ANALYSIS OF THE APPLICATION VALUE OF CA199, CA724 AND CEA IN EARLY DIAGNOSIS AND PROGNOSIS OF GASTRIC CANCER

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ABSTRACT

Objective*: To analyze the value of macromolecular carbohydrate antigen 199 (CA199), macromolecular carbohydrate antigen 72-4 (CA724) and carcinoembryonic antigen (CEA) in the early diagnosis and prognosis of gastric cancer.*

Methods: *A total of 154 patients with gastric cancer admitted to our hospital from January 2019 to January 2020 were included in the gastric cancer group, 63 patients with benign gastric disease were included in the benign gastric disease group, and 40 healthy people who had a physical examination in the physical examination center of our hospital during the same period were selected as the control group. According to pTNM staging, the patients were divided into group I-II (n=73), group III (n=51) and group IV (n=30). Patients were divided into the good prognosis group (n=85) and poor prognosis group (n=69) according to their prognoses. In the morning, 3mL of fasting venous blood was collected from all subjects, and serum CA199, CA724 and CEA levels were detected by electrochemical luminescence immunoassay. The serum CA199, CA724 and CEA levels for the groups were compared. ROC curves were used to analyze the value of CA199, CA724 and CEA in the early diagnosis and prognosis of gastric cancer.*

Results: *The serum levels of CA199, CA724 and CEA in the gastric cancer group and the benign gastric disease group were significantly higher than those in the control group, and the serum levels of CA199, CA724 and CEA in the gastric cancer group were significantly higher than those in the benign gastric disease group (P<0.05). The serum CA199, CA724 and CEA levels in groups IV and III were markedly higher than those in group I-II, and serum CA199, CA724 and CEA levels in group IV were significantly higher than those in the group III (P<0.05). The serum CA199, CA724 and CEA levels of gastric cancer patients in the poor prognosis group were significantly higher than those in the good prognosis group (P<0.05). ROC curve analyses showed that the area under the curve (AUC), sensitivity and specificity of CA199 for the early diagnosis of gastric cancer were 0.758, 78.64% and 75.21%, respectively. The AUC, sensitivity and specificity of CA724 in the early diagnosis of gastric cancer were 0.702, 72.64% and 68.34%, respectively, whereas the AUC, sensitivity and specificity of CEA in the early diagnosis of gastric cancer were 0.628, 65.39% and 67.94%, respectively. Finally, the AUC, sensitivity and specificity of the combination of these three indicators in the diagnosis of early gastric cancer were 0.878, 89.34% and 85.14%, respectively. The AUC, sensitivity and specificity of CA199 in gastric cancer prognosis were 0.736, 73.65% and 76.94%, respectively. The AUC, sensitivity and specificity of CA724 in gastric cancer prognosis were 0.715, 73.64% and 75.54%, respectively, whereas the AUC, sensitivity and specificity of CEA in gastric cancer prognosis were 0.658, 68.31% and 66.49%, respectively. Finally, the AUC, sensitivity and specificity of the combined indicators in gastric cancer prognosis were 0.859, 86.37% and 84.15%, respectively.*

Conclusion: *The levels of serum CA199, CA724 and CEA in gastric cancer patients were significantly high and changed with the severity of the disease and the prognosis of the patients. Therefore, the serum levels of CA199, CA724 and CEA in gastric cancer patients are of certain value in the early diagnosis and prognosis of gastric cancer; however, the combination of the three indicators was of high value in diagnoses and could be widely used in clinical practice.*

Keywords: *CA199, CA724, CEA, gastric cancer, early diagnosis, prognosis assessment, application, value.*

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Introduction

Gastric cancer is a type of malignant tumor originating in the gastric mucosal epithelium that is characterized by a high incidence rate and high mortality. Gastric cancer is second only to prostate cancer and lung cancer in global incidence inf men and has a very high incidence in women. Therefore, it is of great concern to medical scholars all over the world[1]. Helicobacter pylori infection, dietary habits, family history, genetics and regional differences are all related factors affecting the occurrence of gastric cancer[2]. Early gastric cancer means that the cancer tissue is limited to the gastric mucosa and submucosa.

The 5-year survival rate of patients with early gastric cancer after surgical treatment is significantly higher than that of patients with advanced gastric cancer[3]. However, due to limited early gastric cancer screening, most patients are already in the middle and advanced stages at the time of detection and have poor prognoses. Therefore, early diagnosis and early treatment are of great significance in the effective treatment of gastric cancer patients, improvement in their quality of life and extension of their life cycles.

Tumor markers are substances produced by host stimulation of the tumor or abnormal secretions of malignant tumor cells that are found widely in malignant tumor tissues. Studies have shown that the detection of tumor markers in the blood and tissues of tumor patients can indirectly indicate the existence and progression of tumors as well as analyze the therapeutic effect[4, 5]. In clinic, many tumor markers have been used in the routine diagnosis and monitoring of gastric cancer, including macromolecular carbohydrate antigen 199 (CA199), macromolecular carbohydrate antigen 724 (CA724) and carcinoembryonic antigen (CEA), which are used in the screening and efficacy monitoring of early gastric cancer.

However, the sensitivity and specificity of any single indicator is low, leading to missed diagnoses and misdiagnoses, so single indicators cannot be used widely in clinical practice (6). In this study, 154 patients with gastric cancer admitted to our hospital from January 2019 to January 2020 were selected to participate in this study, which aimed to analyze the value of CA199, CA724 and CEA in the early diagnosis and prognosis of gastric cancer.

Data and methods

General information

A total of 154 patients with gastric cancer admitted to our hospital from January 2019 to January 2020 were included in the gastric cancer group.

The inclusion criteria for the gastric cancer group were:

• Meeting the diagnostic criteria of gastric cancer in the 'Guidelines for standardized diagnosis and treatment of gastric cancer' formulated by the National Health and Family Planning Commission of the People's Republic of China[7];

• Gastric cancer confirmed by gastroscopy and/or histopathological examination;

• Informed consent form signed by the patients and their family members.

The exclusion criteria for the gastric cancer group were:

• Incomplete clinical data;

• Previous gastrectomy, chemotherapy and related tumor therapy;

• Serious disfunction of the heart, liver, kidneys or other important organs;

• Other malignant tumors;

• Refused to participate in this study or terminated the study for other reasons.

Sixty-three patients with benign gastric disease were included in the benign gastric disease group.

The inclusion criteria for the benign gastric disease group were:

• Confirmed to have benign gastric disease via gastroscopy and/or histopathological examination;

• Informed consent signed by the patient and their family.

The exclusion criteria for the benign gastric disease group included:

• Incomplete clinical data;

• Serious disfunction of the heart, liver, kidneys or other important organs;

• Other malignant tumors;

• Refused to participate in this study or terminated the study for other reasons.

Forty healthy people who received physical examinations in the physical examination center of our hospital during the same period were selected as the control group.

The inclusion criteria for the control group were:

• No obvious gastric disease;

• No serious disfunction of the heart, liver, kidneys or other important organs;

• Informed consent signed by the patient and their family members.

In the gastric cancer group, there were a total of 154 patients, including 77 males and 77 females, with an average age of 45.06±9.78 years old and an average BMI of 20.05±0.98 Kg/m^2. There were 63 patients in the benign gastric disease group, including 32 males and 31 females, with an average age of 45.11±9.85 years old and an average BMI of 20.12±0.94 Kg/m^2.

A total of 40 patients were included in the control group, including 21 males and 19 females, with a mean age of 45.12±9.56 years old and an average BMI of 20.53±1.02 Kg/m^2. Using the postoperative pathologic staging results (TNM staging of gastric cancer is based on the 8th edition of the clinical oncology manual prepared by the International Union Against Cancer)[8], the patients were divided

into group I-II, group III and group IV. There were 73 patients in group I-II, including 37 males and 36 females, with an average age of 45.11±9.54 years old and an average BMI of 20.25±1.03 Kg/m^2.

There were 51 patients in group III, including 26 males and 25 females, with a mean age of 45.21±9.11 years old and an average BMI of 20.21±1.05 Kg/m^2. There were 30 patients in group IV, including 14 males and 16 females, with an average age of 45.01±9.68 years old and an average BMI of 20.02±0.68 Kg/m^2.

Patients were divided into a good prognosis group and a poor prognosis group according to their prognoses.

A total of 85 patients were included in the good prognosis group, including 43 males and 42 females, with an average age of 45.01±9.65 years old and an average BMI of 20.02±0.56 Kg/m^2. In the poor prognosis group, there were a total of 69 patients, including 34 males and 35 females, with a mean age of 45.11±9.89 years old and an average BMI of 20.25±1.02 Kg/m^2. There were no statistically significant differences in age, sex and BMI among the groups (P>0.05).

Observational indexes

Serum testing

3mL of fasting venous blood was collected from the subjects; for admitted patients, the samples were collected 24h after admission, while samples were taken from control group members during their physical examinations.

All blood samples were placed at room temperature for 20min. The blood was then centrifuged at 3000r/min for 10min, and the serum was carefully separated and stored at -70°C to avoid repeated freeze-thaw cycles. Serum CA199, CA724 and CEA levels were detected by electrochemical luminescence immunoassay.

Statistical methods

In this study, the SPSS20.0 software package was used for the statistical analyses.

The measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$), and t tests were used for comparisons between groups. The counting data were expressed as percentages, and χ^2 tests were used for comparisons between groups.

ROC curves were used to analyze the value of CA199, CA724 and CEA in the early diagnosis and prognosis of gastric cancer. P<0.05 indicated that the statistical results were statistically significant.

Results

Comparison of serum CA199, CA724 and CEA levels between groups of subjects

The serum levels of CA199, CA724 and CEA in the gastric cancer group and the benign gastric disease group were significantly higher than those in the control group, and the serum levels of CA199, CA724 and CEA in the gastric cancer group were significantly higher than those in the benign gastric disease group (P<0.05). The results are shown in Table 1.

Group	Cases	CA199	CA724	CEA
Control group	40	6.31±1.45	2.35±0.85	1.89±0.84
Benign gastric disease group	63	9.64±4.12^a	5.78±1.46^a	4.39±0.25^a
Gastric cancer group	154	20.46±9.31^{ab}	26.35±4.12^{ab}	18.71±3.64^{ab}

Table 1: Comparisons of the serum CA199, CA724 and CEA levels in groups of subjects ($\bar{x}\pm s$).

Notes: a means that when compared with the control group, $^aP<0.05$; b means that when compared with the benign gastric disease group, $^bP<0.05$.

Comparisons of serum CA199, CA724 and CEA levels among gastric cancer patients with different conditions

The serum CA199, CA724 and CEA levels in groups IV and III were significantly higher than those in group I-II, and serum CA199, CA724 and CEA levels in group IV were significantly higher than those in group III (P<0.05). The results are shown in Table 2.

Group	Cases	CA199	CA724	CEA
Group I-II	73	17.69±2.15	23.46±3.01	6.98±2.15
Group III	51	20.15±2.85a	26.86±4.15^a	13.95±3.14*
Group IV	30	24.36±3.18^{ab}	30.15±4.91^{ab}	20.64±4.16^{ab}

Table 2: Comparisons of serum CA199, CA724 and CEA levels among gastric cancer patients with different conditions ($\bar{x}\pm s$).

Notes: a means that when compared with the control group, $^aP<0.05$; b means that when compared with the benign gastric disease group, $^bP<0.05$.

Comparisons of serum CA199, CA724 and CEA levels among gastric cancer patients with different prognoses

The serum CA199, CA724 and CEA levels of gastric cancer patients in the poor prognosis group were significantly higher than those in the good prognosis group (P<0.05). The results are shown in Table 3.

Group	Cases	CA199	CA724	CEA
Good prognosis group	85	16.31±3.46	20.37±3.21	15.34±3.15
Poor prognosis group	69	25.49±4.18	31.06±3.25	22.84±3.64
t		14.912	14.912	13.701
P		<0.001	<0.001	<0.001

Table 3: Comparisons of serum CA199, CA724 and CEA levels among gastric cancer patients with different prognoses ($\bar{x}\pm s$).

Value of CA199, CA724 and CEA in the early diagnosis and prognosis of gastric cancer

A ROC curve analysis showed that the area under the curve (AUC), sensitivity and specificity of CA199 for the early diagnosis of gastric cancer were 0.758, 78.64% and 75.21%, respectively. The AUC, sensitivity and specificity of CA724 in the early diagnosis of gastric cancer were 0.702, 72.64% and 68.34%, respectively, whereas the AUC, sensitivity and specificity of CEA in the early diagnosis of gastric cancer were 0.628, 65.39% and 67.94%, respectively. Finally, the AUC, sensitivity and specificity of the combined indicators for the early diagnosis of gastric cancer were 0.878, 89.34% and 85.14%, respectively.

The AUC, sensitivity and specificity of CA199 for the prognosis of gastric cancer were 0.736, 73.65% and 76.94%, respectively. The AUC, sensitivity and specificity of CA724 for gastric cancer prognosis were 0.715, 73.64% and 75.54%, respectively, while the AUC, sensitivity and specificity of CEA for gastric cancer prognosis were 0.658, 68.31% and 66.49%, respectively. The AUC, sensitivity and specificity of the combined indicators for gastric cancer prognosis were 0.859, 86.37% and 84.15%, respectively. The results are shown in Table 4.

Item	*AUC*	*95% CI*	*P*	Sensitivity	Specificity
Early diagnosis					
CA199	0.758	0.701-0.804	0.001	78.64%	75.21%
CA724	0.702	0.659-0.758	0.025	72.64%	68.34%
CEA	0.628	0.589-0.689	0.012	65.39%	67.94%
Combined detection	0.878	0.825-0.922	0.001	89.34%	85.14%
Prognosis					
CA199	0.736	0.689-0.789	0.028	73.65%	76.94%
CA724	0.715	0.662-0.769	0.002	73.64%	75.54%
CEA	0.658	0.601-0.714	0.035	68.31%	66.49%
Combined prognosis	0.859	0.809-0.908	0.006	86.37%	84.15%

Table 4: Value of CA199, CA724 and CEA in the early diagnosis and prognosis of gastric cancer.

Discussion

Gastric cancer is a malignant tumor with the second highest mortality rate in the world, and its 5-year survival rate is extremely low, which is partly due to the inadequate large-scale detection and screening of early gastric cancer and the failure to provide patients with early diagnoses and targeted treatment[9]. In addition, the early symptoms of gastric cancer are not obvious, and diagnoses are mainly made by means of imaging and endoscopies. However, this examination method is expensive and causes different degrees of pain in patients, so it cannot be widely used. With the rapid development of molecular biology in recent years, a large number of biological molecules tied to the occurrence and development of tumors have been discovered and now play important roles in the search for, and diagnosis of, gastric cancer.

CA199 is a mucus-containing macromolecular glycoprotein that appears in a variety of tumor cells, and studies have shown that CA199 is a highly sensitive marker for pancreatic cancer[10]. In recent years, it has been discovered that CA199 is significantly highly expressed in the serum of gastric cancer patients and is a highly sensitive marker for gastric cancer[11].

CA724 is currently the most recognized tumor marker associated with gastric cancer, and studies have shown that its sensitivity as a marker for gastric cancer can reach about 65%[12]. A study conducted by Yu[13] showed that the content of CA724 in the blood of patients with gastric cancer was highly correlated with the clinical stage of gastric cancer, the size of the tumor itself, and the involvement of distant organs and lymph nodes. CEA is a carcinoembryonic antigen of glycoproteins.

Under normal circumstances, CEA is polar when entering the gastrointestinal tract, making it difficult to detect. However, cancer cells can secret a large amount of CEA into the blood, so CEA is highly specific for gastric cancer, liver cancer, colorectal cancer and other cancers of the digestive system, and its detection rate is high[14]. In this study, the serum levels of CA199, CA724 and CEA in the gastric cancer group and the benign gastric disease group were significantly higher than those in the control group, and the serum levels of CA199, CA724 and CEA in the gastric cancer group were significantly higher than those in the benign gastric disease group. The serum CA199, CA724 and CEA levels in groups IV and III were

significantly higher than those in group I-II, and the serum CA199, CA724 and CEA levels in group IV were significantly higher than those in group III. The serum CA199, CA724 and CEA levels of gastric cancer patients in the poor prognosis group were significantly higher than those in the good prognosis group. These results suggest that the serum CA199, CA724 and CEA levels in gastric cancer patients are significantly highly expressed, are closely related to the development and prognosis of gastric cancer and may play important roles in the diagnosis of early gastric cancer and prognoses. These results are similar to those obtained by Zhong et al.[15].

In order to further analyze the value of CA199, CA724 and CEA in the early diagnosis and prognosis of gastric cancer, ROC curve analyses were conducted. The area under the curve (AUC), sensitivity and specificity of CA199 for the early diagnosis of gastric cancer were 0.758, 78.64% and 75.21% respectively; these same measurements for CA724 in the early diagnosis of gastric cancer were 0.702, 72.64% and 68.34%, respectively; and those of CEA in early diagnosis of gastric cancer were 0.628, 65.39% and 67.94%, respectively.

The AUC, sensitivity and specificity of the combined indicators in the diagnosis of early gastric cancer = 0.878, 89.34% and 85.14%, respectively. The AUC, sensitivity and specificity of CA199 for gastric cancer prognosis were 0.736, 73.65% and 76.94%, respectively; those of CA724 for gastric cancer prognosis were 0.715, 73.64% and 75.54%, respectively; and those of CEA for gastric cancer prognosis were 0.658, 68.31% and 66.49%, respectively. The AUC, sensitivity and specificity of the combined indicators for gastric cancer prognosis were 0.859, 86.37% and 84.15%, respectively. These results suggest that CA199, CA724 and CEA serum levels have predictive value in the early diagnosis and prognosis of gastric cancer.

The combined indicators had a better predictive value for the early diagnosis and prognosis of gastric cancer than any single index, meaning that the combined indicators can help physicians in the early diagnosis of gastric cancer, prognoses and taking corresponding measures, which is of great significance for the effective treatment of patients.

In conclusion, the serum levels of CA199, CA724 and CEA in gastric cancer patients were significantly high and changed with the severity of the disease and prognosis. Therefore, the serum levels of CA199, CA724 and CEA in gastric cancer patients had certain value in the early diagnosis and prognosis of gastric cancer, while the combination of indicators was of high value and could be widely used in clinical practice.

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