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Macrophage inhibitory cytokine-1 versus carbohydrate antigen 19–9 as a biomarker for diagnosis of pancreatic cancer

A PRISMA-compliant meta-analysis of diagnostic accuracy studies

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Abstract

Background: Because of the high malignant degree of pancreatic cancer (PC), the early diagnosis of PC is of great concern. Macrophage inhibitory cytokine-1 (MIC-1) was reported to be a potential diagnostic biomarker, but its diagnostic value is indeterminate. Therefore, we performed this meta-analysis to compare it to carbohydrate antigen 19–9 (CA19–9), the most frequently used serum biomarker in PC.

Material and Methods: After a systematic review of the relevant studies, the pooled diagnostic indices, including sensitivity, specificity, positive/negative likelihood ratio (PLR/NLR), diagnostic odds ratio (DOR), summary receiver operating characteristic curve (sROC), and area under the SROC curve (AUC) were used to evaluate the diagnostic value of MIC-1 and CA19–9 for PC. These indices were pooled with random-effects models. We explored the heterogeneity by meta-regression.

Results: Fourteen studies comprising a total of 2826 subjects were included in our meta-analysis. The summary estimates for MIC-1 and CA19–9 are listed as follows: sensitivity, 80% [95% confidence interval (CI) 78–82] versus 71% (95% CI 68–73); specificity, 85% (95% CI 83–87) versus 88% (95% CI 86–90); DOR, 24.57 (95% CI 14.00–43.10) versus 17.65 (95% CI 11.65–26.76); area under sROC (AUC), 0.8945 versus 0.8322; PLR, 5.18 (95% CI 3.24–8.26) versus 5.34 (95% CI 3.78–7.54); and NLR, 0.23 (95% CI 0.19–0.29) versus 0.32 (95% CI 0.28–0.37).

Conclusion: These data demonstrate that serum MIC-1 has a comparable diagnostic accuracy to CA19–9 for PC.

Abbreviations: AUC = area under the SROC curve, CA125 = carbohydrate antigen 125, CA19–9 = carbohydrate antigen 19–9, CA242 = carbohydrate antigen 242, CA72–4 = carbohydrate antigen 72–4, CBM = Chinese Biomedical Literature Database, CEA = carcinoembryonic antigen, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, CT = computed tomography, DOR = diagnostic odds ratio, ERCP = Endoscopic Retrograde Cholangiopancreatography, EUS = Endoscopic ultrasonography, EUS-FNA = Endoscopic ultrasonography-guided fine-needle aspiration, LAMC2 = laminin γC, MDCT = multidetector-row CT, MIC-1 = Macrophage inhibitory cytokine-1, MRCP = magnetic resonance cholangiopancreatography, MRI = magnetic resonance imaging, NLR = negative likelihood ratio, PC = pancreatic cancer, PET = positron emission tomography, PLR = positive likelihood ratio, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2, ROC = receiver operating characteristic, sROC = summary receiver operating characteristic curve, TGF-b = transforming growth factor b, TUS = transabdominal ultrasonography.

Keywords: antigens, carbohydrate, meta-analysis, growth differentiation factor 15, pancreatic neoplasms, tumor-associated

1. Introduction

Pancreatic cancer (PC) is one of the most malignant carcinoma with the 5-year survival rate of <5%.[1,2] The incidence of PC is ranked tenth among all cancers, while PC is the fourth leading cause of cancer death in western countries and the eighth in China.[3,4] Lacking of early diagnosis leads that 80% patients could not get surgical treatment. The prognosis of the other part of the patients is severely poor in spite of the surgery.[5] The most effective therapeutic method for PC is surgery at the initial stage, while the majority of patients are diagnosed at an advanced stage with distant metastasis and lose the opportunity for radical resection even chemoradiotherapy.[5,6] Therefore, early diagnosis of PC may be the only chance to improve the survival of patients. Although radiological imaging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), and so on, have been obviously advanced, early diagnosis of PC remains a challenge.[7–9] Nevertheless, an accurate serological test may contribute to the early diagnosis of PC greatly. In addition to early diagnosis, it can screen the high-risk population of patients

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at an early stage of PC and improve the monitoring of patients undergoing treatment.[10]

Carbohydrate antigen 19–9 (CA19–9), a glycolipid and an O-linked glycoprotein expressed on the surface of cancer cells, is the most frequently used biomarker for the diagnosis of PC in daily clinical practice in spite of plenty of limitations.[11,12] The diagnostic value of CA19–9 cannot meet our expectation for the reason that CA19–9 rises obviously in patients suffering from chronic pancreatitis, cholangitis, and even gastrointestinal cancers.[13,14]

Macrophage inhibitory cytokine-1 (MIC-1) is a divergent member of the transforming growth factor b (TGF-b) family of cytokines, and it was originally identified as a gene expressed in the context of macrophage activation.[15] MIC-1 is substantially upregulated in several pathological conditions such as injury inflammation and kinds of cancers including colon and prostate cancer.[16–19]

Previously, Koopmann et al[20] reported that MIC-1 was differentially expressed in PC tissues and elevated in the serum of PC patients compared with both healthy controls and those with benign pancreatic neoplasms. It was found to have higher sensitivity (71%) as that to CA19–9 (59%) in differentiating PC from other benign diseases and healthy controls but lower specificity.[20] Serum MIC-1 was found to be superior to CA19–9 in differentiating patients with resectable PC from controls.[21,22] But the data from the study with a small number of samples cannot make sure the diagnostic value of the MIC-1 for PC. So, we performed this meta-analysis.

2. Material and methods

The approval from an ethics committee or institutional review board is not required for the reason that our meta-analysis was based on previously published clinical trials.

2.1. Literature search

Without any restrictions in terms of language, year of publication, and publication status, all relevant primary studies published on or before May 1, 2017, that focused on the diagnostic value of MIC-1 for PC were searched from the following electronic databases: PubMed, Embase, the Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (CBM), and Wan Fang Data. Our search strategy included "pancreatic tumor or pancreatic cancer or pancreatic carcinoma or pancreatic neoplasm" and "MIC-1 or Macrophage Inhibitory Cytokine-1."

2.2. Inclusion and exclusion criteria

Two independent authors screened all relevant articles on the basis of titles and abstracts and skimmed the full text for any reasonable eligibility. Any disagreement was resolved by discussion with the third author to reach a final consensus. The inclusion criteria of the current systematic review and meta-analysis were studies that evaluated the diagnostic accuracy of serum or plasma MIC-1 and CA19–9 in diagnosis of PC; sample size of PC and non-PC patients was more than 20, knowing that small sample size studies may be vulnerable to selection bias; and 2×2 tables for both MIC-1 and CA19–9 could be constructed from the sensitivity and specificity reported or could be obtained from the receiver operating characteristic (ROC) curve. The exclusion criteria were applied: animal studies; non-English and non-Chinese publications; conference, abstracts, or letters to editors, because they usually presented limited data for analysis; studies had insufficient data to calculate sensitivity and specificity; and samples came from tissues or other body fluids. For duplicate reports, only the study with more detailed information was included.

2.3. Data extraction and quality assessment

The same 2 independent authors extracted the data and reached a consensus on all items. If disagreements arose, a consensus was reached after a full discussion with a third senior reviewer. The following data were extracted: first author, publication year, country where the study was conducted, number of patients and controls, patient characteristics, assay method of the biomarkers, cut-off values, and raw data in a 4-fold table format.

The quality of eligible studies was independently assessed using the revised Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool, which is considered reliable for the quality assessment of diagnostic accuracy test. The QUADAS-2 consists of 4 key domains that are supported by signaling questions to aid judgment on the risk of bias, including "patient selection," "index test," "reference standard," and "flow and timing." Simultaneously, the QUADAS-2 rates the risk of bias and applicability concern as "high," "unclear," or "low" and handles studies in which the reference standard consists of follow-up.[23] Any disagreement in quality assessment was resolved by consensus.

2.4. Statistical analysis

Previously published guidelines and methods on conducting meta-analysis of diagnostic test evaluations were used.[24–26] The meta-analysis was performed using Meta DiSc statistical software v1.4 (http://www.hrc.es/investigacion/metadisc_en.htm) and we used Word and Review Manager 5.2 to descriptively analyze the study characteristics and QUADAS-2 quality assessment. The following measures of test accuracy, including sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and corresponding 95% confidence interval (CI) were calculated using the DerSimonian–Laird method and presented in the form of forest plots. A summary ROC (SROC) curve covering all the studies was plotted to analyze test accuracy[27,28] and to calculate the area under curve (AUC). The area under the SROC curve (AUC) was used for grading the overall diagnostic performance of MIC-1 and CA19–9 as a potential summary of the SROC curve. Heterogeneity is usually caused by threshold effect and nonthreshold effect. There are many ways to determine whether the threshold effect exists or not, such as observing the ROC plane plots, which illustrate that threshold effect exists when the points show a curvilinear pattern. And Spearman correlation coefficient was also calculated to determine the threshold effect.[29] Heterogeneity induced by nonthreshold effect was assessed by means of the Cochran Q method and the test of inconsistency (I^2). If $P < .05$ or $I^2 > 50\%$, heterogeneity exists.[30] To explore the sources of heterogeneity, we did a meta-regression analysis. We used 4 variables (country of origin, publication year, quality of including studies, and case number) in this meta-analysis.

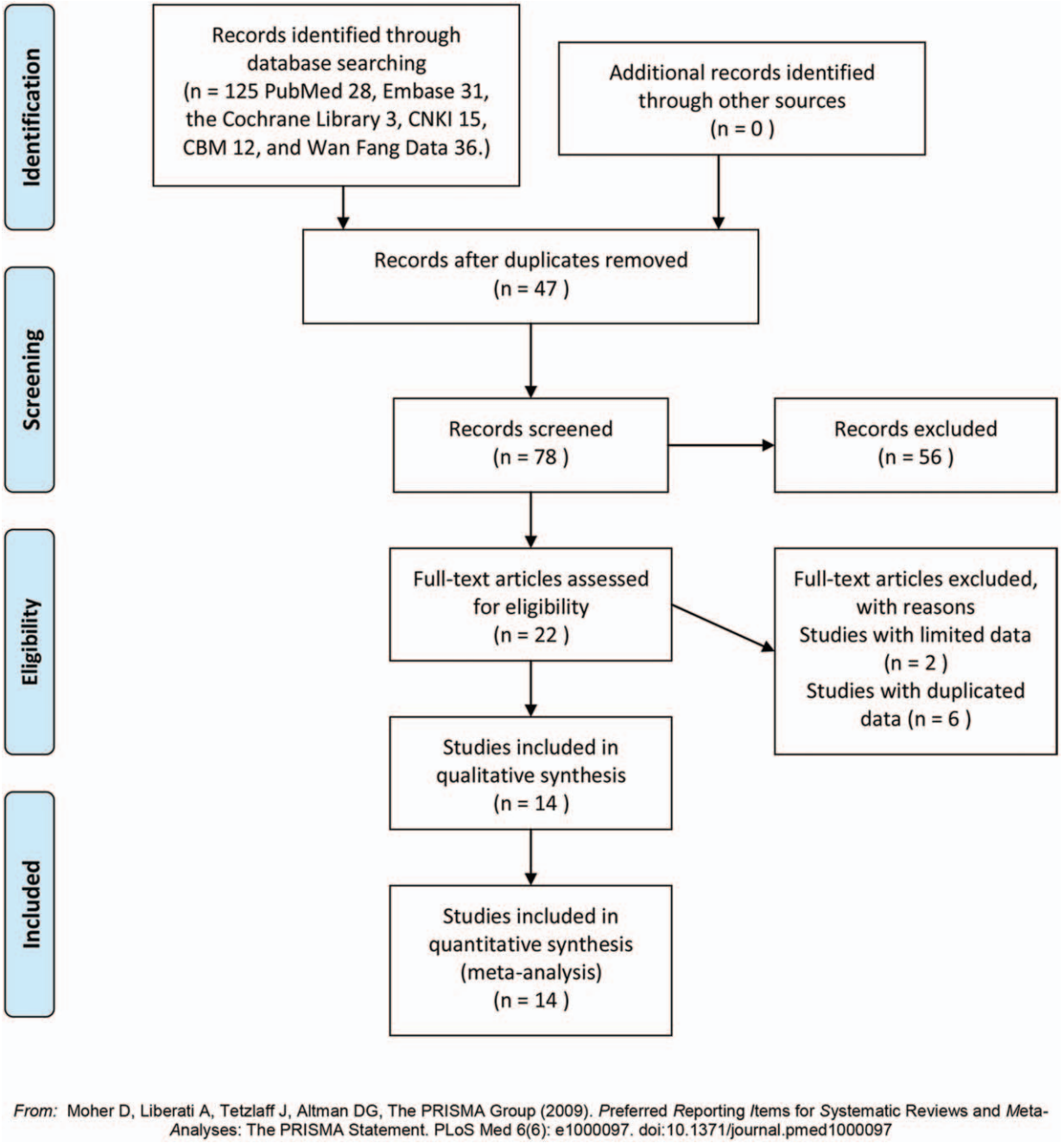

Figure 1. The flow diagram of literature search: 14 eligible studies were included in our meta-analysis.

3. Results

3.1. Literature search

A total of 125 potentially relevant studies were found after searching the databases. We scanned the title, keywords, and abstract of these studies, and removed 103 researches consisting of the repeated studies, reviews, or the studies whose theme is prognosis, treatment, or pathology of PC. The remaining 22 articles were read in detail, and it resulted that 20 articles were quite consistent with our meta-analysis. The 2 articles that were excluded were from the studies by Ma et al [31] and Wang et al.[32] The former is lack of specificity of CA19–9 and MIC-1, the latter is lack of sensitivity and specificity of CA19–9. Then, we read the full texts of the remaining 20 articles. Eventually, 14 studies[20,22,33–44] were included and the other 6 was excluded because of potential duplicate data. The flow diagram of searching is shown in Fig. 1. Table 1 summarizes the essential information of the including studies.

3.2. Quality of the studies

The result of the assessment of all the including studies by QUADAS-2 is presented in Fig. 2. The primary bias of these eligible researches are concentrated with the patient selection and index text. Especially, the patient selection augmented the risk of bias in 14 studies[20,22,33–44] due to the case–control study design

Table 1

Main characteristics of the studies included in this meta-analysis.

Ref.	Year	Country	PC	Gender (M/F)	Mean age, y	Control				Sample
						NPC	Healthy	Gender (M/F)	Mean age	
Mohamed et al[36]	2015	Egypt	50	32/18	63	0	20	11/9	62	Serum
Özkan et al[44]	2011	Turkey	56	37/19	63.1	0	33	16/17	57.4	Serum
Koopmann et al[20]	2004	Australia	80	45/35	66.4	119	97	NA	NA	Serum
Koopmann et al[22]	2006	Australia	50	22/28	67.6	0	50	14/36	61.1	Serum
Kaur et al[32]	2013	USA	91	55/36	65.5	0	24	4/20	56	Plasma
Zhou et al[43]	2014	China	152	101/51	56	0	96	72/24	58	Serum
Zeng et al[42]	2012	China	42	31/11	59.82	0	30	15/15	45.54	Serum
Fu et al[31]	2011	China	118	76/42	58	32	120	85/67	47	Serum
Li et al[35]	2014	China	129	75/54	31–72	0	120	67/53	18–66	Serum
Shao et al[37]	2007	China	101	68/33	58.77	0	50	26/24	40.89	Serum
Tao et al[38]	2015	China	86	47/39	63.4	0	90	48/42	50.6	Serum
Wang et al[39]	2007	China	171	108/63	60	27	0	5/22	42.48	Serum
Wang et al[40]	2011	China	552	305/217	57.5	0	200	124/76	47.5	Serum
Yang et al[41]	2014	China	20	10/10	53	0	20	10/10	53	Serum

M/F = male/female, NPC = nonpancreatic cancer, including chronic pancreatitis, adenoma, and benign diseases, PC = pancreatic cancer.

and 1 study[20] lacking the information about whether consecutive or random samples of patients were enrolled. For the risk of bias in the index text, 3 studies[22,40,43] did not pre-set the threshold. Even though the results of index test were interpreted without knowledge of the results of the reference standard, we considered these studies to have a high risk of bias. Regarding the domain of reference standard, all the studies used histopathological method that the world medical community agrees to be the gold standard to diagnose PC blindly. For patient flow and timing domains, all patients received the same reference standard and there was an appropriate interval between index test and reference standard. In relation to applicability concerns, all the 3 domains (patient selection, index text, and reference standard) scored well for all the including studies.

3.3. Heterogeneity assessment

It is indispensable for any meta-analysis to do an examination of the potential sources of heterogeneity before pooling the data from the included studies into summary assessments.[45] In all meta-analysis, the heterogeneity within the studies was determined, which is crucial to the comprehension of the potential factors that greatly influence accuracy assessments and the appraisal of the appropriateness of statistical pooling of the diagnostic accuracy from the various studies.[46] There are 2 causes of heterogeneity. One is the threshold effect, which is primary and important, and the other one is nonthreshold effect. We used a Spearman test to explore whether the heterogeneity caused by the threshold effect of MIC-1 and CA19–9 exists or not in all researches. With regard to the MIC-1 researches, Spearman correlation coefficient was −0.018 and P value was .952. In addition, regarding to CA19–9 researches, Spearman correlation coefficient was 0.244 and P value was .401. In conclusion, the Spearman test that we did made it clear that there was no heterogeneity caused by threshold effect. Another vital reason that may be dedicated to the heterogeneity among the researches is nonthreshold effect. We assessed nonthreshold effect by the means of the Cochran Q method, Chi-squared test, and the test of inconsistency (I^2). Cochran Q values, x^2 values, I^2 values for diagnostic performance indices were shown in the forest plots. The I^2 values were more than 50% as shown in figures, which suggested high heterogeneity from nonthreshold effect among the included studies.

3.4. The summary diagnostic accuracy of MIC-1 versus CA19–9 for pancreatic cancer

The result of the including researches is listed in Table 2 and Figs. 3 to 6 show the forest plots of diagnostic indices of MIC-1 and

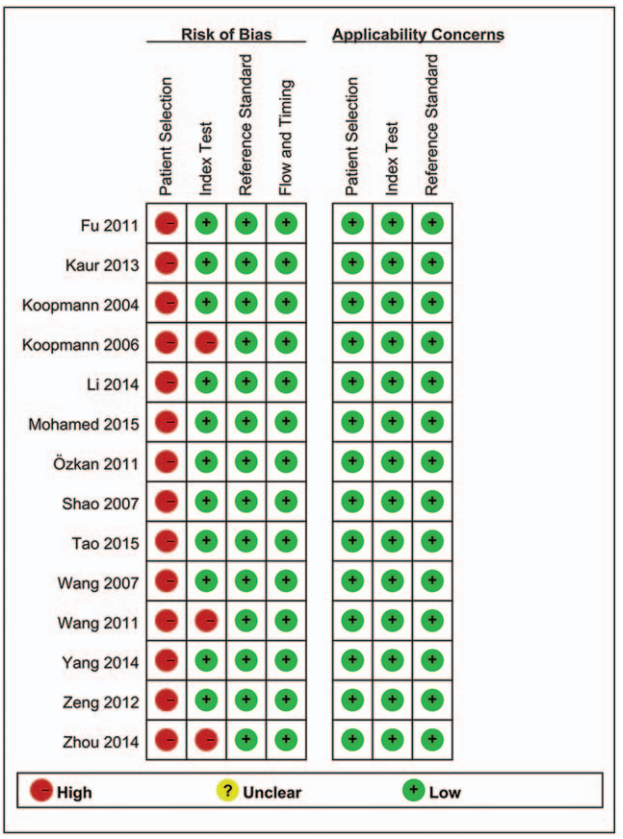

Figure 2. The quality assessment of the included studies by QUADAS-2.

Table 2

Diagnostic performance of MIC-1 and CA19–9 from individual studies.

Author	Year	Tumor marker	Test method	Cutoff level	Sen%	Spe%	TP	FP	FN	TN	AUC	95% CI
Mohamed et al[36]	2015	MIC-1	ELISA	2070 pg/mL	94	45.8	47	11	3	9	0.917	NA
		CA19–9	NA	55 U/mL	82	66.7	41	7	9	13	0.904	NA
Özkan et al[44]	2011	MIC-1	ELISA	1259 pg/mL	81	73	45	9	11	24	0.88	0.78–0.94
		CA19–9	ELISA	34.3 U/mL	81	97	45	1	11	32	0.93	0.85–0.97
Koopmann et al[20]	2004	MIC-1	ELISA	1070 pg/mL	71	78	57	48	23	168	0.81	0.75–0.86
		CA 19–9	ELISA	70 U/mL	59	88	47	26	33	190	0.77	0.69–0.83
Koopmann et al[22]	2006	MIC-1	ELISA	1583 pg/mL	90	94	45	3	5	47	0.99	NA
		CA 19–9	ELISA	37 U/mL	62	80	31	10	19	40	0.78	NA
Kaur et al[32]	2013	MIC-1	ELISA	1070 pg/mL	90	46	82	13	9	11	NA	NA
		CA 19–9	RIA	37 U/mL	83	67	76	8	15	16	NA	NA
Zhou et al[43]	2014	MIC-1	ELISA	642.8 pg/mL	89.9	90.3	137	9	15	87	0.958	0.924–0.992
		CA 19–9	RIA	18.44 U/mL	82	96.8	125	3	27	93	0.883	0.833–0.932
Zeng et al[42]	2012	MIC-1	ELISA	677 pg/mL	83.33	93.33	35	2	7	28	0.96	NA
		CA 19–9	ECLIA	37 U/mL	73.81	90	31	3	11	27	0.85	NA
Fu et al[31]	2011	MIC-1	ELISA	946 pg/mL	80.5	90.1	95	15	23	137	0.918	NA
		CA 19–9	ECLIA	NA	74.6	82.2	88	27	30	125	0.835	NA
Li et al[35]	2014	MIC-1	ELISA	1000 pg/mL	73.6	82.5	95	21	34	99	NA	NA
		CA 19–9	CLIA	37 U/mL	69.8	85.8	90	17	39	103	NA	NA
Shao et al[37]	2007	MIC-1	ELISA	617 pg/mL	8l.2	94	82	3	19	47	0.92	NA
		CA 19–9	ECLIA	37 U/mL	72.4	89.6	71	5	27	43	0.86	NA
Tao et al[38]	2015	MIC-1	ELISA	1000 pg/mL	79.07	78.89	68	19	18	71	NA	NA
		CA 19–9	CLIA	35 U/mL	70.93	85.56	61	13	25	77	NA	NA
Wang et al[39]	2007	MIC-1	ELISA	615.7 pg/mL	83.6	88.9	143	3	28	24	0.923	NA
		CA 19–9	ELISA	37 U/mL	76.6	80.8	131	5	40	21	0.808	NA
Wang et al[40]	2011	MIC-1	ELISA	1000 pg/mL	73.9	97	386	6	136	194	0.945	NA
		CA 19–9	ECLIA	37 U/mL	61.9	97	323	6	199	194	0.836	NA
Yang et al[41]	2014	MIC-1	ELISA	NA	62.32	68.56	12	6	8	14	0.68	NA
		CA 19–9	ELISA	NA	72.45	83.29	14	3	6	17	0.83	NA

95% CI = 95% confidence interval, AUC = area under curve, CA19–9 = carbohydrate antigen 19–9, CLIA = chemiluminescent immunoassay, ECLIA = electrochemiluminescence immunoassay, ELISA = enzyme-linked immunosorbent assay, FN = false negative, FP = false positive, MIC-1 = microphage inhibitory cytokine-1, NA = not available, RIA = radioimmunoassay, Sen = sensitivity, Spe = specificity, TN = true negative, TP = true positive.

CA19–9 for PC. The sensitivity that these studies observed ranged from 60% to 94% (summary 80%; 95% CI 78–82), 59% to 84% (summary 71%; 95% CI 68–73) for MIC-1 (Fig. 3A) and CA19–9 (Fig. 4A) levels in the diagnosis of PC, respectively, while the specificity ranged from 45% to 97% (summary 85%; 95% CI 83–87) (Fig. 3B), 65% to 97% (summary 88%; 95% CI 86–90) (Fig. 4B). As a result of this, the pooled sensitivity of CA19–9 is observably higher than MIC-1, while with regard to the pooled specificity, MIC-1 had a significantly higher result than CA19–9. In addition, the pooled PLR and NLR were 5.18 (95% CI, 3.24–8.26) and 0.23 (95% CI, 0.19–0.29) versus 5.34 (95% CI, 3.78–7.54) and 0.32 (95% CI, 0.28–0.37) for MIC-1 (Fig. 5A, B) and CA19–9 (Fig. 6A, B) levels in the diagnosis of PC, which indicated that each had its own merits.

Overall diagnostic accuracy was assessed by the pooled DOR and AUC. Their values for MIC-1 versus CA19–9 levels in the diagnosis of PC were 24.57 (95% CI, 14.00–43.10) (Fig. 5C) versus 17.65 (95% CI, 11.65–26.76) (Fig. 6C) and 0.8945 (Fig. 7A) versus 0.8322 (Fig. 7B), respectively, suggesting that the diagnostic value of MIC-1 is of a stroke above that of CA19–9. Summary of the pooled diagnostic indices is provided in Table 3.

3.5. Meta-regression

Inconsistency (1-square) values namely I^2 values for the diagnostic performance indices, as the figure follows, were more than 50% without exception, indicating that high heterogeneity from nonthreshold effect among the included studies exists. Therefore, a meta-regression that was based on country of origin (Asia or non-Asia), publication year (before 2010 or after 2010), quality of including studies (high, medium or low), and case number (<100 or ≥ 100) was performed to explore the possible sources of heterogeneity. The results of this meta-regression are summarized in Table 4, indicating that none of the above covariates was found to be the significant source of heterogeneity (all $P > .05$).

4. Discussion

It is critical to identify PC early in the clinical course to provide timely and accurate treatment for patients, for the reason that PC is one of the lethal disease with an unfavorable prognosis. Nevertheless, the patients who are suffering from PC always cannot be diagnosed definitely for the asymptomatic clinical performance until the disease develops to an advanced stage. Therefore, the only thing we have to do is get down to find some powerful markers and confirm its diagnostic value to solve the problem about early diagnosis when we have no idea about that whether PC exists or not. Serum MIC-1 was reported in a few studies to be a promising candidate biomarker to dedicate to the diagnosis of PC in contrast to CA19–9, a traditional serum biomarker. But studies have given confusing results about their diagnostic performance. Some studies[20,22,36] consider that the diagnostic value of MIC-1 for PC is better than that of CA19–9. However, some[41,44] hold the opposite view. To definitize the

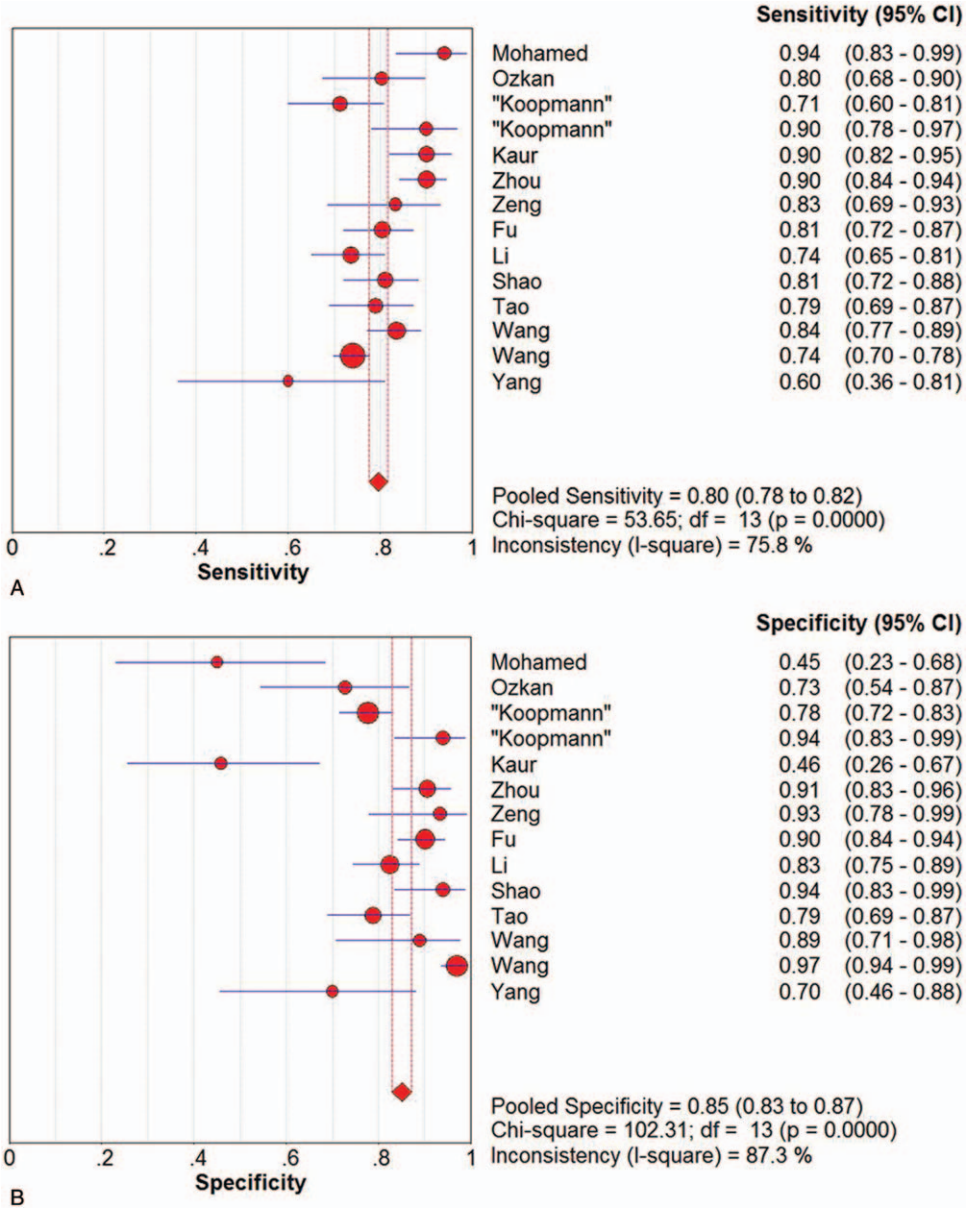

Figure 3. Forest plots of (A) sensitivity and (B) specificity for MIC-1 in the diagnosis of PC of the included 14 studies.

diagnostic performance of the 2 biomarkers, we did this meta-analysis. We found and assessed 14 studies that directly compared the diagnostic accuracy of serum MIC-1 and CA19–9 in the same patient population, and the results demonstrate that MIC-1 is a comparable marker for PC to CA19–9.

Currently, it is universally acknowledged that CA19–9 is the most commonly used and most extensively validated serum biomarker for detecting PC. CA19–9 is a sialylated Lewis blood group antigen, which is absent from the blood stream of 5% to 10% of the population who are unable to express sialylated Lewis antigens.[47] Although CA19–9 is the most commonly used antigen for detecting PC, it is also elevated in a variety of other conditions, including malignancies such as cholangiocarcinoma, hepatocellular carcinoma, and colorectal adenocarcinoma as well as nonmalignant processes such as pancreatitis, pseudocyst, choledocholithiasis, and cirrhosis.[48] Therefore, the diagnostic value of CA19–9 is suboptimal. Our meta-analysis indicated that MIC-1 was performed with a higher sensitivity than CA19–9, with a lower rate of missed diagnoses than CA19–9 in the meantime. As for the specificity, MIC-1 is slightly lower than CA19–9. The rate of misdiagnosis for MIC-1 is 15%, which is higher than CA19–9. These findings demonstrate that MIC-1 and CA19–9 could play different roles in the diagnosis of PC. DOR is a single indicator of test accuracy that combines the data from sensitivity and specificity into a single number. The value of DOR ranges from 0 to infinity, and higher values indicate better discriminatory test performance.[26] In our study, the DOR value for MIC-1 is 24.57, which is obviously higher than that for CA19–9 of 17.65. Another indicator of diagnostic accuracy is AUC that was calculated by SROC curve that assesses overall test

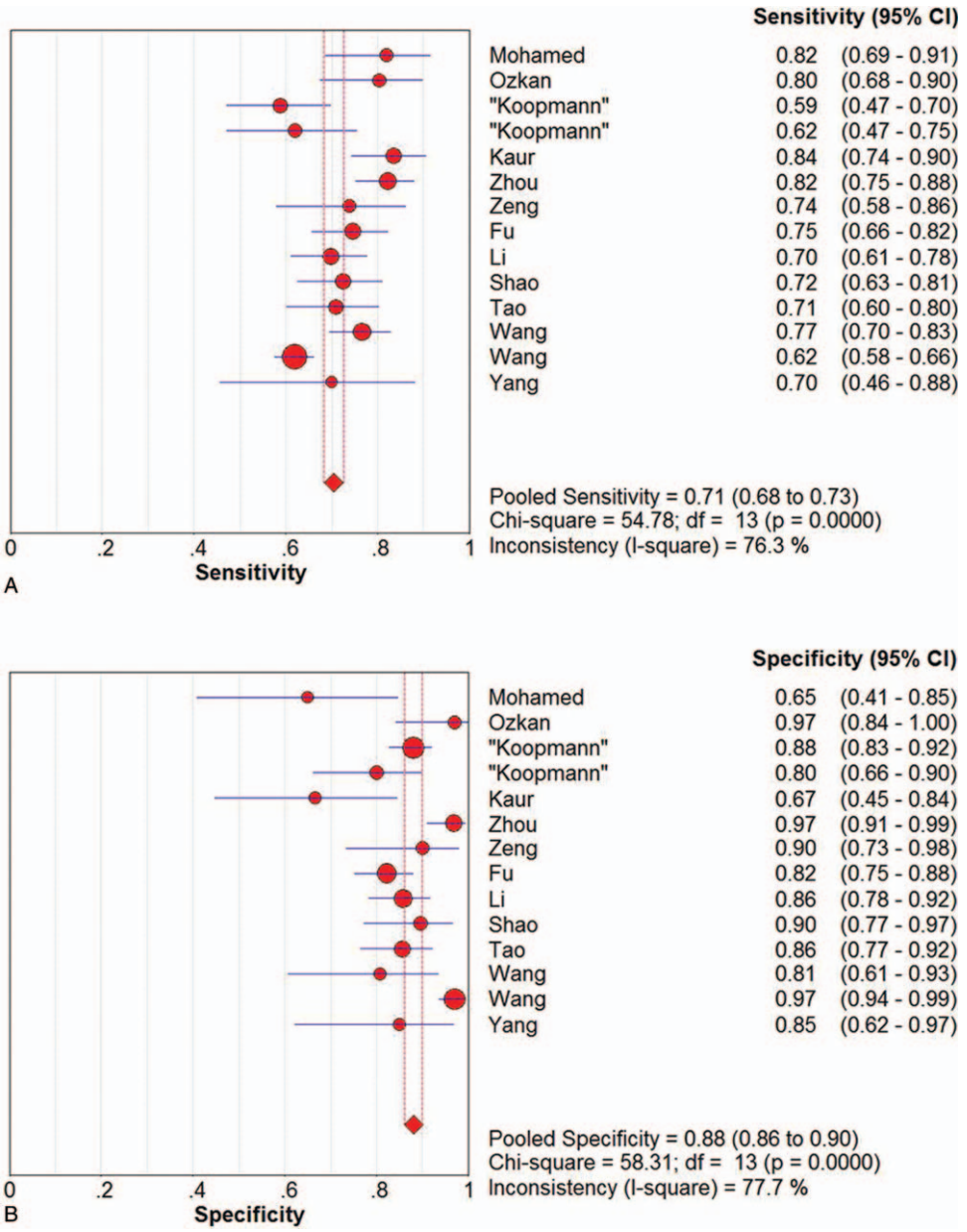

Figure 4. Forest plots of (A) sensitivity and (B) specificity for CA19–9 in the diagnosis of PC of the included 14 studies.

performance by showing the trade-off between sensitivity and specificity.[49] In the same way, MIC-1 had an AUC of 0.8945, more than CA19–9 of 0.8322. Both the findings of DOR and that of AUC prompt that MIC-1 have a more exact diagnostic accuracy for diagnosing PC comparing with CA19–9. We further examined the diagnostic accuracy of MIC-1 and CA19–9 by calculating PLR and NLR, which can be easier to relate to clinical practice than SROC and DOR. The pooled PLR value for MIC-1 of 5.18 suggests that patients with cancer have about 5-fold higher chance of being MIC-1 positive than patients without cancer. In the clinical practice, the larger the PLR value, the better. Thus, CA19–9 is a little better than MIC-1 with the PLR value of 5.34. The pooled NLR for MIC-1 was 0.23, suggesting that a negative MIC-1 result is still 23% likely to be a false negative, which is not low enough to rule out PC. That is to say, the lower the NLR, the easier to rule out PC. Now, we can say that MIC-1 can help to rule out PC more easily than CA19–9 on account of its NLR value of 0.32. Thereby for MIC-1 and CA19–9, each in his own way has made an important contribution in this field in spite of the tiny difference of LR values.

Currently, there are plenty of serum biomarkers such as carcinoembryonic antigen (CEA),[50] carbohydrate antigen 72–4 (CA72–4),[50] carbohydrate antigen 242 (CA242),[51] carbohydrate antigen 125 (CA125),[52] laminin γC (LAMC2)[52] was found to be devoted to clinical diagnosis of PC more or less. These markers sometimes perform alone, sometimes are combined with other markers, and form a panel to identify PC. Although some serum biomarkers or biomarker panels can be of high diagnostic value, it cannot meet the strict diagnostic criteria in clinical practice. In addition to serum biomarkers, other markers such as

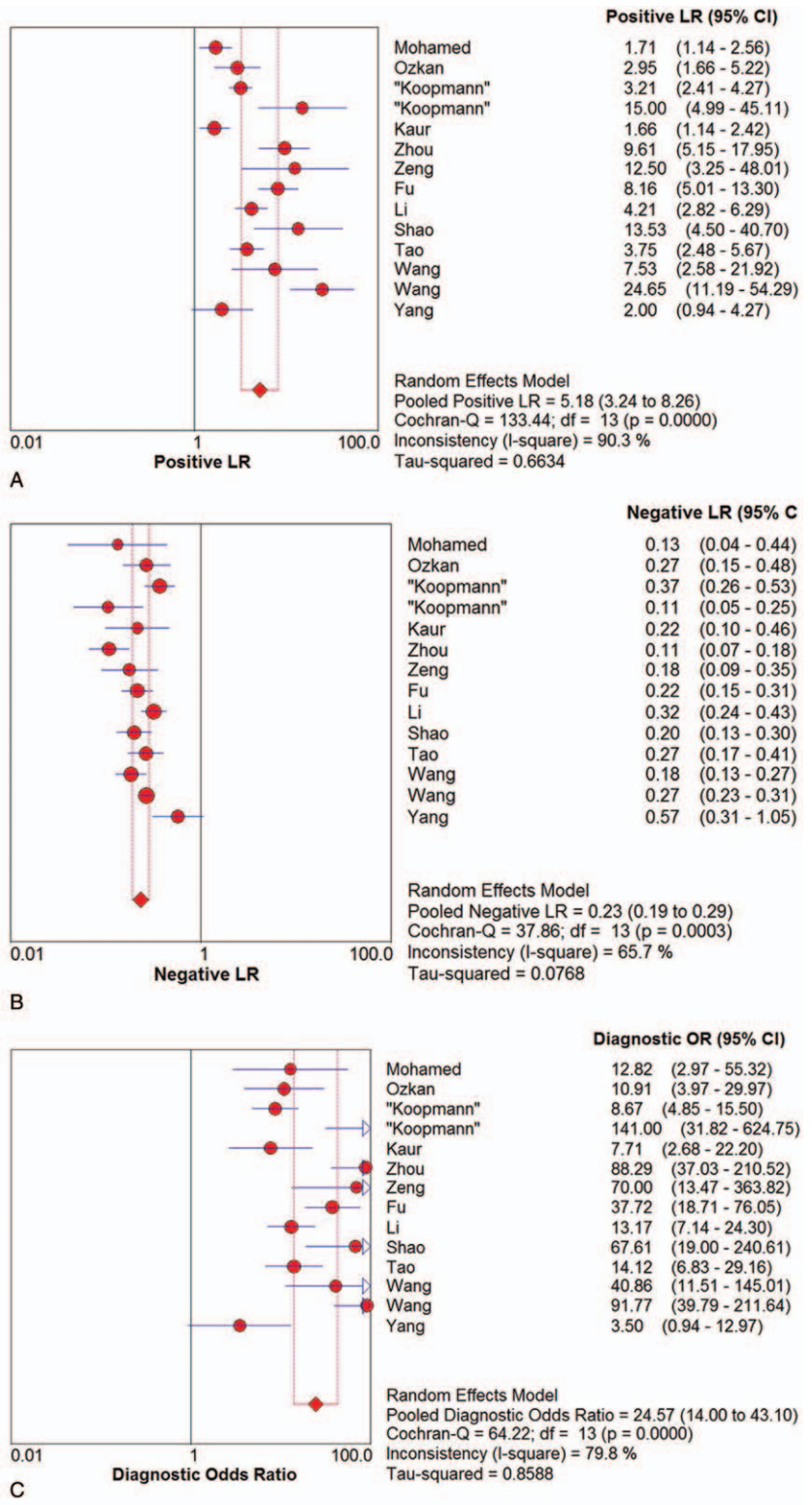

Figure 5. Forest plots of (A) PLR, (B) NLR and (C) DOR for MIC-1 in the diagnosis of PC of the included 14 studies.

clinical presentation, signs, symptoms, imaging characteristics, some signs of invasive examinations, and gene detection are widely used. The study by Keane et al[53] suggested that PC is associated with 12 alarm symptoms: weight loss, abdominal pain, nausea and vomiting, bloating, dyspepsia, new-onset diabetes, changes in bowel habit, pruritus, lethargy, back pain, shoulder pain, and jaundice. Diagnostic ability of ultrasonography greatly depends on the operator's experience and the patient's condition in terms of obesity and bowel gas, which leads to uncertain sensitivity and specificity. It is necessary to combine

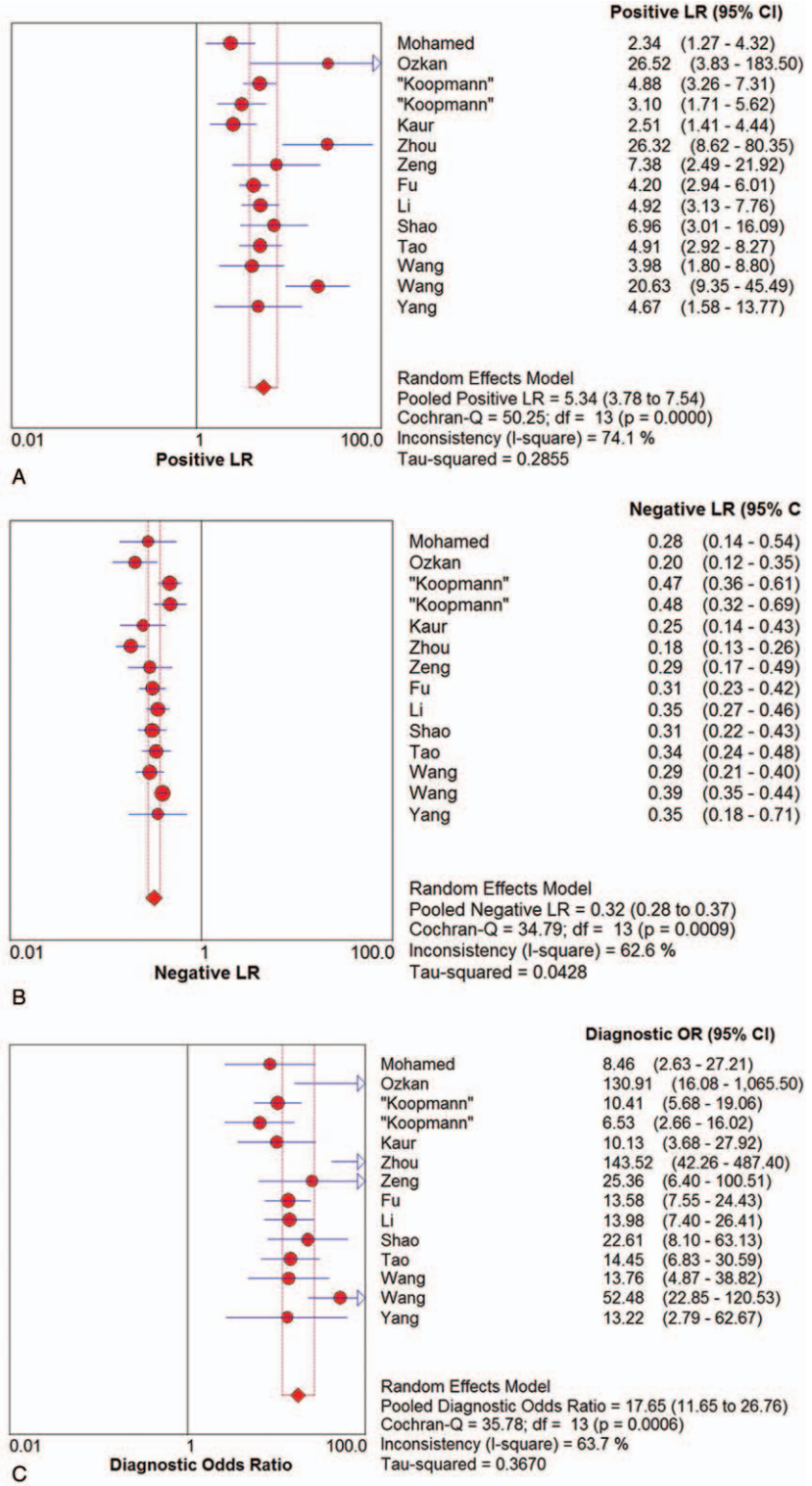

Figure 6. Forest plots of (A) PLR, (B) NLR and (C) DOR for CA19–9 in the diagnosis of PC of the included 14 studies.

some other imaging tests such as CT, multidetector-row CT (MDCT), positron emission tomography (PET), MRI, or magnetic resonance cholangiopancreatography (MRCP) and some invasive examinations such as endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), and endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) with transabdominal ultrasonography (TUS) to evaluate all aspects of PC. There are a number of studies[54] that combine several imaging diagnostic methods to diagnose PC in order to improve the accuracy of the diagnosis, as the individual tests are generally of little value. At last, it was found that EUS and EUS-FNA offer high diagnostic ability for

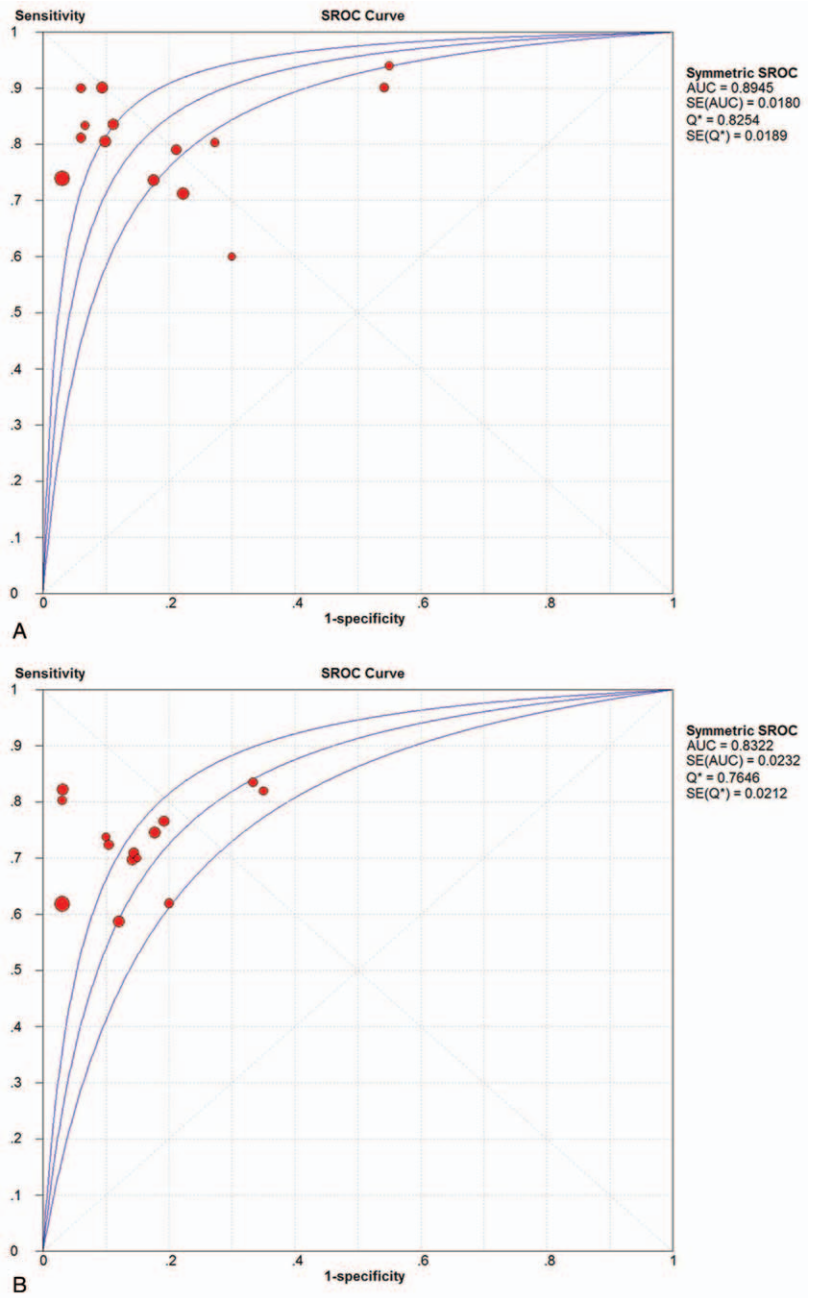

Figure 7. SROC curve for (A) MIC-1 and (B) CA19–9 in the diagnosis of PC of the included 14 studies.

PC.[55] Some patients with PC were found to have gene mutations, such as KRAS, P16INK4A, p53, SMAD4, and so on. What is more, microRNAs can be detected in patients' tissues or plasma. These combined panels can help the diagnosis of PC. Diagnosis of PC is still largely based on histopathological examination, but we just need some accurate noninvasive examinations.

However, our meta-analysis had numerous limitations and we should interpret the results with caution for this reason. In spite of that our meta-analysis was strengthened by the use of a standard protocol, strict inclusion criteria, standardized data extraction, independent reviewers, and a random-effects model,[27] we can do nothing about other uncontrollable factors. These factors are as follows: First, we only included the studies published in English or Chinese in only a few databases. Our results may be biased by our omission of studies published in journals not indexed in the databases we searched, studies published in other languages and unpublished studies. Second, this meta-analysis mostly included case–control studies, which may be prone to spectrum bias because of the limitation of selecting controls. At last, the heterogeneity of our meta-analysis was obvious. Although we had carried on the meta-regression analysis, we could not find the source of heterogeneity.

Table 3

Summary of the pooled diagnostic indices of MIC-1 and CA19–9 for PC.

Summary	MIC-1	95%CI	CA19–9	95% CI
Sen	0.8	0.78–0.82	0.71	0.68–0.73
Spe	0.85	0.83–0.87	0.88	0.86–0.90
PLR	5.18	3.24–8.26	5.34	3.78–7.54
NLR	0.23	0.19–0.29	0.32	0.28–0.37
DOR	24.57	14.00–43.10	17.65	11.65–26.76
AUC	0.8945	–	0.8322	–

AUC = area under the SROC curve, DOR = diagnostic odds ratio, NLR = negative likelihood ratio, PLR = positive likelihood ratio.

Table 4

Meta-regression of the effects of methodological characteristics on diagnostic accuracy.

	MIC-1			CA19–9		
Covariates	Coefficient	SE	*P*	Coefficient	SE	*P*
Country	0.754	0.5957	.2297	0.706	0.3935	.0982
Year	−0.77	0.6575	.2663	0.397	0.4472	.3935
Quality	−0.163	0.5485	.7737	−0.108	0.374	.7777
Case	0.49	0.7705	.5388	−0.036	0.6475	.9566

5. Conclusion

Our meta-analysis found that MIC-1 is a comparable biomarker to CA19–9 as an individual diagnostic tool for PC and each performs its own functions. The diagnostic value of MIC-1 combined with CA19–9 in diagnosis of PC is still worth exploring.

References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10–29.
[2] Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277–300.
[3] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–403.
[4] Li D, Xie K, Wolff R, et al. Pancreatic cancer. Lancet 2004;363:1049–57.
[5] Hidalgo M. Pancreatic cancer. N Engl J Med 2010;362:1605–17.
[6] Conlon KC, Klimstra DS, Brennan MF. Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathologic analysis of 5-year survivors. Ann Surg 1996;223:273–9.
[7] Herreros-Villanueva M, Bujanda L. Non-invasive biomarkers in pancreatic cancer diagnosis: what we need versus what we have. Ann Transl Med 2016;4:134.
[8] Guo J, Xie K, Zheng S. Molecular biomarkers of pancreatic intra-epithelial neoplasia and their implications in early diagnosis and therapeutic intervention of pancreatic cancer. Int J Biol Sci 2016; 12:292–301.
[9] Viterbo D, Gausman V, Gonda T. Diagnostic and therapeutic biomarkers in pancreaticobiliary malignancy. World J Gastrointest Endosc 2016;8:128–42.
[10] International Institute of Anticancer Research. Tumour markers in gastrointestinal cancers–EGTM recommendations. European Group on Tumour Markers [editorial]. Anticancer Res 1999;19:2811–5.
[11] Kaur S, Baine MJ, Jain M, et al. Early diagnosis of pancreatic cancer: challenges and new developments. Biomark Med 2012;6:597–612.
[12] Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. Eur J Surg Oncol 2007;33:266–70.
[13] Brody JR, Witkiewicz AK, Yeo CJ. The past, present, and future of biomarkers: a need for molecular beacons for the clinical management of pancreatic cancer. Adv Surg 2011;45:301–21.
[14] Duffy MJ, Sturgeon C, Lamerz R, et al. Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. Ann Oncol 2010;21:441–7.
[15] Bootcov MR, Bauskin AR, Valenzuela SM, et al. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. Proc Natl Acad Sci U S A 1997;94:11514–9.
[16] Boyle GM, Pedley J, Martyn AC, et al. Macrophage inhibitory cytokine-1 is overexpressed in malignant melanoma and is associated with tumorigenicity. J Invest Dermatol 2009;129:383–91.
[17] Breit SN, Johnen H, Cook AD, et al. The TGF-beta superfamily cytokine, MIC-1/GDF15: a pleotrophic cytokine with roles in inflammation, cancer and metabolism. Growth Factors 2011;29:187–95.
[18] Buckhaults P, Rago C, St Croix B, et al. Secreted and cell surface genes expressed in benign and malignant colorectal tumors. Cancer Res 2001;61:6996–7001.
[19] Welsh JB, Sapinoso LM, Kern SG, et al. Large-scale delineation of secreted protein biomarkers overexpressed in cancer tissue and serum. Proc Natl Acad Sci U S A 2003;100:3410–5.
[20] Koopmann J, Buckhaults P, Brown DA, et al. Serum macrophage inhibitory cytokine 1 as a marker of pancreatic and other periampullary cancers. Clin Cancer Res 2004;10:2386–92.
[21] Misek DE, Patwa TH, Lubman DM, et al. Early detection and biomarkers in pancreatic cancer. J Natl Compr Canc Netw 2007; 5:1034–41.
[22] Koopmann J, Rosenzweig CN, Zhang Z, et al. Serum markers in patients with resectable pancreatic adenocarcinoma: macrophage inhibitory cytokine 1 versus CA19-9. Clin Cancer Res 2006;12:442–6.
[23] Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.
[24] Deville WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. BMC Med Res Methodol 2002;2:9.
[25] Liang QL, Shi HZ, Qin XJ, et al. Diagnostic accuracy of tumour markers for malignant pleural effusion: a meta-analysis. Thorax 2008;63:35–41.
[26] Chappell FM, Raab GM, Wardlaw JM. When are summary ROC curves appropriate for diagnostic meta-analyses? Stat Med 2009; 28:2653–68.
[27] Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 2005;58:982–90.
[28] Glas AS, Lijmer JG, Prins MH, et al. The diagnostic odds ratio: a single indicator of test performance. J Clin Epidemiol 2003;56:1129–35.
[29] Moses LE, Shapiro D, Littenberg B. Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations. Stat Med 1993; 12:1293–316.
[30] Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006;11:193–206.

[31] Ma HB, Huang T, Han F, et al. Study on clinical value of MIC-1 for early diagnosis, metastasis and curative effect of patients with pancreatic cancer. Mod Prev Med 2012;39:2249–50.
[32] Wang XB, Li YF, Tian HM, et al. Macrophage inhibitory cytokine 1 (MIC-1/GDF15) as a novel diagnostic serum biomarker in pancreatic ductal adenocarcinoma. BMC Cancer 2014;14:578.
[33] Fu C, Wang H, Qi J, et al. Application of serum macrophage inhibitory cytokine-1 in pancreatic cancer. Oncol Progr 2011;9:204–8.
[34] Kaur S, Chakraborty S, Baine MJ, et al. Potentials of plasma NGAL and MIC-1 as biomarker(s) in the diagnosis of lethal pancreatic cancer. PLoS One 2013;8:e55171.
[35] Li XM, Wang LZ, Gong GF, et al. Clinical research of serum MIC-1, CA19-9, CA242 and CEA in patients with pancreatic cancer. J Clin Intern Med 2014;31:31–3.
[36] Mohamed AA, Soliman H, Ismail M, et al. Evaluation of circulating ADH and MIC-1 as diagnostic markers in Egyptian patients with pancreatic cancer. Pancreatology 2015;15:34–9.
[37] Shao CJ, Wang XB, Wang Y, et al. Value of macrophage inhibitory cytokine-1 as a novel marker for detecting and diagnosing pancreatic cancer. World Chinese J Digestol 2007;15:3644–8.
[38] Tao GL, Ren CL, Ding QL. Diagnostic value of MIC-1, TSGF combined with CA 19-9 in pancreatic carcinoma(Chinese). Lab Med Clin 2015;12:215–6.
[39] Wang Y. The Relative Factors Affecting the Survival in Pancreatic Cancer, Value of MIC-1 in Pancreatic Cancer and it's Expression in p. pastoris. Chinese Peking Union Medical College; 2007.
[40] Wang XB, Fu C, Wu F, et al. Clinical research of serum macrophage inhibitory cytokine-1 in large numbers of patients with pancreatic cancer. Oncol Progr 2011;9:367–73.
[41] Yang X, Li X. Combined detection of serum OPN, MIC-1 and CA19-9 for diagnosis of pancreatic cancer. World Chinese J Digestol 2014;22: 2966–70.
[42] Zeng L. Clinical Diagnostic Value of MIC-1 and REG4 as Serum Tumor Markers in Pancreatic Cancer. Nanchang University; 2012.
[43] Zhou YF, Xu LX, Huang LY, et al. Combined detection of serum UL16-binding protein 2 and macrophage inhibitory cytokine-1 improves early diagnosis and prognostic prediction of pancreatic cancer. Oncol Lett 2014;8:2096–102.
[44] Ozkan H, Demirbas S, Ibis M, et al. Diagnostic validity of serum macrophage inhibitor cytokine and tissue polypeptide-specific antigen in pancreatobiliary diseases. Pancreatology 2011;11:295–300.
[45] Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. Stat Med 2002;21:1525–37.
[46] Zamora J, Abraira V, Muriel A, et al. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol 2006;6:31.
[47] Goggins M. Molecular markers of early pancreatic cancer. J Clin Oncol 2005;23:4524–31.
[48] Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: an evidence based appraisal. J Gastrointest Oncol 2012;3: 105–19.
[49] Hamza TH, van Houwelingen HC, Heijenbrok-Kal MH, et al. Associating explanatory variables with summary receiver operating characteristic curves in diagnostic meta-analysis. J Clin Epidemiol 2009;62:1284–91.
[50] Carpelan-Holmstrom M, Louhimo J, Stenman UH, et al. CEA, CA 19-9 and CA 72-4 improve the diagnostic accuracy in gastrointestinal cancers. Anticancer Res 2002;22:2311–6.
[51] Lamerz R. Role of tumour markers, cytogenetics. Ann Oncol 1999;10 (Suppl 4):145–9.
[52] Chan A, Prassas I, Dimitromanolakis A, et al. Validation of biomarkers that complement CA19.9 in detecting early pancreatic cancer. Clin Cancer Res 2014;20:5787–95.
[53] Keane MG, Horsfall L, Rait G, et al. A case-control study comparing the incidence of early symptoms in pancreatic and biliary tract cancer. BMJ open 2014;4:e005720.
[54] Tang S, Huang G, Liu J, et al. Usefulness of 18F-FDG PET, combined FDG-PET/CT and EUS in diagnosing primary pancreatic carcinoma: a meta-analysis. Eur J Radiol 2011;78:142–50.
[55] Kamisawa T, Wood LD, Itoi T, et al. Pancreatic cancer. Lancet 2016; 388:73–85.