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Original Article

Value of joint detection of serum TK-1 and tumor markers in gastric cancer screening

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Abstract: Objective: To explore the value of joint detection of serum thymidine kinase-1 (TK-1) and tumor markers in gastric cancer screening. Methods: We included 45 patients with gastric cancer as the cancer group and 160 patients with benign gastric cancer as the benign group from May 2017 to May 2018. In addition, 35 healthy volunteers were recruited as the control group. Levels of carcino-embryonic antigen (CEA), carbohydrate antigen 72-4 (CA72-4) and carbohydrate antigen 19-9 (CA19-9) were determined by electrochemiluminescence immunoassay, and TK-1 level was determined by enzyme-linked immuno sorbent assay (ELISA) for confirming the sensitivity and specificity of joint detection of TK-1 and those tumor markers in gastric cancer diagnosis. Then TK-1 expression levels of the gastric cancer patients with different pathological characteristics as well as the correlation between TK-1 and the three biomarkers were analyzed. Results: The levels of TK-1, CEA, CA72-4 and CA19-9 in patients of the cancer group were significantly higher than those in patients of the benign group and the control group (all $P<0.05$). The areas under the curve (AUC) of TK-1, CEA, CA72-4 and CA19-9 were all greater than 0.7 at respective and joint determination. TK-1 levels in patients with lymph node metastasis, low degree of differentiation or no differentiation, tumor diameter of ≥4 cm, or large depth of invasion were significantly higher than those in patients without the pathological indices (all $P<0.05$). The sensitivity and specificity of CEA, CA19-9, CA72-4 and TK-1 detection alone were significantly lower than joint detection of those four indices ($P<0.05$). TK-1 had obvious correlation with CEA, CA19-9 and CA72-4 ($r=0.685$, 0.659, 0.685, respectively; all $P<0.05$). Conclusion: Serum TK-1, CEA, CA72-4 and CA19-9 can be used as markers for diagnosis of gastric cancer. The joint detection of those four tumor markers can effectively improve the sensitivity and accuracy of gastric cancer, which is conducive to early diagnosis and intervention, presenting a relatively high value in clinical application.

Keywords: TK-1, tumor markers, gastric cancer, joint detection

Introduction

Gastric cancer is one of the most common malignant tumors in clinic, with poor prognosis and adverse affects on health of the patients. Early detection and treatment are at present the keys to improving the recovery rate, quality of life and survival time of patients with gastric cancer among the medical community [1-3]. In 2012, approximately 950,000 new gastric cancer cases and 720,000 deaths were present worldwide, which ranked respectively the 5th in the incidence rate and the 3rd in the mortality rate of malignant tumors, and more than 1/3 of the new cases occurred in China [4]. Patients in the early stage of gastric cancer have no obvious symptoms, and most of them are in the middle or advanced stages when receiving inspection in a hospital, thus missing the best opportunity for treatment [5, 6]. Gastroscopy combined with pathological diagnosis is the gold standard for diagnosis of gastric cancer, but poor tolerance to gastroscopy, high economic costs and low acceptability among patients make it unsuitable for basic screening [7, 8].

Metabolites directly produced by tumor cells and released into body fluids or tissues, or produced by normal cells when fighting against tumors serve as tumor markers, and usually exist as antigens, enzymes or hormones [9]. In the normal condition, such markers show no existence or extremely low content in the body.

Their presence or changes in quantity can reflect the occurrence and progression of tumors, with advantages of convenient detection, strong acceptability and low costs, which improves the detection rate of primary tumors, monitor tumor recurrence or metastasis, and evaluate the prognosis effect [10]. However, tumor markers are not specific antigens of tumors. Wide range of concentration of a single tumor marker in serum lacks strong sensitivity, specificity and accuracy, which is easy to cause misdiagnosis or missed diagnosis, and reduces the clinical application value [11]. Therefore, joint detection of different kinds of malignant tumor markers has high application value for early diagnosis and treatment of gastric cancer [12].

Materials and methods

Patients

Forty-five patients with gastric cancer were included as the cancer group and one hundred and sixty patients with benign gastric cancer as the benign group from May 2017 to May 2018. In addition, thirty-five healthy volunteers in the same period were recruited as the control group. Inclusion criteria: Gastric cancers or benign gastric tumors were confirmed by pathological diagnosis by gastroscopic biopsy or gastric samples after surgery, and the judgement for the pathological diagnosis accorded to 2017 consensus for diagnostic pathology in biopsies of chronic gastritis and epithelial neoplasms released by the Group of Digestive Diseases of Chinese Society of Pathology [13]. All the included patients received neither radiotherapy nor chemotherapy. In addition, gastric cancer in the included patients was pathologically proved to be adenocarcinoma. Exclusion criteria: (1) Patients without complete examination or testing items; (2) Patients with coagulation disorder or endocrine disorders; (3) Patients who were in poor basic condition, complicated with other serious diseases; (4) Patients who were in pregnancy or lactation, or who were blood donors. The study was approved by the Medical Ethics Committee of Baoji Central Hospital, and informed consents were obtained from all the patients or their families.

Methods

A total of 5 mL fasting venous blood was collected from each subject and centrifuged at 3,000 rpm per 10 min for isolating the serum. The levels of carcinoembryonic antigen (CEA; Amyjet, Wuhan, China), carbohydrate antigen 72-4 (CA72-4; Savant, Beijing, China) and carbohydrate antigen 19-9 (CA19-9; Linc-Bio, Shanghai, China) of all subjects were determined by fully automated chemiluminescent immunoassay analyzer (Roche, Switzerland). The level of thymidine kinase-1 (TK-1; Cusabio, Wuhan, China) was determined by enzyme-linked immuno sorbent assay using a Thermo Scientific™ Multiskan™ FC microplate reader. All the procedures were carried out in strict accordance with the instructions of the kits. The pathological data of the patients were obtained from the pathology laboratory of gastric cancer of Baoji Central Hospital. The conditions including lymph node metastasis, tumor size, degree of differentiation, and depth of invasion of the patients were evaluated by professional pathologists for the postoperative samples [14].

Outcome measures

Primary indicators: The expression levels of CEA, CA19-9, CA72-4 and TK-1 in the patients of the three groups were recorded. The correlations between TK-1 and various pathological indices were analyzed. The detection sensitivity, specificity and accuracy of each tumor maker as well as joint detection were calculated. According to the kit instructions, CEA >4.3 ng/mL, CA19-9 >27 U/mL, CA72-4 >6.9 U/mL, TK-1 >2 pmol/L were in the positive range [15]. Single index was positive when its testing value was greater than the critical value, or negative when its testing value was less than or equal to the critical value. While joint detection showed a positive result if at least one index was testing positive, otherwise the detection result was negative.

Secondary indicators: The receiver operating characteristic (ROC) curves of TK-1, CEA, CA19-9 and CA72-4 in diagnosis of gastric cancer were statistically analyzed. Relationships between TK-1 and age, CEA, CA19-9, and CA72-4 were respectively analyzed.

Statistical analysis

The data obtained in this study were analyzed using the SPSS software, version 21.0. Measurement data were tested for normal distribution using a Q-Q Plot, and all measurement

Table 1. Baseline characteristics of the three groups ($\bar{x}$ ± sd) n (%)

	Cancer group (n=45)	Control group (n=35)	Benign group (n=160)	F	P
Age (year)	61.0±8.9	59.9±9.5	59.3±9.7	0.559	0.572
BMI (kg/m^2)	20.46±2.12	19.40±2.44	19.60±2.76	2.215	1.114
Sex (male/female)	25/20	19/16	85/75	0.088	0.957
Complications					
Hypertension	3 (6.67)	2 (5.71)	6 (3.75)	0.803	0.669
Diabetes mellitus	1 (2.22)	2 (5.71)	7 (4.38)	0.653	0.721
Hyperlipidemia	2 (4.44)	2 (5.71)	8 (5.00)	0.067	0.967

Note: BMI, body mass index.

data conformed to normal distribution were expressed as mean ± standard deviation ($\bar{x}$ ± sd). Measurement data between two groups were compared using t tests. Comparison of independent samples of multiple groups was carried out by one-way ANOVA. The post hoc SNK method was used for pair-wise comparisons. Enumeration data were expressed as the number of cases/percentage (n/%), for which a χ^2 test was performed. The correlation analysis was conducted by the Spearman Rank Correlation method. For all analyses, P<0.05 was considered statistically significant.

Results

Baseline characteristics

There were no differences in age, sex, body mass index (BMI) and the number of patients with complications among the three groups, presenting no statistical significances (all P>0.05). See **Table 1**.

Expression levels of tumor markers

The levels of CEA, CA19-9, CA72-4 and TK-1 in the cancer group were significantly higher than those in the benign group and the control group, and the differences were statistically significant (all P<0.05). However, there was no difference between the benign group and the control group (P>0.05). See **Figure 1**.

Expression level of TK-1 and different pathological indices

TK-1 levels in patients with lymph node metastasis, low degree of differentiation or no differentiation, tumor diameter of ≥4 cm, or large depth of invasion (T3-T4) were significantly higher than those in patients with lymph node metastasis, intermediate or high degree of differentiation, tumor diameter of <4 cm, or shallow depth of invasion (T1-T2). The difference was statistically significant (all P<0.05). See **Figure 2**.

Diagnostic value of tumor markers for gastric cancer

The ROC curves of the four included tumor markers were respectively made to obtain the areas under the curve by taking gastric cancer patients as the disease group and healthy patients as the control group. According to the areas under the curve, CEA had moderate diagnostic value for gastric cancer, while CA19-9, CA72-4 and TK-1 presented high diagnostic value. See **Figure 3**.

Sensitivity, specificity and accuracy of TK-1 and tumor markers

The sensitivity and specificity of CEA, CA19-9, CA72-4 and TK-1 detection alone were significantly lower than joint detection of those four indices (P<0.05). See **Table 2**.

Correlations between tumor markers and TK-1

TK-1 had no correlation with the patient's age (P>0.05). However, TK-1 presented obvious correlations with CEA, CA19-9, and CA72-4, and the differences were statistically significant (all P<0.05). See **Figure 4**.

Discussion

Lesions of gastric cancer originate from gastric mucosa epithelial tissue and spread through lymphatics and blood vessels under serosa in the early stage. Early stage gastric cancer often has no specific clinical manifestations, which poses difficulties in distinguishing other diseases like gastritis, gastric ulcer from gastric cancer. The detection rate of early gastric cancer is very low in China. Lack of obvious discomfort symptoms in the early stage with late inspection in a hospital, and imperfection of the early

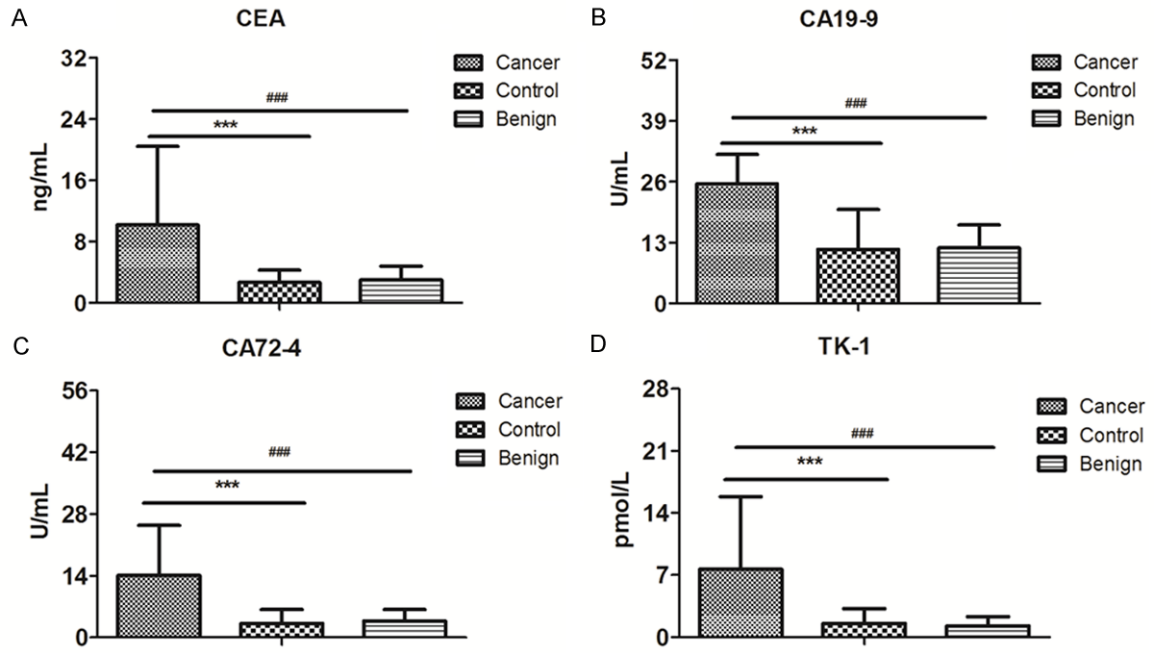

Figure 1. Expression levels of the tumor markers in the three groups ($\bar{x}$ ± sd). Comparison between the cancer group and the control group, ***P<0.001; comparison between the cancer group and the benign group, ###P<0.001. A: CEA level of the three groups; B: CA19-9 level of the three groups; C: CA72-4 level of three groups; D: TK-1 level of three groups. The higher the level, the higher the risk of cancer; TK-1, thymidine kinase-1; CEA, carcinoembryonic antigen; CA72-4, carbohydrate antigen 72-4; CA19-9, carbohydrate antigen19-9.

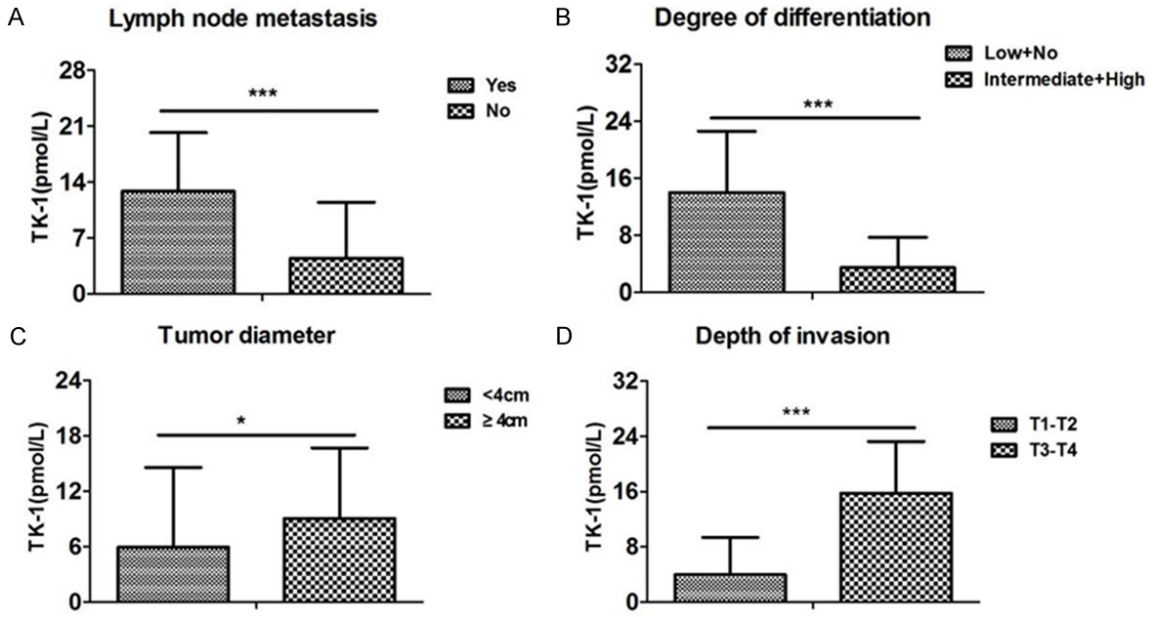

Figure 2. Expression level of TK-1 in gastric cancer patients with different pathological indices. A: TK-1 level in gastric cancer patients with lymph node metastasis or otherwise, the presence or absence of lymph node metastasis is related to the prognosis of the patients; B: Differentiation of tumors, the lower the degree of differentiation, the worse the prognosis of the patients; C: Tumor diameter, the larger the tumor diameter, the more difficulty the surgery presents; D: Depth of invasion, the larger the depth of invasion, the lower the survival rate; TK-1, thymidine kinase-1; *P<0.05, ***P<0.001.

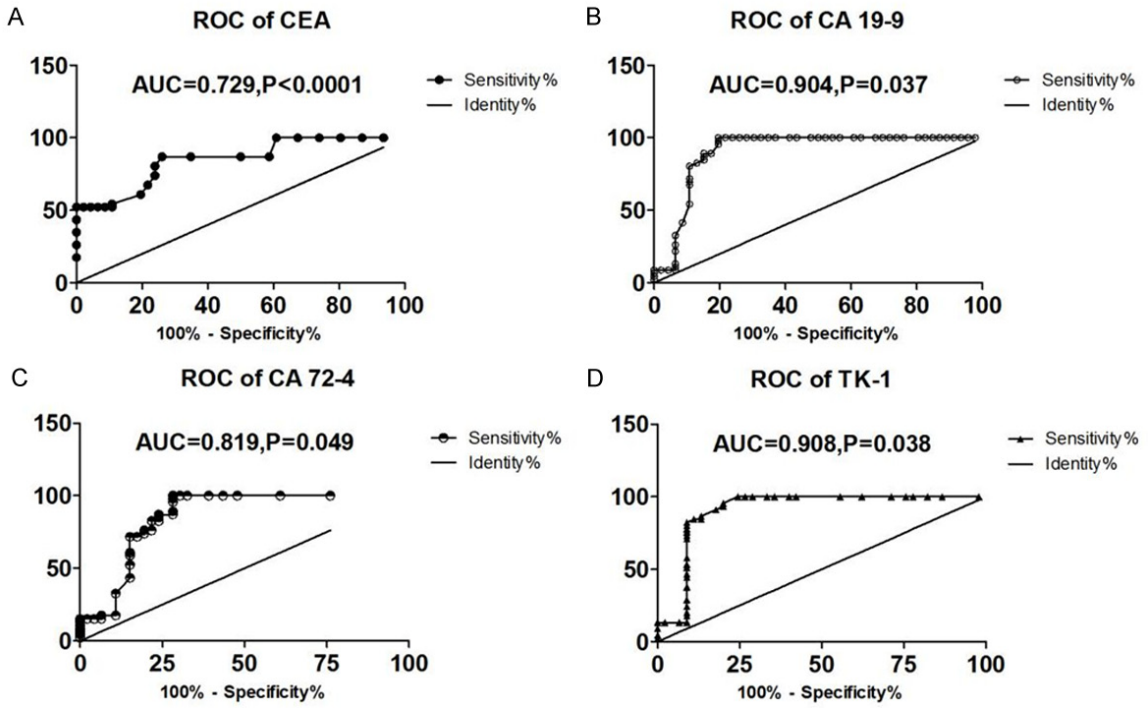

Figure 3. Diagnostic value of the tumor markers for gastric cancer. A: ROC curve of CEA; B: ROC curve of CA19-9; C: ROC curve of CA72-4; D: ROC curve of TK-1; ROC curve, receiver operating characteristic curve; TK-1, thymidine kinase-1; CEA, carcinoembryonic antigen; CA72-4, carbohydrate antigen 72-4; CA19-9, carbohydrate antigen19-9.

Table 2. Comparison between TK-1 and tumor markers in sensitivity, specificity and accuracy

Tumor marker	Sensitivity (%)	Specificity (%)	Accuracy (%)
CEA	29.41	87.59	72.20
CA19-9	31.75	82.39	66.83
CA72-4	35.29	82.47	70.73
TK-1	34.89	81.48	71.71
CEA+CA19-9+CA72-4+TK-1	46.51	99.10	75.12

Note: TK-1, thymidine kinase-1; CEA, carcinoembryonic antigen; CA72-4, carbohydrate antigen 72-4; CA19-9, carbohydrate antigen19-9.

detection system for high-risk groups mainly account for the low detection rate [16]. At present, gastroscopy, cytologic examination of the gastric juice, barium meal and CT are commonly used for gastric cancer detection in clinic, but relatively high economic costs and certain damages to the body lead to low acceptability among patients, with difficulty in clinical popularization [17]. Moreover, sample collection of routine serum tumor markers are convenient with quick detection, but the detection presents low sensitivity, specificity and accuracy. As a result, confirmed cases with gastric cancer often appear in locally progressive or advanced stage, which significantly reduces the overall survival rate in patients [18]. Therefore, how to improve the early detection rate of gastric cancer is a hot issue in current research.

After reading literatures and communicating with relevant experts, we found that CEA, CA72-4, CA19-9 and TK-1 were closely related to gastric cancer, so we took them as the indicators for this study. CEA is a heavily glycosylated protein that belongs to the CEA-related cell adhesion molecule (CEACAM) family, which can reflect invasion and metastasis of a tumor and thus can be used as an indicator to evaluate the patients' prognosis. Current studies have confirmed that CEA presents an expression rate of 20%-80% in gastrointestinal tumors but with poor sensitivity and specificity, and it is no longer used as a biomarker for single detection in cancer screening, and other markers are required for joint detection [19]. CA72-4 is a mucin-like carbohydrate antigen and exists in various malignant tumor tissues such as gas-

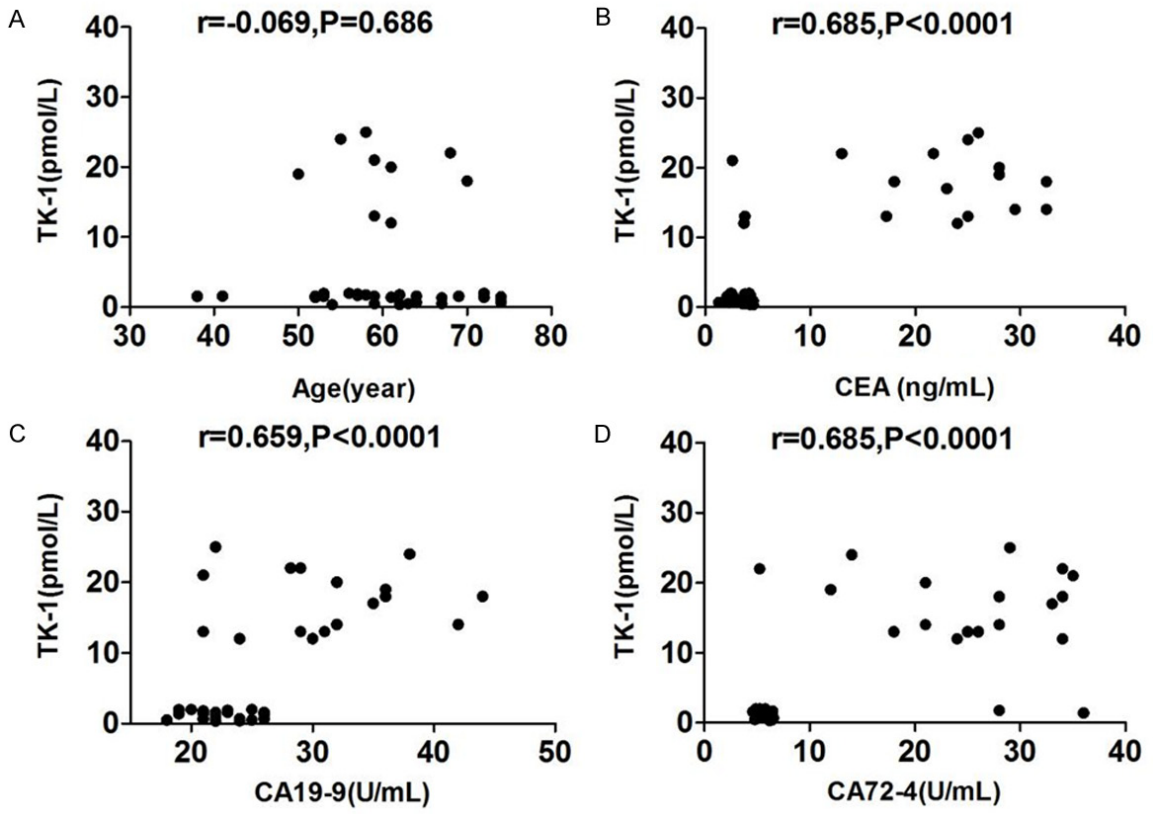

Figure 4. Correlations between the tumor markers and TK-1. A: TK-1 has no correlation with age; B: TK-1 level is positively correlated with CEA level; C: TK-1 level has a positive correlation with the CA19-9 level; D: TK-1 level presents a positive correlation with the CA72-4 level; TK-1, thymidine kinase-1; CEA, carcinoembryonic antigen; CA72-4, carbohydrate antigen 72-4; CA19-9, carbohydrate antigen19-9.

tric cancer. However, CA72-4 does not express in non-epithelial malignant tumors. Studies have proved that the specificity of CA72-4 in diagnosing gastric cancer is over 95%, and the expression level of CA72-4 has obvious correlation with tumor differentiation, clinical stage and degree of invasion. Though CA72-4 serves at present as one of the efficient indicators for diagnosis of gastric cancer, its low sensitivity makes it less helpful for meeting the clinical needs [20]. CA19-9 is a mucin-like glycoprotein. It is specific to various gastrointestinal tumors, and it has the highest sensitivity to pancreatic cancer. TK-1, a soluble protein, can catalyze the conversion of thymidine to thymidine monophosphate, and it is positively correlated with DNA synthesis and can reflect the proliferation of tumor cells. TK-1 presents low content in a healthy body, but its activity and content will be elevated with the rapid proliferation of tumor cells when the body is under cancerization. In recent years, a large number of studies have confirmed that TK-1 is closely related to the occurrence of tumors. Nisman et al. found that TK-1 content was closely related to the tumor stage and grades of lung cancer [21]. Moreover, TK-1 can serve as an independent prognostic factor for leukemia, lymphoma, lung cancer and kidney cancer, but the significance of TK-1 in diagnosis of gastric cancer has not been systematically reported [22].

This study found that the levels of CEA, CA19-9, CA72-4 and TK-1 in the cancer group were significantly higher than those in the benign group and the control group, which is consistent with the findings of Li et al. [23]. Some scholars believe that CA19-9, CA72-4 and CEA have low sensitivity and cannot be used as adjuvant diagnostic indicators for gastric cancer alone, and joint detection of CEA, CA19-9 and CA72-4 is a preferred combination for gastric cancer diagnosis [24]. Felix et al. has confirmed that serum TK-1 has become a new biomarker for prognosis of pancreatic cancer [25]. Besides, Wang et al. confirmed that TK1 expression in

patients with ovarian serous adenocarcinoma was correlated with MDACC grading, pathological stage, lymph node metastasis, the recurrence rates and overall survival rates [26]. Therefore, TK-1 alone for gastric cancer detection presents relatively low specificity. While this study proved that TK-1 levels in patients with lymph node metastasis, low degree of differentiation or no differentiation, tumor diameter of ≥4 cm, or large depth of invasion (T3-T4) were significantly higher than those in patients without the above pathological features, indicating that TK-1 can be used as a relatively potent biomarker for prognosis of gastric cancer. Ning et al. found that joint detection of TK-1 with CEA and CA19-9 that commonly used in clinic could significantly improve the specificity of detection of gastrointestinal tumors [27]. Moreover, TK-1 has obvious correlations with CEA, CA19-9 and CA72-4, and their combinations can further improve the accuracy of gastric cancer detection. Therefore, serum TK-1 has the forewarning function for the diagnosis of precancerous lesions and early-stage tumors, and it can be used as an indicator for tumor screening in physical examination. Plus, TK-1 can obviously improve the sensitivity and specificity of diagnosis of early-stage tumor when included in combination detection with other tumor markers, which is worthy of clinically further promotion [27].

Although joint detection is of significance in guiding clinical diagnosis of gastric cancer, its diagnostic sensitivity is still not high, which accounts for its application in preliminary tumor screening in clinical practice. As a result, patients with positive serum markers require conventional imaging and pathological examination, and patients with negative results need to be diagnosed as soon as possible when discomfort symptoms or abnormal indicators appear. Besides, we also expect to find more ideal biomarkers for gastric cancer detection as well as more economical diagnostic methods with less invasive damages. However, this study has limited sample size, and the contents of tumor markers of the included patients after treatment were not recorded and taken into consideration. In future studies, we will cooperate with several departments to explore the relationship between TK-1 and prognosis and survival time of gastric cancer patients, so as to provide more data to support its application value for large-scale clinical promotion.

In conclusion, serum TK-1, CEA, CA72-4 and CA19-9 can be used as adjuvant biomarkers for diagnosis of gastric cancer. The joint detection of those four tumor markers can effectively improve the sensitivity and accuracy of gastric cancer, which is conducive to early diagnosis and intervention, presenting a relatively high value in clinical application.

Disclosure of conflict of interest

None.

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