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REVIEW

Diagnostic and prognostic value of carcinoembryonic antigen in pancreatic cancer: a systematic review and meta-analysis

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Background: Carcinoembryonic antigen (CEA) is one of the most widely used tumor markers and is increased in 30%–60% of patients with pancreatic cancer. Although carbohydrate antigen 19-9 (CA19-9) is the most important serum biomarker in pancreatic cancer, the diagnostic and prognostic value of CEA is gradually being recognized.

Materials and methods: The MEDLINE, EMBASE, and Web of Science databases were searched for related literature published until January 2017. Diagnostic accuracy variables were pooled using the Meta-Disc software. The pooled hazard ratios (HRs) for prognostic data were calculated and analyzed using Stata software.

Results: A total of 3,650 participants enrolled in 19 studies met our inclusion criteria. The pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of a CEA-based panel were 0.45 (95% confidence interval [CI], 0.41–0.50), 0.89 (95% CI, 0.86–0.91), 5.39 (95% CI, 3.16–9.18), and 0.55 (95% CI, 0.41–0.72), respectively. The area under the curve (AUC, 0.90) and Q-value (0.84) of the CEA-based panel indicated a significantly higher diagnostic accuracy compared with CEA or CA19-9 alone. Moreover, there was also a significant association between high levels of CEA and worse overall survival (HR, 1.43; 95% CI, 1.31–1.56).

Conclusion: Our meta-analysis indicated that elevated serum CEA level, as a vital supplementary to CA19-9, can play an important role in the clinical diagnosis of pancreatic cancer patients and predict poor prognosis.

Keywords: carcinoembryonic antigen, pancreatic cancer, diagnosis, prognosis, meta-analysis

Introduction

Pancreatic cancer is one of the most aggressive malignancies and the fourth leading cause of cancer-related death.[1] Despite advances in diagnostic and therapeutic strategies in the past 2 decades, the outcome of pancreatic cancer remains disappointing, and the 5-year survival rate is approximately 6%.[2,3] Most pancreatic cancer patients are diagnosed at advanced stages due to a lack of specific symptoms and appropriate markers. Failure to identify patients with a high risk of metastasis and recurrence has also resulted in an unsatisfactory prognosis of pancreatic cancer patients.

Carcinoembryonic antigen (CEA), a glycoprotein with a molecular weight of 180–200 kDa, was initially isolated from fetal colon and colon cancer tissue in 1965.[4] CEA is increased not only in colorectal cancer but also in various other types of cancer, including breast cancer,[5] lung cancer,[6] and thyroid cancer.[7] Moreover, the serum level of CEA is increased in 30%–60% of pancreatic cancer patients.[8,9] Carbohydrate antigen 19-9 (CA19-9), the only biomarker currently recommended for clinical use by the National

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Comprehensive Cancer Network guidelines for pancreatic cancer, has several limitations that should be considered when interpreting serum levels in a clinical setting. CA19-9 may lack sufficient sensitivity and specificity for certain patients with specific metastases or jaundice.[10] Furthermore, sialylated Lewis antigen-negative individuals, constituting approximately 5%–10% of the population, have little or no secretion of CA19-9.[11,12] For this proportion of the population, serum CEA was proposed as a potential marker to improve the diagnosis of pancreatic cancer. Thus, elevated CEA levels have been established as an independent predictor of poor survival of pancreatic cancer patients.[13] Preoperative serum panel results of $CEA^+/CA125^+/CA19\text{-}9 \geq 1{,}000$ U/mL helped to identify a subgroup of patients with poor outcomes following surgery.[14]

Although many recent studies have focused on the relationship between CEA and pancreatic cancer, the results are still unclear. Therefore, this review initiated a comprehensive analysis to clarify the precise value of CEA in the diagnosis and prognosis of pancreatic cancer.

Materials and methods

Search strategy

The investigation was conducted by searching the electronic databases such as MEDLINE, EMBASE, and Web of Science for all relevant articles published up to January 2017, using the following terms: "carcinoembryonic antigen" or "CEA," "diagnosis" or "prognosis," and "pancreatic cancer/tumor/adenocarcinoma." The searches were supplemented by studying reference lists of the retrieved articles as well as relevant review articles. Two researchers independently assessed the eligibility of the potential studies following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[15]

Inclusion and exclusion criteria

The eligible studies were selected according to the following inclusion criteria: 1) studied pancreatic cancer based on histopathological confirmation; 2) at least one of the diagnostic or prognostic value of CEA detection in pancreatic cancer patients was reported or able to be calculated from published data; and 3) samples were obtained from the peripheral blood. Exclusion criteria included the following: 1) duplicated studies using the same population or overlapping database; 2) literature published as reviews, case reports, letters, editorials, and expert opinions; and 3) studies published in a non-English language.

Quality assessment

The methodological quality of diagnosis in this review was assessed using the QUADAS-2 (Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews).[16] The criteria consist of four key domains, including 1) patient selection; 2) conduct of the index test; 3) reference standard; and 4) flow and timing. All the four domains address the risk of bias, whereas the first three domains also consider concerns regarding applicability. Assessment results are presented as "low risk," "high risk," and "unclear risk."

The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality of prognosis in this review.[17] In addition, the specific quality assessment of prognostic studies was estimated according to the approach of Hayden et al.[18] This scale is an eight-item instrument that assesses the quality of the selection, comparability, exposure, and outcomes for study participants.

Data extraction

Two reviewers independently extracted the data from the selected studies and decided on controversial issues through discussion. The following information from each article was extracted: name of the first author, year of publication, country of study, number of samples, origin of samples, detection method, time of sampling, cutoff criteria, accuracy of diagnostic value (the number of true positives [TPs]; false positives [FPs]; true negatives [TNs]; false negatives [FNs]), and survival data (hazard ratio [HR]). If not available, data were extracted using the method described by Tierney et al[19] and Parmar et al.[20]

Statistical analysis

Diagnostic variables with corresponding 95% confidence intervals (CIs), such as sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and the summary receiver operating characteristic curve (SROC), were calculated and analyzed using the statistical methods described in the protocol.[21] Pooled HRs of serum CEA levels for overall survival (OS) were calculated. The I^2 value was used to assess the statistical heterogeneity among the studies. A fixed-effects model was used for $I^2 < 50\%$, whereas a random-effects model was used for $I^2 > 50\%$.[22] The latent publication bias was assessed by a funnel plot. Meta-Disc 1.4 (XI Cochrane Colloquium, Barcelona, Spain) and Stata Version 12.0 software (StataCorp LP, College Station, TX, USA) were

used to conduct statistical analysis. All *p*-values were two sided, and statistical significance was set at $p<0.05$.

Results

Literature screening and study characteristics

The flowchart of article selection is shown in Figure 1. We initially retrieved 875 published articles from the databases such as EMBASE, MEDLINE, and Web of Science. A total of 67 studies remained after manual screening of titles, abstracts, and keywords and removal of duplicates or irrelevant studies to the current analysis. A total of 48 articles were further removed according to the inclusion criteria or exclusion criteria. Finally, 19 studies were considered eligible for inclusion in the meta-analysis.

Detailed information on the included studies is summarized in Table 1. A total of 3,650 participants enrolled in 19 studies were analyzed for the association between serum CEA level and pancreatic cancer, and 2,329 (63.8%) were included in 11 studies with prognosis analyses, including HRs, or standardized incidence ratios with 95% CI. All participants enrolled in these studies were from America, Finland, Germany, Greece, Korea, Japan, China, Australia, Italy, and Turkey. A total of 15 studies adopted the critical values of CEA (5 ng/mL) as the cutoff value, with 8.4 ng/mL, 2.5 ng/mL, 12.5 ng/mL, and 3.47 ng/mL used in the other studies. All pancreatic cancer patients were confirmed by pathological examination of resected specimens or by fine-needle aspiration. The results of diagnosis quality assessment using the QUADAS-2 analysis are shown in Figure S1. The results of quality assessment according to NOS are presented in Table S1, and all studies achieved a score over 5.

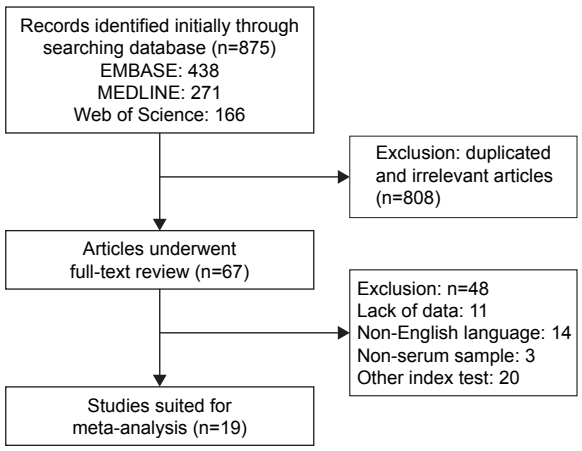

Figure 1 Literature review process.

Meta-analysis results of diagnostic value

Characteristics of the diagnostic analysis of the included studies are summarized in Table 2. Tumor markers, such as CA19-9, CEA, and the CEA-based tumor panel, were detected and evaluated on their diagnostic accuracy. Serum CEA alone had a pooled sensitivity of 0.43 (95% CI, 0.39–0.47), specificity of 0.82 (95% CI, 0.79–0.84), PLR of 2.40 (95% CI, 1.68–3.43), and NLR of 0.71 (95% CI, 0.65–0.78) (Figure S2). Similarly, the pooled accuracy of CA19-9 alone in this meta-analysis was also assessed (Figure S3). In addition, as shown in Figure 2, the overall accuracy of the CEA-based panel showed that the pooled sensitivity was 0.45 (95% CI, 0.41–0.50), specificity was 0.89 (95% CI, 0.86–0.91), PLR was 5.39 (95% CI, 3.16–9.18), and NLR was 0.55 (95% CI, 0.41–0.72). The DOR expressed how much greater the odds of having the disease are for individuals who have a positive test result compared with those who have a negative test result. The pooled DOR of CA19-9, CEA, and the CEA-based panel was 8.44 (95% CI, 5.12–13.91), 3.57 (95% CI, 2.29–5.57), and 19.20 (95% CI, 6.45–57.18), respectively. I^2 values of the diagnostic variables were used to test the heterogeneity of these studies. The pooled indicators were calculated using the random-effects model due to the significant heterogeneity between these studies. The pooled results are summarized in Table 3. The SROC curve for the tumor diagnostic indicators, a comprehensive representative of test accuracy combining sensitivity with specificity, was drawn based on FP rates for the horizontal axis and TP rates for the vertical axis. An area under the curve (AUC) close to 1 reflects a well-performing diagnostic precision.[23] We also determined the Q-value, 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. The Q-value provides an overall measure of the discriminatory power of the diagnostic test. In this meta-analysis, the higher AUC (0.90) and Q-value (0.84) of the CEA-based panel are shown in Figure S4, compared with CA19-9 or CEA alone.

Meta-analysis results of prognostic significance

A total of 11 studies were available for calculating OS and pooled for survival analysis. As shown in Figure 3, the results indicated that a high level of CEA in pancreatic cancer was associated with worse OS (HR, 1.43; 95% CI, 1.31–1.56). A fixed-effects model was applied during calculation due to the moderate but insignificant heterogeneity

Table 1 Summary of the studies included in the meta-analysis

Study	Region	Number of participants	Result	Survival analysis	HR (95% CI)	CEA cutoff criteria (ng/mL)	Detection method	Sample source	Sample time
Benini et al[36]	America	193	–	–	–	8.4	Immunoassay	Serum	BS
Carpelan-Holmstrom et al[39]	Finland	191	–	–	–	5	Immunoassay	Serum	BS
Haas et al[40]	Germany	34	OS	U	2.24 (1.18–4.25)	5	Immunoassay	Serum	BS
Tsavaris et al[45]	Greece	215	OS	M	1.58 (1.14–2.20)	5	NR	Serum	BS
Lee et al[42]	Korea	187	OS	M	1.52 (1.03–2.23)	5	Immunoassay	Serum	BS
Haglund[32]	Finland	201	–	–	–	2.5	Immunoassay	Serum	BS
Sakamoto et al[38]	Japan	61	–	–	–	12.5	Immunoassay	Serum	BS
Kanda et al[44]	Japan	166	OS	U	1.06 (0.79–1.42)	5	NR	Serum	BS
Ni et al[33]	China	205	–	–	–	5	Immunoassay	Serum	BS
Reitz et al[43]	Australia	393	OS	M	1.27 (1.00–1.61)	5	NR	Serum	NR
Imaoka et al[13]	Japan	433	OS	KM	1.77 (1.42–2.20)	5	NR	Serum	BS
Del Favero et al[34]	Italy	139	–	–	–	3.47	Immunoassay	Serum	BS
Liao et al[35]	China	150	–	–	–	5	Immunoassay	Serum	BS
Duraker et al[37]	Turkey	181	–	–	–	5	Immunoassay	Serum	BS
Distler et al[46]	Germany	259	OS	M	1.299 (1.127–1.496)	5	Immunoassay	Serum	BS
Papadoniou et al[47]	Greece	215	OS	M	1.58 (1.14–2.20)	5	NR	Serum	BS
Kim et al[41]	Korea	144	OS	M	2.60 (1.22–5.55)	5	NR	Serum	AS
Gu et al[31]	China	132	OS	KM	1.023 (0.975–3.208)	5	Immunoassay	Serum	BS
Xu et al[48]	China	151	OS	M	2.654 (1.643–4.289)	5	Immunoassay	Serum	AS

Note: –, indicates not mentioned.
Abbreviations: AS, after treatment; BS, before treatment; CEA, carcinoembryonic antigen; HR, hazard ratio; KM, Kaplan–Meier analysis; M, multivariate analysis; NR, not reported; OS, overall survival; U, univariate analysis.

(I^2=56.6%, p=0.011). In the subgroup analyses by ethnicity, six studies were conducted in Asian population (two in China, two in Japan, and two in Korea) and the remaining five in Caucasian population (one in Australia, two in Greece, and two in Germany). Regardless of whether the cases were from Asian or Caucasian populations, a high level of CEA was still a significant predictor of poor OS of pancreatic cancer (Asian: HR, 1.56; 95% CI, 1.35–1.80, Figure S5A; Caucasian: HR, 1.37; 95% CI, 1.23–1.52, Figure S5B).

Publication bias

The publication bias of the included studies was assessed by funnel plots in this meta-analysis. Deeks' tests of publication bias in diagnostic analysis showed that there was no publication bias (p=0.634). Similarly, the publication bias was assessed for the association of CEA and OS in pancreatic cancer patients. Begg's tests showed that publication bias was not significant for the enrolled studies (Begg's test: p=0.213). The funnel plot is shown in Figure S6.

Discussion

Traditional surgical specimens or biopsy tissues are used in the diagnosis of pancreatic cancer and considered the gold standard for clinical examination. However, limitations still exist, because they involve invasive procedures and delayed reflection of tumor dynamic changes.[24,25] Hence, the current

Table 2 Characteristics of the diagnosis part of included studies

Study	Region	Number of participants	CA19-9: TP/FP/FN/TN	CEA: TP/FP/FN/TN	CEA-based tumor panel: TP/FP/FN/TN (panel composition)
Benini et al[36]	America	193	14/25/11/143	10/26/15/142	23/39/2/129 (CEA, CA19-9)
Carpelan-Holmstrom et al[39]	Finland	191	24/31/6/130	9/7/21/154	–
Haglund[32]	Finland	201	74/24/21/82	47/25/40/81	31/1/56/105 (CEA, CA125, CA19-9)
Sakamoto et al[38]	Japan	61	26/2/4/29	20/7/10/24	28/9/2/22 (CEA, CA19-9)
Ni et al[33]	China	205	84/57/21/43	47/25/58/75	39/16/66/84 (CEA, CA19-9)
Del Favero et al[34]	Italy	139	20/33/9/77	8/24/21/86	6/5/23/105 (CEA, CA19-9)
Liao et al[35]	China	150	84/15/28/23	37/2/75/36	40/1/72/37 (CEA, CA19-9, CA50, CA242)
Duraker et al[37]	Turkey	181	100/14/23/44	48/5/75/53	42/3/81/55 (CEA, CA19-9)
Gu et al[31]	China	132	43/33/9/47	28/35/24/45	47/5/5/75 (CEA, CA19-9, CA125, CA242)

Note: –, indicates not mentioned.
Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; FN, false negative; FP, false positive; TN, true negative; TP, true positive.

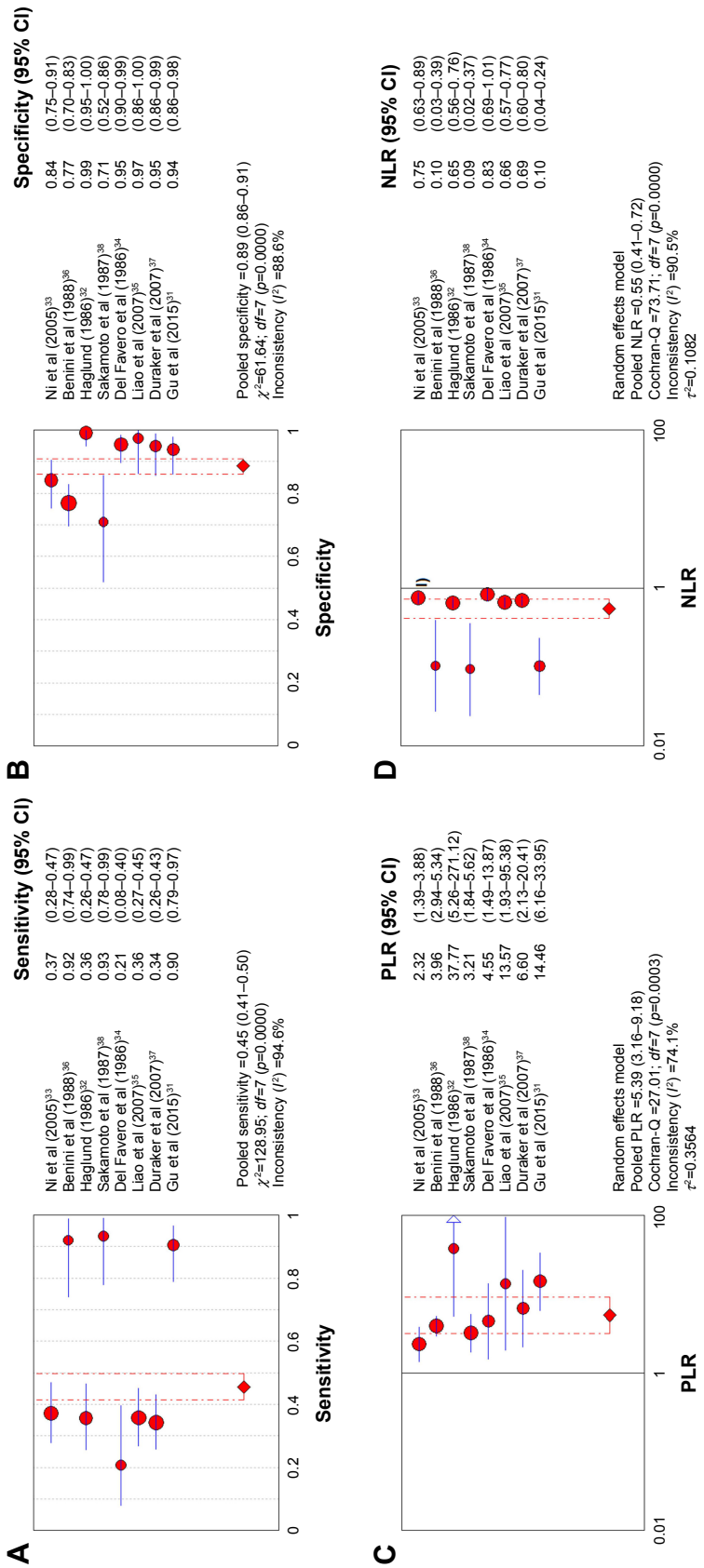

Figure 2 Forest plots of sensitivity (**A**), specificity (**B**), PLR (**C**), and NLR (**D**) for the CEA-based biomarker panel in the diagnosis of pancreatic cancer.
Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; NLR, negative likelihood ratio; PLR, positive likelihood ratio.

Table 3 Pooled diagnostic accuracy

Study participants	Diagnostic biomarker	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (SEM)
PC vs non-PC	CA19-9	0.78 (0.75–0.81)	0.73 (0.69–0.76)	2.77 (1.98–3.87)	0.34 (0.27–0.43)	8.44 (5.12–13.91)	0.81
	CEA	0.43 (0.39–0.47)	0.82 (0.79–0.84)	2.40 (1.68–3.43)	0.71 (0.65–0.78)	3.57 (2.29–5.57)	0.61
	CEA-based panel	0.45 (0.41–0.50)	0.89 (0.86–0.91)	5.39 (3.16–9.18)	0.55 (0.41–0.72)	19.20 (6.45–57.18)	0.90
Heterogeneity, I^2 (p-value)	CA19-9	28.1% (0.194)	90.0% (0.000)	85.9% (0.000)	46.2% (0.061)	68.4% (0.001)	–
	CEA	67.1% (0.002)	89.0% (0.000)	69.2% (0.001)	26.8% (0.205)	56.8% (0.017)	–
	CEA-based panel	94.6% (0.000)	88.6% (0.000)	74.1% (0.000)	90.5% (0.000)	81.7% (0.000)	–

Note: –, indicates not mentioned.
Abbreviations: AUC, area under the curve; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; DOR, diagnostic odds ratio; NLR, negative likelihood ratio; PC, pancreatic cancer; PLR, positive likelihood ratio; SEM, standard error of the mean.

attempts to develop screening tests for early diagnosis have predominantly focused on serum biomarkers. The application of CA19-9, a widespread screening tool for pancreatic cancer, has been restricted due to its low sensitivity and specificity. CA19-9 is elevated in patients with other upper gastrointestinal tumors, biliary obstruction, and other benign conditions.[26] Furthermore, Lewis antigen-negative individuals, constituting approximately 5%–10% of the population, are genetically unable to produce CA19-9.[27] Recently, combinations of biomarkers in a panel screen were shown to have increased power to accurately diagnose pancreatic cancer over any single marker alone.[28–30] Serum CEA is the second most common biomarker used clinically for detecting pancreatic cancer. Many recent studies have shown that CEA, when combined with other biomarkers, including CA19-9, CA125, and CA50, may increase the accuracy in distinguishing cancer from normal patients.[31–39] Moreover, many studies have reported that CEA could also play an important role in predicting survival of pancreatic cancer patients.[13,31,40–48] However, the relationship between CEA and pancreatic cancer still remains unclear. Therefore, it is necessary to conduct a comprehensive analysis to assess the clinical utility of CEA in pancreatic cancer patient diagnosis and prognostic prediction.

In this meta-analysis, evidence showed that CEA-based panels were superior to CEA or CA19-9 alone in terms of test specificity, although the sensitivity of the panels had no obvious advantage. As an evaluation index of the overall performance of diagnostic tests, the pooled DOR of CEA-based panels was 19.20, indicating a significantly higher diagnostic accuracy compared with CEA or CA19-9 alone. Similarly, CEA-based panels had a better diagnostic capability (AUC =0.90) to indicate the risk of pancreatic cancer according to the suggested guidelines for the interpretation of the area under summary

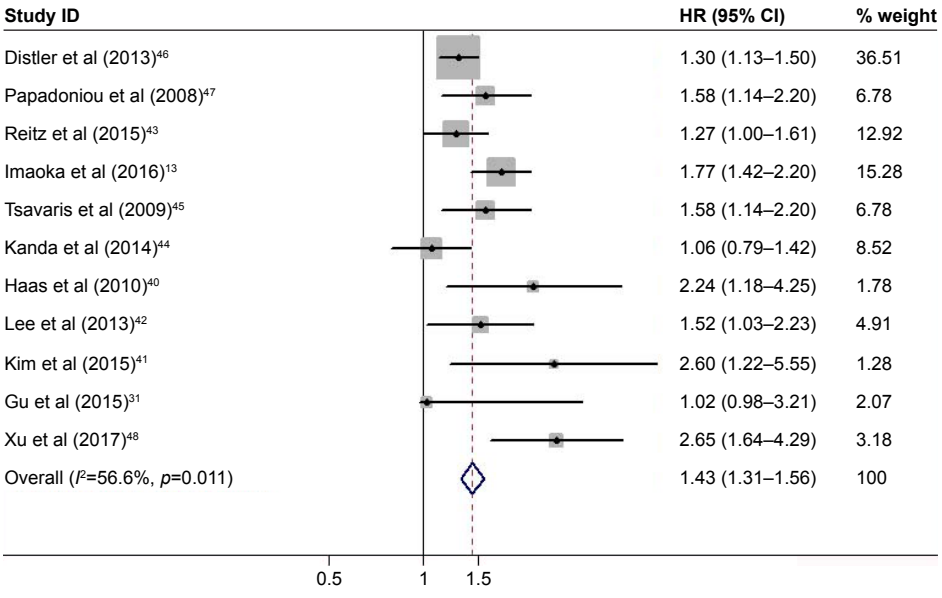

Figure 3 Forest plot of the HRs for survival with high serum CEA levels in pancreatic cancer.
Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio.

receiver operating characteristic curve value.[49] Hence, these results demonstrate the promising clinical value of the CEA-based diagnostic panel as a diagnostic biomarker.

With regard to prognostic value, the expression of CEA was significantly associated with OS of pancreatic cancer patients. Papadoniou et al[47] found that increased levels of the markers CEA and CA19-9, which indicate a higher tumor burden, were also associated with a worse prognosis. Reitz et al[43] reported that a linear combination of CEA and CA19-9 is significantly better for prognostic prediction compared with single tumor markers. Imaoka et al[13] showed that CEA level is an independent prognostic factor in patients with metastatic pancreatic cancer, and a combination chemotherapy regimen (such as Folfirinox and nab-paclitaxel plus gemcitabine) may offer only a modest survival benefit in cases with high CEA. In this field, our team has published two relevant studies.[14,48] We previously showed that increases in serum CEA in combination with CA19-9 could significantly enhance the prognostic value of CA19-9.[48] A CEA$^+$/CA125$^+$/CA19-9≥1,000 U/mL serum signature could better identify a subgroup of patients with poor response to radical resection.[14]

Several limitations in this meta-analysis study should be addressed. First, a relatively small number of studies with a limited number of subjects were included in this meta-analysis, which may reduce the statistical power for determining the diagnostic role of CEA for pancreatic cancer. Second, through subgroup analysis of ethnicity, we found that the differences in patient characteristics (age, country, and other variables) and cutoff criteria of the included studies may be another potential source of heterogeneity. Third, our study selected English language-only publications or unpublished articles, which may result in certain publication bias. Finally, the findings of this meta-analysis need to be confirmed by further multicenter, prospective clinical studies to enable a definitive conclusion to be made.

Conclusion

The current meta-analysis showed that a CEA-based panel is better at diagnosing pancreatic cancer than CA125 or CA19-9 alone. Furthermore, high levels of serum CEA are significantly related to poor prognosis of patients with pancreatic cancer. Thus, the measurement of serum CEA, as a vital supplementary to CA19-9, is inexpensive, convenient, and necessary for monitoring this disease.

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Disclosure

The authors report no conflicts of interest in this work.

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