Quantitative assessment of the diagnostic role of mucin family members in pancreatic cancer: a meta-analysis

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Background: The use of mucins (MUC) as specific biomarkers for various malignancies has recently emerged. MUC1, MUC4, MUC5AC, and MUC16 can be detected at different stages of pancreatic cancer (PC), and can be valuable for indicating the initiation and progression of this disease. However, the diagnostic significance of the mucin family in patients with PC remains disputed. Herein, we assessed the diagnostic accuracy of mucins in PC using a meta-analysis.

Methods: We searched the PubMed, Cochrane Library, Institute for Scientific Information (ISI) Web of Science, Embase, and Chinese databases from their date of inception to June 1, 2020 to identify studies assessing the diagnostic performance of mucins in PC. The estimations of diagnostic indicators in selected studies were extracted for further analysis by Meta-DiSc software. Publication bias was assessed using Deeks' funnel plot asymmetry test.

Results: Our meta-analysis included 34 studies. The pooled accuracy indicators of MUC1 in PC including the sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) (with 95% confidence intervals) were 0.84 (0.82–0.86), 0.60 (0.56–0.64), 18.37 (9.18–36.78), 2.62 (1.79–3.86), and 0.22 (0.15–0.33), respectively. The area under the summary receiver operating characteristic (SROC) curve was 0.8875 and the Q index was 0.8181. Quantitative random-effects meta-analysis of MUC4 in PC using the summary (ROC) curve model revealed a pooled sensitivity of 0.86 (95% confidence interval, 0.82–0.89) and specificity of 0.88 (95% confidence interval, 0.85–0.91). In addition, the meta-analysis of MUC5AC in PC diagnosis also showed a high sensitivity and specificity of 0.71 (95% confidence interval, 0.65–0.76) and 0.60 (95% confidence interval, 0.53–0.66), respectively. Regarding MUC16, the area under the summary ROC curve and Q index were 0.9185 and 0.8516, respectively.

Conclusions: In summary, our results suggested a good diagnostic accuracy of several crucial mucins in PC. Mucins may serve as optional indicators in PC examination, and further research is warranted to investigate the role of mucins as potential clinical biomarkers.

Keywords: Pancreatic cancer (PC); MUC1; MUC4; MUC5AC; MUC16; diagnosis

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Introduction

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in the United States, with a dismal overall prognosis and a 5-year survival rate of 8% (1). The only curative treatment for patients with PC is surgery; however the 5-year survival rate of patients

who undergo surgical resection is unfavorable (2). Due to the difficulty in diagnosing PC early, more than 80% of patients are diagnosed in the late stage, and only 20% of patients can undergo radical surgery with an initial diagnosis of resectable tumors (3). The clinical methods used to diagnose PC mainly rely on computed tomography, magnetic resonance imaging, endoscopic ultrasonography, and the detection of cancer biomarkers in peripheral blood. Commonly, serum carbohydrate antigen (CA)-199 is used to diagnose PC (4); however, the area under the curve (AUC) is 0.7 when CA-199 is used to discriminate patients with PC from healthy controls (5). Serum CA125, alpha fetoprotein (AFP), and carcinoembryonic antigen (CEA) are also important indices for PC assessment, but their sensitivities are inferior to that of CA19-9 (6,7). Consequently, better PC treatment requires identifying novel diagnostic markers to facilitate early detection and improve prognosis in patients with PC.

Mucins (or MUC) are a family of high-molecular-weight glycosylated proteins, which form a protective barrier of epithelial cells (8). At present, more than 20 mucins have been identified. Mucins can be divided into two groups according to their structure and function: transmembrane mucins (MUC1, MUC4, MUC12, and MUC16) and secreting mucins (MUC2, MUC5AC, and MUC6) (9,10). The subcellular distribution and expression level of mucins change according to the different disease stages, indicating their roles in tumorigenesis, malignant transformation, and cancer progression (11). The expression level of mucins has been shown to participate in the progression and metastasis of different cancers, including colon carcinoma, ovarian malignancy, renal tumors, breast cancer, and lung carcinoma (9,12-15).

With regards to PC, mucins have been demonstrated to be strongly involved in carcinogenesis and progression, suggesting that the abnormal expression of mucins might be a predictive marker in PC (16). The correlation between MUC1 and PC has been explored in many studies. MUC1 is a major component of ductal cells in healthy pancreatic tissue but is aberrantly expressed in PC cells. MUC1 exposes tumor-associated epitopes and provokes cellular and humoral immune responses. MUC1 is expressed in more than 60% of PC cases, and its high expression is correlated with poor prognosis (17). Moreover, studies have demonstrated that MUC4 is involved in several oncogenic properties and has been shown to be expressed in 32%, 89%, and 79% of PC cases in different studies, respectively (18-20). Furthermore, when combined with CA19-9, MUC5AC has been reported to improve the diagnostic sensitivity of pancreatic malignancies (21). Moreover, the expression level of MUC16 increases from low-grade to high-grade dysplasia in pancreatic tissue (22).

However, findings regarding the application of mucins as a diagnostic indicator of PC remain conflicting. Systematic analyses of these data might be valuable to verify the diagnostic accuracy of mucin family members in PC. Therefore, the purpose of our quantitative meta-analysis was to investigate the diagnostic potential of mucin family members that have been widely explored in PC (MUC1, MUC4, MUC5AC, and MUC16), which has not been reported previously. We present the following article in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting checklist (23) (available at http://dx.doi.org/10.21037/atm-20-5606).

Methods

Search strategy

We performed systematic literature searches of the PubMed, Institute for Scientific Information (ISI) Web of science, the Cochrane Library, and Embase databases, along with the Wanfang and China National Knowledge Infrastructure databases, from the date of initiation of the database to June 2020. The primary aim of our literature search was to access original articles that focused on mucins in the diagnosis of PC. Keywords included ("mucin" OR "mucins" OR "MUC") AND ("pancreatic cancer" OR "pancreatic carcinoma" OR "pancreatic tumor" OR "pancreatic neoplasm") AND ("diagnostic "OR "diagnosis"). References cited by the selected literatures were also manually searched to find additional studies.

Inclusion and exclusion criteria

The inclusion criteria for studies were as follows: (I) research about the detection of PC with MUC by immunohistochemistry; (II) cases pathologically confirmed as PC (the gold standard criterion); (III) complete quadruplex table data available from the full text or abstract of the literature to calculate the diagnostic parameters; (IV) inclusion of a control group with healthy or benign patients. Studies were excluded based on the following

criteria: (I) those reporting on malignancies other than PC or metastatic PC; (II) cases confirmed with non-pathological evidence; (III) MUC detected by methods other than immunohistochemistry; (IV) lack of diagnostic quadruple table data; (V) case reports or review articles. All included publications were independently evaluated by two reviewers, and discrepancies were resolved through discussion and consensus.

Data extraction and quality assessment

Two reviewers independently examined eligible studies and extracted data concerning the author, country, year of publication, case numbers, MUC phenotype, detection method, and histological type with the true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) results. Each study was assessed by two independent researchers for inclusion or exclusion, and discrepancies were resolved by a third investigator for re-evaluation. The quality of included articles was scored by the 14 items Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (24).

Diagnostic efficiency index

The diagnostic efficiency evaluation indexes used were sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR), negative likelihood ratio (NLR), area under the curve (AUC) of the summary receiver operating characteristic (SROC) curve, and the Q index. An AUC close to 1 implies a good differential ability to separate patients from healthy controls. Also, a higher Q index indicates a higher accuracy of the diagnostic test.

Statistical analysis

The standard protocol recommended for the meta-analysis of diagnostic accuracy was adopted (25). Data such as diagnostic quadruple tables and critical values were extracted and entered into the Meta-DiSc 1.4 software (26). Heterogeneity caused by the threshold effect was checked by Spearman's correlation analysis. I^2>50% indicated the presence of heterogeneity in the studies, and a random effects model was applied in the pooled analysis. A fixed effects model was used to aggregate the accuracy indicators (27,28), while 95 % confidence intervals (CIs) were used for all pooled data. P values are two-tailed, and a P value <0.05 was considered statistically different. Deeks' funnel plot was employed to assess publication bias. Meta-DiSc 1.4 and Stata 12.0 were employed to perform the analyses.

Results

Search results

After a comprehensive literature search to identify related studies published before June 2020, 746 records were initially screened for inclusion. A further 17 studies were acquired through other sources. After excluding 194 duplicates, we screened the abstracts of 569 studies, and excluded 434 that did not meet the inclusion criteria. We also excluded articles that were unrelated to our main subject, along with abstracts, reviews, case reports, and non-English or non-Chinese language articles. The full texts of the remaining 135 studies were further evaluated. Of these, 101 articles were excluded due to lack of sufficient data to calculate sensitivity and specificity, overlapped data, or lack of control groups in the study. Finally, 34 observational studies involving 3,900 patients were included in our review (18,19,29-40). The study selection process is detailed in *Figure 1* (41-60).

Study characteristics

The basic information of all included studies is summarized in *Tables 1*,*2*. In total, 34 eligible studies published between 1993 and 2019 were included. No prospective or randomized controlled trials (RCTs) were included. All included studies evaluated the expression level of MUC in both PC and negative controls using immunohistochemistry. There were 23 studies that investigated the diagnostic accuracy of MUC1 for PC, 8 studies that reported on MUC4, 9 studies that reported on MUC5AC, and 4 studies that reported on MUC16. The QUADAS tool was employed to assess the quality of the studies, and the final score of each study is shown in *Tables 1* and *2*.

Quantitative data analysis of MUC1

Twenty-three studies involving 1,797 patients provided data for this analysis. Spearman's correlation coefficient results yielded an rs of 0.404 and a P of 0.069, suggesting that sensitivity and specificity were positively correlated, and therefore, there was no threshold effect. Also, the heterogeneity test results suggested that there was heterogeneity in the sensitivity (I^2=86.9%), specificity

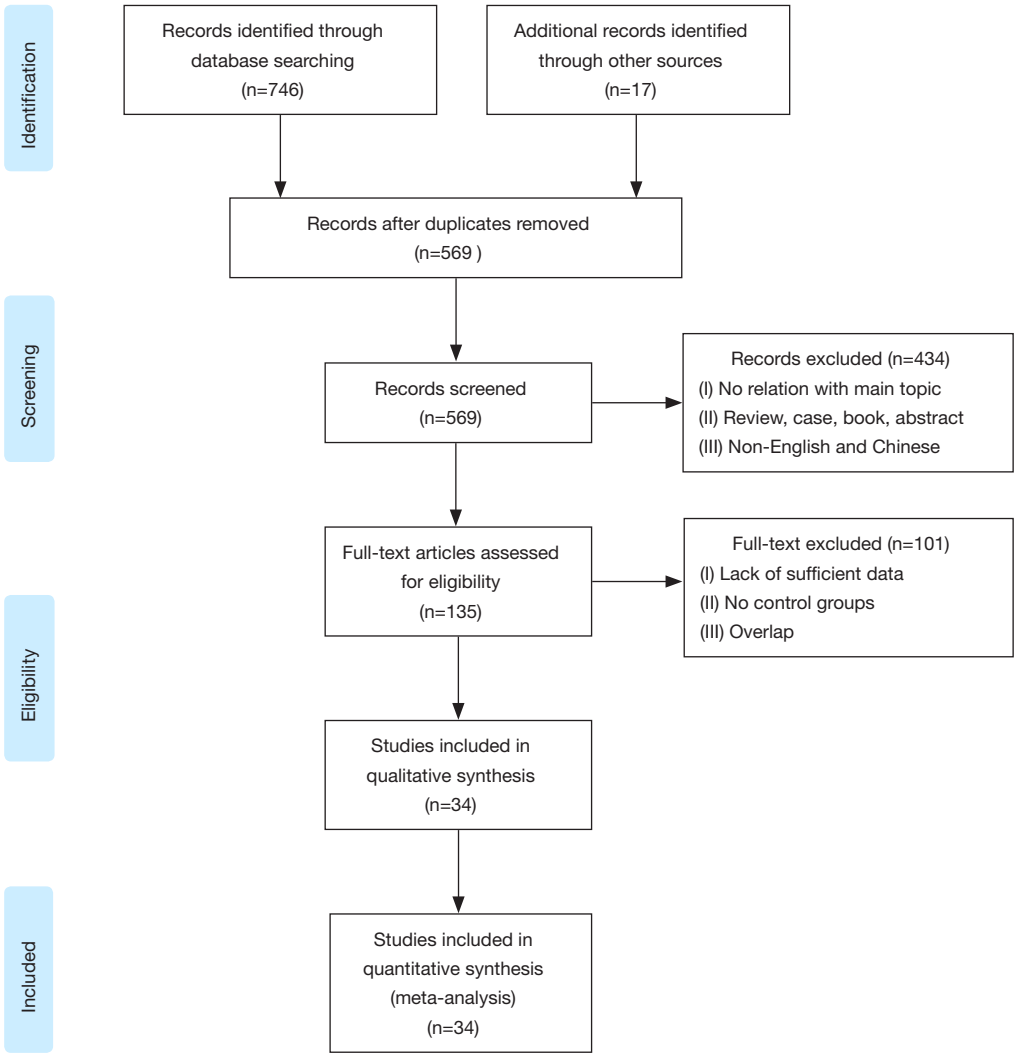

Figure 1 Flow diagram of included studies.

(I^2=91.6%), and DOR (I^2=72.4%) among the studies, so the random effects model was employed to combine effect quantities. The pooled sensitivity and specificity of MUC1 in the diagnosis of PC were 0.84 (95% CI, 0.82–0.86) and 0.60 (95% CI, 0.56–0.64), respectively. The PLR, NLR, and DOR were 2.62 (95% CI, 1.79–3.86), 0.22 (95% CI, 0.15–0.33), and 18.37 (95% CI, 9.18–36.78), respectively. The recalculated sensitivity and specificity are shown in *Figure 2*, and the PLR, NLR, and DOR for MUC1 in PC diagnosis are shown in *Figure 3*. The AUC was 0.8875 and the Q index was 0.8181. The SROC graph displays the summary values of sensitivity and specificity of MUC1 in PC diagnosis (*Figure 4*).

Quantitative data analysis of MUC4

Eight studies containing 909 cases investigated the diagnostic accuracy of MUC4 in PC. A random effects model was used, and the pooled sensitivity and specificity were 0.86 (95% CI, 0.82–0.89) and 0.88 (95% CI, 0.85–0.91), respectively. In addition, the PLR, NLR, and DOR were 6.95 (95% CI, 2.33–20.69), 0.20 (95% CI, 0.14–0.30), and 36.64 (95% CI, 9.49–141.46), respectively. The pooled DOR was 36.64 (95% CI, 9.49–141.46). The Q index was

Table 1 Characteristics of included studies of MUC1 for the detection of pancreatic cancer

Author	Year	Country	Method	Blind	Patient number	TP (a)	FP (b)	FN (c)	TN (d)	Quality score
Osako	1993	Japan	IHC	No	47	33	0	3	11	11
Terada	1996	Japan	IHC	No	52	25	25	0	2	10
Masak	1999	Japan	IHC	No	64	55	3	0	6	9
Luttges	2001	Germany	IHC	No	84	35	20	0	29	10
Adsay	2002	USA	IHC	No	251	86	23	50	92	11
Kim	2002	USA	IHC	No	195	51	94	13	37	10
Terris	2002	France	IHC	No	147	79	11	11	46	12
Yonezawa	2002	Japan	IHC	No	79	44	4	2	29	9
Chhieng	2003	USA	IHC	No	35	23	1	1	10	11
Hiroyuki	2004	Japan	IHC	No	88	46	42	0	0	9
Tajiri	2005	Japan	IHC	No	18	10	0	0	8	10
Ueda	2005	Japan	IHC	No	45	21	6	0	18	11
Zhang	2005	China	IHC	No	82	40	10	12	20	9
Gao	2006	China	IHC	No	58	29	3	14	12	9
Giorgadze	2006	USA	IHC	No	43	25	7	5	6	8
Ohuchida	2006	Japan	IHC	No	62	23	18	0	21	12
Okada	2006	Japan	IHC	No	47	9	3	5	30	11
Wang	2007	China	IHC	No	54	31	4	7	12	10
Sabrina	2013	USA	IHC	No	57	30	26	0	1	9
Shi	2014	USA	IHC	No	62	43	11	0	8	10
Marek	2016	Poland	IHC	No	141	101	40	0	0	10
Meritxell	2018	Portugal	IHC	No	24	19	3	2	0	9
Catalina	2019	Mexico	IHC	No	62	34	1	16	11	11

IHC, immunohistochemistry; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

0.8353 and the AUC was 0.9038 (*Figure 5*).

Quantitative data analysis of MUC5AC

Nine articles including 515 cases were analyzed for the accuracy of MUC5AC expression for PC diagnosis. Pooled analyses revealed heterogeneity in the included research, so a random effects model was utilized. Results showed that the sensitivity and specificity of MUC5AC were 0.71 (95% CI, 0.65–0.76) and 0.60 (95% CI, 0.53–0.66), respectively. Moreover, the PLR, NLR, and DOR were 1.81 (95% CI, 0.81–4.11), 0.41 (95% CI, 0.16–1.06), and 6.18 (95% CI, 0.81–47.36), respectively. The SROC curve showed that the AUC was 0.7735 and the Q index was 0.7131 (*Figure 6*).

Quantitative data analysis of MUC16

MUC16 was mentioned in four articles. Due to heterogeneity, a random effects model was employed to analyze the combined effect quantities. The final pooled values of sensitivity, specificity, and DOR were 0.72 (95% CI, 0.67–0.76), 0.87 (95% CI, 0.83–0.90), and 32.94 (95% CI, 1.51–717.78), respectively. The PLR and NLR were 12.16 (95% CI, 0.56–266.28) and 0.36 (95% CI, 0.17–0.78), respectively. The area under the SROC curve was 0.9185 and the Q index was 0.8516 (*Figure 7*).

Table 2 Main characteristics of the included publications about MUC4, MUC5AC, and MUC16

Author	Year	Country	Method	Blind	Patient number	TP (a)	FP (b)	FN (c)	TN (d)	Quality score
MUC4										
Mahefatiana	2001	USA	IHC	No	26	12	0	4	10	10
Michael	2002	USA	IHC	No	274	25	0	3	246	12
Park	2003	USA	IHC	No	171	65	8	17	81	11
Nirag	2006	USA	IHC	No	65	41	0	4	20	10
Atul	2007	USA	IHC	No	89	55	4	16	14	9
Sabrina	2013	USA	IHC	No	55	24	17	5	9	9
Marek	2016	Poland	IHC	No	141	91	26	10	14	10
Carlos	2017	Sweden	IHC	No	88	73	0	5	10	11
MUC5AC										
Suguru	1999	Japan	IHC	No	58	29	5	0	24	12
Yonezawa	2002	Japan	IHC	No	56	32	7	8	9	9
Hiroyuki	2004	Japan	IHC	No	62	5	20	33	4	9
Ohuchida	2006	Japan	IHC	No	43	29	8	1	5	12
Giorgadze	2006	USA	IHC	No	71	15	30	23	3	8
Wang	2007	China	IHC	No	56	32	7	8	9	10
Sabrina	2013	USA	IHC	No	88	34	0	12	42	9
Marek	2016	Poland	IHC	No	57	25	5	5	22	10
Meritxell	2018	Portugal	IHC	No	24	19	0	2	3	9
MUC16										
Dhanya	2011	USA	IHC	No	152	38	38	38	38	11
Mirte	2012	USA	IHC	No	315	163	3	37	112	11
Lucie	2016	France	IHC	No	62	23	0	8	31	8
Jiang	2017	USA	IHC	No	212	66	4	31	111	10

IHC, immunohistochemistry; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

Publication bias

Deeks' funnel plot asymmetry test was carried out to assess the publication bias. The result indicated that there was no obvious publication bias present (P=0.47) (*Figure 8*).

Discussion

PC manifests with extremely malignant effects and a high mortality rate. According to the latest epidemiological data from the United States, the 5-year survival rate of PC is less than 10% (2). Patients with PC have a dismal prognosis, partially due to delays in diagnosis. The most widely applied clinical detection method is immunological analysis of serum tumor markers, such as CA19-9, CEA, and AFP glycoproteins. These belong to tumor-associated antigens, which are widely expressed in the digestive, urinary, and respiratory tracts of PC patients, as well as in pancreatitis and benign pancreatic lesions, and thus lack specificity (61). Consequently, it is necessary to identify novel diagnostic markers to facilitate a breakthrough in the accurate diagnosis of PC, which will lead to improvements in the poor outcomes of PC patients. To the best of our knowledge, this is the first meta-analysis to focus on mucin family expression for the diagnosis of PC based on

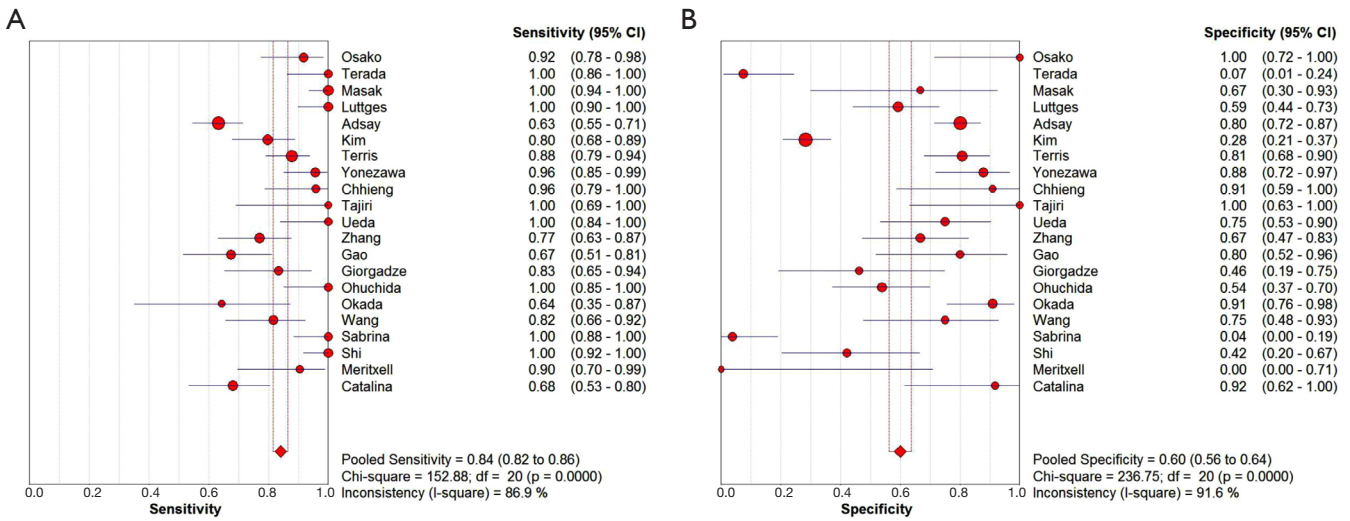

Figure 2 Forest plot of pooled sensitivity (A) and specificity (B) of MUC1 for the diagnosis of PC. PC, pancreatic cancer.

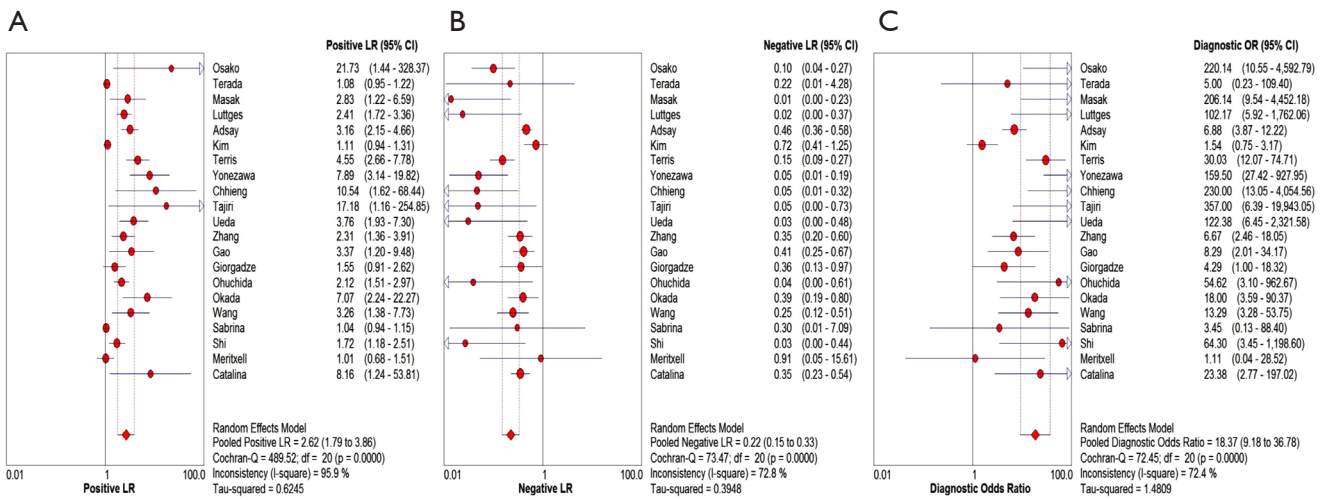

Figure 3 Forest plot of pooled PLR (A), NLR (B), and DOR (C) of MUC1 for the diagnosis of PC. PC, pancreatic cancer; DOR, diagnostic odds ratio; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

published reports.

MUC1, a heterodimeric oncoprotein, is aberrantly upregulated in various malignancies, including PC (14,62,63). Previous studies have revealed that MUC1 is highly expressed in PC tissues and exerts an important role in the oncogenesis of PC, participating in several signaling pathways such as hypoxia-inducible factor-1, Slug, AKT, mitogen-activated protein kinase, and Wnt/β-catenin (10,64). It has already been confirmed that the level of MUC1 expression is elevated in PC tissues compared to negative controls (30). In addition, MUC1 is involved in epithelial-mesenchymal transition, the process through which tumor cells acquire their invasive potential (65,66). In pathological cases, such as those of colon cancer and stomach carcinoma, MUC1expression has been found vary in expression (63). Our meta-analysis is the most comprehensive study that supports MUC1 as a potential diagnostic marker based on quantitative assessments in patients with PC. MUC1 could be used to differentiate patients with PC from controls and manifested a pooled

sensitivity of 0.84 (95% CI, 0.82–0.86), a specificity of 0.60 (95% CI, 0.56–0.64), an AUC of 0.8875, and a Q index of 0.8181, demonstrating its potential diagnostic value. The AUC is regarded as the overall test performance, and an AUC of the SROC curve of approximately 1 suggests excellent diagnostic accuracy (67). Taken together, although the specificity of MUC1 was moderate, the sensitivity was high, and the Q index ranging from 0.7 to 0.9 indicated a good accuracy for diagnosing PC.

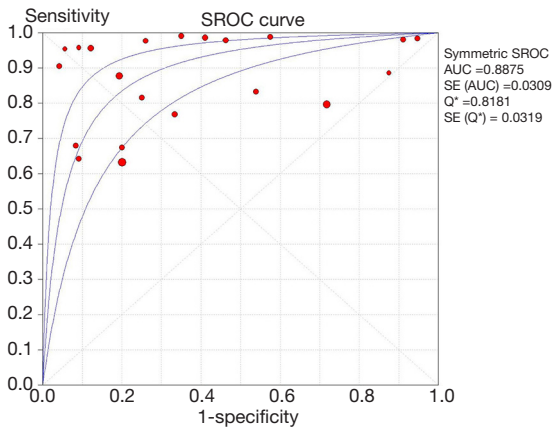

Figure 4 Summary receiver operating characteristic curve of MUC1 for the diagnosis of PC. PC, pancreatic cancer.

Regarding MUC4, *de novo* expression has been observed in PC but not in healthy tissue (16,52). MUC4 participates in the oncogenesis process by enhancing cellular growth, differentiation, and immune recognition, primarily via its transmembrane ligand for the receptor tyrosine kinase, ErbB2 (68,69). In the present study, MUC4 had a high PLR of 6.95 (95% CI, 2.33–20.69) and a low NLR of 0.20 (95% CI, 0.14–0.30), which implies that it performed well in excluding cancer within the pancreas. In addition, MUC4 expression was also verified as an indicator for overall survival in patients with PC receiving gemcitabine-based chemotherapy and as a novel tumor antigen in PC immunotherapy (54,70). In our analysis, MUC4 performed better than MUC5AC, with a higher sensitivity and Q index.

MUC5AC was first identified as an overexpressed gene in PC tissue compared with benign controls by Iacobuzio-Donahue *et al.* in 2003 (71). Moreover, the messenger ribonucleic acid level of MUC5AC in pancreatic juice exhibited good diagnostic performance in identifying PC (38). A panel of MUC3, MUC5AC, and MUC6 provided the ability to discriminate PC from a normal pancreas (50). Clinically, Kaur *et al.* investigated the

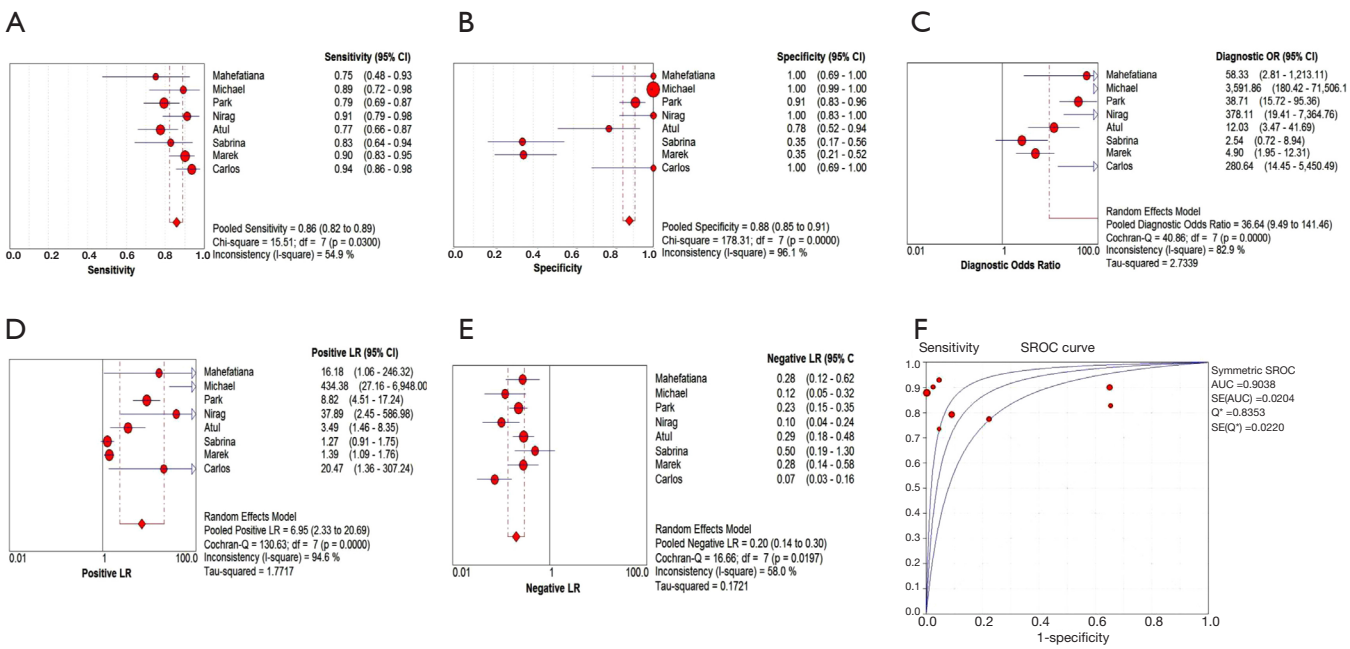

Figure 5 Forest plot of pooled sensitivity (A), specificity (B), DOR (C), PLR (D), NLR (E), and SROC (F) of MUC4 for the diagnosis of PC. PC, pancreatic cancer; DOR, diagnostic odds ratio; PLR, positive likelihood ratio; NLR, negative likelihood ratio; SROC, summary receiver operating characteristic.

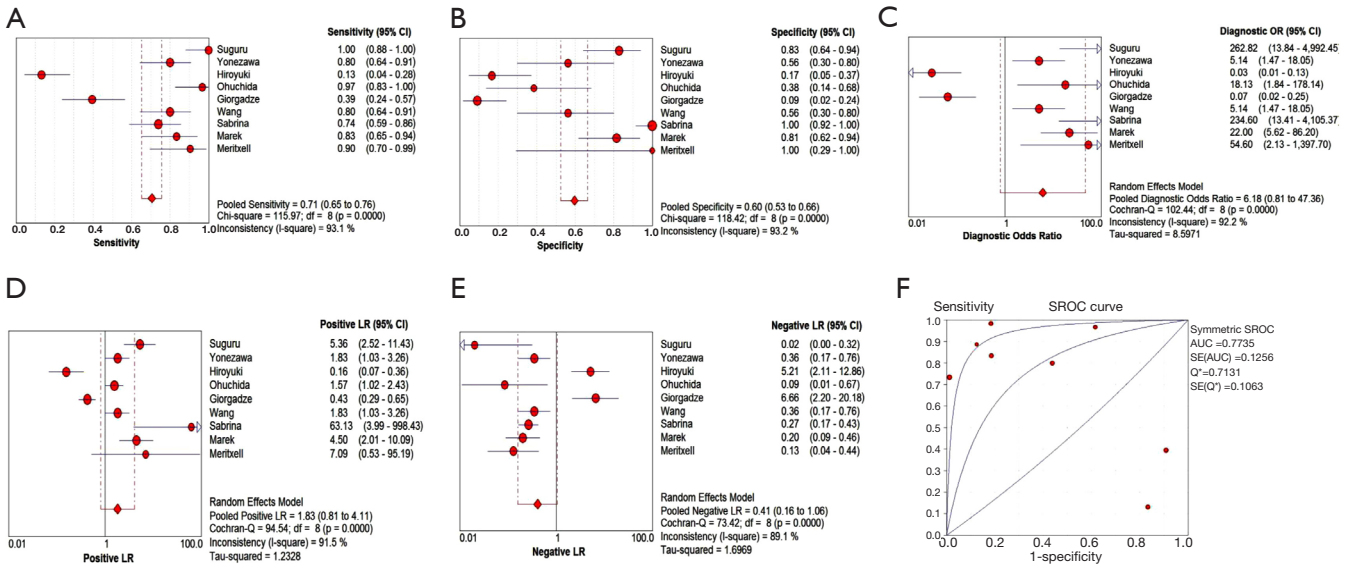

Figure 6 Forest plot of pooled sensitivity (A), specificity (B), DOR (C), PLR (D), NLR (E), and SROC (F) of MUC5AC for the diagnosis of PC. PC, pancreatic cancer; DOR, diagnostic odds ratio; PLR, positive likelihood ratio; NLR, negative likelihood ratio; SROC, summary receiver operating characteristic.

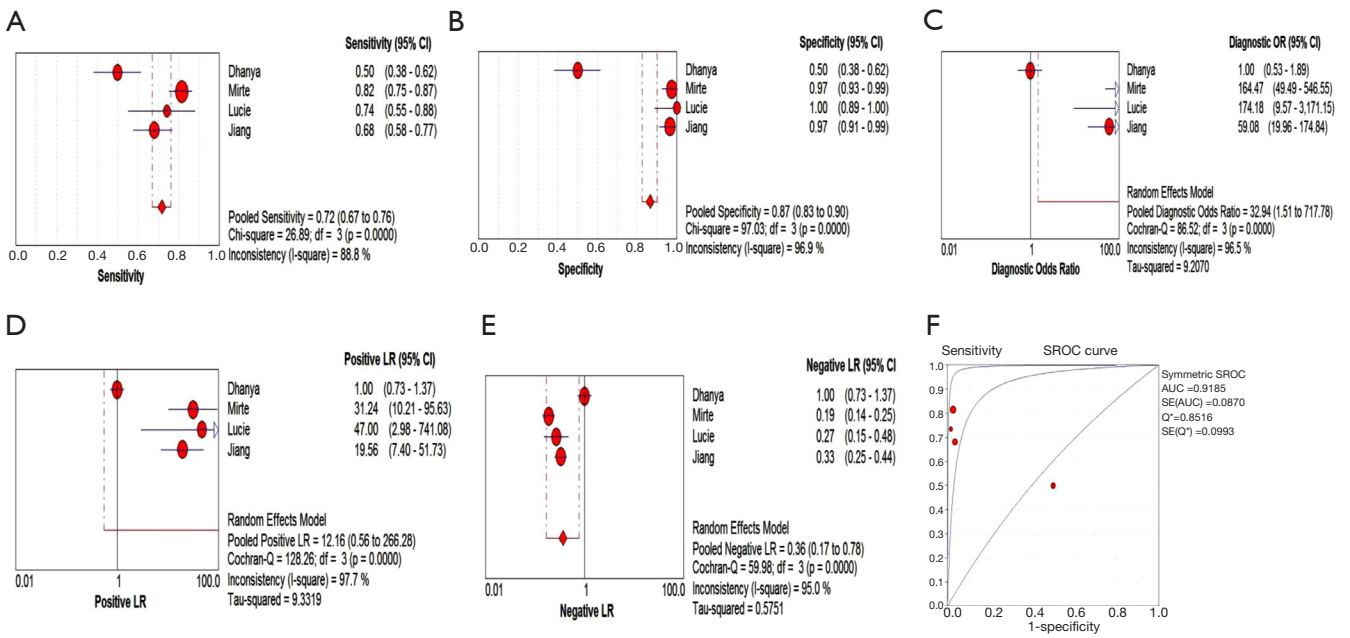

Figure 7 Forest plot of pooled sensitivity (A), specificity (B), DOR (C), PLR (D), NLR (E), and SROC (F) of MUC16 for the diagnosis of PC. PC, pancreatic cancer; DOR, diagnostic odds ratio; PLR, positive likelihood ratio; NLR, negative likelihood ratio; SROC, summary receiver operating characteristic.

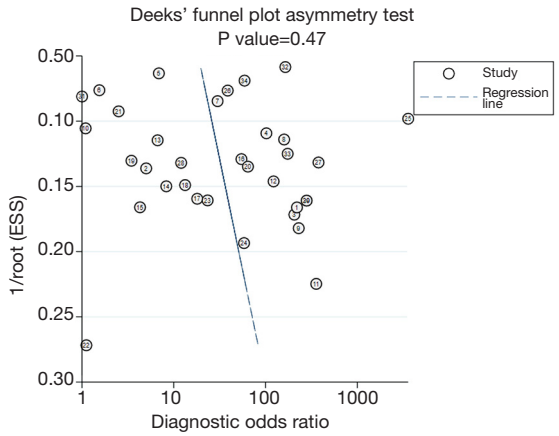

Figure 8 Detection of publication bias.

potential of MUC5AC in combination with CA19-9 to improve the diagnostic accuracy in a Caucasian population (21). In addition, Zhang *et al.* showed that the same panel could also benefit the accurate diagnosis of PC in Asian individuals (72). In addition to early diagnosis, MUC5AC also presented the ability to monitor the response to chemo/radiotherapy in patients with PC.

Moreover, molecular cloning of CA125 led to the discovery of MUC16 in 2001 (73). MUC16 is used as a specific marker not only for ovarian malignancy, but also in gastric carcinoma, colorectal cancer, cholangiocarcinoma, and more recently in PC (57,74). The diagnostic dilemma of MUC16 application as a diagnostic biomarker for PC is based on its presence in patients with benign pancreatic neoplasms and pancreatitis (58). Our results showed a sensitivity of 0.72 (95% CI, 0.67–0.76) and specificity of 0.87 (95% CI, 0.83–0.90) for MUC16. The AUC of the SROC was 0.9185, which was approximately 1, indicating its diagnostic potential. However, the number of included studies might not have been adequate.

Mucins not only serve as diagnostic markers, but also participate in important biological processes, including adhesion, immune regulation, chemoresistance, and intracellular signaling transductions (10,54,75). As for CA19-9, which is the most popular tumor biomarker in the diagnosis of PC, its epitope is produced only on the MUC-1/Y core protein, indicating that the CA19-9 epitope may be a specific marker for the MUC-1/Y protein (76). The expression of mucins is accompanied by the evolution of the disease, with its level changing in accordance with the progression of healthy tissue to precursor lesions to PC. Moreover, mucins can also regulate signal pathways such as p53, PI3K-AKT (phosphatidylinositide-3-kinase/AKT), JAK-STAT (Janus kinase-signal transducer and activators of transcription), RAS-ERK (Ras-extracellular signal-regulated kinase), and MAP (mitogen-activated protein) kinase (75). In some studies, mucins have been reported to be associated with clinicopathological characteristics such as histological pattern, tumor location, or vascular invasion (77,78). Moreover, some mucins have also been significantly correlated with the prognosis of PC patients (79,80).

The combination of mucin panels provides considerable functional value in differentiated diagnosis. For instance, MUC1 to MUC6 expression in lung carcinoma was correlated with tumor differentiation and histologic subtypes, while MUC5AC was found capable of differentiating primary lung cancer from metastatic PC in the lung (81). As for colon cancer, several studies detected the MUC1, MUC2, MUC5AC, and MUC6 expression using tissue microarrays and demonstrated their clinical significance (82,83). In PC, Dai *et al.* (84) demonstrated that MUC14 plus MUC15 serves as a prognostic marker for stomach adenocarcinoma through bioinformatics analysis. As can be seen, mucin combinations have frequently been applied in clinical diagnosis. However, there is currently no commercial mucin chip. A more in-depth investigation of mucin panels may produce the means to provide an early diagnosis of different cancers.

Some limitations to our study should also be noted. (I) The studies included in this meta-analysis were observational or retrospective studies, while the RCTs regarding pathological staining lack real-world value. Furthermore, there were only a few studies related to this topic, and the data presented in these articles did not correspond to large sample sizes, making them prone to produce erroneous conclusions. Future larger sample size studies and results are needed to verify this conclusion. (II) There was inevitably a selection bias in the published literature. In all included studies, the interpretation of mucin expression was dependent on the gold standard; however, there was a lack of blinding. (III) Although there was no threshold effect, the threshold settings of the included studies were different. The results of the immunohistochemistry tests were evaluated by combining the percentage of colored cells and the grading of coloring intensity. However, in some studies, the results were evaluated only based on the numerical value of the percentage of colored cells. The standards and methods of each study were different and could not be unified; therefore, we adopted a random effects model

in circumstances where heterogeneity existed between the studies. We also conducted the Deeks' funnel plot asymmetry test to assess the publication bias.

Overall, the detection of mucin family expression offers potential value for the diagnosis of PC. Clinically, the expression level of mucins in PC tissue may also function as a prognostic marker and therapeutic target in the future. Further analyses must be conducted to calculate mucin levels with clinicopathological parameters to comprehensively ascertain the role of mucins in PC.

Conclusions

Our meta-analysis is the first study to examine the value of mucins in the diagnosis of PC. We demonstrated that mucins yield acceptable sensitivity and specificity for distinguishing patients with PC from healthy controls, which indicates that they may be a potential innovative biomarker for PC diagnosis. Considering the limitations in our analysis, further scientific studies with larger sample sizes and high-quality evidence are needed to evaluate this topic more accurately.

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