Carbohydrate antigen 19-9 for differential diagnosis of pancreatic carcinoma and chronic pancreatitis

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Core tip: Pancreatic carcinoma and chronic pancreatitis show similar clinical manifestations. Differential diagnosis of pancreatic carcinoma and chronic pancreatitis remains a challenge, particularly in patients with pancreatic masses that may be benign (inflammatory) or malignant. Carbohydrate antigen 19-9 (CA19-9) shows promise for differentiating the diseases. We evaluated the usefulness of CA19-9 in this systematic review.

Introduction. Pancreatic carcinoma is the fourth leading cause of cancer deaths in the United States [1]. Currently, the most effective treatment is surgical resection [2, 3]. However, approximately 80% of tumors are unresectable at diagnosis, and these patients show a 5-year survival rate below 5% [1]. The clinical manifestations of pancreatic carcinoma resemble those of chronic pancreatitis. In fact, chronic pancreatitis is strongly associated with pancreatic malignancy and may help to cause it. For example, individuals in parts of Southern India with idiopathic chronic pancreatitis unassociated with alcohol abuse show a high incidence of pancreatic carcinoma [4].

Differential diagnosis of pancreatic carcinoma and chronic pancreatitis remains a challenge, particularly in patients with pancreatic masses that may be benign

(inflammatory) or malignant. This differentiation is important in order to avoid unnecessary resection in patients with inflammatory masses: 5%-10% of patients subjected to pancreatic resection are ultimately diagnosed with pancreatitis rather than pancreatic carcinoma [5]. Differentiation is also important in order to identify correctly pancreatic masses as cancerous and avoid leaving behind malignant masses. Pancreatic carcinoma is incurable in many patients who also have chronic pancreatitis, because the cancer is multicentric or advanced.

Carbohydrate antigen 19-9 (CA19-9) is the most popular serum-based marker for diagnosis of pancreatic cancer, and it is useful for detecting disease recurrence after surgery [6, 7]. However, this biomarker has limited diagnostic power. CA19-9 level can be normal in patients with localized disease, therefore, it is less effective for screening for early pancreatic cancer. High CA19-9 levels can also occur in benign diseases, including chronic pancreatitis and nonmalignant jaundice [6, 7, 8].

Diagnosis of pancreatic cancer at an early, resectable stage is especially difficult when the patient also presents with chronic pancreatitis [9, 10], therefore, we wondered whether CA19-9 might be useful for differentiating the two diseases. We performed a systematic review and meta-analysis of the utility of CA19-9 as a serum tumor marker and its sensitivity and specificity for distinguishing pancreatic carcinoma and chronic pancreatitis.

Materials and methods.

Search strategies. In June 2013 we searched MEDLINE (1980 to May 2013), EMBASE (1980 to May 2013), Web of Science (1990 to May 2013) and Cochrane databases. Although no language restrictions were imposed initially, for the full-text review and final analysis only English language articles were included. Additional articles were searched using the "Related articles" function in PubMed and by manually searching reference lists of identified articles and review articles. The following search terms were used: "pancreatic carcinoma" or "pancreatic cancer" and "chronic pancreatitis" and "carbohydrate antigen 19-9" and "diagnosis" or "sensitivity" or "specificity". We contacted experts in the field to ask about studies

that we may have missed in the databases. Conference abstracts and letters to the editor were excluded because of the limited data they contained.

***Study inclusion criteria*.** A study was included when it provided both the sensitivity (true-positive rate) and specificity (true-negative rate) of using serum CA19-9 levels to diagnose pancreatic carcinoma or chronic pancreatitis in patients of any age. Studies were also included if they reported CA19-9 values in a scatter plot format that allowed patient-level data to be extracted. Studies had to involve at least 10 patients with pancreatic carcinoma or chronic pancreatitis in order to reduce selection bias due to a small number of participants. Patients had to be diagnosed with pancreatic carcinoma based on cytology and/or histology of pancreatic tissue, or diagnosed with chronic pancreatitis based on clinical information alone or in combination with histopathological resection, radiology (endoscopic retrograde cholangiopancreatography and computed tomography) and/or endoscopic ultrasonography. Two reviewers (Su SB and Jiang HX) independently determined study eligibility, and disagreements were resolved by consensus.

Data extraction and quality assessment. These same two reviewers independently confirmed the eligibility of the final set of studies and extracted the following data: first author, publication year, participant characteristics, assay methods, sensitivity and specificity data, cut-off values, and methodological quality. Serum CA19-9 values provided in scatter plots were extracted by placing scalar grids over the plots. A receiver operating characteristic (ROC) curve was calculated for each study.

To enable us to assess the methodological quality of the included studies, we extracted data on the following study design characteristics: (1) cross- sectional or case-control design; (2) consecutive or random sampling of patients; (3) blinded (single or double) or non-blinded interpretation of experimental and reference measurements; and (4) prospective or retrospective data collection. Su SB and Jiang HX independently assessed the methodological quality of studies using the Standards for Reporting Diagnostic Accuracy (STARD) guidelines [11] (maximum score of 25) and the Quality Assessment for Studies of Diagnostic Accuracy (QUADAS)

guidelines [12] (maximum score of 14). Average inter-rater agreement on the methodological quality checklists was 0.96. If primary studies did not report information needed to assess methodological quality, we contacted the authors in an effort to obtain the data. If the authors did not respond, we changed the response for the relevant items from "not reported" to "no" on the assessment instruments.

***Statistical analysis*.** Standard methods recommended for meta-analyses of diagnostic test evaluations were used [13]. Analyses were performed using Meta-DiSc for Windows (XI Cochrane Colloquium; Barcelona, Spain) and Stata 12.0 (Stata Corporation, College Station, TX, United States). The following measures of test accuracy were analyzed for each study: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR). A summary ROC (SROC) curve [14] was generated for each study based on a single test threshold for sensitivity and specificity [13, 15]. A random-effects model was adopted to calculate the average sensitivity, specificity, and other measures across studies [16, 17].

To assess the effects of STARD and QUADAS scores on the diagnostic power of CA19-9, we included them as covariates in univariate, inverse variance- weighted meta-regression. We also analyzed the effects of other covariates on DOR, such as cross- sectional design, consecutive or random sampling of patients, single- or double-blinded interpretation of experimental and reference measurements, and prospective or retrospective data collection. The relative DOR (RDOR) was calculated to analyze the change in diagnostic precision in each study per unit increase in the covariate [18, 19]. $P<0.05$ was considered to show statistical significance.

The heterogeneity, or variability, across studies was assessed for statistical significance using the χ^2 and Fisher exact tests. Publication bias can pose problems for meta-analyses of diagnostic studies, therefore, we tested for the potential presence of this bias using funnel plots and the Egger test [20].

Results.

***Selection and summary of studies*.** We identified 345 citations *via* electronic searches, and 106 were retrieved for detailed analysis (Figure 1). Of these, 47 studies were excluded for failing to satisfy the inclusion criteria, and another 17 were excluded because they failed to provide sufficient information for meta-analysis. Five studies were duplicate publications. Two articles were meta-analyses, and one was excluded for involving fewer than 10 participants. In the end, 34 publications were included in the analysis [21–54], involving 3125 patients with pancreatic carcinoma and 2061 patients with chronic pancreatitis. The average sample size of the studies was 153 patients (range: 24-941). Table 1 summarizes the clinical characteristics of participants in each study; the numbers of true-positive, false-positive, false- negative and true-negative results; and STARD and QUADAS scores.

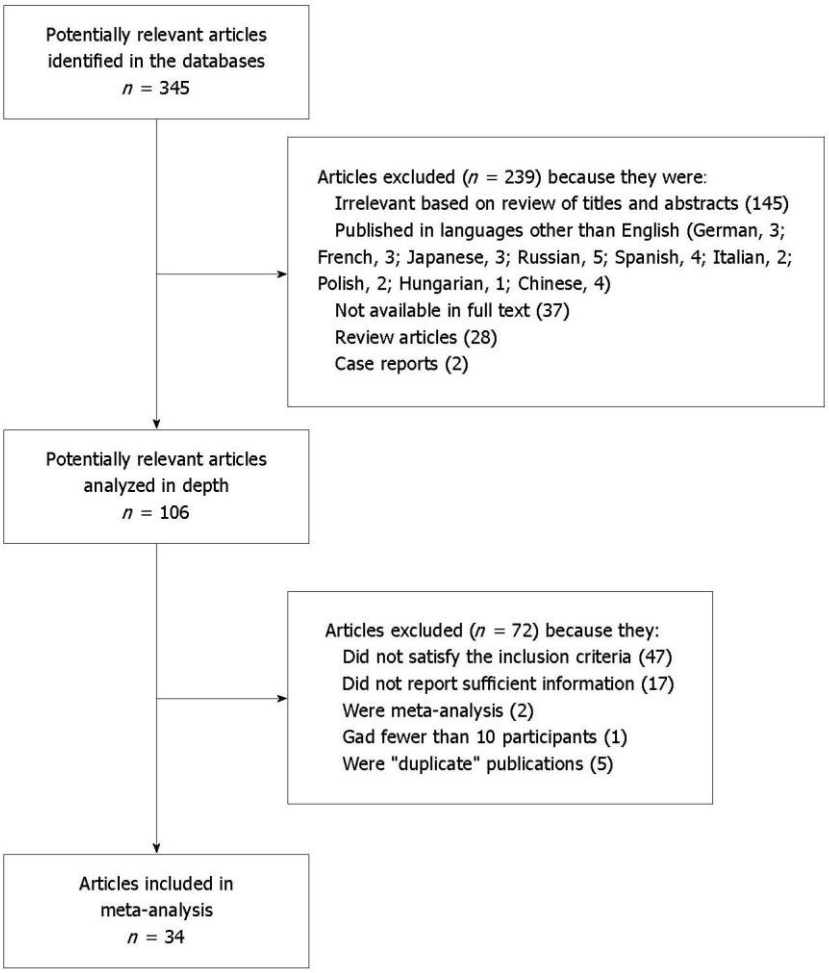

Fig. 1. Flowchart of study selection.

Table 1 Summary of carbohydrate antigen 19-9 assay methods, results, and overall methodological quality of included studies

Ref.	Number of patient	Assay method	Cut-off for elevated CA19-9 (U/mL)	Assay results				Quality score	
				TP	FP	FN	TN	STARD	QUADAS
Wang *et al*[21], 1986	58	RIA	37	20	0	4	34	15	10
Safi *et al*[22], 1987	191	RIA	37	80	28	7	76	16	10
Sakamoto *et al*[23], 1987	57	RIA	37	26	1	4	26	18	12
Friess *et al*[24], 1993	154	ELISA	37	53	14	6	81	17	11
Röthlin *et al*[25], 1993	97	RIA	37	54	8	14	21	17	12
Haglund *et al*[26], 1994	199	RIA	37	148	3	31	17	16	11
Kuno *et al*[27], 1994	117	RIA	37	41	10	6	60	19	13
Pasquali *et al*[28], 1994	103	RIA	37	47	2	11	43	12	9
Satake *et al*[29], 1994	941	RIA	37	454	56	118	244	19	13
Hámori *et al*[30], 1997	94	RIA	37	48	4	14	28	11	7
Safi *et al*[31], 1997	647	RIA	37	296	48	51	252	18	12
Hayakawa *et al*[32], 1999	76	RIA	37	21	14	6	35	16	11
Kim *et al*[33], 1999	160	ELISA	37	69	9	21	61	19	13
Manes *et al*[34], 1999	58	RIA	37	30	3	4	21	17	11
Slesak *et al*[35], 2000	122	LIA	37	32	14	14	60	18	12
Maire *et al*[36], 2002	78	ELISA	37	43	4	4	27	17	11
Akashi *et al*[37], 2003	46	RIA	37	15	7	5	19	12	9
Mu *et al*[38], 2003	24	RIA	37	4	3	5	12	15	10
Cwik *et al*[39], 2004	150	RIA	37	82	5	16	47	16	11
Jiang *et al*[40], 2004	148	ELISA	37	82	7	14	45	17	12
Ventrucci *et al*[41], 2004	81	EIA	60	45	2	15	19	18	12
Teich *et al*[42], 2005	59	ELISA	22	27	3	3	13	12	9
Chang *et al*[43], 2007	111	ELISA	37	63	11	9	28	18	12
		ELISA	100	57	7	15	32	18	12
Kuhlmann *et al*[44], 2007	62	EIA	37	17	4	11	30	16	11
Liao *et al*[45], 2007	150	ELISA	37	84	15	28	23	15	10
Bedi *et al*[46], 2009	84	ELISA	37	23	15	11	35	17	12
		ELISA	100	14	7	20	43	17	12
Firpo *et al*[47], 2009	107	ELISA	37	58	2	17	30	18	12
Liao *et al*[48], 2009	102	RIA	37	47	22	11	22	16	10
Morris-Stiff *et al*[49], 2009	188	ELISA	37	70	31	3	84	19	13
Talar-Wojnarowska *et al*[50], 2010	157	ELISA	37	71	18	14	54	17	12
Zapico-Muñiz *et al*[51], 2010	102	LIA	100	35	7	12	48	16	11
Chung *et al*[52], 2011	78	NR	30	40	2	15	21	12	9
Gold *et al*[53], 2013	284	EIA	37	180	16	54	34	18	11
Kaur *et al*[54], 2013	114	RIA	37	76	9	15	14	17	11

CA19-9: Carbohydrate antigen 19-9; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent assay; FN: False negative; FP: False positive; LIA: Luminescent immunoassay; NR: Not reported; RIA: Radioimmunoassay; TN: True negative; TP: True positive.

***Methodological quality of the included studies*.** Of the 34 studies in the meta-analysis, 30 had STARD scores > 13, and 29 had QUADAS scores ^ 10. All studies collected data from consecutive patients using a prospective design. No study reported interpretation of CA19-9 measurements in which analysts were blinded to the corresponding reference measurements (Table 2).

***Diagnostic accuracy*.** As shown in Figure 2, a Forest plot of serum CA19-9 levels in all 34 included studies showed that the sensitivity of this biomarker to differentiate between pancreatic carcinoma and chronic pancreatitis ranged from 0.44 to 0.96 [mean: 0.81, 95%CI: 0.80-0.83; $\chi^2 = 77.23$, $P < 0.001$), while the specificity ranged from 0.50 to 1.0 (mean: 0.81, 95%CI: 0.79-0.82; $\chi^2 = 111.98$, $P < 0.001$). The PLR was 4.08 (95%CI: 3.39-4.91; $j^2 = 113.62$, $P < 0.001$), NLR was 0.24 (95%CI: 0.21-0.28; $\chi^2 = 86.13$, $P < 0.001$) and DOR was 19.31 (95%CI: 14.4-25.9; $\chi^2 = 94.02$, $P < 0.001$). These χ^2 values and associated P-values indicate significant heterogeneity among studies.

These measures of differential diagnostic power varied with different CA19-9 assays and cut-off values used to define CA19-9 levels as elevated or normal (Table 3). Data from the 11 studies that relied on the enzyme-linked immunosorbent assay (ELISA) method, involving 1396 patients, gave a sensitivity of 0.83 and specificity of 0.79. Data from the 17 studies using the radioimmunoassay method, involving 3074 patients, gave a sensitivity of 0.82 and specificity of 0.81. Data from the three studies that relied on an enzyme immunosorbent assay (EIA) gave a sensitivity of 0.75 and specificity of 0.79. Data from the 30 studies (4879 patients) using a cut-off value of 37 U/mL gave a sensitivity of 0.82 and specificity of 0.80. Data from the three studies using a cut-off value of 100 U/mL gave corresponding values of 0.69 and 0.85. These variations in sensitivity and specificity with CA19-9 assay and cut-off values did not achieve statistical significance (P > 0.05, Table 4), suggesting that high cut-off values such as 100 U/mL may better increase the specificity for differential diagnosis of pancreatic carcinoma.

Instead of assessing diagnostic power using the traditional ROC plot, we calculated an SROC plot to reveal the effect of varying thresholds on sensitivity and

specificity within each study. In this plot, different studies appear as different data points, allowing SROC curves to provide a global summary of test performance and illustrate the trade-off between sensitivity and specificity. Figure 3 shows an SROC curve for rates of true- and false-positive results obtained with the CA19-9 assay in individual studies. From this plot we determined the *Q* value, which was defined as the point of intersection of the SROC curve with a diagonal line extending from the left upper corner to the right lower corner of the plot. The *Q* value indicates the highest identical value of sensitivity and specificity, thereby serving as an overall measure of the discriminatory power of a test. Our SROC curve was desirably positioned near the upper left corner, and the maximum joint sensitivity and specificity was 0.81. The area under the curve (AUC) was 0.88 (Figure 3A), indicating high overall accuracy. SROC plots differed based on the CA19-9 assay method and cutoff values, but all plots were positioned near the upper left corner with AUCs near 0.88 (Figure 3B-F), again indicating high overall accuracy.

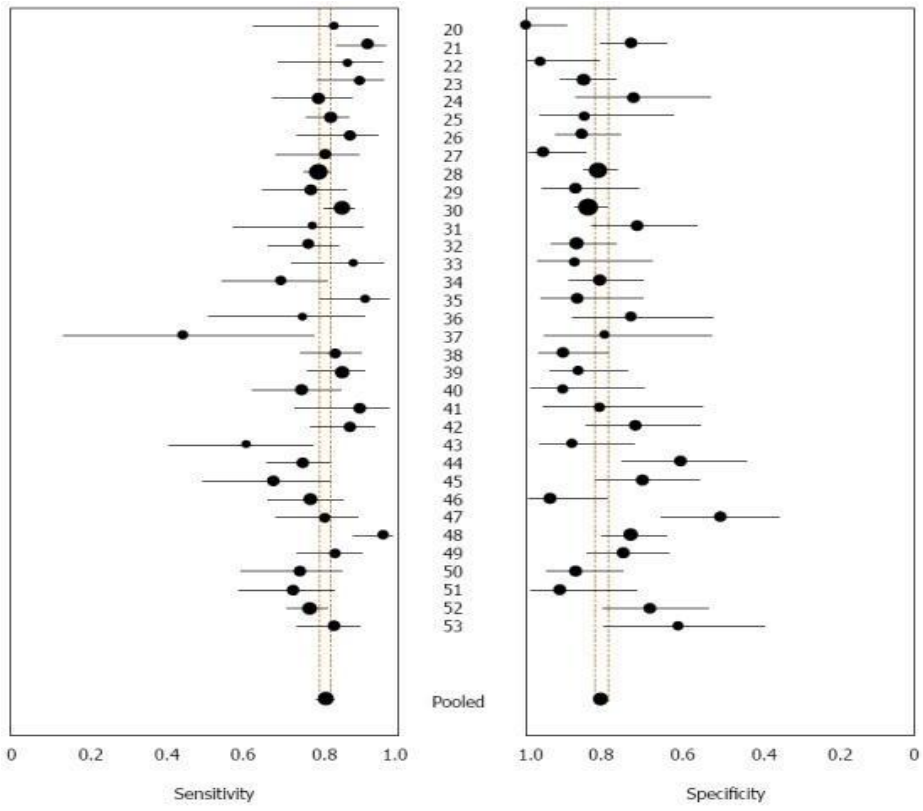

Fig. 2. Forest plot showing sensitivity and specificity of carbohydrate antigen 19-9 in the diagnosis of pancreatic carcinoma. The point estimates of sensitivity and

specificity from each study are shown as solid circles. Horizontal error bars indicate 95%CI. Numbers between the plots refer to references. Pooled estimates for the serum carbohydrate antigen 19-9 assay were 0.81 for sensitivity (95%CI: 0.80-0.83) and 0.81 for specificity (95%CI: 0.79-0.82).

Table 2 Additional characteristics of patients and methodology in the included studies

Ref.	Country/area	PC/CP, *n*	PC reference	Cross-sectional design	Consecutive or Random sampling	Blinded design	Prospective design
Wang *et al*[21], 1986	Taiwan	24/34	His or Cyt	No	Yes	No	Yes
Safi *et al*[22], 1987	Germany	87/104	His	Yes	Yes	No	Yes
Sakamoto *et al*[23], 1987	Japan	30/27	His	No	Yes	No	Yes
Friess *et al*[24], 1993	Germany	59/95	His	Yes	Yes	No	Yes
Röthlin *et al*[25], 1993	Switzerland	68/29	His	No	Yes	No	Yes
Haglund *et al*[26], 1994	Finland	179/20	His	No	Yes	No	Yes
Kuno *et al*[27], 1994	Japan	47/70	His	Yes	Yes	No	Yes
Pasquali *et al*[28], 1994	Italy	58/45	His	No	No	NR	Yes
Satake *et al*[29], 1994	Japan	641/300	His	Yes	Yes	No	Yes
Hámori *et al*[30], 1997	Hungary	62/32	His	No	Yes	No	Yes
Safi *et al*[31], 1997	Germany	347/300	His or Bio	Yes	Yes	No	Yes
Hayakawa *et al*[32], 1999	Japan	27/49	His (Bio, Aut)	No	Yes	No	Yes
Kim *et al*[33], 1999	Korea	90/70	His	Yes	Yes	No	Yes
Manes *et al*[34], 1999	Italy	34/24	His or Cyt	Yes	Yes	No	Yes
Slesak *et al*[35], 2000	Poland	48/74	His	No	Yes	No	Yes
Maire *et al*[36], 2002	France	47/31	His or Cyt	No	Yes	No	Yes
Akashi *et al*[37], 2003	Japan	20/26	His or Aut	No	Yes	No	Yes
Mu *et al*[38], 2003	China	9/15	His or Cyt	No	Yes	No	Yes
Cwik *et al*[39], 2004	Lublin	98/52	His	NR	Yes	NR	Yes
Jiang *et al*[40], 2004	China	96/52	His	Yes	Yes	No	Yes
Ventrucci *et al*[41], 2004	Italy	60/21	His	Yes	Yes	No	Yes
Teich *et al*[42], 2005	Germany	30/16	His	No	No	No	Yes
Chang *et al*[43], 2007	Taiwan	72/39	His	Yes	Yes	No	Yes
	New York, United States	28/34	His	No	Yes	NR	Yes
Kuhlmann *et al*[44], 2007	China	112/38	His	No	Yes	No	Yes
Liao *et al*[45], 2007	India	34/50	His or Bio	Yes	Yes	No	Yes
Bedi *et al*[46], 2009	United States	75/32	His or Cyt	Yes	Yes	No	Yes
	Taiwan	58/44	His	Yes	Yes	No	Yes
Firpo *et al*[47], 2009	United Kingdom	73/115	His	Yes	Yes	No	Yes
Liao *et al*[48], 2009	Poland	85/72	His	Yes	Yes	No	Yes
Morris-Stiff *et al*[49], 2009	Spain	47/55	His	Yes	Yes	No	Yes
Talar-Wojnarowska *et al*[50], 2010	Korea	55/23	His	Yes	Yes	No	Yes
Zapico-Muñiz *et al*[51], 2010	New York, United States	234/50	His or Cyt	Yes	Yes	No	Yes
Chung *et al*[52], 2011	Germany	91/23	His	No	Yes	No	Yes

Aut: Autopsy; Bio: Biopsy; CP: Chronic pancreatitis; Cyt: Cytology; PC: Pancreatic carcinoma; His: Histology; NR: Not reported.

Table 3 Bivariate estimates of diagnostic precision based on different carbohydrate antigen 19-9 assay methods and cut-off values

Assay method or cut-off value	Number of studies	Number of participants	Sensitivity (95%CI)	Specificity (95%CI)	PLR (95%CI)	NLR (95%CI)	DOR (95%CI)
ELISA	11	1396	0.83 (0.80-0.86)	0.79 (0.75-0.82)	3.97 (2.96-5.33)	0.20 (0.15-0.28)	22.64 (12.44-41.22)
RIA	17	3074	0.82 (0.80-0.84)	0.81 (0.79-0.83)	4.16 (3.09-5.60)	0.23 (0.19-0.27)	20.14 (13.27-30.55)
EIA	3	427	0.75 (0.70-0.80)	0.79 (0.70-0.86)	3.84 (1.82-8.10)	0.34 (0.27-0.43)	10.29 (4.96-21.34)
LIA	2	224	ND	ND	ND	ND	ND
Cut-off of 37 U/mL	30	4879	0.82 (0.80-0.83)	0.80 (0.78-0.82)	3.94 (3.24-4.78)	0.24 (0.21-0.28)	18.79 (13.67-25.82)
Cut-off of 100 U/mL	3	297	0.69 (0.61-0.76)	0.85 (0.79-0.91)	4.35 (2.86-6.61)	0.38 (0.18-0.77)	11.53 (4.47-29.77)
All studies	34	5115	0.81 (0.80-0.83)	0.81 (0.79-0.82)	4.08 (3.39-4.91)	0.24 (0.21-0.28)	19.31 (14.40-25.90)

DOR: Diagnostic odds ratio; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent assay; LIA: Luminescent immunoassay; ND: Not done; NLR: Negative likelihood ratio; PLR: Positive likelihood ratio; RIA: Radioimmunoassay.

Table 4 Weighted meta-regression of the effects of study design, methodological quality and assay parameters on diagnostic accuracy of carbohydrate antigen 19-9

Covariate	Number of studies	Coefficient	RDOR (95%CI)	*P* value
Study design and quality				
STARD ⩾ 13	30	0.564	1.76 (0.14-22.68)	0.652
QUADAS ⩾ 10	29	-0.666	0.51 (0.06-4.11)	0.514
Consecutive or random design	32	0.924	2.52 (0.26-24.68)	0.411
Cross-sectional design	18	-0.512	0.60 (0.28-1.28)	0.178
Blinded design	0	ND	ND	ND
Prospective design	34	ND	ND	ND
Assay method or cut-off value				
RIA	17	-0.619	0.54 (0.12-2.51)	0.413
ELISA	11	-0.737	0.48 (0.10-2.26)	0.336
EIA	3	0.425	1.53 (0.29-8.14)	0.604
Cut-off of 37 U/mL	30	0.553	1.74 (0.36-8.36)	0.474
Cut-off of 100 U/mL	3	0.890	2.43 (0.72-8.26)	0.146

EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent assay; ND: Not done; RIA: Radioimmunoassay; STARD: Standards for Reporting Diagnostic Accuracy; QUADAS: Quality Assessment for Studies of Diagnostic Accuracy.

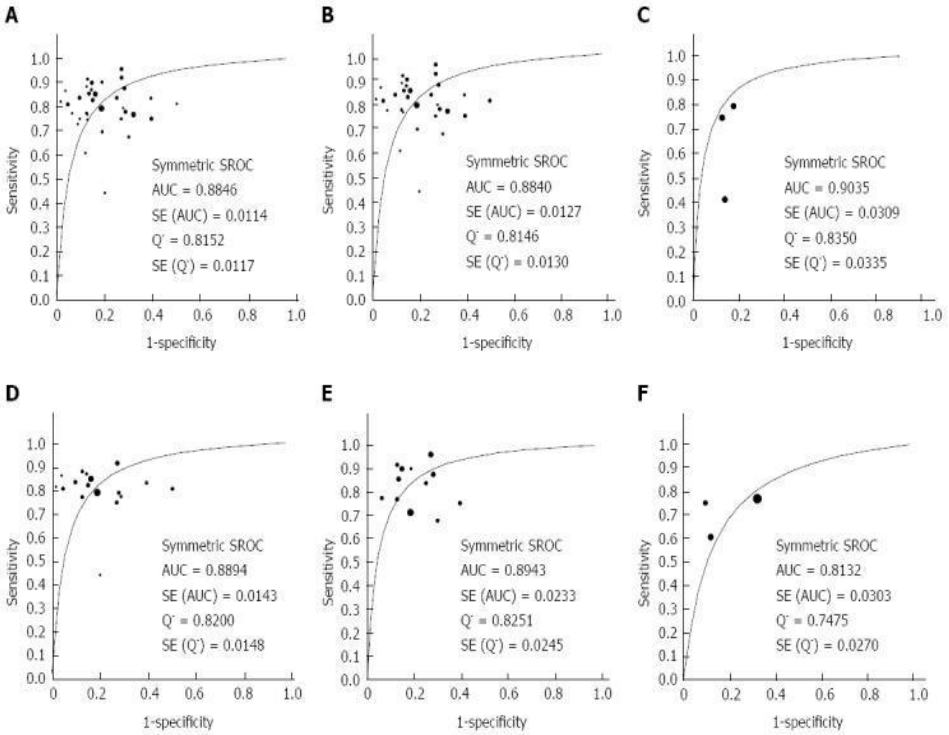

Fig. 3. Summary receiver operating characteristic curves for carbohydrate antigen 19-9 assays for differential diagnosis of pancreatic carcinoma and chronic pancreatitis. Solid circles represent each study included in the meta-analysis, with circle size proportional to the number of participants in the study. SROC curves summarize the overall diagnostic accuracy for all included studies (A), studies using a cut-off of 37 U/mL carbohydrate antigen 19-9 (CA19-9) (B), studies using a cut-off of 100 U/mL CA19-9 (C), studies based on the radioimmunoassay method to assay CA19-9 (D), studies based on the ELISA method (E), and studies based on the enzyme immunoassay method (F). ELISA: Enzyme-linked immunosorbent assay; SROC: Summary receiver operating characteristic.

***Multiple regression analysis and publication bias*.** Quality scores based on the STARD [11] and QUADAS [12] guidelines were generated for every study on the basis of the title and introduction, methods, results and discussion (Table 1). These scores were used in meta-regression to assess the effect of study quality on the RDOR of CA19-9 in the differential diagnosis of pancreatic carcinoma and chronic pancreatitis. Studies of higher quality (STARD score $\geq$ 13; QUADAS score $\geq$ 10)

produced RDOR values similar to those of lower- quality studies. In addition, RDOR values did not differ significantly as a function of blinding, cross-sectional or case-control design, consecutive or random sampling, prospective or retrospective design, CA19-9 assay method, or cut-off values ($P > 0.05$). These results suggest that study design did not significantly affect diagnostic accuracy and that the risk of detection bias was low.

The Egger test showed no significant evidence of publication bias in reports about CA19-9 assays for differential diagnosis of pancreatic carcinoma ($P = 0.944$).

Discussion.

Timely and accurate diagnosis of pancreatic carcinoma is critical for patient prognosis, but it remains a challenge because the signs and symptoms of pancreatic cancer overlap considerably with those of chronic pancreatitis. Compounding this challenge is the fact that acute or chronic pancreatitis increases the risk of pancreatic carcinoma, as well as the fact that this cancer can induce secondary inflammatory processes. In this systematic review, we find evidence that although CA19-9 levels on their own are inadequate for differentiating pancreatic carcinoma and chronic pancreatitis, elevated CA19-9 may complement other clinical tests to help confirm a diagnosis of pancreatic carcinoma.

CA19-9 is a sialylated Lewis (Le^a) blood-group antigen, which was first identified as a ligand bound by monoclonal antibody 1116 NS 19-9 [55]. CA19-9 levels are elevated in > 80% of patients with advanced pancreatic cancer [56]. However, up to 40% of patients with chronic pancreatitis also have elevated CA19-9 levels, suggesting that these levels do not reliably differentiate between patients with pancreatic carcinoma and those with chronic pancreatitis [57]. In contrast to these earlier findings, our meta-analysis shows that the mean sensitivity of a CA19-9 assay was 0.81; mean specificity, 0.81; maximum joint sensitivity and specificity, 0.81; and AUC, 0.88. These values suggest high overall accuracy. These sensitivity and specificity values are similar to the corresponding values of 0.79-0.81 and 0.82-0.90 reported in two previous meta-analyses [6, 58]. Interestingly, both previous meta-

analyses examined the ability of serum CA19-9 to differentiate pancreatic carcinoma from benign pancreatic diseases in general, not specifically chronic pancreatitis.

DOR is an indicator of test accuracy that combines sensitivity and specificity data into a single number [59]. The DOR is the ratio of the odds of positive test results in the patient with disease relative to the odds of positive test results in the patient without disease. Thus, higher DOR values indicate better discriminatory test performance. The mean DOR in our study was 19.31, implying that CA19-9 levels may be useful in diagnosing pancreatic carcinoma.

Although SROC and DOR meta-analyses provide evidence that CA19-9 can help differentiate between pancreatic cancer and chronic pancreatitis, these diagnostic indicators are difficult to interpret and relate to clinical practice. Therefore, we examined the differential diagnostic power of CA19-9 using the more clinically meaningful likelihood ratio [60]. PLRs and NLRs of > 10 or < 0.1 indicate high accuracy. The overall PLR value in our meta-analysis was 4.08, indicating that patients with pancreatic carcinoma are ~ 4-fold more likely to have elevated CA19-9 than patients with chronic pancreatitis. On the other hand, NLR in our meta-analysis was 0.24, meaning that a patient without elevated CA19-9 would still have a 24% chance of having pancreatic carcinoma, or that 24% of patients with pancreatic carcinoma would not have elevated CA19-9. This proportion is too high to rule out pancreatic cancer in patients who do not have elevated CA19-9. These findings suggest that serum CA19-9 levels are insufficient on their own to differentiate between pancreatic carcinoma and chronic pancreatitis. A better approach may be a combined diagnostic strategy drawing on clinical information as well as findings from cytology and histology of pancreatic tissue, radiology and/or endoscopic ultrasonography.

The present meta-analysis had several limitations. First, the exclusion of conference abstracts, letters to the editor, and non-English-language studies may have led to publication bias, although our bias analysis suggests that this was not a significant problem. Second, nonrandom misclassification bias may have occurred given that different studies used different approaches to diagnose chronic pancreatitis,

including histology of pancreatic tissue, radiology, endoscopic ultrasonography and/or clinical information alone. Third, CA19-9 is not routinely measured when patients present with chronic pancreatitis, so the individuals in our meta- analysis may not be completely representative of this patient population. Fourth, 5%-10% of patients lacked the Lewis enzyme, fucosyltransferase, and so cannot present elevated CA19-9 even when tumor burden is high. Finally, we did not identify any large, blinded randomized controlled trials that satisfied our inclusion criteria.

In conclusion, our meta-analysis suggests that although CA19-9 showed considerable sensitivity and specificity for differentiating pancreatic carcinoma and chronic pancreatitis, the relatively high NLR means that CA19-9 levels by themselves have insufficient diagnostic accuracy. At the same time, elevated CA19-9 should increase suspicion of pancreatic carcinoma and may complement other clinical and histological findings to help confirm a diagnosis of cancer.

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Carbohydrate antigen 19-9 for differential diagnosis of pancreatic carcinoma and chronic pancreatitis

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Aim. To evaluate the utility of carbohydrate antigen 19-9 (CA19-9) for differential diagnosis of pancreatic carcinoma and chronic pancreatitis.

Methods. We searched the literature for studies reporting the sensitivity, specificity, and other accuracy measures of serum CA19-9 levels for differentiating pancreatic carcinoma and chronic pancreatitis. Pooled analysis was performed using random-effects models, and receiver operating characteristic (ROC) curves were generated. Study quality was assessed using Standards for Reporting Diagnostic Accuracy and Quality Assessment for Studies of Diagnostic Accuracy tools.

Results. A total of 34 studies involving 3125 patients with pancreatic carcinoma and 2061 patients with chronic pancreatitis were included. Pooled analysis of the ability of CA19-9 level to differentiate pancreatic carcinoma and chronic pancreatitis showed the following effect estimates: sensitivity, 0.81 (95% CI: 0.80–0.83); specificity, 0.81 (95% CI: 0.79–0.82); positive likelihood ratio, 4.08 (95% CI: 3.39–4.91); negative likelihood ratio, 0.24 (95% CI: 0.21–0.28); and diagnostic odds ratio, 19.31 (95% CI: 14.40–25.90). The area under the ROC curve was 0.88. No significant publication bias was detected.

Conclusion. Elevated CA19-9 by itself is insufficient for differentiating pancreatic carcinoma and chronic pancreatitis, however, it increases suspicion of

pancreatic carcinoma and may complement other clinical findings to improve diagnostic accuracy.