SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 17: 3227-3232, 2019

Diagnostic value of apolipoprotein C-I, transthyretin and apolipoprotein C-III in gastric cancer

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Received September 21, 2018; Accepted January 8, 2019

DOI: 10.3892/ol.2019.9957

Abstract. Diagnostic value of apolipoprotein C-I (ApoC-I), transthyretin (TTR) and ApoC-III in gastric cancer were evaluated. Retrospective analysis methods were used to collect 60 patients with gastric cancer first diagnosed in The First Affiliated Hospital of Jiaxing University. There were 60 patients with chronic atrophic gastritis in the benign lesion group and 60 healthy individuals in the control group. The expression levels of serum ApoC-I, TTR and ApoC-III was detected by enzyme-linked immunosorbent assay. Differences existed in the expression levels of ApoC-I, TTR and ApoC-III in the gastric cancer group, benign lesion group and control group ($P<0.001$), with the expression levels of ApoC-I, TTR and ApoC-III in the gastric cancer group being lower than that of the benign lesion group ($P<0.05$), and the expression levels of ApoC-I, TTR and ApoC-III in the benign lesion group being lower than that of the control group ($P<0.05$). The expression levels of ApoC-I, TTR and ApoC-III in the gastric cancer group were to a certain degree correlated with the clinical stage, lymph node metastasis and differentiation of patients in the gastric cancer group ($P<0.05$). The specificity and negative predictive value of combined detection were proven to be higher than the separate detection of the three factors ($P<0.05$). The detection of serum ApoC-I, TTR and ApoC-III was of great significance in the diagnosis of gastric cancer and the estimation of its severity. The method of combined detection is worth a further in-depth study as it could improve the specificity of diagnosis and have a higher negative predictive value.

Introduction

As a highly invasive and destructive malignant tumor of the digestive tract (1), gastric cancer has a very high morbidity and mortality rate worldwide (2) and greatly threatens human health. The increase of pressure on life and work, changes in the eating habits of individuals and the reoccurring food safety issues have caused the incidence age of gastric cancer to be younger (3). However, the potential incidence of gastric cancer is often ignored by patients and medical staff because the early stage of gastric cancer lacks specific symptoms and is wrongly considered as chronic gastritis or gastric ulcer (4). Consequently, most of the clinically diagnosed gastric cancer patients are in advanced stage. Studies have shown that the five-year survival of patients with advanced gastric cancer is not optimistic (5), so how to diagnose gastric cancer in its early stage has become the key to improving the prognosis of gastric cancer patients.

At present, the common diagnostic methods for cases of suspected gastric cancer are gastroscopy, CT and X-ray barium meal (6,7), this involves pain and risks of which may easily arouse patients' resistance and hinder clinical deployment. However, the specificity and sensitivity of common serological tumor markers such as carcinoembryonic antigen, cancer antigen 19-9 are not satisfactory when applied to the diagnosis of early gastric cancer (8), so is pepsin PGI and PGII which are related to the course of chronic atrophic gastritis (9). Therefore, finding a non-invasive serum biomarker that is easy to detect has become a hot-spot in gastric cancer research due to a lack of high-efficiency, non-invasive serum tumor markers for gastric cancer in clinical practice (10). Apolipoprotein (Apo), which can bind to free lipids to form lipoproteins and transport lipids through the lymphatic and circulatory systems to regulate lipid metabolism in serum and plasma (11), is closely related to the formation and progression of malignant tumors such as prostate cancer and non-small cell lung cancer (12,13). It is found that ApoC-I and ApoC-III show low expression in gastric cancer (14). Transthyretin (TTR), a liver-derived secreted protein also known as prealbumin, is known for its role in the carrier of thyroid hormone, thyroxine, and triiodothyronine (15), and is used as a biomarker to reflect the nutritional status and disease progression of patients with colorectal cancer (16,17). It is currently recommended to screen for colorectal cancer in patients with gastric cancer since the colorectal and stomach both belong to the digestive system and share synchronized morbidity risk (18). In this study, the expression levels of ApoC-I, TTR and ApoC-III in the serum of patients with gastric cancer were detected by

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Key words: apolipoprotein C-I, transthyretin, apolipoprotein C-III, gastric cancer, diagnostic value

enzyme-linked immunosorbent assay (ELISA), and analysis and discussion were made to investigate the value of ApoC-I, TTR and ApoC-III in diagnosing early gastric cancer.

Patients and methods

Experimental subjects. Retrospective analysis was made of 60 patients with gastric cancer first diagnosed in the First Affiliated Hospital of Jiaxing University (Jiaxing, China) from March 2015 to April 2016. They were enrolled into the gastric cancer group, 60 patients with chronic atrophic gastritis first diagnosed in the same hospital during the same period were enrolled into the benign lesion group, and 60 healthy volunteers in the health service center of the First Affiliated Hospital of Jiaxing University were enrolled into the control group. The gastric cancer group consisted of 39 males and 21 females, aged 25-76 years, with a mean age of 62.58±10.47 years; the benign lesion group consisted of 35 males and 25 females, aged 23-72 years, with a mean age of 41.83±10.84 years; the control group consisted of 36 males and 24 females, aged 21-78 years, with a mean age of 41.63±11.26 years. The general data of the three groups were not statistically different (P>0.05).

Inclusion criteria: i) The gastric cancer group was confirmed by clinical histopathology to meet the diagnostic criteria for gastric cancer (19); ii) the benign lesion group was diagnosed as chronic atrophic gastritis by gastroscopy, CT and X-ray barium meal, and the possibility of gastric cancer was excluded; and iii) the gastric cancer group had not received any radiotherapy or chemotherapy for nearly 6 months, the benign lesion group had not received antibiotics or related treatment ever, and the control group was healthy.

Exclusion criteria: i) Individuals with heart, brain, liver and kidney dysfunction; ii) individuals with coagulation disorders or malignant tumor with the digestive tract and/or other systems; and iii) individuals with severe mental disorders, communication disorders or mental confusion.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Jiaxing University, and all the examinees were explained the experiment contents in detail and then they signed the informed consent.

Experimental methods

Experimental apparatus and reagents. Human APO-C1 ELISA Kit (CSB-E13807h; Cusabio Biotech Co., Ltd., Wuhan, China); Human APO-CIII ELISA Kit (SBJ-H1035; Nanjing SenBeiJia Biological Technology Co., Ltd., Nanjing, China); human TTR ELISA Kit (HZ-TTR-Hu; Shanghai Huzhen Industrial Co., Ltd., Shanghai, China); FLUOstar Omega automatic multi-function microplate reader (FLUOstar Omega; Bio-Gene Technology Ltd., Melbourne, Australia); spectrophotometer (OD-1000+; Shanghai Genesci Medical Technology Co., Ltd., Shanghai, China).

Determination of the concentration of ApoC-I, TTR and ApoC-III in the serum by ELISA. After 8 h, blood samples (3 ml each) were taken in the morning from the patients' elbow venous blood using a vacuum lancet and were placed at room temperature for 2 h. The agglutinated blood samples were then placed in a centrifuge at the speed of 2,900 x g for 15 min. The supernatant was carefully aspirated to obtain serum, which was dispensed and stored in a -80˚C medical refrigerator.

The concentration of ApoC-I, TTR and ApoC-III in the serum samples to be tested was determined by ELISA. First, blank control wells, sample wells and standard wells were set, adding 285 μl of the dilution to the sample wells, then adding 15 μl of the sample, mixed gently, and set the standard wells according to the instructions. The sample wells and standard wells were sealed with the supplied tape and incubated for 2 h at 37˚C. Second, the tape was removed, the liquid was discarded from the reaction wells, and 100 μl of biological antibody (1X) was added to each well; the wells were sealed again and incubated at 37˚C for 1 h. Third, the liquid was discarded from the wells, and then the wells were washed with 200 μl of wash buffer and diluted with distilled water twice for 3 min each time. Fourth, 100 μl of the enzyme labeling reagent in the kit was added to each reaction well except the blank well, and the wells were sealed and incubated at 37˚C for 1 h. Then the washing was repeated 5 times. Fifth, 50 μl of TMB developer was added to each well and the wells were incubated at 37˚C for 30 min in the dark. Finally, 50 μl of the stop solution was added into each well and the liquid in each well was gently mixed to terminate the reaction. A blank well was used as a zero reference value, and the optical density value (OD value) in each reaction well was measured using a spectrophotometer with a wavelength of 450 nm. Then the sample protein concentration was calculated according to the standard curve.

Statistical analysis. The experimental data were statistically analyzed using SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA). The comparison of the enumeration data (%) between groups was performed using Chi-square test. The comparison of measurement data (mean ± SD) between two groups was performed using the t-test, and the comparison between multiple groups was performed using one-way analysis of variance with Least Significant Difference test and the receptor operating characteristic curve (ROC curve). Statistical significance was set at P<0.05.

Results

Expression of ApoC-I, TTR and ApoC-III in the serum of the gastric cancer, benign lesion and control groups. The expression levels of ApoC-I, TTR and ApoC-III in the gastric cancer group, benign lesion group and control group were different from each other (P<0.01), with the expression levels of ApoC-I, TTR and ApoC-III in the gastric cancer group being lower than that of the benign lesion group (P<0.05), and the expression levels of ApoC-I, TTR and ApoC-III in the benign lesion group being lower than that of the control group (P<0.05). Specific data are shown in Table I.

Relationship between the three factors and clinicopathological features of gastric cancer. The expression levels of ApoC-I, TTR and ApoC-III in the gastric cancer group had certain correlation with the clinical stage, lymph node metastasis and differentiation of patients in the gastric cancer group (P<0.05), and no association with patients' sex or age (P>0.05). Specific data are shown in Tables II-IV.

Comparison of diagnostic value. According to the ROC curves of the expression levels of ApoC-I, TTR and ApoC-III

Table I. Comparison of the expression levels of ApoC-I, TTR and ApoC-III in the serum in the three groups.

Items	Gastric cancer group (n=60)	Benign lesion group (n=60)	Control group (n=60)	F-value	P-value
ApoC-I (g/l)	9.53±2.57	12.83±2.52[a]	17.39±6.2[3a,b]	54.160	<0.001
TTR (mg/l)	168.34±26.34	204.48±52.73[a]	253.37±36.47[3a,b]	68.230	<0.001
ApoC-III (g/l)	17.35±3.57	22.72±5.34[a]	30.17±6.27[3a,b]	92.600	<0.001

[a]P<0.05 compared with the gastric cancer group; [b]P<0.05 compared with the benign lesion group. ApoC-I, apolipoprotein C-I; TTR, transthyretin.

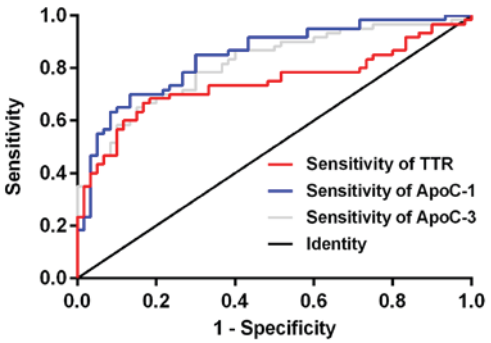


Figure 1. ROC curve of ApoC-I, TTR and ApoC-III in diagnosing gastric cancer. According to the ROC curves of the expression levels of ApoC-I, TTR and ApoC-III in the serum of patients from the gastric cancer group and benign lesion group, the AUC areas of ApoC-I, TTR and ApoC-III were 0.844 (0.775-0.914), 0.743 (0.651-0.836), and 0.814 (0.738-0.891), respectively, the diagnostic critical values were 11.75 g/l, 189.50 mg/l and 21.19 g/l. ApoC-I, apolipoprotein C-I; TTR, transthyretin; ROC, receptor operating characteristic.

Table II. Relationship between ApoC-I and clinicopathological features of gastric cancer (mean ± SD).

Variables	Case	ApoC-I (g/l)	t-test	P-value
Sex			0.340	0.735
Male	39	9.56±2.38		
Female	21	9.34±2.42		
Age			0.223	0.825
≤60 years	32	9.46±2.72		
>60 years	28	9.62±2.84		
Clinical stage			2.331	0.023
I+II stage	36	9.92±3.14		
III+IV stage	24	8.21±2.13		
Lymph node metastasis			2.556	0.013
Without metastasis	42	9.72±3.81		
With metastasis	18	7.28±2.04		
Degree of differentiation			2.440	0.018
High/moderate level	43	10.34±3.73		
Low level	17	8.34±2.45		

ApoC-I, apolipoprotein C-I; TTR, transthyretin.

in the serum of patients from the gastric cancer group and benign lesion group, the AUC areas of ApoC-I, TTR and ApoC-III were 0.844 (0.775-0.914), 0.743 (0.651-0.836) and 0.814 (0.738-0.891), respectively. The diagnostic critical values were 11.75 g/l, 189.50 mg/l and 21.19 g/l (P<0.001), as shown in Fig. 1. The diagnostic critical value was used as a positive indicator to calculate the sensitivity, specificity, diagnostic coincidence rate, positive predictive value and negative predictive value of ApoC-I, TTR, ApoC-III and the combined detection (any of the three indexes at the diagnostic critical value was regarded as positive for the combined detection). The specificity and negative predictive value of combined detection were proven to be higher than the separate detection of the three factors (P<0.05) (Table V).

Discussion

As one of the most common malignant tumors in developing countries, gastric cancer poses a serious threat to human health (20). The survival of patients with gastric cancer at an advanced and moderate stage is generally frustrating and the pain induced by cancer causes a heavy physical and mental burden to patients and their families (21), whereas gastric cancer at an early stage can achieve better long-term clinical efficacy by endoscopic resection (22). So early diagnosis and effective treatment are essential for the survival of patients with gastric cancer.

In recent years, biological markers have played an increasingly important role in the discovery of gastrointestinal malignancies (23). Tumor markers can reflect tumorigenesis or tumor progression, with more than one kind of tumor marker being able to mark one certain tumor. Early detection of tumor markers in serum has important reference significance for early diagnosis, timely treatment and prognosis of the disease (24).

In this study, the expression levels of ApoC-I, TTR and ApoC-III in the serum of patients with gastric cancer were analyzed. The results showed that the expression levels of serum ApoC-I, TTR and ApoC-III in the gastric cancer group were lower than those in the benign lesion group, and levels of serum ApoC-I, TTR and ApoC-III in the benign lesion group were lower than those in the control group, which indicated that ApoC-I, TTR and ApoC-III showed low expression in gastric cancer. After analyzing the serum samples of 103 gastric cancer patients and cancer-free individuals by mass spectrometry, Cohen *et al* (14) found that the identificated peptides were fragments of ApoC-I and ApoC-III, which could be used as the basis for the diagnosis of gastric cancer patients when combined with other clinical indicators. TTR (25) is not only a key indicator for assessing nutritional status, but also a sign of good prognosis for patients with malnutrition. Recent

Table III. Relationship between TTR and clinicopathological features of gastric cancer (mean ± SD).

Variables	Cases	TTR (mg/l)	t-test	P-value
Sex			0.390	0.698
Male	39	169.61±25.13		
Female	21	166.82±28.83		
Age			1.009	0.317
≤60 years	32	162.73±28.14		
>60 years	28	169.72±25.14		
Clinical stage			3.289	0.002
I-II stage	36	183.41±31.35		
III-IV stage	24	158.62±23.83		
Lymph node metastasis			2.358	0.022
Without metastasis	42	171.38±37.72		
With metastasis	18	148.57±24.30		
Degree of differentiation			3.626	0.001
High/moderate level	43	174.83±31.75		
Low level	17	153.32±14.42		

TTR, transthyretin.

Table IV. Relationship between ApoC-III and clinicopathological features of gastric cancer (mean ± SD).

Variables	Cases	ApoC-III (g/l)	t-test	P-value
Sex			0.427	0.671
Male	39	17.63±3.23		
Female	21	17.24±3.63		
Age			0.210	0.835
≤60 years	32	17.42±3.12		
>60 years	28	17.25±3.14		
Clinical stage			2.459	0.017
I-II stage	36	18.72±4.13		
III-IV stage	24	16.25±3.27		
Lymph node metastasis			2.391	0.020
Without metastasis	42	18.54±3.82		
With metastasis	18	16.03±3.49		
Degree of differentiation			2.088	0.041
High/moderate level	43	18.39±3.32		
Low level	17	16.62±2.81		

ApoC-III, apolipoprotein C-III.

research findings (26) indicated that TTR could be used as an independent prognostic risk factor for gastric cancer, which can now provide side verification for the results of this study. The expression levels of ApoC-I, TTR and ApoC-III in the serum of patients with gastric cancer at clinical III/IV stage, lymph node metastasis and high/medium differentiation were higher than those with poorly differentiated gastric cancer at clinical I/II stage and without lymph node metastasis. On the one hand, APOC-I can mediate the proliferation and apoptosis of the cancer cells and regulate the cell cycle by controlling the signal pathways for Survivin, p21 and caspase-3 (27). On the other hand, as important regulators of lipoprotein metabolism in humans, ApoC-I and ApoC-III can delay the clearance of triglycerides in many aspects: ApoC-I can inhibit the binding of lipoproteins to LDL receptors to directly interfere with the uptake of fatty acids; ApoC-III inhibits fat degradation by interfering with the binding of lipoproteins to glycosaminoglycan on the cell surface (28). Literature has shown that patients with gastric cancer have lower serum lipid levels than normal individuals and disordered lipoprotein metabolism. Blood lipids and lipoprotein levels can be used as important indicators to reflect the progression and prognosis of gastric cancer (29), so constant monitoring of the blood lipid levels of gastric cancer patients is of great guiding significance to the prognosis of patients (30). The low expression of ApoC-I and ApoC-III indicates the decrease of the body's ability to degrade triglyceride, the timely degradation of the serum and the decreased blood lipid level, which may reflect the fact that the higher severity of the disease causes a worse prognosis. As mentioned above, TTR is important for the nutritional status of patients. Low expression of TTR often reflects malnutrition

Table V. Comparison of the diagnostic values of ApoC-I, TTR and ApoC-III [n(%)].

Items	Sensitivity	Specificity	Diagnostic coincidence rate	Positive predictive value	Negative predictive value
ApoC-I	86.67 (52/60)[a]	70.00 (42/60)	78.33 (94/120)	74.29 (52/70)	84.00 (42/50)[b]
TTR	81.67 (49/60)[a]	68.33 (41/60)	75.00 (90/120)	72.06 (49/68)	78.85 (41/52)[b]
ApoC-III	83.33 (50/60)[a]	66.67 (40/60)	75.00 (90/120)	71.43 (50/70)	80.00 (40/50)[b]
Combined detection	100.00 (60/60)	53.33 (32/60)	76.67 (92/120)	68.18 (60/88)	100.00 (32/32)

[a]Compared with the combined detection, the sensitivity of ApoC-I was lower (χ^2=8.571, P=0.003), so was the sensitivity of TTR (χ^2=12.110, P=0.001), and the sensitivity of ApoC-III (χ^2=10.910, P=0.001); [b]the negative predictive value of ApoC-I (χ^2=5.674, P=0.017), the negative predictive value of TTR (χ^2=7.789, P=0.005), and the negative predictive value of ApoC-III (χ^2=7.289, P=0.007) were all lower than that of the combined detection. ApoC-I, apolipoprotein C-I; TTR, transthyretin.

in patients (25), which seriously affects the overall survival of patients with gastric cancer (31). The lower the expression level of TTR is, the poorer nutritional status the gastric cancer patient is in, so the low expression of TTR may indicate the severity of the disease progression of gastric cancer. The specificity and negative predictive value of combined detection were proven to be higher than the separate detection of the three factors. It was suggested that ApoC-I, TTR and ApoC-III may be potential biomarkers of gastric cancer, enjoying higher diagnostic value when used for combined detection of gastric cancer. Closely related to the occurrence and development of various malignant tumors such as breast cancer, ApoC-I has a certain anticancer effect on breast tumor cells, and has the ability to inhibit the expression of PCNA, Ki-67 and Bcl-2 proteins, enhance Bax protein expression, and inhibit cell proliferation (32). ApoC-III has been found to be a potential target for the diagnosis and treatment of hepatocellular carcinoma (33), and also a potential biomarker for pancreatic cancer (34). Previous studies have shown that TTR combined with other factors can diagnose the severity of gastric cancer, and can make a supplementary diagnosis of patients with gastroscopy evaluation (35). The prognosis of patients with high expression of TTR in serum is better than the prognosis of patients with low expression of TTR (26). These studies showed that ApoC-I, TTR, ApoC-III were closely related to the occurrence of many malignant tumors, and could be used as potential biomarkers for several tumors, having great reference value in the early diagnosis and treatment of gastric cancer when used in combined detection.

However, this study has shortcomings: the sample size is too small due to the limited experimental conditions, and needs expanding or multi-center research.

In summary, the expression levels of ApoC-I, TTR and ApoC-III in the serum of patients in the gastric cancer group were lower than those of patients in the benign lesion group and healthy volunteers from the control group. The combined detection of serum ApoC-I, TTR and ApoC-III of gastric cancer deserves further study as it can improve the specificity and the positive predictive value of diagnosis, having great significance in diagnosing gastric cancer and concluding the pathological pattern.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MW and JW performed ELISA. MW and HJ collected and analyzed the general data of the patients. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First Affiliated Hospital of Jiaxing University (Jiaxing, China) and written informed consents were signed by the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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