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Correlation between serum CA724 and gastric cancer: multiple analyses based on Chinese population

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Abstract Serum tumor biomarker carbohydrate antigen 724 (CA724) is noticeable for gastric cancer. Correlation between CA724 and gastric cancer was investigated based on Chinese population. Chinese Biomedical Database, Chinese Journal Full-text Database and PubMed were searched. Gastric cancer patients were proven by biopsy, and control included health volunteers or benign gastric diseases. Participants received at least one test of CA724, CA125, CA153, CA199, CA242 or CEA. Meta-analysis, summary ROC (SROC) and post hoc analysis were performed by RevMan 5.0 and SPSS 11.5. Totally, 33 eligible studies were analyzed. Meta-analysis showed CA724 had the highest odds ratio 32.86 compared to control, orderly followed by CA242, CA199, CEA, CA125 and CA153. Accumulated accuracy rate of CA724 was 77 %, superior to others. In SROC analysis, specificity of all studies was above 0.70, but sensitivity of few studies was above 0.70; CA724 was selected as the preferable single test, followed by CA242, CA199, CEA, CA125 and CA153. If threshold of both specificity and sensitivity up to 0.70, CA153 was unacceptable; if up to 0.80, only CA724 and CA242 were considerable. In CA724-combined patterns, CA724+CEA+CA199 combination performed best by increasing sensitivity to 0.74 without impairing specificity, while CA724 + CA199 pattern was not a proper combination. CA724 was the most correlative serum tumor biomarker for gastric cancer in Chinese population. Sensitivity of serum CA724 is limited, but CA724+CEA+CA199 combination is considerable to improve sensitivity without impairing specificity.

Keywords Gastric cancer · CA724 · CEA · CA199 · Tumor biomarker · Meta-analysis · Summary ROC · Chinese

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Introduction

Gastric cancer was still one of the most common malignancies and a major health problem in the worldwide [1, 2]. Although its incidence trended to decline in the Western, gastric cancer kept high incidence in some eastern countries, such as Japan, Korea and China [3–5]. In China, the incidence rate of early gastric cancer is really low which cause most patients are detected at advanced stage and of poor prognosis [6]. Therefore, an effective tumor biomarker for screening, diagnosis and follow-up monitoring of gastric cancer is still desired.

As well known, serum alpha1-fetoprotein (AFP) is the most effective biomarker to screen and diagnose primary hepatic cancer, and also serum carcinoembryonic antigen (CEA) is a useful biomarker for colorectal cancer. However, by now, there is still no either sensitive or specific tumor biomarker for gastric cancer [7]. The commonly researched serum tumor biomarkers in gastric cancer have been CEA, CA199 and CA724 [8, 9]. Some other serum cancer-associated biomarkers, such as CA125 and CA242 can be elevated in the digestive system tumors [8]. Recently, CA724 has been paid more attention for gastric cancer as been considered to be potentially more sensitive and specific [9]. Although they are tumor-associated but tumor-specific, the sensitivity and specificity of the studies were quite diverse. The present research was aimed to find out the relatively useful biomarker including CA724 and some others to use as supplementary test for the diagnosis of gastric cancer patients based on the Chinese population.

Methods

Search strategy

We searched the electronic databases of Chinese Biomedical Database (CBM) and Chinese Journal Full-text Database (CJFD), as well as Pub-Medline from 1999 to 2009. The search strategy of Pub-Medline was ("Stomach Neoplasms"[Mesh] and "Carcinoma"[Mesh]) and ("Tumor Biomarkers, Biological"[Mesh] or "Antigens, Tumor-Associated, Carbohydrate"[Mesh] or "CA-72-4 Antigen"[Substance name] or "carcinoembryonic antigen"[Mesh] or "CA-125 Antigen"[Mesh] or "CA-19-9 Antigen"[Mesh] or "CA-15-3 Antigen"[Mesh] or "CA 242 antigen"[Substance name]). The search strategy of Chinese databases was accordant to that of Pub-Medline.

Inclusion and exclusion criteria

The present meta-analysis included the diagnostic studies containing either single test or multiple tests. The patients all were diagnosed of gastric cancer proved by biopsy, and control arm included the health volunteers or benign gastric diseases. All the participants received the test of serum tumor biomarker, at least one of CA724, CA125, CA153, CA199, CA242 or CEA. CA153 is generally not regarded as a gastrointestinal cancer-associated biomarker, and hereby selected as a control biomarker to refer to.

The studies had reported results by eligible outcome measures. The positive expression of serum tumor biomarkers in patients with gastric cancer was judged as true positive (TP), while the negative expression in patients with gastric cancer as false negative (FN). On the other hand, the negative expression in control arm was judged as true negative (TN), while the positive expression in control arm as false positive (FP).

The studies contaminated with other gastric malignancies, such as lymphoma, gastrointestinal stromal tumor, neuroendocrine carcinoma, were ineligible. The extractable data of results were mandatory to every study, or else to be excluded. There was no limitation of age or gender. Any disagreement was discussed and solved by third party.

Data extraction

The data of the outcome measures mentioned above were extracted, including events numbers in TP, FN, TN and FP arms for categorical variables. The number of events could be calculated if the percentage reported.

Statistical analysis

The comparison was performed among the single tests, i.e. CA724, CEA, CA125, CA153, CA199 and CA242. Outcomes of eligible studies will be statistically synthesized by Reviewer Manager (RevMan Version 5.0, 2008, The Nordic Cochrane Centre, Cochrane Collaboration). The statistical method was referred to the Cochrane Handbook for Systematic Reviews [10].

In each single test, meta-analysis was performed to compare the biomarkers positive rate of gastric cancer with that of control. Odds ratio (OR) plus 95 % confidence interval (CI) was calculated in fixed effects model initially. The Mantel–Haenszel (M–H) test was used to test significance, with $p < 0.05$ considered statistically significant [10]. Heterogeneity between comparable studies was tested in all analyses using a standard Chi-square test for between-study heterogeneity and considered significant at $p < 0.1$ [10]. If heterogeneity existed, the analysis used the random effects model.

For multiple single test or combination tests analysis, summary ROC (SROC) plots was involved. Each SROC curve had to contain no less than five studies, or else the synthesis couldn't be done. In addition, plots of SROC curve, based on the Littenberg and Moses linear regression model can be presented [11]. In SROC curves, average operating points including 95 % confidence intervals and 95 % prediction regions can also be produced, but the p values couldn't be calculated by the RevMan 5.0 software [10]. The SROC curves were created by symmetric model for analysis among single tests, while asymmetric model for analysis of combination tests. SROC analyses were weighted by sample size of studies. The curve, which was the nearest one to the left upper point, represented the preferable test in the comparison, and moreover, the one nearest to the right lower point was the unfavorable test. In

Table 1 The results of meta-analysis in each single test based on Chinese population

Biomarkers	Studies number	Participants	Gastric cancer		Control		Model	Odds ratio	(95 % CI)	Accumulated accuracy rate	Sensitivity[a] Mean ± SD	Specificity[b] Mean ± SD
			Positive	Total	Positive	Total						
CA724	19	3,444	800	1,535	62	1,909	Random	32.86	(16.34–66.09)	0.77	0.49 ± 0.19	0.96 ± 0.06
CA242	11	2,039	327	922	31	1,117	Random	15.07	(7.99–28.41)	0.69	0.38 ± 0.19	0.97 ± 0.02
CA199	25	4,210	861	1,876	145	2,334	Random	12.60	(7.75–20.48)	0.72	0.44 ± 0.15	0.92 ± 0.08
CEA	25	4,296	781	1,876	144	2,420	Random	10.02	(6.48–15.52)	0.71	0.41 ± 0.16	0.93 ± 0.05
CA125	10	1,728	194	721	60	1,007	Random	5.50	(3.37–8.97)	0.66	0.32 ± 0.16	0.93 ± 0.05
CA153	5	1,108	36	516	18	592	Fixed	4.37	(1.97–9.70)	0.55	0.10 ± 0.10	0.97 ± 0.03

CI confidence interval, *SD* standard deviation

[a] One-way ANOVA LSD's post hoc test: CA724 significantly higher than CA125 ($p = 0.007$) and CA153 ($p < 0.001$); CA153 significantly lower than CA724, CA242 ($p = 0.002$), CA199 ($p < 0.001$), CEA ($p = 0.001$) and CA125 ($p = 0.016$)

[b] One-way ANOVA LSD's post hoc test: CA242 significantly higher than CA199 ($p = 0.044$)

sensitivity analysis, the thresholds of preference for both sensitivity and specificity were set as ≥0.70 and ≥0.80.

Since the RevMan 5.0 can't provide quantitative comparison in SROC analysis, the one-way ANOVA LSD's post hoc test was used to compare the mean of sensitivity and specificity of six biomarkers. The data of sensitivity and specificity were extracted from individual study. SPSS 11.5 software (SPSS, Inc., USA) was used for LSD's post hoc test, and two-sided p value less than 0.05 was considered as significance.

Results

Literatures

There were totally 33 eligible studies included for meta-analysis, of which there were 2,390 cases in gastric cancer arm and 2,893 cases in control arm, respectively [12–44]. In each single test, CA724 included 19 studies with 1,535 versus 1,909 cases, CA242 11 studies with 922 versus 1,117 cases, CA199 25 studies with 1,876 versus 2,334 cases, CEA 25 studies with 1,876 versus 2,420 cases, CA125 10 studies with 721 versus 1,007 cases and CA153 five studies with 516 versus 592 cases, respectively (Table 1). The median sample size of included studies was 138 cases with the range from 30 to 538.

Single biomarker analysis

Meta-analysis

Meta-analysis showed that positive serum CA724 in gastric cancer patients had the apparently high OR 32.86 (95 % CI, 16.34–66.09) compared to control (Fig. 1). The median and range of sensitivity and specificity of serum CA724 among included studies were 0.51 (0.14–0.90) and 0.98 (0.75–1), respectively (Fig. 1). The accumulated accuracy rate of serum CA724 was 77 % (Table 1). Funnel plot analysis didn't show obvious publication bias of serum CA724 for gastric cancer (Fig. 2). All these results indicated serum CA724 was the best one of selected six biomarkers for gastric cancer against the others.

The OR of CA724 was the highest one, orderly followed by CA242 (OR: 15.07), CA199 (OR: 12.60), CEA (OR: 10.02), CA125 (OR: 5.50) and CA153 (OR: 4.37) (Table 1). It meant CA724 was highly correlated with gastric cancer. The ORs of CA125 and CA153 were less 10 and seemed not correlated with gastric cancer. Moreover, 95 % CI of CA724 (16.34–66.09) was completely superior to those of CEA (6.48–15.52), CA125 (3.37–8.97) and CA153 (1.97–9.70) (Table 1). The accumulated accuracy rate of CA724 (77 %) was the top one of the six selected

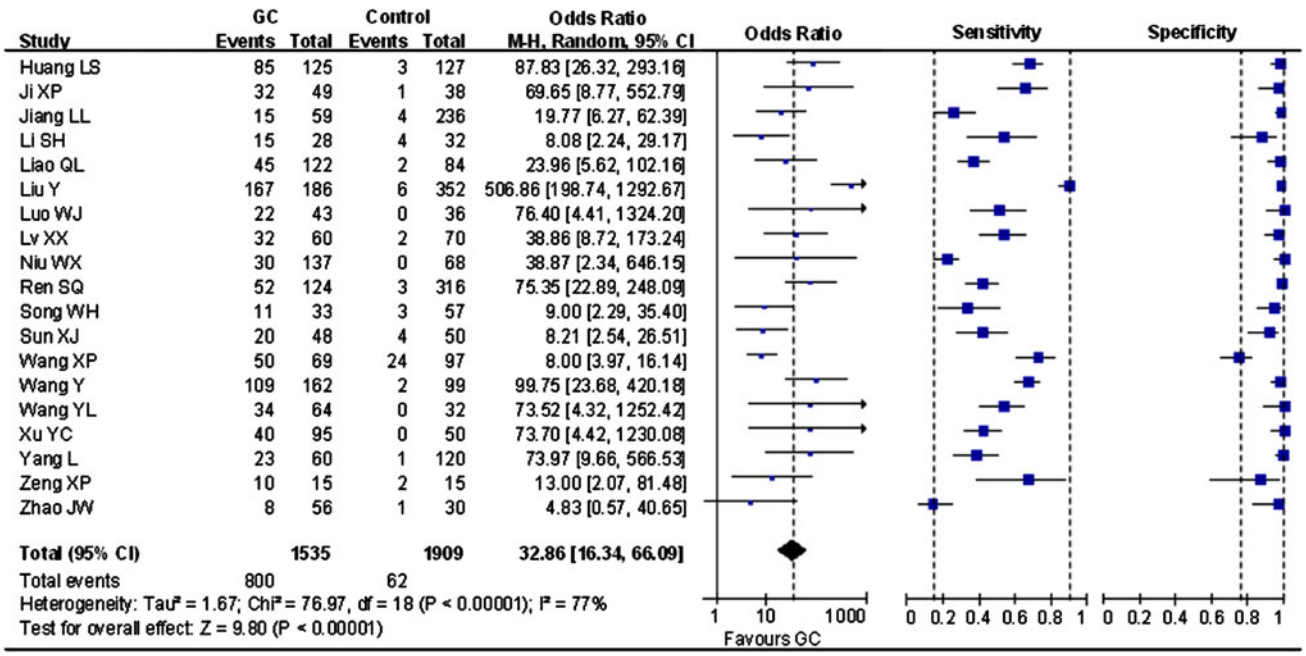

Fig. 1 Meta-analysis of serum CA724 positive rate between gastric cancer patients and control [12–30]

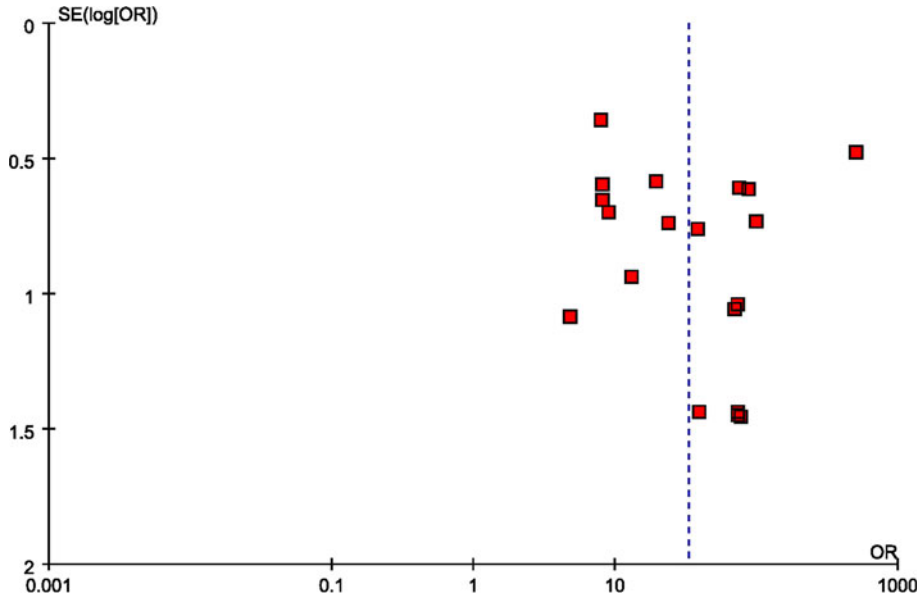

Fig. 2 Funnel plot of odds ratio of positive serum CA724 in gastric cancer against control

biomarkers, while that of CA153 was the worse (55 %) (Table 1).

SROC analysis

In symmetric SROC curve analysis of multiple tests, the specificity of all studies was more than 0.70, but the sensitivity of few studies was more than 0.70 (Fig. 3). It implied that single test pattern can't meet the requirement of diagnostic accuracy. Moreover, by the SROC curve, CA724 was selected as the preferable single test, followed by CA242, CA199, CEA and CA125 subsequently, while CA153 was the unfavorable one (Fig. 3). If threshold of both specificity and sensitivity were up to 70 %, CA153 was unacceptable for gastric cancer; if up to 80 %, only CA724 and CA242 were considerable serum biomarkers (Fig. 3).

Post hoc analysis

The mean of sensitivity (49 %) of serum CA724 among included studies were the highest, and significantly higher than CA125 ($p = 0.007$) and CA153 ($p < 0.001$); the

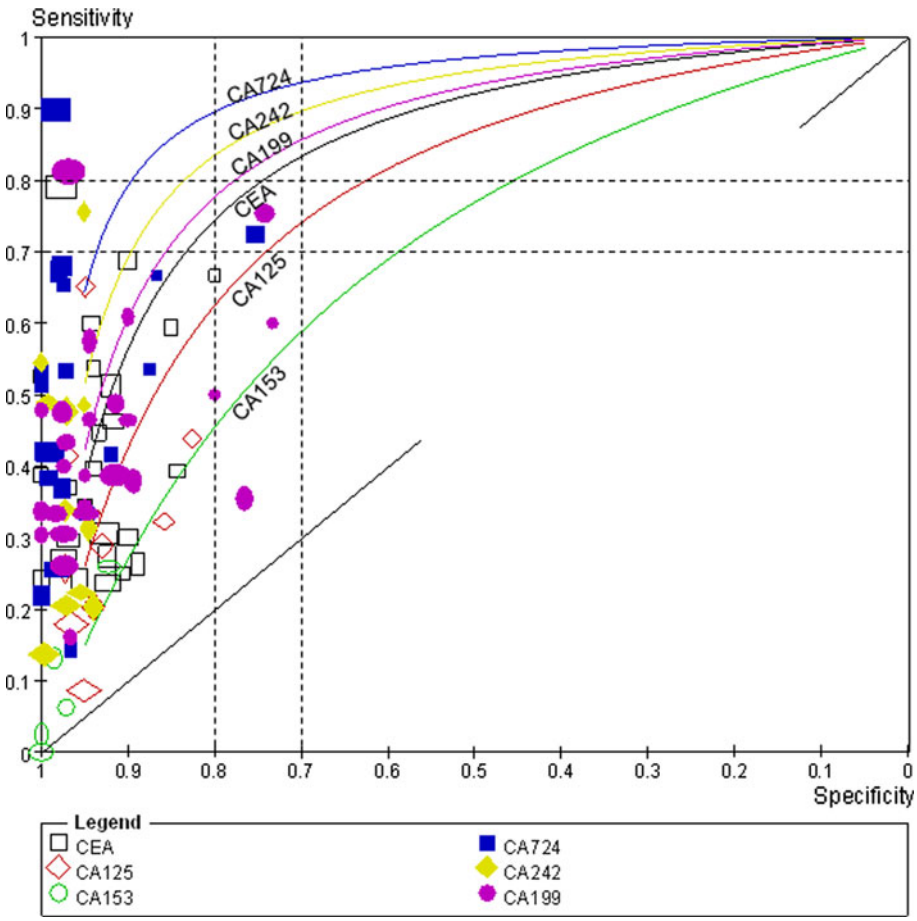

Fig. 3 SROC plot of single biomarker including CA724 and other five serum markers for gastric cancer based on Chinese population

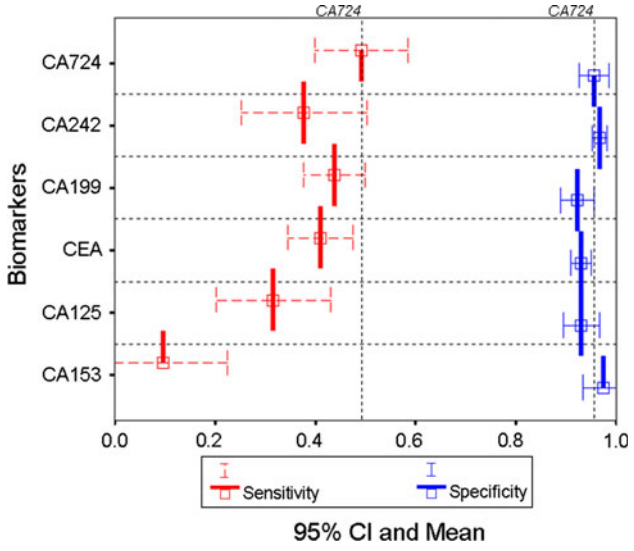

Fig. 4 Error bar of sensitivity and specificity of six serum biomarkers for gastric cancer among included studies

sensitivity of CA199, CEA and CA242 were lower than that of CA724 but without statistical significance; the sensitivity of CA153 was significantly lower than those of CA724, CA242 ($p = 0.002$), CA199 ($p < 0.001$), CEA ($p = 0.001$) and CA153 ($p = 0.016$) (Table 1; Fig. 4). The means of specificity were all more than 90 % and commonly comparable among six biomarkers except CA242 higher than CA199 ($p = 0.044$), only with narrow interval between their specificity (Table 1; Fig. 4).

Biomarkers combination analysis

Due to the limited sensitivity of single test of serum CA724, the CA724-combined multiple tests was considered as a way to improve the sensitivity. CA724+CEA+CA199 combination was the commonly reported pattern. To examine the value of combination tests based on CA724, 10 studies reported comparisons between CA724 single pattern and binary pattern (CA724+CA199, CA724+CEA) or triple pattern (CA724+CEA+CA199) were selected for further post hoc analysis and SROC analysis[13, 15, 16, 18, 19, 21, 23, 27, 29, 30].

Post hoc analysis

Combination tests all had trends to increase the sensitivity, and the triple pattern CA724+CEA+CA199 could increase most from 0.47 ± 0.15 to 0.74 ± 0.11 (Table 2). Post hoc analysis

Table 2 Sensitivity and specificity comparison between combination test patterns and CA724 single test

	Mean ± SD	*p* value[a]		
		CA724+CA199	CA724+CEA	CA724+CEA+CA199
Sensitivity				
CA724 only	0.47 ± 0.15	0.118	0.013	0.003
CA724+CA199	0.61 ± 0.21	–	0.442	0.196
CA724+CEA	0.68 ± 0.10	–	–	0.564
CA724+CEA +CA199	0.74 ± 0.11	–	–	–
Specificity				
CA724 only	0.96 ± 0.05	0.025	0.211	0.118
CA724+CA199	0.77 ± 0.24	–	0.289	0.427
CA724+CEA	0.86 ± 0.11	–	–	0.771
CA72+CEA+CA199	0.84 ± 0.15	–	–	–

[a] One-way ANOVA LSD's post hoc test

found CA724+CEA and CA724+CEA+CA199 patterns could significantly increase sensitivity, but CA724+CA199 pattern was not able to (Table 2). It implied that CEA might be a synergetic biomarker to increase sensitivity with CA724, but CA199 influenced less in improvement of sensitivity. Combination tests increased the sensitivity, but impaired the specificity according to general rule. CA724+CA199 pattern reduced the specificity most from 0.96 ± 0.05 to 0.77 ± 0.24 ($p = 0.025$), but CA724+CEA and CA724+CEA+CA199 patterns didn't significantly reduced the specificity (Table 2). It implies that CA199 might play a negative role in specificity but CEA not. What's more, comparison between CA724+CEA and CA724+CEA+CA199 patterns didn't show significant difference (Table 2).

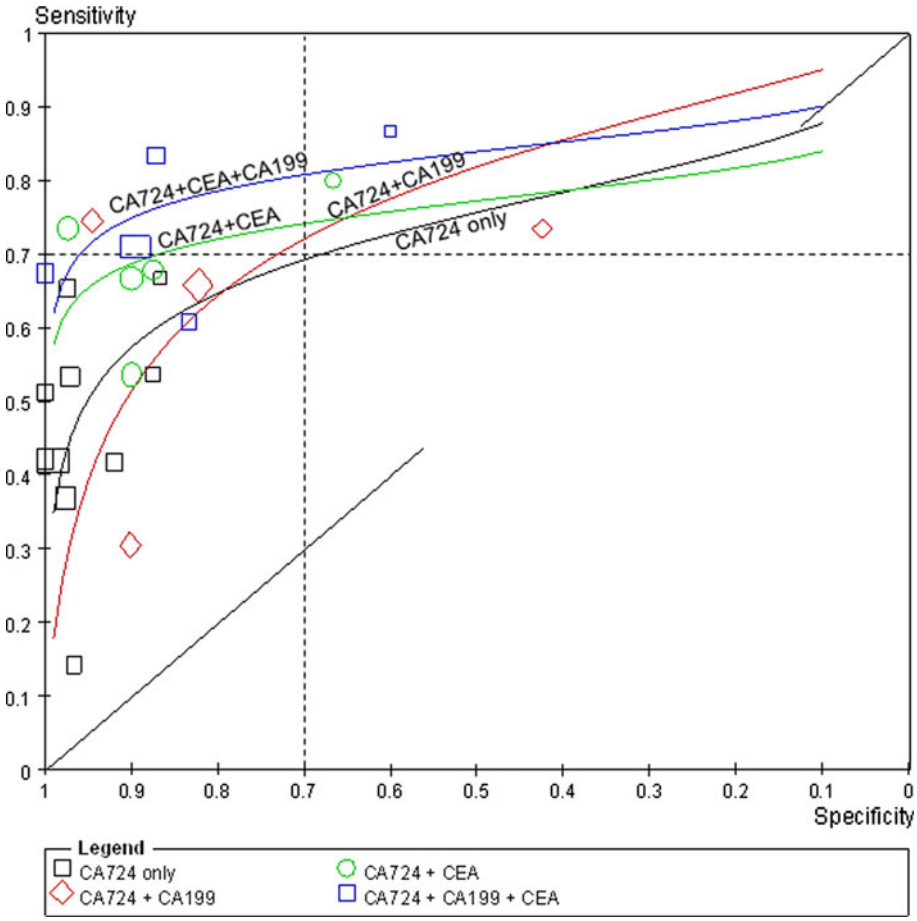

Fig. 5 SROC plot of serum CA724 and CA724-combined multiple tests

SROC analysis

Finally, asymmetric SROC curve analysis showed that the curve of CA724+CEA+CA199 combination test was the one nearest to the left upper point, and indicated that CA724+CEA+CA199 combination was still preferable to CA724 only, as well as CA724+CA199 and CA724+CEA patterns (Fig. 5).

Summary

Through multiple statistical analyses, serum CA724 was the most correlative tumor biomarker for gastric cancer in Chinese population among CA724, CA242, CA199, CEA, CA125 and CA153, and significantly superior to the others. However, actually, the sensitivity of serum CA724 was still limited as single test. CA724+CEA+CA199 combination pattern performed best, since it could significantly improve the sensitivity for gastric cancer, but without significant impairment of the specificity. Moreover, CA125 and CA153 appeared not to be associated with gastric cancer.

Discussion

The prognosis of advanced gastric cancer is relatively poor, but the 5-year survival rate of early gastric cancer is usually reported as more than 90 % [45, 46]. An early detection of primary gastric cancer is often difficult in asymptomatic patients and therefore gastric cancers are often detected at a relatively advanced stage, when symptoms lead to a diagnostic evaluation [47]. Even though techniques of extended surgery and perioperative chemoradiotherapy are improving, the overall survival outcome of gastric cancer cannot be obviously improved by now [48, 49]. Therefore, an useful tumor biomarker for gastric cancer is still fairly desired in the field of screening, diagnosis and follow-up monitoring. It means there hasn't been a commonly recommended and accepted gastric cancer-associated biomarker by now. In some previous research, CA724 has been suggested to be the most sensitive and specific biomarker for gastric cancer [50]. Our results of multiple analyses based on Chinese population corroborate previous findings and also indicated that the single test of serum CA724 could perform the best accuracy and sensitivity, as well as acceptable specificity, for the detection of gastric cancer. Maybe, CA724 is the most correlative biomarker with gastric cancer.

However, the single test of serum CA724 is actually limited in the aspects of sensitivity around 50 % and accuracy no more than 80 %. Therefore, apparently, single test of serum CA724 couldn't meet the requirement of clinical practice. Research found the combination of several biomarkers could improve the diagnostic accuracy in gastrointestinal tract malignancies compared with single biomarkers alone [51]. A few of studies have investigated several CA724-combined modules on their efficacy of improving the sensitivity, and the most focused module is CA724, CEA and CA199 [51, 52]. Another biomarker CA242 also has relatively high sensitivity up to 44 % in gastric cancer and can be considered as useful one for CA724 to combine with [51]. Thus, the choice of combination module is required further investigation on how to improve the sensitivity and accuracy of gastric cancer detection.

Furthermore, gastric cancer has an extremely variable prognosis; thus, the identification of new prognostic parameters may be useful for selecting patients to more tailored therapies [47]. Tumor biomarker CA724 trended to be considered as an independent prognostic factor in addition to stage and histological type of gastric cancer [8]. In resectable gastric cancer, preoperative serum CA199 and CEA levels may associate with stage, but neither has been proven as an independent prognostic factor [7]. Some studies have compared the prognostic value of CEA, CA199 and CA724 in gastric cancer, and the results have been quite conflicting [9, 53, 54]. Interestingly, the combined test of CEA, CA199 and CA724 preoperative serum levels could provide certain prognostic information in patients with resected gastric cancer; patients with preoperative positivity for one of these three biomarkers should be considered at high risk of recurrence even in early gastric cancer [55].

In a short, we found serum CA724 was the most correlative tumor biomarker for gastric cancer in Chinese population among CA724, CA242, CA199, CEA, CA125 and CA153, and significantly superior to the others. However, actually, the sensitivity of serum CA724 was still limited as single test. CA724-combined module (CA724+CEA+CA199) could improve the sensitivity for gastric cancer without impairing the specificity.

By now, NCCN Clinical Practice Guideline in Gastric Cancer 2010 and ESMO Clinical Recommendations for Gastric Cancer 2009 haven't mentioned any tumor biomarker or combined biomarkers for gastric cancer in the aspects of screening, diagnosis and follow-up monitoring [3, 56]. Thus, we regard the strategy of tumor biomarkers for gastric cancer need some standardized criteria in the future. Serum CA724 or CA724-combined module (CA724+CEA+CA199) could be considered of diagnostic value for gastric cancer patients, and further investigation on the correlation between screening, disease progress or staging, follow-up monitoring and serum CA724 or CA724-combined module (CA724+CEA+CA199) is required.

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