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Diagnostic Value of VEGF, CA 19-9, and CEA in Pancreatic Cancer and Risk Factors of Vascular Invasion

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Abstract: *Background:* Pancreatic cancer is a malignant tumor of the gastrointestinal tract. Due to its insidious onset, most patients with newly diagnosed pancreatic cancer have missed the opportunity for radical surgery, which offers patients the best chance of survival. The 5-year survival rate of patients with pancreatic cancer can be improved with early diagnosis, and serum tumor makers are an inexpensive and convenient diagnostic tool that is widely used in the diagnosis of malignancies. *Objective:* To determine the diagnostic value of vascular endothelial growth factor (VEGF), carbohydrate antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA) in patients with pancreatic cancer and the risk factors of vascular invasion. *Methods:* An experimental group comprising 52 patients with pancreatic cancer admitted to our department from July 2021 to July 2022 and a control group comprising 21 patients with benign pancreatic diseases during the same period were included in our study. Their serum VEGF, CA 19-9, and CEA levels were detected and compared between the two groups, and the correlation between the three markers in the invaded vessel and non-invaded vessel groups was investigated. The diagnostic value of a single tumor marker and in combination for pancreatic cancer was analyzed, and the three tumor marker levels of the experimental group in different pathological characteristics were detected and compared. *Results:* The experimental group had higher serum VEGF, CA 19-9, and CEA levels than the control group ($P < 0.05$). Through a receiver operating characteristic (ROC) curve analysis, the combined detection had the highest value for the diagnosis of pancreatic cancer, in which the area under the curve (AUC) was 0.9158 (95% CI: 0.8415–0.9900), while the sensitivity and specificity were 76.19% and 98.08%, respectively. Serum VEGF and CA 19-9 levels were higher in stage III–IV pancreatic cancer patients and those with tumor metastasis compared with stage I–II patients and those without metastasis ($P < 0.05$), respectively. Binary logistic regression analysis was performed to determine the risk factors of vascular invasion in pancreatic cancer, and the results showed that only serum VEGF was a risk factor ($P < 0.05$), OR (95% CI): 1.001–1.006. *Conclusion:* Patients with pancreatic cancer have significantly higher serum VEGF, CA 19-9, and CEA levels, and the combined detection of tumor markers is of high clinical value in its diagnosis. In addition, serum VEGF is an independent risk factor of vascular invasion in pancreatic cancer, which can predict vascular invasion to a certain extent.

Keywords: Pancreatic cancer; Tumor markers; Vascular endothelial growth factor; Carcinoembryonic antigen; Carbohydrate antigen 19-9

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1. Introduction

Pancreatic cancer is a common but highly malignant digestive tract tumor. There are 216,000 new cases of pancreatic cancer worldwide each year, with the number of deaths exceeding 200,000 per year [1]. Although

complete resection of the primary lesion offers patients with localized pancreatic cancer the best chance of survival in the long run, 80% of newly diagnosed pancreatic cancer patients have missed the best opportunity for radical surgery because of its insidious onset [2]. Hence, patients with pancreatic cancer are known to have poor prognosis, of which the 5-year survival rate is only about 8% [3,4]. However, with early diagnosis and active and effective treatment, the 5-year survival rate of patients can be improved to a certain extent. Therefore, looking for an effective diagnostic method is of great significance for improving the diagnostic rate of pancreatic cancer and prolonging the survival period. Serum tumor markers are an inexpensive and convenient diagnostic tool that is widely used in the diagnosis of various malignant tumors, including pancreatic cancer [5,6]. However, due to the difficulty of early diagnosis by single CA 19-9 detection, new tumor markers are needed [7]. Based on this, we explored the diagnostic value of vascular endothelial growth factor (VEGF), carbohydrate antigen 19-9 (CA 19-9), and carcinoembryonic antigen (CEA) in patients with pancreatic cancer as well as the risk factors of vascular invasion in pancreatic cancer.

2. Materials and methods

2.1. Baseline data

From July 2021 to July 2022, 52 patients diagnosed with pancreatic cancer and confirmed by histological examination were recruited into the experimental group, while 21 patients with benign pancreatic diseases during the same period were recruited into the control group. The experimental group consisted of 22 female and 30 male patients, age ranging from 38 to 88, with an average age of 64.10 ± 10.50 years; the patients were divided into the invaded vessel group (20 patients) and the non-invaded vessel group (32 patients); tumor location: 35 cases in the head and neck, and 17 cases in the body and tail; tumor diameter: 1.2–8.3 cm (average: 3.16 ± 1.39 cm), with 23 cases < 3 cm, and 29 cases ≥ 3cm; TNM staging: 24 cases in stage I–II, and 28 cases in stage III–IV; metastatic status: 30 cases with metastasis, and 22 cases without metastasis. The control group consisted of 14 female and 7 male patients, age ranging from 25 to 86, with an average age of 60.48 ± 17.38 years. The difference between the two groups was not statistically significant ($P > 0.05$).

2.2. Methods

The collection and processing of serum samples were as follows: 5 mL of fasting morning venous blood was collected from the patients following admission and centrifuged at 3000 r/min for 10 min to separate the serum; VEGF levels were detected using a chemiluminescence instrument and related kits (purchased from Shandong Kanghua Biomedical Technology Co., Ltd.); CA 19-9 and CEA levels were also detected using a chemiluminescence instrument and related kits (purchased from Roche Company). All operations were completed in strict accordance with relevant standards.

2.3. Observation indicators and judgment criteria

Serum VEGF, CA 19-9, and CEA levels were compared between the two groups, and the relationship between the three tumor marker levels and the pathological characteristics of the pancreatic cancer patients was analyzed. Receiver operating characteristic (ROC) curves were used to evaluate the predictive value of VEGF, CA 19-9, and CEA for the diagnosis of patients with pancreatic tumors. The reference values of the three tumor markers were as follows: VEGF > 160.00 pg/mL; CA 19-9 > 27.00 U/mL; CEA > 5.20 ng/mL.

2.4. Statistical analysis

The measurement data (VEGF, CA 19-9, and CEA) were tested by paired or independent sample t-test with SPSS 26.0 and expressed as $\bar{x}$ ± s. The ROC curves were used to analyze the diagnostic value of VEGF,

CA 19-9, and CEA in pancreatic cancer, the area under the curve (AUC), 95% confidence index (CI), cut-off value, sensitivity, specificity, *etc*.; binary logistic regression fitting was performed for joint prediction; the return prediction probability logit (p) was obtained and used as an independent test variable for ROC analysis; ROC curves was drawn using GraphPad Prism 9 and used to analyze the predictive value charts of different tumor markers alone and in combination. Binary logistic regression analysis was performed to explore whether the different factors were risk factors for vascular invasion. $P < 0.05$ indicated statistically significant difference.

3. Results

3.1. Comparison of serum VEGF, CA 19-9, and CEA levels between the two groups

The serum VEGF, CA 19-9, and CEA levels of the experimental group were higher than those of the control group, all $P < 0.05$ (see **Table 1**).

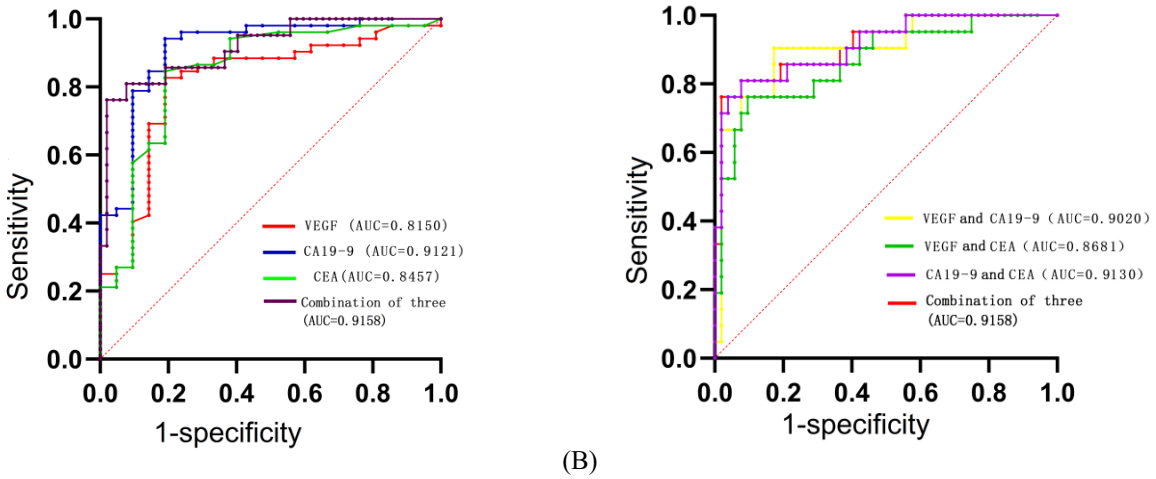
Table 1. Comparison of serum VEGF, CA 19-9, and CEA levels between the two groups ($\bar{x} \pm s$)

Group	Number	VEGF (pg/mL)	CA 19-9 (U/mL)	CEA (ng/mL)
Control group	21	179.03 ± 64.85	55.09 ± 30.59	2.05 ± 0.48
Experimental group	52	662.89 ± 78.90	960.53 ± 210.16	7.74 ± 1.54
t-value	–	4.738	4.263	3.519
P-value	–	0.000	0.000	0.001

Abbreviations: CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; VEGF, vascular endothelial growth factor.

3.2. Value analysis of VEGF, CA 19-9, and CEA levels in the diagnosis of patients with pancreatic cancer

Through ROC curve analysis, the combined detection of VEGF, CA 19-9, and CEA showed the highest value in the diagnosis of pancreatic cancer (**Figure 1**). The AUC was 0.9158; 95% CI: 0.8415–0.9900; sensitivity and specificity were 76.19% and 98.08%, respectively. Although the AUC value of CA 19-9 detection alone was high, its specificity was only 80.95%, which is far inferior to the combined detection of three tumor markers.



(A) (B)

Figure 1. ROC curves of VEGF, CA 19-9, and CEA in the diagnosis of patients with pancreatic cancer. (A) Single detection and combined detection. (B) Pairwise joint detection and combined detection. Abbreviations: AUC, area under the curve; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ROC, receiver operating characteristic; VEGF, vascular endothelial growth factor.

3.3. Relationship between serum VEGF, CA 19-9, and CEA levels and pathological characteristics of patients with pancreatic cancer

The serum VEGF and CA 19-9 levels in stage III–IV pancreatic cancer patients were higher than those in stage I–II patients (both $P < 0.05$); the serum VEGF and CA 19-9 levels in patients with tumor metastasis were similar with those without tumor metastasis (both $P < 0.05$), see **Table 2**.

Table 2. Relationship between serum VEGF, CA 19-9, and CEA levels and the pathological characteristics of patients with pancreatic cancer ($\bar{x} \pm s$)

Pathological characteristics	Classification	Number	VEGF (pg/mL)	CA 19-9 (U/mL)	CEA (ng/mL)
Age	< 60	18	675.94 ± 166.50	918.14 ± 381.55	5.41 ± 2.37
	≥ 60	34	655.98 ± 84.55	982.98 ± 254.26	8.98 ± 1.99
Gender	male	30	666.69 ± 131.92	1,088.73 ± 309.97	6.25 ± 1.54
	Female	22	660.11 ± 98.66	785.71 ± 264.74	9.77 ± 2.99
Tumor location	Neck	35	647.81 ± 91.64	860.72 ± 254.32	7.19 ± 1.44
	Body and tail	17	693.95 ± 154.46	1,166.04 ± 379.13	8.89 ± 3.75
Tumor diameter (cm)	< 3	23	644.07 ± 129.99	957.58 ± 394.92	4.01 ± 0.76
	≥ 3	29	677.82 ± 98.91	962.88 ± 216.95	10.70 ± 2.59
Staging	I–II	24	419.49 ± 90.25	277.41 ± 88.17	5.98 ± 2.20
	III–IV	28	875.81 ± 110.68*	1,546.07 ± 348.93*	9.25 ± 2.16
Metastasis	Metastasis	30	846.9 ± 106.33	1,466.23 ± 330.35	8.92 ± 2.02
	No metastasis	22	413.10 ± 96.38*	270.96 ± 93.70*	6.14 ± 2.40

Note: Comparing stage III–IV with stage I–II and between the metastasis group and no metastasis group, there were significant differences, *$P < 0.05$. Abbreviations: CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; VEGF, vascular endothelial growth factor.

3.4. Analysis of the risk factors related to vascular invasion

Binary logistic regression analysis was performed to determine whether gender, age, tumor location, and serum CA 19-9, CEA, and VEGF are risk factors for vascular invasion in pancreatic cancer. The results showed that only serum VEGF is a risk factor, $P < 0.05$, OR (95% CI): 1.001–1.006 (**Table 3**), indicating that the higher the VEGF level in patients with pancreatic cancer, the higher the possibility of vascular invasion.

Table 3. Relationship between different factors and vascular invasion in pancreatic cancer

Factor	*P*	OR (95%CI)
Gender	0.811	–
Age	0.328	–
Tumor location	0.372	–
CA 19-9	0.943	–
CEA	0.242	–
VEGF	0.006	1.001–1.006

Abbreviations: CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; VEGF, vascular endothelial growth factor.

4. Discussion

A timely and accurate diagnosis of pancreatic cancer is crucial for the prognosis of patients. However, there are very few noticeable symptoms in the early stage of pancreatic cancer. Due to its insidious onset, pancreatic cancer is often discovered at an advanced stage and thus cannot be surgically removed. Therefore, making an early diagnosis is the focus for improving the treatment effect and prognosis of pancreatic cancer. The detection of serum tumor markers is a non-invasive method that is used clinically to detect various malignant tumors. Although CA 19-9 is the most common serum marker used for diagnosing pancreatic cancer and the only diagnostic marker approved by the Food and Drug Administration (FDA), its diagnostic value is limited due to its poor sensitivity and specificity [8]. However, combining CA 19-9 with other markers can improve the diagnostic accuracy. Studies have shown that 80% of patients with advanced pancreatic cancer have elevated levels of CA 19-9 [7] but up to 40% of patients with chronic pancreatitis also have elevated levels of CA 19-9 [9], indicating that patients with pancreatic cancer cannot be reliably distinguish from those with other pancreatic conditions based on CA 19-9 levels. VEGF, which is now called VEGF-A, is a member of a protein family that also includes VEGF-B, VEGF-C, VEGF-D, VEGF-E (encoded by viruses), and placenta growth factor (PlGF). Given the dominant role VEGF-A plays in regulating angiogenesis and disease, it is referred to as VEGF. VEGF is overexpressed in most malignant tumors and plays an important role in angiogenesis [10,11]. CEA, on the other hand, is one of the most widely recognized tumor markers in clinical practice. CEA is a stable molecule, which is often seen at extremely low levels in the blood of healthy people but highly expressed in tumors [12]. It is non-specific and is often combined with other tumor markers to make a diagnosis since CEA detection test alone has low sensitivity.

This study showed that the experimental group had higher serum VEGF, CA 19-9, and CEA levels than the control group. This indicates that the three tumor markers may provide some guidance in the diagnosis of pancreatic cancer. In addition, serum VEGF was found to be an independent risk factor for vascular invasion in this study, indicating that the higher the serum VEGF level in patients with pancreatic cancer, the greater the possibility of vascular invasion. This may provide some guidance in imaging judgment and preoperative surgical planning. Angiogenesis is a key process in tumor progression. Newly formed blood vessels provide tumors with nutrients and oxygen, thus helping them grow. Studies have shown that the endothelial cells in neovascularization play a role in promoting tumor metastasis, allowing the translocation of invasive cancer cells into the lumen of blood vessels [13]. VEGF plays a dominant role in regulating angiogenesis, which may be the reason that serum VEGF is a risk factor for vascular invasion. According to the ROC curve, it was found that the combined detection of VEGF, CA 19-9, and CEA had the highest value in predicting malignancy in patients with pancreatic tumors, suggesting that the combined detection of the aforementioned markers has high specificity, which can significantly reduce misdiagnosis and missed diagnosis as well as improve the diagnostic value. In addition, this study showed that stage III–IV patients and those with tumor metastasis had higher serum VEGF and CA 19-9 levels compared to stage I–II patients and those without tumor metastasis, respectively.

In conclusion, patients with pancreatic cancer have significantly higher serum VEGF, CA 19-9, and CEA levels, and the combined detection of these three tumor markers is of high clinical value in the diagnosis of pancreatic cancer. In addition, VEGF provides a certain basis for reference in preoperative and intraoperative judgment of vascular invasion in pancreatic cancer.

Disclosure statement

The authors declare no conflict of interest.

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