DIAGNOSTIC VALUE OF SERUM CYFRA21-1, VEGF, AFP, CA19-9 AND SCC IN ESOPHAGEAL CANCER

Jing Jiang[1,#], Gang Xiao[2,#], Lu Luo[1], Jing Li[1], Junming Hou[3], Hui Wei[4], Dezhen Yang[5,*]
[1]The Fourth Ward of Cancer Hospital, Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, Xianyang 712000, Shaanxi Province, Shaanxi Province, China - [2]Department of General Surgery, Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, Xianyang 712000, Shaanxi Province, China - [3]Department of Integrated Traditional Chinese and Western Medicine, Shaanxi University of Traditional Chinese Medicine, Xianyang 712000, Shaanxi Province, China - [4]Department of Internal Medicine-Oncology, Cancer Hospital, Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, Xianyang 712000, Shaanxi Province, China - [5]Department of Oncology, Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000
[#]These authors contributed equally to this work as co-first author

ABSTRACT

Objective: *To investigate serum cytokeratin 19 fragments (CYFRA21-1), vascular endothelial growth factor (VEGF), alpha-fetoprotein (AFP), carbohydrate antigen 19-9 (CA19-9), and squamous cell carcinoma antigen (SCC) detection of the diagnosis and clinical value of esophageal cancer.*

Methods: *From April 2015 to April 2019, 92 cases of patients with esophageal cancer admitted to our hospital were selected as esophageal cancer patients. There were 84 cases of benign esophageal disease group and 88 cases of healthy physical examination in the same period as the control group. Comparison of Three groups of serum CYFRA21-1, VEGF, AFP, CA19-9, SCC levels and the above indicators' levels of esophageal cancer patients in different The receiver operating characteristic curve (ROC curve) was used to evaluate the diagnostic value of five indicators and their combined detection for different TNM staging and with or without lymph node metastasis. The receiver operating characteristic curve (ROC curve) was used to evaluate the diagnostic value of five indicators and their combined detection for esophageal cancer. cancer group was higher than those in the benign esophageal disease group and the control group (P<0.05), while the above-mentioned levels of the There was no statistical significance (P>0.05). The serum levels of five serum indicators in patients with stage III~IV esophageal cancer were higher than those in stage I~II. The serum levels of five patients with lymph nodes The ROC curve showed that the area under the curve (AUC), sensitivity, and specificity for the diagnosis of esophageal cancer were CYFRA21-1 of 0.749, 77.2%, 71.4%, VEGF was 0.852, 82.6%, 85.7%, and AFP was 0.631, 63.0%, 67.9%, CA19 -9 was 0.819, 83.7%, 81.0%, SCC was 0.717, 72.8%, 72.6%; and the five combined diagnoses had an AUC of 0.960, a sensitivity of 90.2%.*

Conclusion: *The combined detection of serum CYFRA21-1, VEGF, AFP, CA19-9 and SCC can effectively The combined detection of serum CYFRA21-1, VEGF, AFP, CA19-9 and SCC can effectively diagnose esophageal cancer and evaluate the condition, which provides a basis for clinical diagnosis and treatment.*

Keywords: *Esophageal cancer, cytokeratin 19 fragment, vascular endothelial growth factor, alpha-fetoprotein, carbohydrate antigen 19-9, squamous cell carcinoma antigen.*

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Introduction

Esophageal cancer is a common clinical malignant tumor of the gastrointestinal tract, which has no specific symptoms in the early stage of development and develops in the middle and late stage when diagnosed, with a poor prognosis and a 5-year survival rate of less than 20%[(1)]. Therefore, early diagnosis to control the disease is especially critical to improve the prognosis. Gastroscopy is currently performed in patients with the suspected disease (dysphagia, etc.), but it is invasive and difficult to confirm the diagnosis[(2)]. In recent years, serological indexes have received a lot of attention in the early diagnosis of malignant tumors due to their convenience, rapidity, the possibility of repeated measurements in a short period, and the economy. Cytokeratin 19 fragment (CYFRA21-1),

carbohydrate antigen 19-9 (CA19-9), and squamous cell carcinoma antigen (SCC) are cancer cells SCC is a cellular fragment secreted by cancer cells during proliferation, and studies at[3-4] have found that all three are aberrantly expressed with alpha-fetoprotein (AFP) in gastrointestinal tumors. Vascular endothelial growth factor (VEGF) can be involved in tumor lymphangiogenesis. Although some current studies have investigated the application value of each of the five indicators, there is no conclusion about the combined diagnostic value of the five indicators.

Based on this, this study investigated the diagnostic and clinical value of serum CYFRA21-1, VEGF, AFP, CA19-9, and SCC for esophageal cancer, to provide a reference basis for clinical application. The results are reported as follows.

Data and methods

General information

Ninety-two patients with esophageal cancer admitted to our hospital from April 2015 to April 2019 were selected as the esophageal cancer group.

Inclusion criteria:

• Esophageal cancer confirmed by pathological examination;

• No anti-tumor and immunotherapy before receiving serological index test in this study;

• Age > 18 years.

Exclusion criteria:

• Metastatic esophageal cancer;

• Combined with other malignant tumors;

• Hematological system diseases;

• Serious liver, kidney and other important organ dysfunction;

• Autoimmune diseases;

• Pregnant and lactating women.

• 92 patients, 58 males and 34 females;

• Age 37-76 years, mean (57.69±7.48) years;

• Pathological type: 89 cases of squamous carcinoma and 3 cases of adenocarcinoma;

• Site of origin.

The cervical segment in 12 cases, and upper thoracic segment in 31 cases, a middle thoracic segment in 22 cases, and the lower thoracic segment in 27 cases; degree of differentiation: 44 cases with low differentiation, 27 cases with middle differentiation, and 21 cases with high differentiation; TNM stage: 20 cases in stage I, 32 cases in stage II, 21 cases in stage III, and 19 cases in stage IV. Eighty-four patients with benign esophageal disease admitted at the same time were selected as the benign esophageal disease group, including 53 males and 31 females; ages ranged from 35 to 74 years, with a mean of (56.97±7.35) years; 19 cases of cardiac failure, 9 cases of benign esophageal tumor, 16 cases of the esophageal diverticulum, 27 cases of reflux esophagitis and 13 cases of esophageal hiatal hernia. In addition, 88 cases were selected as the control group, 57 males and 31 females, aged 34-75 years old, with an average of (57.41±7.43) years.

There was no statistically significant difference in the general information of the three groups (P>0.05), which was comparable. The study was approved by the medical ethics committee of the hospital, and all study subjects signed informed consent.

Methodology

Before a treatment or during physical examination, 5 mL of fasting elbow venous blood was collected in the morning, centrifuged at 3000 r/min for 10 min, the serum was separated, and the supernatant was collected and stored at -80 °C for measurement.

The serum levels of CYFRA21-1 and SCC were measured by electrochemiluminescence method and supporting reagents, and the serum levels of VEGF, AFP and CA19-9 were measured by enzyme-linked immunosorbent assay using a Roche Cobas E601 automatic electrochemiluminescence immunoassay. All operations were performed according to the kit instructions.

Statistical analysis

The statistical software SPSS22.0 was used to process the data, and the count data were expressed as (n, %), and the χ^2 test was performed.

The diagnostic value was assessed using the receiver operator characteristic curve (ROC curve), and the area under the curve (AUC) of 0.5~0.7 had low diagnostic accuracy, 0.7~0.9 had some accuracy, and >0.9 had higher accuracy[5]. P<0.05 was considered a statistically significant difference.

Results

Comparison of serum CYFRA21-1, VEGF, AFP, CA19-9 and SCC levels in the three groups

The serum CYFRA21-1, VEGF, AFP, CA19-9, and SCC levels in the esophageal cancer group were higher than those in the benign esophageal disease group and the control group, and the differences were statistically significant (P<0.05), while none of the

above levels in the benign esophageal disease group compared with the control group were statistically significant (P>0.05). See Table 1.

Group	*n*	CYFRA21-1 (μg/L)	VEGF (pg/mL)	AFP (ng/L)	CA19-9 (U/mL)	SCC (μg/L)
Esophageal cancer group	92	4.45±1.58*#	177.62± 39.72*#	6.21± 2.14*#	46.07± 12.14*#	1.43± 0.61*#
Benign esophageal disease group	84	2.89±1.60	113.99± 35.89	5.06± 2.07	29.42± 12.26	0.83± 0.42
Control group	88	2.51±0.96	107.24± 19.83	4.77± 1.24	26.48± 6.59	0.69± 0.25
F-value		47.319	124.566	14.930	88.448	50.130
P-value		<0.001	<0.001	<0.001	<0.001	<0.001

Table 1: Comparison of serum CYFRA21-1, VEGF, AFP, CA19-9 and SCC levels in the three groups.
*Note: Compared with the control group, *P<0.05; compared with the group with the benign esophageal disease, #P<0.05.*

Comparison of serum CYFRA21-1, VEGF, AFP, CA19-9 and SCC levels in esophageal cancer patients with different TNM stages

Serum CYFRA21-1, VEGF, AFP, CA19-9, and SCC levels were higher in patients with stage III-IV esophageal cancer than in patients with stage I-II, and the differences were statistically significant (P<0.05). See Table 2.

TNM Staging	Number of cases	CYFRA21-1 (μg/L)	VEGF (pg/mL)	AFP (ng/L)	CA19-9 (U/mL)	SCC (μg/L)
Phase I~II	52	3.70± 1.05	155.06± 28.74	5.69± 2.41	40.29± 8.74	1.18± 0.42
III~IV stage	40	5.42± 1.63	206.95± 45.87	6.89± 2.87	53.58± 9.27	1.75± 0.81
t-value		6.137	6.642	2.178	7.042	4.372
P-value		<0.001	<0.001	0.032	<0.001	<0.001

Table 2: Comparison of serum index levels of esophageal cancer patients with different TNM stages.

Comparison of serum CYFRA21-1, VEGF, AFP, CA19-9 and SCC levels in esophageal cancer patients with and without lymph node metastasis

Serum CYFRA21-1, VEGF, AFP, CA19-9, and SCC levels were higher in esophageal cancer patients with lymph node metastasis than in patients without lymph node metastasis, and the difference was statistically significant (P<0.05). See Table 3.

Diagnostic value of serum CYFRA21-1, VEGF, AFP, CA19-9 and SCC for esophageal cancer

The ROC curves showed that the AUCs of serum CYFRA21-1, VEGF, AFP, CA19-9, and SCC for diagnosing esophageal cancer were 0.749, 0.852, 0.631, 0.819, and 0.717, respectively, with AFP having relatively low diagnostic accuracy; the maximum cut point of the Yordon index was used as the optimal threshold, and the diagnostic sensitivity and specificity at this point were. 77.2% and 71.4% for CYFRA21-1, 82.6% and 85.7% for VEGF, 63.0% and 67.9% for AFP, 83.7% and 81.0% for CA19-9, and 72.8% and 72.6% for SCC, which have some diagnostic value.

The above five indicators were included in the logistic regression model, and the calculation model of the five-indicator combination was fitted according to the regression coefficients: five-indicator combination = CYFRA21-1+0.036/0.892 * VEGF+0.178/0.892 * AFP+0.092/0.892 * CA19-9+1.307/0.892 * SCC, which was analyzed by The ROC curve showed that the AUC of the combined diagnosis of the five items was 0.960, with a sensitivity of 90.2% and specificity of 91.7%, which was higher than that of the individual tests of each index, suggesting that the combined test could improve the diagnostic value of esophageal cancer. See Table 4 and Figure 1.

Projects	Number of cases	CYFRA21-1 (μg/L)	VEGF (pg/mL)	AFP (ng/L)	CA19-9 (U/mL)	SCC (μg/L)
With lymph node metastasis	28	5.76± 1.78	214.31± 49.17	7.34± 2.83	58.92± 9.71	1.92± 0.99
No lymph node metastasis	64	3.88± 1.24	161.57± 36.42	5.72± 2.29	40.45± 8.54	1.22± 0.65
t-value		5.828	5.724	2.901	9.152	4.023
P-value		<0.001	<0.001	0.005	<0.001	<0.001

Table 3: Comparison of serum index levels in patients with esophageal cancer with and without lymph node metastasis.

Inspection items	AUC	Standard error	Asymptotic significance level	95% Confidence interval		Optimal threshold	Sensitivity	Specificity	Yoden Index
				Lower limit value	Upper limit value				
CYFRA21-1	0.749	0.038	<0.001	0.675	0.823	3.650	0.772	0.714	0.486
VEGF	0.852	0.031	<0.001	0.792	0.912	133.31	0.826	0.857	0.683
AFP	0.631	0.043	0.003	0.548	0.715	6.315	0.630	0.679	0.309
CA19-9	0.819	0.034	<0.001	0.752	0.886	33.59	0.837	0.810	0.647
SCC	0.717	0.040	<0.001	0.639	0.794	1.385	0.728	0.726	0.454
Five joint	0.960	0.015	<0.001	0.931	0.989	16.2015	0.902	0.917	0.819

Table 4: Diagnostic value of serum CYFRA21-1, VEGF, AFP, CA19-9, SCC and the combination of the five tests for esophageal cancer.

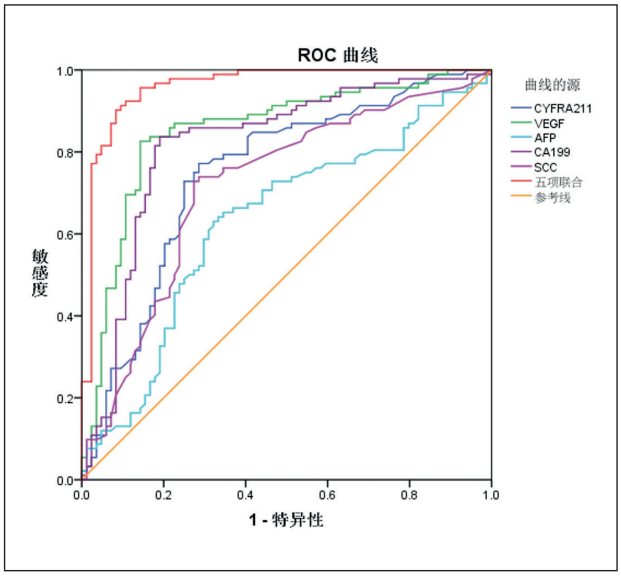

Figure 1: ROC curves of serum CYFRA21-1, VEGF, AFP, CA19-9, SCC and the combination of five items for the diagnosis of esophageal cancer.

Discussion

CYFRA21-1 is an important molecular structure of the cytoskeleton. Under normal physiological conditions, the expression of CYFRA21-1 in peripheral blood is low; when cells become cancerous, activation of proteases will accelerate the degradation of cytokeratin, generating a large amount of soluble CYFRA21-1 and releasing it into the blood, causing an increase in CYFRA21-1 expression in blood[6-7]. CA19-9 is a member of the glycoprotein superfamily. CA19-9 is a member of the glycoprotein superfamily with low levels in normal esophageal tissues. However, related studies have shown that CA19-9 expression is also abnormally elevated in esophageal cancer[8]. SCC is a glycoprotein fragment, mostly found in cancerous tissues of the pharynx and esophagus, and is a specific antigen for squamous cells, which is used as a marker for squamous cancer.

Data show that the altered expression of SCC is closely related to the tissue activity of esophageal cancer cells, and its positive rate increases with disease progression[9-10]. VEGF is a pro-angiogenic factor, which can promote angiogenesis, accelerate cancer cell proliferation, and promote cancer cell invasion and metastasis. Current studies have shown that VEGF is relatively highly expressed in esophageal cancer tissues, involved in tumorigenesis and associated with lymph node metastasis[11-12]. AFP is a glycoprotein belonging to the albumin family, which is mainly used clinically for diagnosis and efficacy assessment of hepatocellular carcinoma, but it is widely expressed and has been studied[13] as a positive monitoring indicator for many GI tumors.

This study showed that serum CYFRA21-1, VEGF, AFP, CA19-9, and SCC levels were higher in the esophageal cancer group than in the benign esophageal disease group and the control group. It was suggested that the five were relatively highly expressed in esophageal cancer patients and involved in the pathogenesis of the disease.

It is considered to be mainly related to the release of the above factors into the blood circulation during the abnormal differentiation and proliferation of tumor cells, such as intracellular skeletal components and metabolites of cell membrane fragments[14-15]. Lymph node metastasis is an important way for tumor cells to metastasize and is also a risk factor for recurrence of metastasis and death of patients after surgical treatment[16]. Lymph node metastasis can appear in the early stage of esophageal cancer, but the delay in diagnosis due to the lack of specific symptoms in the early stage is detrimental to the prognosis of patients. Therefore, the search for specific indicators to assess the condition of esophageal cancer has become a hot topic of research. In this study, the serum levels of CYFRA21-1, VEGF, AFP, CA19-9 and SCC were higher in patients with stage III-IV esophageal cancer than in patients with stage I-II cancer.

The ROC curve analysis showed that the AUC, sensitivity and specificity of the five indices for a single diagnosis of esophageal cancer were not high, especially the diagnostic efficacy of AFP was low; while the AUC of the combined diagnosis of the five indices was 0.960, sensitivity 90.2% and specificity 91.7%, which was higher than that of The AUC of the combined test was 0.960, with a sensitivity of 90.2% and specificity of 91.7%, which was higher than the single test of each index.

This suggests that the combined test can improve the diagnostic value of esophageal cancer. The analysis is that the combined test of multiple indices can avoid the risk of missing diagnosis due to the insensitivity of single indices, make up for the shortcomings of single diagnosis, improve the quick and accurate diagnosis, and promote the early detection and diagnosis of esophageal cancer. However, some studies[17] showed that AFP has no significant diagnostic value for esophageal cancer, which is related to the different considerations of this study with the sample size, study population, individual patient differences and other factors.

The study by Jinxian He et al.[18] showed that AFP levels and positive rates were significantly higher in patients with esophageal cancer compared with healthy patients and that its combination with tumor markers such as CA19-9 could improve the diagnostic accuracy of esophageal cancer.

Another foreign study showed that elevated and positive AFP expression was associated with esophageal adenocarcinoma development, metastasis, and carcinoma in the lower esophagus[19-20]. It indicates that AFP can be used in the diagnosis and evaluation of primary liver cancer, but also combined with CYFRA21-1, VEGF, CA19-9 and SCC for the early adjuvant diagnosis of esophageal cancer.

In conclusion, the combined test of serum CYFRA21-1, VEGF, AFP, CA19-9, and SCC can effectively diagnose esophageal cancer and evaluate the disease, providing a basis for clinical diagnosis and treatment. The inadequacy of this study is the sample size limitation, which may affect the generalizability of the results, and will be further tested in a large sample and multicenter study in the future.

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Corresponding Author:
Dezhen Yang
No. 2, Weiyang West Road, Qindu District, Xianyang City, Shaanxi Province, China
Email: 258131990@qq.com
(China)