivity, specificity, positive LR, negative LR and DOR. Therefore, we performed meta-regression analysis of contrast agent dosage, scan phase, number of patients, continent and type of contrast agent to determine the reason for this inconsistency. Meta-regression analysis revealed that only the number of patients affected diagnostic ability. Therefore, we performed a subgroup analysis of the number of patients. The results indicated that the significant inconsistency between sensitivity and negative LR was improved, suggesting that the small

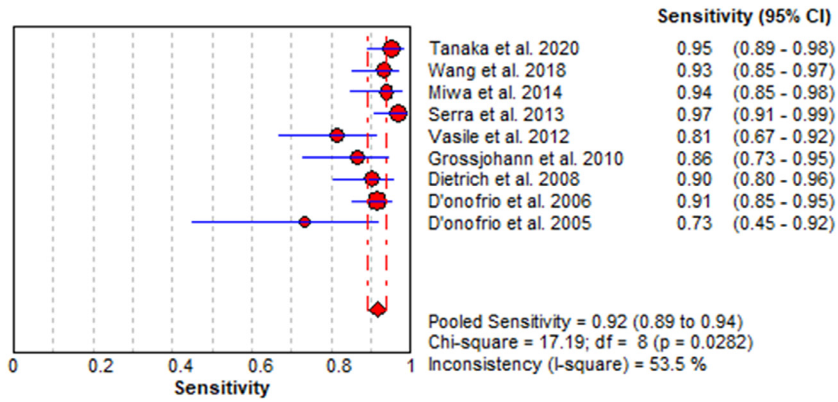


Fig. 4. Forest plots of the pooled sensitivity of contrast-enhanced transabdominal ultrasound for diagnosis of pancreatic cancer. The pooled estimate of sensitivity for the diagnosis of pancreatic cancer was 92% (95% confidence interval [CI]: 89%–94%).

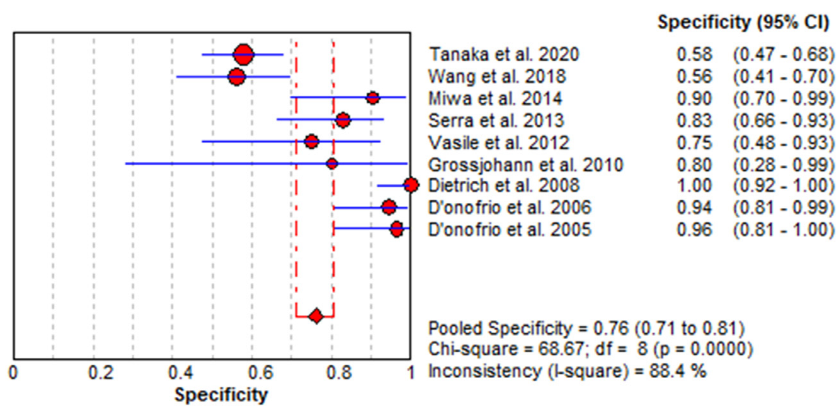


Fig. 5. Forest plots of the pooled specificity of contrast-enhanced transabdominal ultrasound for diagnosis of pancreatic cancer. The pooled estimate of specificity for the diagnosis of pancreatic cancer was 76% (95% confidence interval [CI]: 71%–81%).

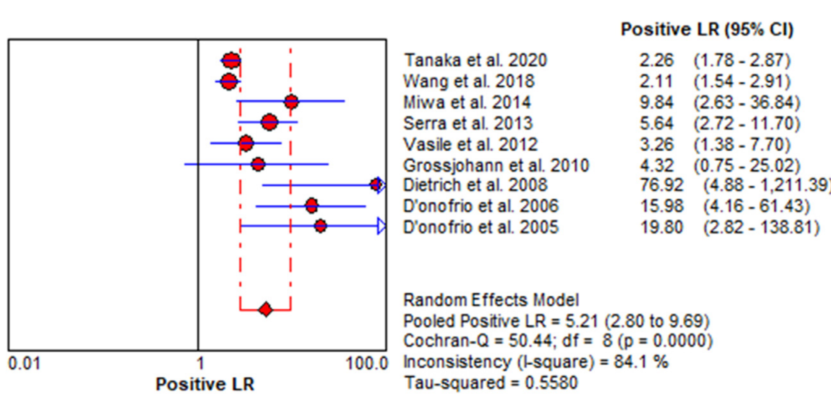


Fig. 6. Forest plots of the pooled positive likelihood ratios of contrast-enhanced transabdominal ultrasound for diagnosis of pancreatic cancer. The pooled positive likelihood ratio (LR) was 5.21 (95% confidence interval [CI]: 2.80–9.69).

number of cases reported in three studies caused the variability in the results. However, it is difficult to detect significant inconsistencies in specificity, positive LR and DOR using meta-regression analysis.

The area under the SROC was 0.95, which is close to 1. These data indicate that CEUS has good performance in the diagnosis of pancreatic cancer. Unfortunately, there were few reports comparing

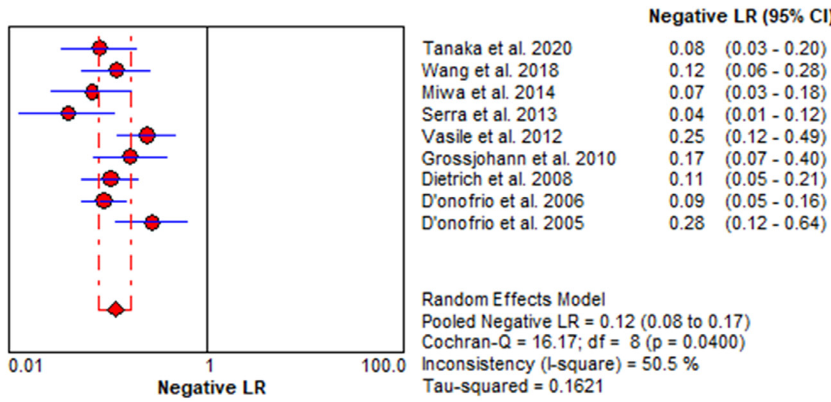


Fig. 7. Forest plots of the pooled negative likelihood ratios of contrast-enhanced transabdominal ultrasound for diagnosis of pancreatic cancer. The pooled negative likelihood ratio (LR) was 0.12 (95% confidence interval [CI]: 0.08−0.17).

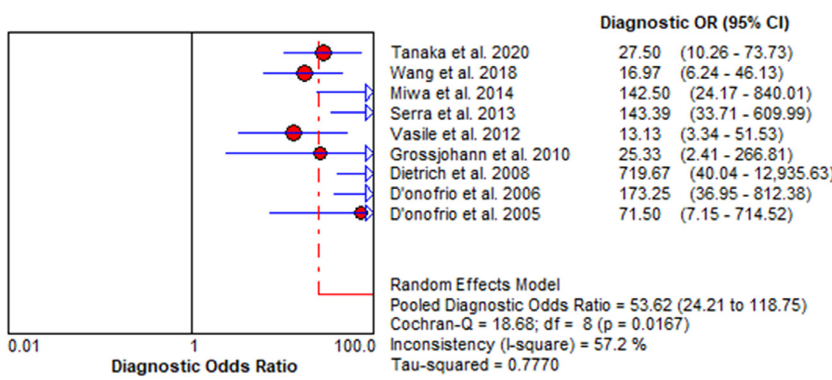


Fig. 8. Forest plot of the diagnostic odds ratio of contrast-enhanced transabdominal ultrasound for diagnosis of pancreatic cancer. CE-US was useful for diagnosis of pancreatic cancer, with a high value for the odds ratio (53.62).

CEUS with CE endoscopic ultrasound (CEEUS) for diagnosis of PC. Indeed, no study compared these two imaging methods in same article, which is insufficient for meta-analysis. However, a previous meta-analysis with the same second-generation contrast agents revealed that the area under the SROC of CEEUS for PC was 0.97 (Yamashita et al. 2019). Therefore, CEUS has good diagnostic ability for PC, similar to that of CEEUS.

The QUADAS-2 assessment indicated that most studies had a low risk of bias; indeed, funnel plots revealed no publication bias. Moreover, CEUS is advantageous when patients have contraindications to magnetic resonance imaging and computed tomography (CT) contrast agents (*e.g.,* renal failure or contrast allergy) (Reddy et al. 2011). Contrast-enhanced ultrasound (CEUS) also allows for dynamic and repeat examinations because it does not expose the patient to ionizing radiation (Chung and Kim 2015). In addition, a previous study reported that CEUS is useful for diagnosis of small pancreatic lesions, which were not detected by CT (Tanaka et al. 2020). Therefore, we conclude that CEUS is more accurate than CT because it can detect smaller pancreatic cancers.

The results of this analysis are similar to the findings of three previous meta-analyses (Lin et al. 2016; Ran et al. 2017; Li et al. 2018), although the three previous reports were limited with respect to reference selection. First, some studies cited in the previous meta-analyses included pancreatic cystic lesions. The vascularity of these cystic lesions was not assessed because it is difficult to include both solid and cystic lesions in a meta-analysis because of the different classifications of contrast enhancement. Second, the previous meta-analyses included various reports that used heterogeneous methods to analyze images, such as such as the presence of vessels in the tumor, a heterogeneous enhancement pattern and time−intensity curves. Therefore, we included only reports that used enhancement pattern as a diagnostic criterion because it is the most common clinical criterion for a diagnosis of PC by CEUS. Third, high-mechanical-index CEUS suffers from problems related to real-time depiction, repeat examinations and spatial resolution (Chung and Kim 2015). By contrast, low-mechanical-index CEUS allows visualization of microvessels and provides detailed information on parenchymal perfusion; this results in high spatial resolution and real-time depiction, along with the option of repeat

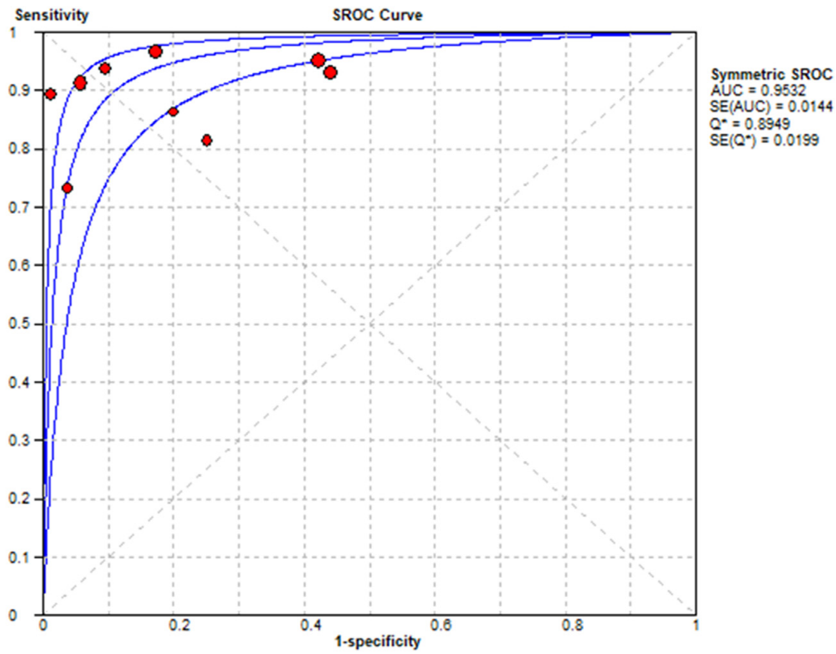


Fig. 9. Summary receiver operating characteristic (SROC) curve for the diagnostic accuracy of contrast-enhanced transabdominal ultrasound. AUC = area under the curve; SE = standard error; $Q$ = the point at which sensitivity and specificity are equal. The area under the SROC was 0.95.

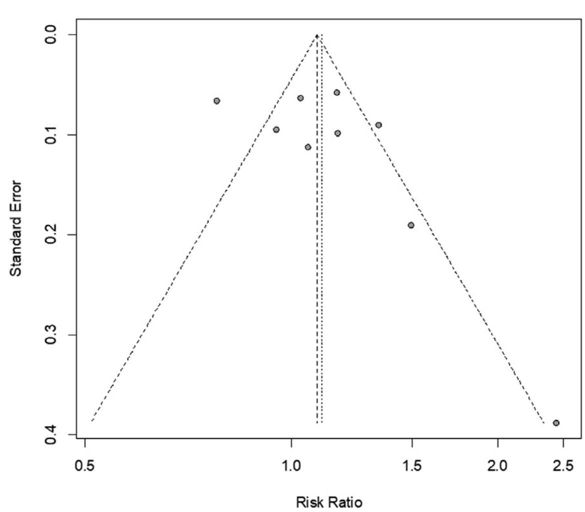


Fig. 10. Funnel plot of publication bias. Funnel plots did not identify publication bias.

Table 3. Meta-regression to identify potential sources of heterogeneity

| Characteristic | Relative diagnostic odds ratio (95% CI) | $p$ Value |
|---|---|---|
| Region (Asia/Europe) | 0.94 (0.06−12.5) | 0.957 |
| Sonazoid/ SonoVue | 0.56 (0.05−5.82) | 0.570 |
| Contrast agent dosage (continuous variable) | 3.6 (0.59−22.06) | 0.121 |
| Scan phase (early/late phase) | 0.26 (0.01−8.89) | 0.386 |
| No. of patients (≤80/>80) | 0.17 (1.46−45.63) | 0.024 |

CI = confidence interval.
There was significant relationship between the diagnostic odds ratio and number of patients.

Table 4. Subgroup analyses with outliers excluded

| | Pooled value(95% CI) | $p$ Value | $I^2$(%) |
|---|---|---|---|
| Sensitivity | 0.93 (0.91−0.95) | 0.45 | 0 |
| Specificity | 0.74 (0.69−0.79) | 0.00 | 91.6 |
| Positive likelihood ratio | 5.23 (2.46−11.13) | 0.00 | 88.9 |
| Negative likelihood ratio | 0.09 (0.07−0.12) | 0.65 | 0 |
| Diagnostic odds ratio | 75.55 (27.25−209.45) | 0.01 | 66.8 |

CI = confidence interval.
The significant inconsistency between sensitivity and negative likelihood ratio improved.

examination if needed. Therefore, low-mechanical-index CEUS is the most accurate technique for investigating pancreatic lesions. Based on the aforementioned facts, we focused on studies of low-mechanical-index CEUS imaging techniques and the enhancement pattern (hypo-enhancement).

This study has some limitations. First, significant heterogeneity might have affected interpretation of the data and the conclusions reached. However, a random-effects model (DerSimonian−Laird method) was used and when significant heterogeneity was detected. We also performed the meta-regression analysis or subgroup analysis to determine the reason of obvious inconsistency. Second, exclusion of conference abstracts, case−control studies, case reports, reviews, editorials and unpublished data may have resulted in publication bias, so that our results may have overestimated the actual diagnostic performance.

## CONCLUSIONS

We determined that low-mechanical-index CEUS is a useful tool for diagnosis of pancreatic cancer, with high sensitivity and accuracy, regardless of the second-generation US contrast agent used, continent, contrast agent dosage and scan phase. Thus, low-mechanical-index CEUS may improve diagnostic accuracy in PC in clinical practice.

*Conflict of interest disclosure*—Mirko D'Onofrio has received honoraria for speaking lectures in conferences from Hitachi Medical Systems, Bracco Imaging, and Siemens Healthineers. Masatoshi Kudo has received honoraria for speaking lectures in conferences from GE Healthcare and GE Medical Systems. The other authors declare that there is no conflict of interest regarding the publication of this article.

## REFERENCES


Bell A, Fairbrother M, Jones K. Fixed and random effects models: Making an informed choice. Qual Quant 2019;53:1051–1074.

Chung YE, Kim KW. Contrast-enhanced ultrasonography: Advance and current status in abdominal imaging. Ultrasonography 2015;34:3–18.

Dietrich CF, Braden B, Hocke M, Ott M, Ignee A. Improved characterisation of solitary solid pancreatic tumours using contrast enhanced transabdominal ultrasound. J Cancer Res Clin Oncol 2008;134:635–643.

D'Onofrio M, Malagò R, Zamboni G, Vasori S, Falconi M, Capelli P, Mansueto G. Contrast-enhanced ultrasonography better identifies pancreatic tumor vascularization than helical CT. Pancreatology 2005;5:398–402.

D'Onofrio M, Zamboni G, Tognolini A, Malago R, Faccioli N, Frulloni L, Pozzi Mucelli R. Mass-forming pancreatitis: Value of contrast-enhanced ultrasonography. World J Gastroenterol 2006;12:4181–4184.

D'Onofrio M, Barbi E, Dietrich CF, Kitano M, Numata K, Sofuni A, Principe F, Gallotti A, Zamboni GA, Mucelli RP. Pancreatic multicenter ultrasound study (PAMUS). Eur J Radiol 2012;81:630–638.

Global Burden of Disease Study 2017 (GBD) Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990−2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2019;4:934–947.

Grossjohann HS, Rappeport ED, Jensen C, Svendsen LB, Hillingsø JG, Hansen CP, Nielsen MB. Usefulness of contrast-enhanced transabdominal ultrasound for tumor classification and tumor staging in the pancreatic head. Scand J Gastroenterol 2010;45:917–924.

Li XZ, Song J, Sun ZX, Yang YY, Wang H. Diagnostic performance of contrast-enhanced ultrasound for pancreatic neoplasms: A systematic review and meta-analysis. Dig Liver Dis 2018;50:132–138.

Lin LZ, Li F, Liu Y, Xing LX, Du LF. Contrast-Enhanced Ultrasound for differential diagnosis of pancreatic mass lesions: A meta-analysis. Med Ultrason 2016;18:163–169.

Martínez-Noguera A, D'Onofrio M. Ultrasonography of the pancreas: 1. Conventional imaging. Abdom Imaging 2007;32:136–149.

Miwa H, Numata K, Sugimori K, Kaneko T, Sakamaki K, Ueda M, Fukuda H, Tanaka K, Maeda S. Differential diagnosis of solid pancreatic lesions using contrast-enhanced three-dimensional ultrasonography. Abdom Imaging 2014;39:988–999.

Ran L, Zhao W, Zhao Y, Bu H. Value of contrast-enhanced ultrasound in differential diagnosis of solid lesions of pancreas (SLP): A systematic review and a meta-analysis. Medicine 2017;96:e7463.

Reddy NK, Ioncica AM, Saftoiu A, Vilmann P, Bhutani MS. Contrast-enhanced endoscopic ultrasonography. World J Gastroenterol 2011;17:42–48.

Serra C, Felicani C, Mazzotta E, Piscitelli L, Cipollini ML, Tomassetti P, Pezzilli R, Casadei R, Morselli-Labate AM, Stanghellini V, Corinaldesi R, De Giorgio R. Contrast-enhanced ultrasound in the differential diagnosis of exocrine versus neuroendocrine pancreatic tumors. Pancreas 2013;42:871–877.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.

Tanaka S, Fukuda J, Nakao M, Ioka T, Ashida R, Takakura R, Okagaki S, Katayama K, Ohkawa K, Ikezawa K, Nagata S. Effectiveness of contrast-enhanced ultrasonography for the characterization of small and early stage pancreatic adenocarcinoma. Ultrasound Med Biol 2020;46:2245–2253.

Vasile TA, Feier D, Socaciu M, Anton OM, Seicean A, Iancu C, Zaharie T, Badea R. Contrast enhanced ultrasound and computer tomography diagnosis of solid and mixed pancreatic tumors —Analysis of confounders. J Gastrointestin Liver Dis 2012;21:285–292.

Wang Y, Yan K, Fan Z, Ding K, Yin S, Dai Y, Yang W, Wu W. Clinical value of contrast-enhanced ultrasound enhancement patterns for differentiating focal pancreatitis from pancreatic carcinoma: A comparison study with conventional ultrasound. J Ultrasound Med 2018;3:551–559.

Yamashita Y, Shimokawa T, Napoléon B, Fusaroli P, Gincul R, Kudo M, Kitano M. Value of contrast-enhanced harmonic endoscopic ultrasonography with enhancement pattern for diagnosis of pancreatic cancer: A meta-analysis. Dig Endosc 2019;31:125–133.