Cellular and Molecular Biology

Journal homepage: www.cellmolbiol.org

Analysis of levels and Clinical value of CA19-9, NLR and SIRI in patients with Pancreatic Cancer with different Clinical Features

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ARTICLE INFO

Original paper

Article history:
Received: July 29, 2021
Accepted: October 25, 2021
Published: December 15, 2021

Keywords:
pancreatic cancer; serum cancer antigen 19-9; peripheral blood neutrophil/lymphocyte ratio; systemic immune-inflammatory index; clinical value

ABSTRACT

This study aimed to investigate the levels of cancer antigen 19-9 (CA19-9), neutrophil/lymphocyte ratio (NLR) and systemic immune-inflammatory index (SIRI) in patients with pancreatic cancer with different clinical features and their clinical value. For this purpose, 78 patients with pancreatic cancer treated in our hospital from January 2018 to January 2021 were divided into two groups according to the NLR and SIRI calculated by blood routine and biochemical examination before operation. To observe and analyze the relationship between serum CA19-19 levels, clinical features and NLR and SIRI values in patients with different clinical stages and tumor diameter, and the diagnostic value of CA19-9, NLR and SIRI in pancreatic cancer. The results showed that the level of serum CA19-9 in patients with stage IV pancreatic cancer was significantly higher than that in patients with stage I, II and III, and the level of CA19-9 in patients with stage III was higher than that in patients with stage I and II, and the level of CA19-9 in patients with stage II was higher than that in patients with stage I. The level of CA19-9 in patients with pancreatic cancer with tumor diameter ≥ 5cm was significantly higher than that in patients with tumor diameter < 5cm. The percentage of patients with age ≤ 60 years old in high NLR group (83.78%) was significantly higher than that in low NLR group (63.41%), and the rate of patients with tumor diameter ≥ 5cm in the high SIRI group (54.05%) was significantly higher than that in low NLR group (26.83%). The rate of patients with tumor diameter ≥ 5cm in the high SIRI group (61.92%) was significantly higher than that in the low SIRI group (31.58%). Among the single indexes, the sensitivity of CA19-9 in the diagnosis of pancreatic cancer was the highest (93.10%). The specificity of Siri in the diagnosis of pancreatic cancer was 89.70%. The sensitivity and specificity of combined detection were 89.7% and 70.00%, respectively. In general, the level of serum CA19-9 in patients with pancreatic cancer increases gradually with the increase of clinical stage and tumor diameter. NLR value is related to patient age and tumor diameter, and SIRI value is related to tumor diameter. Combined detection of CA19-9, NLR and SIRI are of higher value in the early diagnosis of pancreatic cancer.

DOI: http://dx.doi.org/10.14715/cmb/2021.67.4.41

Introduction

Pancreatic cancer is a common malignant tumor in the clinic (1). Foreign investigation results show that pancreatic cancer ranks fourth in tumor mortality and is the digestive system tumor with the worst prognosis (2). Due to the absence of special clinical manifestations in the early stage of pancreatic cancer, the disease has reached the middle and late stage when most patients are diagnosed clinically, and only 15%~20% of patients can be treated with surgical resection, and about 50% of patients can be complicated with distant metastasis (3). The incidence of pancreatic cancer is related to genetic and environmental factors (4). Previous studies have shown that chronic pancreatitis, family inheritance and smoking can increase the risk of pancreatic cancer (5, 6). In addition, Fernandez et al. (7) have shown that diabetes and obesity are closely related to the occurrence of pancreatic cancer and may be risk factors for the occurrence of pancreatic cancer. At present, the clinical diagnosis of pancreatic cancer is mainly through imaging examination and pathological examination. The former has certain requirements for tumor growth, while the latter can cause damage to the patient's body, both of which have certain defects. Tumor markers are substances released into the blood by tumor cells that can reflect the progression of a patient's disease. Among them, serum cancer antigen

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19-9 (CA19-9) is a common indicator for early diagnosis, disease evaluation and prognosis of tumors. Neutrophil/lymphocyte ratio (NLR) is a common indicator of inflammation, which is related to the prognosis of gastric cancer, liver cancer and other digestive system tumors (8, 9). Studies have shown that preoperative CA19-9 and platelet-to-lymphocyte ratio (PLR) are independent factors for predicting the carcinogenesis risk of intraductal papillary mucinous tumors of the pancreas, and the combined application of CA19-9 and PLR has better efficacy (10). In recent years, some scholars proposed the concept of systemic immune-inflammation index (SIRI) based on the role of neutrophil, lymphocyte and platelet count in inflammatory response. Studies have shown that SIRI is an independent prognostic factor available for patients with pancreatic ductal carcinoma before surgery, and can be used as an indicator to predict the overall survival of patients after Whipple (11-14). At present, there are few clinical studies on the expression of CA19-9, NLR and SIRI in pancreatic cancer patients with different clinical characteristics (15). This study observed and analyzed the levels of CA19-9, NLR and SIRI and their clinical value in patients with pancreatic cancer with different clinical characteristics. Details are as follows.

Materials and methods

General Information

A total of 78 patients with pancreatic cancer admitted to our hospital from January 2018 to January 2021 were selected. The study was approved by the hospital Ethics Committee. There were 47 males and 31 females aged 33-73 years, with an average age of (47.86±10.33) years. A total of 80 healthy people, 52 males and 28 females, aged from 29 to 69 years old, with an average age of (45.76±12.99) years old, were collected from our hospital at the same time. There was no statistical difference in gender and age between the two groups ($P > 0.05$). Pancreatic body tail tumor in 24 cases, pancreatic head tumor in 54 cases; Hermreck pathological stages were used, including stage I in 20 cases, stage II in 23 cases, stage III in 27 cases and stage IV in 8 cases. There were 35 patients with tumor diameter ≥5cm, and 43 patients with tumor diameter < 5cm.

Inclusion and exclusion criteria

Inclusion criteria were meeting the diagnostic criteria in guidelines for the diagnosis and treatment of pancreatic cancer (16), and diagnosed as pancreatic cancer after imaging and pathological examination. All patients underwent radical resection of pancreatic cancer and patients and their families were informed of the study and voluntarily signed informed consent.

Exclusion criteria included patients with serious dysfunction of the heart, liver and kidney, patients with immune or coagulation dysfunction, complicated with other malignant tumors, digestive system inflammation and digestive tract malformation, and patients with mental illness.

Detection Method

3mL of fasting venous blood was collected from all patients in the morning before surgery, placed in a 5mL centrifuge tube at room temperature for 30min and centrifuged at 3000r/min for 5min. The upper serum was taken and stored at -80°C for testing. The experiment is performed by professional inspectors according to the instrument and reagent instructions. Serum CA19-9 levels were detected by electrochemiluminescence and Dx1800 automatic chemiluminescence immune analyzer (BECKMAN COULTER) was used.

NLR and SIRI were calculated based on the neutrophil count, lymphocyte count, and platelet count in routine blood tests, SIRI= platelet count × neutrophil/lymphocyte. NLR≥2.4 was considered as a high NLR group, and NLR < 2.4 was considered as a low NLR group. SIRI > 1.27 was considered as the high SIRI group, and SIRI≤1.27 was considered as the low SIRI group.

Observation Indicators

The serum CA19-9 levels of patients with different pathological stages and tumor diameters were observed, and the relationship between clinical characteristics and NLR and SIRI values were observed to analyze the diagnostic value of CA19-9, NLR and SIRI in pancreatic cancer.

Statistical methods

SPSS23.0 statistical software was used for data analysis, in which count data was represented by (%) or (n), X2 test was used, measurement data was

represented by (± S), an inter-group comparison was performed by T test, and P<0.05 was considered statistically significant.

Results and discussion

Comparison of serum CA19-9 levels in patients with different pathological stages and tumor diameters

The level of serum CA19-9 in patients with stage IV was significantly higher than that in patients with stage I, II and III, and the level of serum CA19-9 in patients with stage III was significantly higher than that in patients with stage I and II, and the level of serum CA19-9 in patients with stage II was higher than that in patients with stage I, with statistical significance (P<0.05). The level of CA19-9 in pancreatic cancer patients with tumor diameter ≥5cm was significantly higher than that in patients with tumor diameter < 5cm, the difference was statistically significant (P<0.05). See Table 1 for details.

Table 1. Comparison of serum CA19-9 levels in patients with different pathological stages and tumor diameter (x±s, U/mL)

Pathological stage and tumor diameter		CA19-9 (U/mL)	*F/t*	*P*
The pathological staging	I	197.22±143.44	13.524	0.023
	II	823.28±324.61		
	III	1072.22±679.35		
	IV	1138.05±936.67		
Tumor diameter	≥5cm	997.57±342.24	14.614	0.006
	<5cm	311.62±92.85		

Relationship between clinical characteristics of patients and NLR

There were no significant differences in gender, tumor site, clinical stage and differentiation degree between the high NLR group and the low NLR group (P>0.05). The proportion of patients aged ≤60 years in the high NLR group (83.78%) was significantly higher than that in the low NLR group (63.41%), and the proportion of patients with tumor diameter ≥5cm (54.05%) was significantly higher than that in the low NLR group (26.83%), with statistically significant differences (P<0.05), as shown in Table 2.

Relationship between patient clinical features and SIRI

There were no significant differences in gender, age, tumor site, clinical stage and differentiation degree between the high SIRI group and the low SIRI group (P>0.05). The proportion of patients with tumor diameter ≥5cm in the high SIRI group (61.92%) was significantly higher than that in the low SIRI group (31.58%), and the difference was statistically significant (P<0.05), as shown in Table 3.

Table 2. Relationship between clinical characteristics and NLR of patients (n, %); Gender (A), Age (B), Tumor diameter (C), Tumor site (D), Clinical staging (E), The degree of differentiation (F)

Clinical features		Low NLR group (n=41)	High NLR group (n=37)	χ^2	P
A	Male	24 (58.54)	23 (62.16)	0.634	0.215
	Female	17 (41.46)	14 (37.84)		
B	≤60	26 (63.41)	31 (83.78)	7.614	0.034
	>60	15 (36.59)	6 (16.22)		
C	<5cm	30 (73.17)	17 (45.95)	10.524	0.021
	≥5cm	11 (26.83)	20 (54.05)		
D	Pancreatic head	25 (60.98)	29 (78.38)	0.684	0.341
	Pancreatic body tail	16 (39.02)	8 (21.62)		
E	I ~ II period	22 (53.66)	21 (56.76)	0.524	0.263
	III ~ IV period	19 (46.34)	16 (43.24)		
F	Low differentiation	12 (29.27)	14 (37.84)	0.934	0.428
	High differentiation	29 (70.73)	23 (62.16)		

Table 3. Relationship between clinical characteristics and SIRI of patients; Gender (A), Age (B), Tumor diameter (C), Tumor site (D), Clinical staging (E), The degree of differentiation (F)

Clinical features		Low NLR group (n=41)	High NLR group (n=37)	χ^2	P
A	Male	34 (59.65)	13 (61.90)	0.864	0.152
	Female	23 (40.35)	8 (38.10)		
B	≤60	43 (75.44)	14 (66.67)	0.974	0.354
	>60	14 (24.56)	7 (33.33)		
C	<5cm	39 (68.42)	8 (38.10)	10.842	0.013
	≥5cm	18 (31.58)	13 (61.90)		
D	Pancreatic head	40 (70.17)	14 (66.67)	0.685	0.075
	Pancreatic body tail	17 (29.82)	7 (33.33)		
E	I ~ II period	34 (59.65)	12 (57.14)	0.854	0.431
	III ~ IV period	23 (40.35)	9 (42.86)		
F	Low differentiation	17 (29.82)	6 (28.57)	0.634	0.242
	High differentiation	40 (70.17)	15 (71.43)		

Diagnostic value of CA19-9, NLR and SIRI in pancreatic cancer

ROC curve method was used to analyze ca19-9, NLR and SIRI indexes in healthy people and patients with pancreatitis, and to explore their value in the diagnosis of pancreatic cancer. The sensitivity of CA19-9 to the diagnosis of pancreatic cancer was 93.10%, and the specificity of SIRI was 89.70% (P<0.05). The sensitivity and specificity of the combined assay were 89.7% and 70.00% higher than

that of ca19-9, NLR or SIRI alone. See Table 4 and Figure 1 for details.

Table 4. the value of CA19-9, NLR and SIRI in the diagnosis of pancreatic cancer

Indicators	Cutoff value	Sensitivity (%)	Specificity (%)	AUC (95%CI)	P
CA19-9	0.481	0.931	0.450	0.822 (0.735~0.908)	0.000
NLR	0.341	0.617	0.724	0.711 (0.602~0.820)	0.001
SIRI	0.414	0.517	0.897	0.766 (0.668~0.865)	0.000
Joint detection	0.597	0.897	0.700	0.857 (0.781~0.937)	0.000

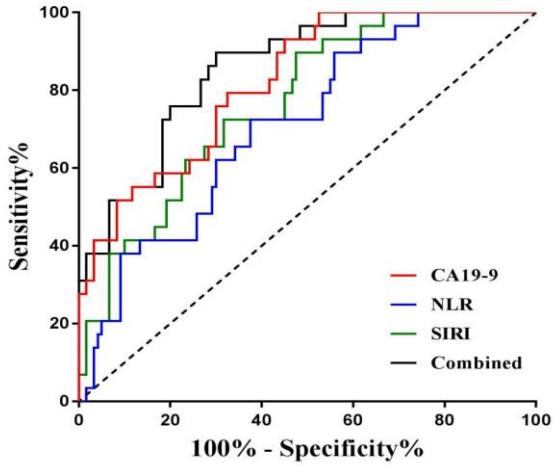

Figure 1. ROC curves of CA19-9, NLR and SIRI and their combination for the diagnosis of pancreatic cancer

Pancreatic cancer is the most malignant tumor of the digestive system. It has been reported that the 5-year survival rate of pancreatic cancer is 6%-10% (17). Due to its insidious onset and rapid progression, the prognosis of patients is often poor. According to epidemiological survey results, the prevalence rate of pancreatic cancer in China ranked 7th in 2011 (18). Studies have also shown that in 2017, the number of patients with pancreatic cancer in China was 83,600, and the prevalence rate was 5.92/100,000, an increase of 230.94% and 180.45% compared with 1990, respectively, and the mortality rate of patients increases with age (19). At present, the pathogenesis of pancreatic cancer is not completely clear. The development of tumors is usually related to genetic mutations, immunity and environmental factors. Studies have shown that the level of tumor-associated macrophages (TAM) is significantly increased in pancreatic cancer tissues (20). In the process of tumor development, monocytes are the main immune cells infiltrating into the tumor microenvironment. The tumor microenvironment can secrete a variety of factors to recruit monocytes and stimulate their differentiation into macrophages. Macrophages have two subtypes, M1 and M2 respectively. M1 can make helper T cell 1 reaction and delayed hypersensitivity reaction, so as to remove pathogenic microorganisms and tumor cells in cells (21). M2 can cause helper T cell 2 reaction and hyperacute hypersensitivity reaction, which can not only remove pathogenic microorganisms but also promote tumor cell growth (22). Therefore, there is a large concentration of M2 in the periphery of pancreatic ductal adenocarcinoma, which is related to tumor size, lymphatic invasion, and prognosis. Since most patients with pancreatic cancer have missed the best time for surgical treatment, early diagnosis is very important to improve the prognosis and survival of patients. This study observed and analyzed the levels of CA19-9, NLR and SIRI and their clinical value in patients with pancreatic cancer with different clinical characteristics.

Ca19-9 is a common clinical non-specific oligosaccharide tumor-associated antigen, and its main components include salivary glycolipids and salivary glycoproteins. Ca19-9 plays an important role in the diagnosis and prognosis of many tumors. Yin et al. (23) showed that compared with patients with gastric benign diseases, serum CA19-9 levels in gastric cancer patients were increased, which was negatively correlated with the degree of tumor differentiation and positively correlated with the clinical stage. Combined detection with other tumor markers had a high diagnostic value for gastric cancer. Wang et al. (24) showed that CA19-9 is associated with liver metastasis of colorectal cancer, and its combined detection with carcinoembryonic antigen has high diagnostic efficiency for liver metastasis of colorectal cancer. During the development of pancreatic cancer, mucin activation is partially regulated by the carcinogenesis of pancreatic duct epithelial cells, thus stimulating the secretion and release of CA19-9. At the same time, tumor cells continue to block pancreatic duct and pancreatic duct, resulting in CA19-9 entering circulation through the surrounding stroma, and increasing the level of serum CA19-9.

NLR is the ratio of neutrophils to lymphocytes. The increase of NLR can reflect the relative increase of

neutrophil content and the relative decrease of lymphocytes in blood. Neutrophils account for 50%~60% of the total number of white blood cells. They have the function of phagocytosis and sterilization and are related to the generation of substances such as vascular endothelial growth factor and tissue inhibitor protease. A large number of previous studies have shown that tumor-associated neutrophils (TAN) play an important role in tumor growth, invasion, pathological angiogenesis and immune escape. Kwantwi et al. (25) showed that TAN invasion density was negatively correlated with tumor-free survival in breast cancer tissues, and positively correlated with tumor pathological grade, lymph node and distant metastasis. Lymphocytes play an important role in the body's immune response. Under normal circumstances, mature lymphocytes can be stimulated by antigen to differentiate and proliferate to perform an immune function. In tumor tissue, lymphocytes can inhibit tumor proliferation and metastasis and affect angiogenesis by mediating cytotoxicity and releasing cytokines. Therefore, when the body is immune to dysfunction, there may be a decrease in the number of lymphocytes. NLR is an indicator of the balance between pro-inflammatory and anti-tumor inflammatory states and has important value in predicting tumor prognosis. Ye et al. (26) showed that preoperative serum D-dimer and peripheral blood NLR were correlated with the clinicopathological characteristics and average overall survival of ovarian cancer, and d-dimer and NLR scores could be used as indicators to evaluate the prognosis of ovarian cancer.

SIRI is an indicator that combines NLR and PLR to comprehensively reflect patients' immune and inflammatory balance. The increased number of neutrophils and platelets can promote tumor growth and invasion, while lymphocytes can inhibit tumor cell growth and proliferation. Increased SIRI is often associated with decreased immune function and increased inflammatory response. And it can be used as an effective indicator to predict the prognosis of some tumors. Wang et al. (27) showed that SIRI was an independent predictor of brain metastasis after PCI in patients with small-cell lung cancer, and a high level of SIRI was associated with poor postoperative overall survival.

The results of this study showed that the serum CA19-9 level in patients with pancreatic cancer stage IV was higher than that in patients with pancreatic cancer stage I, II and III, and the serum CA19-9 level increased gradually with the increase of clinical stage. Ca19-9 levels in pancreatic cancer patients with tumor diameter ≥5cm were higher than those in patients with tumor diameter < 5cm. The results showed that serum CA19-9 level was related to tumor stage and tumor size. In the continuous growth process of tumor tissue, the increase of its volume can make the ca19-9 in the tissue enter the blood, so as to increase the expression level of serum CA19-9. Compared with the low NLR group, the proportion of patients with age ≤60 years and tumor diameter ≥5cm in the high NLR group was higher. The proportion of patients with tumor diameter ≥5cm in the high-siri group was higher than that in the low-siri group. These results suggest that the increase of NLR and SIRI is associated with the increase of tumor diameter, suggesting that patients with larger tumor have increased inflammatory response and poor immune function. The sensitivity and specificity of ca19-9, NLR and SIRI combined were 89.7% and 70.00% higher than that of CA19-9, NLR or SIRI alone. Compared with single index detection, combined detection has higher accuracy in the diagnosis of pancreatic cancer.

In conclusion, serum CA19-9 level in patients with pancreatic cancer is related to clinical stage and tumor diameter, and the serum CA19-9 level gradually increases with the increase of clinical stage and tumor diameter. High NLR was associated with patients' age ≤60 and tumor diameter ≥5cm, and high SIRI was associated with tumor diameter ≥5cm. Increased NLR and SIRI could reflect the aggravation of patients' disease to a certain extent. The combined detection of CA19-9, NLR and SIRI is of greater value for early diagnosis of pancreatic cancer.

Acknowledgments

None.

Interest conflict

The authors declare no conflict of interest.

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