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Review Article

Tumor markers CA19-9, CA242 and CEA in the diagnosis of pancreatic cancer: a meta-analysis

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Abstract: Background: Pancreatic cancer has the worst prognosis and early detection is crucial for improving patient prognosis. Therefore, we performed a meta-analysis to evaluate and compare the sensitivity and specificity of single test of CA19-9, CA242, and CEA, as well as combination test in pancreatic cancer detection. Methods: We searched PubMed, Embase, Medline, and Wanfang databases for studies that evaluated the diagnostic validity of CA19-9, CA242, and CEA between January 1990 and September 2014. Data were analyzed by Meta-Disc and STATA software. Results: A total of 21 studies including 3497 participants, which fulfilled the inclusion criteria were considered for analysis. The pooled sensitivities for CA19-9, CA242, and CEA were 75.4 (95% CI: 73.4-77.4), 67.8 (95% CI: 65.5-70), and 39.5 (95% CI: 37.3-41.7), respectively. The pooled specificities of CA19-9, CA242, and CEA were 77.6 (95% CI: 75.4-79.7), 83 (95% CI: 81-85), and 81.3 (95% CI: 79.3-83.2), respectively. Parallel combination of CA19-9+CA242 has a higher sensitivity (89, 95% CI: 80-95) without impairing the specificity (75, 95% CI: 67-82). Conclusions: Our meta-analysis showed that CA242 and CA19-9 have better performance in the diagnosis of pancreatic cancer than CEA. Furthermore, parallel combination test of CA19-9+CA242 could be of better diagnostic value than individual CA242 or CA19-9 test.

Keywords: CA19-9, CA242, CEA, meta-analysis, pancreatic cancer

Introduction

Pancreatic cancer, a lethal malignancy, is the fourth or fifth commonest cause of cancer mortality [1]. Approximately 330,300 people are diagnosed with the disease and die from it per year worldwide, with a cancer prevalence of 211,500 cases in 2012 [2]. This is in part due to the fact that pancreatic cancer has a very poor prognosis. No early detection tests are available and most patients are not diagnosed until late stage [3]. In a study from Japanese Registry, it was reported that patients with stage I tumors (<2 cm size) had a better survival than patients with stage IIb tumors (58% vs. 17% alive at 5 years) [4]. Therefore, many researchers have focused on the development of early detection methods for pancreatic cancer.

Imaging modalities are used for the diagnosis of pancreatic cancer, including endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), 18F-fluorodeoxyglucose-positron emission tomography (18F-FDGPET), and laparoscopy/laparotomy. However, these complex and expensive imaging modalities have failed in the early screening of pancreatic cancer. Therefore, simple and cost-effective modalities that can be used in early screening of pancreatic cancer are urgently needed.

Various tumor markers have been studied in connection with pancreatic cancer, including carbohydrateantigen19-9 (CA19-9), CA242, and carcinoembryonic antigen (CEA) [5]. CA19-9 is an isolated form of Lewis antigen, which is widely used for pancreatic cancer diagnosis in clinical setting. However, CA19-9 may be elevated in patients with nonmalignant diseases or other gastrointestinal cancers [6]. CEA was

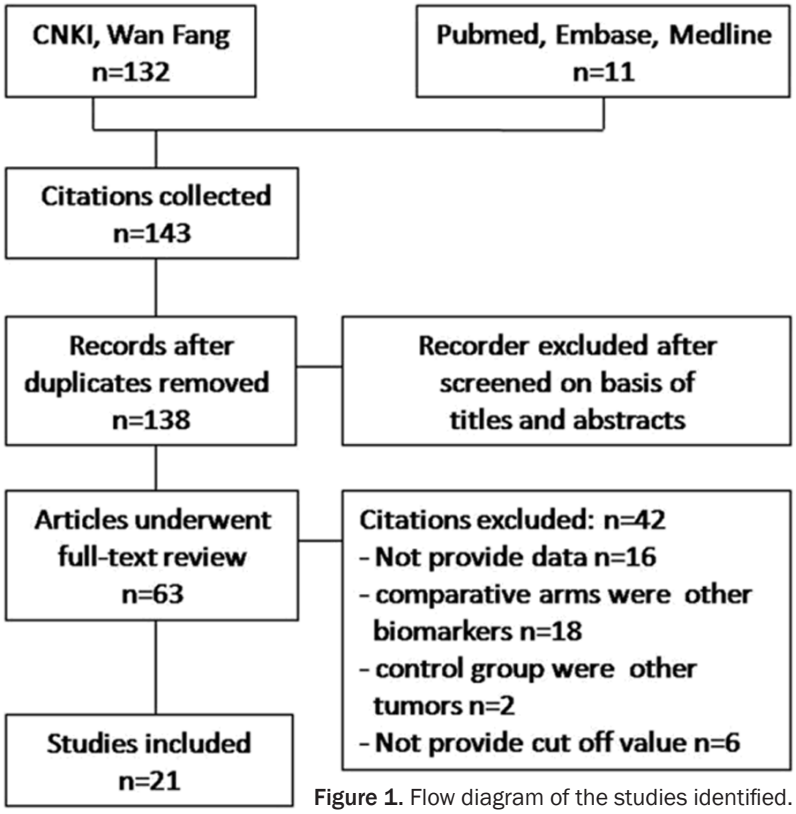

Figure 1. Flow diagram of the studies identified.

found in gastrointestinal tissue during fetal development and colorectal carcinoma, and has been used to diagnose colon cancer, pancreatic cancer, and gastric cancer. However, it may also become positive in heavy smokers and people with nonspecific colitis. CA242 was obtained by immunization of mice with human cell line COLO205 fused with the Sp 2/0 mouse myeloma cell line [7]. It is also an important serum tumor marker for the diagnosis of pancreatic cancer. However, to date there has been no systematic evaluation of the diagnostic potency of the three makers individually or in combination. Accordingly, we performed a meta-analysis to evaluate the sensitivity and specificity of CA19-9, CA242, and CEA in diagnosing pancreatic cancer.

Methods

Search strategy and inclusion criteria

A literature search for human studies was performed to screen publications on the diagnostic performance of CA19-9, CA242, and CEA for pancreatic cancer. PubMed, Medline, Embase, and Wanfang databases were searched for relevant publications in Chinese or in English from January 1990 to September 2014. The keywords "CA19-9 OR carbohydrate antigen 19-9", "CA242 OR carbohydrate antigen 242", "CEA OR carcinoembryonic antigen", "pancreatic cancer OR pancreatic tumor OR pancreatic carcinoma" were used.

Two reviewers independently reviewed each publication. The abstracts were scanned to identify potentially eligible articles and then the full texts of these articles were read to determine whether they should be included in our study. Any disagreement was discussed and solved by a third reviewer. The inclusion criteria were: (1) Compare the sensitivity and specificity of CA19-9, CA-242, and CEA in pancreatic cancer; (2) Have reported or provided sufficient data to allow us to calculate the true positive (TP), false negative (FN), false positive (FP) and true negative (TN) values; (3) Patients with pancreatic cancer were confirmed by surgical and pathological characteristics or radiographic examination.

Data extraction and quality assessment

The following information from each study was extracted independently by 2 reviewers: (1) First author name; (2) Year of publication; (3) Number of patients; (4) Detection methods; (5) Event numbers in TP, FN, TN and FP arms; (6) Cut off value of CA19-9, CA242, and CEA. The QUADAS score was used to assess the quality of included studies.

Data analysis

The pooled sensitivity, specificity, diagnostic odds ratio (DOR) and the likelihood ratios [positive likelihood ratio (PLR) and negative likelihood ratio (NLR)] for single test or combination tests were calculated by Meta-Disc version 1.4. The I-squared value (I^2) was used to assess the statistical heterogeneity among the studies. The estimate below 25% was regarded as low

Table 1. Main characteristics of the studies included in the meta-analysis

Study (year)	Case	Control	CA199			CA242			CEA		
			Method	Cutoff	TP/FP/FN/TN	Method	Cutoff	TP/FP/FN/TN	Method	Cutoff	TP/FP/FN/TN
Wang L (2000) [9]	130	B	ELISA	37	40/27/5/58	ELISA	21	37/34/8/51	ELISA	3.2	32/61/13/24
Liu CM (2004) [10]	74	H	ELISA	37	26/6/7/34	ELISA	20	24/5/10/35	ELISA	5	14/7/20/33
Cui LH (2008) [11]	74	B	ELISA	35	30/4/10/30	ELISA	20	28/5/12/29	ELISA	5	24/6/16/28
Dong AP (2009) [12]	165	B/H	RIA	37	45/24/9/86	RIA	20	44/26/11/84	RIA	10	36/36/19/74
Wang P (2003) [13]	64	B	CLIA	60	30/4/12/18	ELISA	20	29/6/13/16	CLIA	5	20/2/22/20
Li XM (2014) [14]	249	H	CLIA	37	90/17/39/103	ELISA	20	83/28/46/92	CLIA	5	54/41/75/79
Yang YC (2007) [15]	244	B	ELISA	37	134/20/39/51	ELISA	20	110/17/63/54	ELISA	5	53/6/120/65
Cheng J (2012) [16]	466	B/H	CLIA	35	171/6/94/195	CLIA	20	150/3/115/198	CLIA	5	102/7/163/194
Li XM (2013) [17]	229	H	CLIA	35	88/21/21/99	ELISA	20	78/19/31/101	CLIA	5	47/37/62/83
Li N (2001) [18]	123	B	CLIA	35	50/23/13/37	CLIA	20	47/10/16/50	CLIA	5	27/12/36/48
Lu C (2005) [19]	95	B/H	CLIA	37	31/16/7/41	CLIA	20	30/9/8/48	CLIA	5	23/22/15/35
Xia F (2006) [20]	138	B	CLIA	35	58/8/23/49	CLIA	20	59/6/22/51	CLIA	5	50/10/31/47
Li FM (2010) [21]	125	B	ECLIA	35	38/22/7/58	ECLIA	10	32/9/13/71	ECLIA	10	15/15/30/65
You YQ (2012) [22]	100	B	ECLIA	37	39/21/11/29	ECLIA	25	40/18/10/22	ECLIA	5	21/19/29/31
Liao Q (2007) [23]	150	B	ELISA	37	84/15/28/23	ELISA	20	66/10/46/28	ELISA	5	37/2/75/36
Zhang LZ (2008) [24]	160	B	CLIA	37	71/9/24/56	ELISA	20	71/5/24/60	CLIA	10	40/8/55/57
Yan H (2005) [25]	98	H	CLIA	35	56/6/10/26	CLIA	20	52/5/14/27	CLIA	5	45/8/21/24
Gao YC (2005) [26]	496	B	CLIA	37	236/71/79/110	RIA	20	222/52/93/129	CLIA	10	74/7/241/174
Huang BX (2011) [27]	75	B	CLIA	37	37/4/8/26	CLIA	20	28/7/17/23	CLIA	10	18/6/27/24
Zhang M (2005) [28]	146	H	MEIA	37	38/21/8/79	MEIA	20	35/11/11/89	MEIA	5	12/20/34/80
Jiang A (2011) [29]	96	H	ECLIA	35	39/12/9/36	ECLIA	20	34/11/14/37	ECLIA	5	22/13/26/35

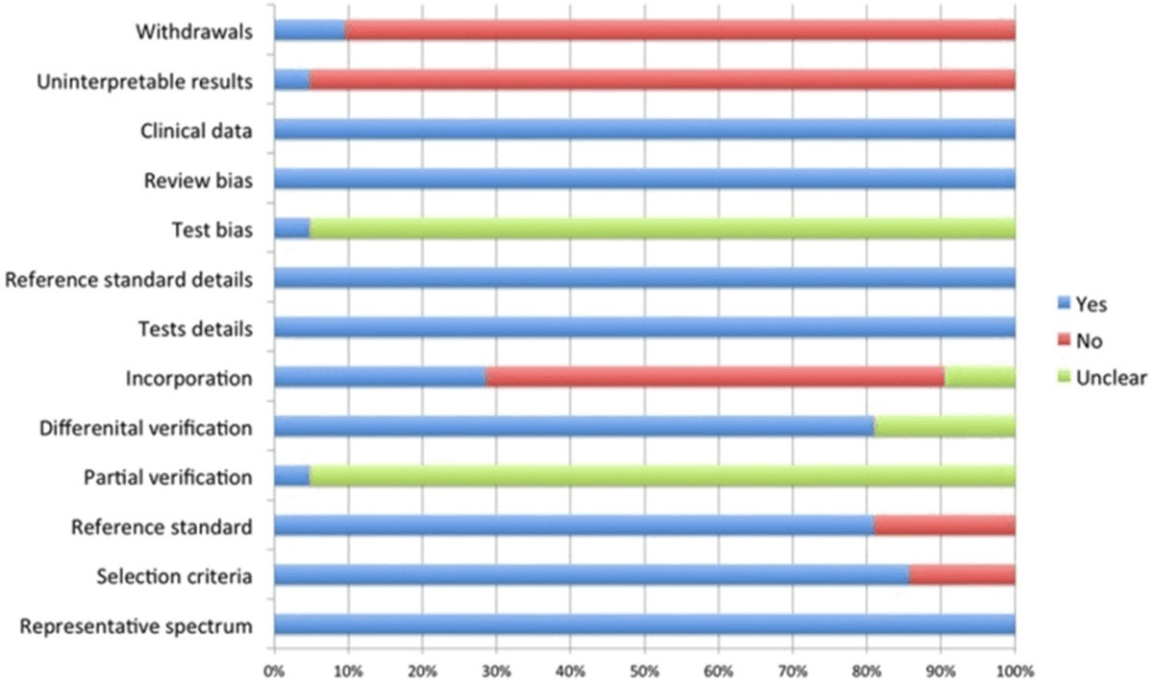

Figure 2. The QUADAS score of included studies.

heterogeneity and above 75% was labeled as high heterogeneity [8]. If heterogeneity existed, a random effect model was used for meta-analysis; otherwise, a fixed effect model was chosen. In addition, subgroup analyses were performed according to the detection method (ELISA vs. CLIA), control groups (benign vs. healthy), and cut off value to assess potential sources of variation in the study results. Publication bias was analyzed by STATA12 software (Stata Corp, College Station, TX, USA).

Results

Literatures

A total of 143 citations were obtained via database searches; and among them, twenty-one met the inclusion criteria for this study (**Figure 1**). These studies included 1896 pancreatic cancer cases, 940 benign pancreatic diseases cases and 661 healthy cases (**Table 1**). The quality assessment of included studies was shown in **Figure 2**.

Single biomarker analysis

The results of the meta-analysis are stated in **Table 2**. The pooled sensitivities for CA19-9, CA242, and CEA were 75.4 (95% CI: 73.4-77.4), 67.8 (95% CI: 65.5-70) and 39.5 (95% CI: 37.3-41.7), respectively. The pooled specificities of CA19-9, CA242, and CEA were 77.6 (95% CI: 75.4-79.7), 83 (95% CI: 81-85), and 81.3 (95% CI: 79.3-83.2), respectively. CA19-9 showed the highest sensitivity, followed by CA242. While for specificity, CA242 gave the highest result, followed by CEA. The pooled DOR for CA19-9, CA242, and CEA were 13.2 (95% CI: 9.33-18.66), 11.91 (95% CI: 0.39-16.91), and 3.53 (95% CI: 2.53-4.93), respectively. Because of the heterogeneity in the study, we used the random effects model to generate the ROC curves. The areas under the curve (AUCs) of CA19-9, CA242, and CEA were 0.85, 0.84, and 0.7, respectively.

Subgroup analysis

Since heterogeneity existed in this study, we performed subgroup analysis to assess the source of heterogeneity. The results of subgroup analysis showed that for CA19-9 and CA242, the specificity was higher when the control group was healthy people. However, for CEA, the specificity was higher with benign cases as control, while the sensitivity was higher with healthy control. It was also found that

Table 2. Meta-analysis of CA19-9, CA242, and CEA for detecting pancreatic cancer

Pooled estimates	CA19-9	CA242	CEA
overall			
Study numbers	19	18	20
I^2 (%)	69.6	68.1	70.6
Sensitivity (%) (95% CI)	75.4 (73.4-77.4)	67.8 (65.5-70)	39.7 (37.4-41.9)
Specificity (%) (95% CI)	77.6 (75.4-79.7)	83 (81-85)	81.3 (79.3-83.3)
PLR (95% CI)	3.58 (2.82-4.54)	4.10 (3.21-5.18)	2.39 (1.84-3.11)
NLR (95% CI)	0.31 (0.28-0.35)	0.38 (0.34-0.45)	0.71 (0.66-0.77)
DOR (95% CI)	13.2 (9.33-18.66)	11.91 (0.39-16.91)	3.63 (2.56-5.12)
ROC area	0.85	0.84	0.7
Control groups			
Benign			
Study numbers	11	10	11
I^2 (%)	63.1%	59.3	51
Sensitivity (%) (95% CI)	76.8 (74.1-79.3)	68.4 (65.6-71.3)	35.7 (32.8-38.7)
Specificity (%) (95% CI)	70.2 (66.8-73.4)	78.8 (75.2-81.9)	86.6 (83.8-89.1)
PLR (95% CI)	2.79 (2.216-3.52)	3.35 (2.56-4.37)	2.86 (1.99-4.1)
NLR (95% CI)	0.33 (0.28-0.39)	0.4 (0.34-0.46)	0.71 (0.64-0.78)
DOR (95% CI)	9.76 (6.51-14.62)	8.86 (5.85-13.4)	4.28 (2.84-6.45)
ROC area	0.82	0.81	0.73
Healthy			
Study numbers	6	5	6
I^2 (%)	0	59.7	47.9
Sensitivity (%) (95% CI)	78.2 (74-80)	70.8 (66-75.3)	44.9 (40.2-49.7)
Specificity (%) (95% CI)	82 (78.1-85.4)	83.5 (79.6-86.9)	72.6 (68.3-76.6)
PLR (95% CI)	4.28 (3.5-5.24)	4.46 (3.07-6.48)	1.54 (1.22-2)
NLR (95% CI)	0.27 (0.21-.033)	0.34 (0.27-0.44)	0.77 (0.65-0.91)
DOR (95% CI)	17.13 (12.15-24.15)	13.38 (7.44-24.06)	2.1 (1.37-3.2)
ROC area	0.88	0.85	0.62
Methods			
ELISA			
Study numbers	5	8	4
I^2 (%)	50.7	61.7	0
Sensitivity (%) (95% CI)	77.9 (73.5-81.9)	66.6 (63.1-70)	35.7 (30.7-40.9)
Specificity (%) (95% CI)	73.1 (67.4-78.3)	81.4 (77.7-84.7)	88.5 (83-92.8)
PLR (95% CI)	2.97 (2.13-4.15)	3.53 (2.62-4.77)	3.29 (2.14-5.06)
NLR (95% CI)	0.31 (0.24-0.39)	0.41 (0.34-0.48)	0.71 (0.62-0.8)
DOR (95% CI)	11.11 (6.13-20.14)	9.12 (5.67-14.68)	5.19 (3.03-8.9
ROC area	0.84	0.82	0.75
CLIA			
Study numbers	10	7	10
I^2 (%)	80.5	79.7	80.6
Sensitivity (%) (95% CI)	73.6 (71-76.1)	67.4 (64.1-70.5)	39.8 (37-42.6
Specificity (%) (95% CI)	80.4 (77.7-82.9)	85.1 (82.1-87.8)	83 (80.4-85.3)
PLR (95% CI)	4.36 (2.81-6.76)	5.17 (2.87-9.31)	2.67 (1.73-4.11)
NLR (95% CI)	0.32 (0.28-0.37)	0.37 (0.31-0.44)	0.69 (0.61-0.78)
DOR (95% CI)	15.24 (8.76-26.53)	15.79 (7.56-32.99)	4.13 (2.38-7.15)
ROC area	0.87	0.87	0.72

Cut off value	37 U/ml	20 U/ml	10 ng/ml
Study numbers	11	18	5
I^2 (%)	65.9	68.1	23
Sensitivity (%) (95% CI)	76.4 (73.8-78.9)	67.8 (65.5-70)	33 (29.1-37.1)
Specificity (%) (95% CI)	72.9 (69.7-75.9)	83 (81-85)	84.7 (81.1-87.9)
PLR (95% CI)	3.04 (2.37-3.91)	4.10 (3.21-5.18)	2.68 (1.7-4.22)
NLR (95% CI)	0.32 (0.28-0.38)	0.38 (0.34-0.45)	0.72 (0.63-0.84)
DOR (95% CI)	10.56 (7-15.93)	11.91 (0.39-16.91)	4.13 (2.7-6.33)
ROC area	0.83	0.84	0.72
Cut off value	35 U/ml	-	5 ng/ml
Study numbers	8	-	16
I^2 (%)	56.3	-	73.8
Sensitivity (%) (95% CI)	73.9 (70.5-77.1)	-	42.2 (39.5-44.9)
Specificity (%) (95% CI)	83.9 (80.8-86.6)	-	79.9 (77.5-82.2)
PLR (95% CI)	4.57 (2.83-7.36)	-	2.26 (1.67-3.05)
NLR (95% CI)	0.29 (0.24-0.35)	-	0.71 (0.65-0.78)
DOR (95% CI)	18 (10.93-29)	-	3.41 (2.25-5.15)
ROC area	0.88	-	0.69

Table 3. Sensitivity and specificity of combination test

Biomarkers	Sensitivity	Specificity
Parallel combination		
CA19-9+CA242	0.89 (0.80-0.95)	0.75 (0.67-0.82)
CA19-9+CEA	0.85 (0.75-0.92)	0.71 (0.63-0.79)
CA242+CEA	0.76 (0.65-0.85)	0.71 (0.62-0.78)
CA19-9+CA242+CEA	0.9 (0.81-0.96)	0.64 (0.56-0.72)
Serial combination		
CA19-9+CA242	0.66 (0.59-0.73)	0.87 (0.81-0.92)
CA19-9+CEA	0.52 (0.45-0.6)	0.8 (0.74-0.86)
CA242+CEA	0.58 (0.5-0.65)	0.89 (0.83-0.93)
CA19-9+CA242+CEA	0.5 (0.42-0.57)	0.93 (0.88-0.97)

for CA19-9, raising the cut off value from 35 U/ml to 37 U/ml may decrease the specificity. In contrast, raising the cut off value from 5 ng/ml to 10 ng/ml increased the specificity but decreased the sensitivity of CEA. However, it seemed that the detection method was not a potential source of variation.

Biomarkers combination analysis

Due to the limited sensitivity of single serum tumor marker test, combined multiple markers tests were considered to be able to improve the sensitivity. It was defined as positive for parallel combined test if the value of any of the tumor markers was higher than the cut off value. A positive result for serial combined testing was defined only when the values of all the tested tumor markers were higher than the corresponding cut off value. Due to the limited number of included studies, patients with benign pancreatic diseases were used as the control group for the combination test.

The meta-analysis results indicated that parallel combination patterns of CA19-9+CA242+CEA and CA19-9+CA242 had similar sensitivity (90, 95% CI: 81-96 and 89, 95% CI: 80-95, respectively), however, parallel combination pattern of CA19-9+CA242 had a higher specificity (75, 95% CI: 67-82) (**Table 3**). On the other hand, the specificity of all four combination patterns increased while the sensitivity decreased significantly in serial combination test.

Publication bias

Deek's funnel plot asymmetry test was used to examine publication bias. Publication bias was conducted by a regression of lnDOR against 1/ESS1/2, with $P<0.05$ for the slope coefficient indicating significant asymmetry [30]. The Deek's asymmetry test result showed that there was no obvious publication bias in this study (**Figure 3**).

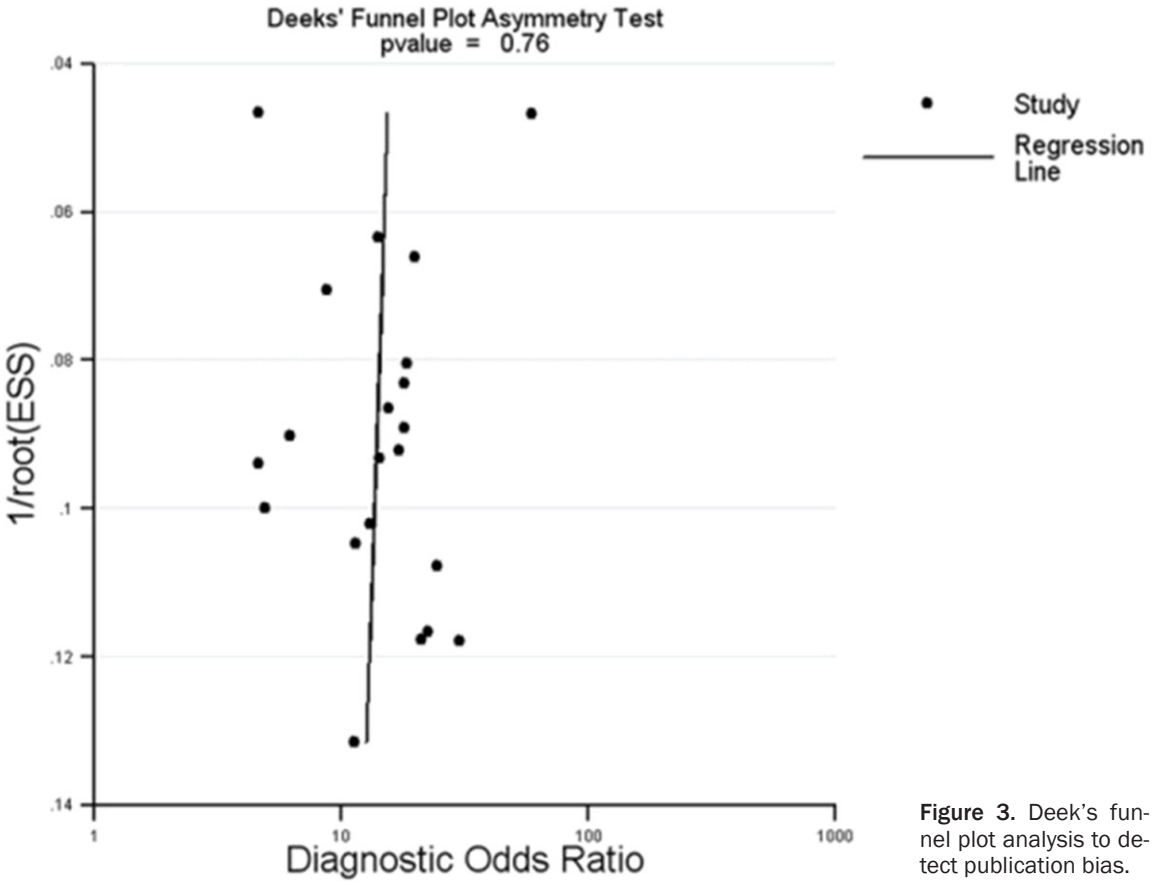

Figure 3. Deek's funnel plot analysis to detect publication bias.

Discussion

This meta-analysis aimed to compare the diagnostic power of CA19-9, CA242 and CEA. In general, CA19-9 has the highest sensitivity and CA242 gives the highest specificity. Parallel combination test pattern of CA19-9+CA242 can increase sensitivity without impairing the specificity. It is well known that CA19-9 was the first choice as biomarker for pancreatic cancer. In subsequent validation studies, CA242 and CEA have also been found to be related with pancreatic cancer, and were gradually accepted as biomarkers for pancreatic cancer. Our meta-analysis indicated that the sensitivity of CA19-9 was significantly higher than those of CA242 and CEA, while the specificities of CA242 and CEA were higher than that of CA19-9.

There was significant heterogeneity in this study. The different study design can influence the pooled estimate. To account for these potential variations, subgroup analyses were performed. According to our meta-analysis, CA19-9 had a higher specificity when healthy people were used as control, and CEA had a higher specificity when patients with benign pancreatic diseases were used as control. The status of patient did not seem to influence the diagnostic capacity of CA242, as the serum level of CA242 does not increase during cholestasis or acute pancreatitis [31].

However, the single serum biomarker test has limited sensitivity and specificity. Therefore, we analyzed the different combination patterns of CA19-9, CA242, and CEA. Subgroup analyses were then performed according to the positive result definition (parallel and serial). Parallel combination usually increased the diagnostic sensitivity but decreased the specificity, while serial combination decreased the diagnostic sensitivity but increased the specificity. Among the different combination patterns, parallel combination pattern of CA19-9+CA242 could increase sensitivity without impairing the specificity.

There are some limitations in our study. Firstly, heterogeneity existed in this study. Through subgroup analysis, it was found that besides

the status of control (with or without benign pancreatic disease), different cut off values of the included studies may be another potential source of heterogeneity. Secondly, the blinded test was not documented in most studies. Studies lacking a blinded design were likely to report a better performance. Thus, this may influence the accuracy of the meta-analysis results. Thirdly, we are unable to perform subgroup analysis according to the stage of pancreatic cancer, because only a few studies reported sensitivity and specificity of these tumor biomarkers according to the different stage of pancreatic cancer. Fourthly, the sample size for the combination test was small due to the limited number of studies. Therefore, large, double-blinded, multiple center randomized controlled trials are needed. Still, despite these limitations, we believe that our analysis could contribute to the comprehensive evaluation of biomarkers in pancreatic cancer diagnosis.

In conclusion, our meta-analysis showed that CA242 and CA19-9 have better performance in the diagnosis of pancreatic cancer than CEA. Furthermore, parallel combination pattern of CA19-9+CA242 could be considered of better diagnostic value for pancreatic cancer patients. Further large scale studies are needed to verify our findings.

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Disclosure of conflict of interest

None.

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