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CA72-4 combined with CEA, CA125 and CAl9-9 improves the sensitivity for the early diagnosis of gastric cancer

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ABSTRACT

Background/aims: To determine whether the combination of tumor markers (CA72-4, CA125, CA19-9 and CEA) could increase the sensitivity and accuracy for in the diagnosis of gastric cancer (GC).
Methods: This study is a retrospective analysis. A total of 426 patients, including 106 patients with GC, 149 patients with benign gastric diseases and 171 healthy people, who visited Zhejiang Xiaoshan Hospital from January 2011 to December 2013, were measured by serum markers, including CA72-4, CA125, CA19-9 and CEA. Statistical analyses including area under curve (AUC) of receiver operating characteristic (ROC) curve, and logistic regression analysis, were performed to evaluate the diagnostic value of these markers on GC.
Results: Serum levels of CA72-4, CEA, CA125 and CA19-9 were higher in the GC group than those in the benign gastric disease group and the healthy control group ($P < 0.005$). The sensitivities of CA72-4, CEA, CA125 and CA19-9 at the recommended cut-off level for all patients were 33.0%, 25.5%, 31.1% and 38.7%, respectively. However, when all four markers were used in combination the sensitivity increased to 66.0%. But by using an optimal cut-off value, the sensitivities of all four markers for the diagnosis of GC were improved. Especially the sensitivity of CEA increased to 73.6% and the sensitivity of the combination of the tumor markers increased to 75.5%. The age and gender had no effects on the diagnostic value of these markers.
Conclusions: With the help of optimal cut-off values based on ROC curve and logistic regression analysis, the combination of these markers could improve the sensitivity for the diagnosis of GC based on common serum tumor markers.

1. Introduction

Gastric cancer (GC) is still one of the most common malignancies and a major health problem worldwide [1]. In the world, the highest incidence and mortality rate of GC is in China. Therefore, we must find an easy and quick way to differentiate the syndromes of GC from benign gastric diseases. Up to now, few effective biomarkers for GC have been applied in the diagnosis of GC [2]. As we know, the diagnosis of GC mainly depends on invasive examination, such as gastroscopy and biopsy. The detection of serum tumor marker is a simple and easy approach, which have been becoming a common clinical method for screening tumor. Tumor markers, such as alpha fetoprotein (AFP), carcinoembryonic antigen (CEA), cancer antigen 72-4 (CA72-4) and cancer antigen 19-9 (CA19-9), have been widely used for the diagnosis of different types of cancers, including primary liver cancer, colorectal cancer and pancreatic cancer. However, so far, there is still neither sensitive nor specific tumor biomarker for GC [3–8]. The commonly researched serum biomarkers in GC are CEA, CA19-9 and CA125. Some other serum cancer-associated tumor markers, such as CA72-4 and CA242, can be elevated in the digestive system tumors. Herein, we hypothesized that the combined use of these tumor markers may increase the sensitivity and accuracy for the early diagnosis of GC. Thus, the aim of this study is to detect the serum levels of CA72-4, CA125, CEA and CA19-9 in 106 patients with GC, 149 patients with benign gastric diseases, and 171 healthy people. Then we performed statistical analysis to evaluate the diagnostic value of these markers for GC. Our results showed that the determination of optimal cut-off values of these markers could increase the sensitivity in the diagnosis of GC.

2. Methods

2.1. Patients

A total of 426 patients visiting Zhejiang Xiaoshan Hospital from January 2011 to December 2013 were enrolled and divided into three groups. The first group was the GC group, which consisted of 106 patients with GC (77 males, 29 females, ranging from 24 to 88 y, mean 59.7 y), including 21 patients with early GC, 85 advanced GC, 50 poorly differentiated adenocarcinoma, 51 moderately differentiated adenocarcinoma, 5 highly differentiated adenocarcinoma, 50 gastric antrum carcinoma, 43 gastric body cancer, 9 gastric cardia-bottom cancer, and 4 multiple site

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Table 1
Serum levels of CA72-4, CEA, CA125 and CA19-9 in these subjects.

	GC (n = 106)	Benign gastric disease (n = 149)	Healthy people (n = 171)	*P*
Age (y)	59.7 ± 13.4	55.2 ± 14.4	48.4 ± 13.0	0.013
Gender (M/F)	77/29	85/64	115/56	0.011
CA72-4 (kU/l)	87.25 ± 206.6	4.8 ± 10.0	3.65 ± 4.8	0.000
CEA (ng/ml)	132.9 ± 671.3	3.14 ± 9.37	1.68 ± 1.43	0.000
CA125 (U/ml)	78.28 ± 183.3	16.26 ± 36.58	12.81 ± 7.17	0.000
CA19-9 (U/ml)	1175 ± 4088	17.74 ± 29.59	10.66 ± 7.10	0.000
CA72-4 positive cases (%)	35 (33.0%)	6 (4.0%)	3 (1.8%)	0.000
CEA positive cases (%)	27 (25.5%)	3 (2.0%)	0	0.000
CA125 positive cases (%)	33 (31.1%)	4 (2.7%)	0	0.000
CA19-9 positive cases (%)	41 (38.8%)	11 (7.4%)	4 (2.3%)	0.000
Combination positive cases (%)	70 (66.0%)	22 (14.8%)	7 (4.1%)	0.000

cancer (>2 sites). The second group was the benign gastric disease group, which consisted of 149 patients (85 males, 64 females, ranging from 22 to 96 y, mean 55.3 y), including 32 patients with gastric ulcer, 71 duodenal ulcer, 16 complex ulcer, 23 non-atrophic gastritis, and 7 atrophic gastritis. The third group consisted of 171 healthy people (115 males, 56 females, ranging from 26 to 84 y, mean 48.4 y). The GC and benign gastric diseases were diagnosed by endoscopy and confirmed by biopsy. This study was approved by the Medical Ethics Committee of Zhejiang Xiaoshan Hospital. All patients were informed about the study and gave their consent.

2.2. Serum tumor marker detection

Venous blood sample for marker determination was separated by centrifugation, and aliquots were stored at −20 °C until assayed. Markers were detected by an E-170 automatic analyzer made by Roche. The cut-off values of 19.3 kU/l, 10.0 ng/ml, 35 U/ml and 37 U/ml were taken for CA72-4, CEA, CA125 and CA19-9, respectively. Once the tumor markers increased above the upper limit, reexamination should be performed within another instrument made by Beckman on the same day and 1 week later again.

2.3. Statistical analysis

The data were expressed as mean ± standard deviation. A value of $P < 0.05$ was considered statistically significant. The area under curve (AUC) of receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of serum tumor markers. Multivariate logistic regression analysis was used to establish the diagnostic mathematical model. On the basis of this model, the prediction value was calculated followed by ROC curve analysis. The statistical analysis was performed using SPSS17.0 statistical software.

3. Results

3.1. The results of CEA, CA125, CA19-9 and CA72-4 in the study subjects

The statistical data, such as age and gender, and the results of 4 serum biomarkers in the three groups of this subject were shown in Table 1. The results were expressed as mean ± standard deviation. There was statistical significance in the average value and positive rate among the three groups.

3.2. Positive rates of serum tumor markers in GC of different clinicopathological features

According to the baseline information of GC, we subdivided the GC group and calculated positive rates of 4 serum tumor markers. We found that there were no significant differences in the positive rate of serum tumor markers among GC with location and different differentiations (Table 2). However, there was a statistical difference in stage only when the four tumor markers were applied at the same time.

Table 2
Positive rates of 4 tumor markers with GC baseline information.

Cases		Positive cases (%)				
		CA72-4	CEA	CA125	CA19-9	Qualitative combined
Stage						
Early stage	21	6 (28.5%)	2 (9.5%)	4 (19.0%)	5 (23.8%)	12 (57.1%)
Advanced stage	85	29 (34.2%)	25 (29.4%)	29 (34.1%)	36 (42.3%)	76 (89.4%)
χ^2		0.234	3.509	1.869	2.441	14.548
P		0.628	0.061	0.172	0.118	0
Location						
Cardia	9	3 (33.3%)	5 (55.6%)	2 (22.2%)	6 (66.7%)	7 (77.8%)
Gastric body	43	11 (25.6%)	12 (27.0%)	15 (34.9%)	11 (25.6%)	30 (69.8%)
Gastric antrum	50	20 (40.0%)	10 (20.0%)	16 (32.0%)	24 (48.0%)	37 (72.0%)
Multi-site	4	1 (25.0%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0%)
χ^2		2.569	6.581	2.441	10.437	4.536
P		0.463	0.087	0.486	0.015	0.209
Differentiation						
High	5	2 (40.0%)	2 (40.0%)	2 (40.0%)	3 (60.0%)	3 (60.0%)
Moderate	51	13 (25.5%)	12 (23.5%)	13 (25.5%)	17 (33.3%)	31 (56.4%)
Poor	50	18 (36.0%)	13 (26.0%)	16 (32.0%)	23 (46%)	36 (72.0%)
χ^2		0.258	0.665	0.81	2.325	1.501
P		0.879	0.717	0.667	0.313	0.472