Am J Cancer Res 2023;13(11):5405-5417
www.ajcr.us /ISSN:2156-6976/ajcr0151534

Original Article

Elevated serum MMP-1 associated with advanced disease stage and lymph node metastasis in patients with pancreatic carcinoma

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Received June 1, 2023; Accepted October 8, 2023; Epub November 15, 2023; Published November 30, 2023

Abstract: Pancreatic cancer is a malignancy with extremely poor prognosis. This study aimed to investigate the application value of tumour markers and matrix metalloproteinase-1 (MMP-1) in predicting clinical staging and lymph node metastasis of pancreatic cancer. Totally, 130 pancreatic cancer patients and 40 healthy controls admitted to Haian Hospital Affiliated to Nantong University from January 2018 to January 2022 were collected. The expression of MMP-1, carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), and carbohydrate antigen 125 (CA125) were detected in their serum. MMP-1 was highly expressed in pancreatic cancer tissue, and MMP-1, CA199, CA125, and CEA could serve as diagnostic markers for pancreatic cancer. MMP-1 and CA199 had higher diagnostic value for early pancreatic cancer. Additionally, MMP-1 also demonstrated high predictive value for lymph node metastasis. Multivariate Cox regression analysis identified TNM staging, differentiation, MMP-1, and CA199 as independent risk factors affecting the overall survival of pancreatic cancer patients. The risk score model constructed based on Cox regression coefficients could better predict the prognosis of pancreatic cancer patients. MMP-1 demonstrates promising application value in determining clinical staging and lymph node metastasis of pancreatic cancer.

Keywords: MMP-1, CA199, CA125, CEA, pancreatic carcinoma, risk model

Introduction

Malignant tumour of the pancreas, especially pancreatic carcinoma, is a common type of digestive system tumour that poses significant challenges for patients and medical workers. It is characterized by highly malignant and insidious onset [1]. Pancreatic ductal adenocarcinoma is the most common pancreatic carcinoma, accounting for 90% of pancreatic malignant tumours [2]. The detection rate of pancreatic malignant tumour has been greatly improved with the progress of medical examination technologies, and the incidence rate is increasing year by year [3]. According to the statistics from a professional organization in the United States in 2021, pancreatic carcinoma ranks 10th among male malignant tumours and 9th among females, and is the fourth most common cause of cancer-related death [4]. In China, pancreatic carcinoma ranks as the 7th most common malignant tumour in males and the 11th in females. It is also the 6th leading cause of cancer-related deaths [5]. It is estimated that by 2030, pancreatic carcinoma will become the second leading cause of cancer-related death in the United States [6]. Despite the progress in treatment methods and effects, the prognosis of pancreatic carcinoma remains concerning.

In order to predict the survival period of patients and provide better treatment guidance, scientists have studied many factors that affect the prognosis, such as TNM staging of tumours, the possibility of radical resection, and systemic chemotherapy [7]. Hematological marker,

CA199, has been widely used in the assessment of pancreatic carcinoma, with a specificity of approximately 82%. However, its limitation is that not only patients with pancreatic carcinoma will have an elevated level, but also patients with inflammation of the biliary system, gastrointestinal tumours, etc. have a similar situation as well [8]. In recent years, researchers have attempted to make breakthroughs at the gene and protein levels and found some biomarkers that affect the prognosis [9]. However, due to the limitations such as cost, detection methods, and equipment, many detection items are difficult to popularize in clinic [10]. Effectively utilizing existing laboratory and examination data, given their low cost and easy availability, has become a challenge in and evaluating the prognosis of pancreatic carcinoma.

Matrix metalloproteinase-1 (MMP-1) is a neutral protease with a molecular weight of 55 kD, which can degrade natural type I and X fibrillar collagen, generate 3/4 N-terminal fragments and 1/4 C-terminal fragments, and transform them into gelatin at room temperature [11]. MMP-1 plays a key role in the invasion and metastasis of malignant tumour cells as well as in tumour angiogenesis [12]. Studies [13, 14] have shown that MMP-1 is expressed in breast carcinoma, lung carcinoma, gastric carcinoma, and other tumours, and it is found that plasma MMP-1 is an independent prognostic factor of colon carcinoma. However, there are relatively few reports about MMP-1 in pancreatic carcinoma, and its relationship with the prognosis of pancreatic carcinoma is not clear. Therefore, it is particularly important to explore the relationship between MMP-1 and clinicopathologic features of pancreatic carcinoma.

This study aimed to analyse the predictive value of MMP-1 and tumour markers in assessing therapeutic efficacy and prognosis of patients with pancreatic carcinoma, and to provide new biological markers for clinical prognosis evaluation.

Materials and methods

Subject recruitment

From January 2018 to January 2022, 219 patients with pancreatic carcinoma treated in Haian Hospital Affiliated to Nantong University were recruited as the subjects for this study. To clarify the research content, we drew a flow chart (**Figure 1**).

Inclusion criteria: (1) Patients who met the diagnostic criteria for pancreatic carcinoma according to the 8th edition of AJCC [15]; (2) Patients who were diagnosed with malignant pancreatic tumour based on postoperative pathological results at our hospital; (3) Patients with complete medical records; (4) Patients who underwent various serological examinations, including serum tumour markers, on the second day after admission; (5) Patients who were confirmed by pathology to have pancreatic ductal adenocarcinoma.

Exclusion criteria: (1) Patients with an expected survival time of less than 3 months; (2) Patients with diseases that affect tumour marker levels, such as pelvic inflammatory disease, endometriosis, other gynecological benign diseases, liver cirrhosis, obstructive jaundice, hepatitis, colitis, pulmonary fibrosis, teratoma, and autoimmune diseases; (3) Patients with concurrent tumours in other systems; (4) Patients who received anti-tumour or other related treatments before surgery.

According to the inclusion and exclusion criteria, we screened 130 patients with pancreatic carcinoma who met the criteria as a patient group of this study. In addition, 40 healthy people who underwent physical examination in the physical examination centre of our hospital during the same period were collected as a normal group. This research was ratified by the Medical Ethics Committee of Haian Hospital Affiliated to Nantong University. All the subjects had provided informed consent.

Collection of clinical data

Clinical data were collected, including gender, age, body mass index (BMI), lesion location, tumour diameter, TNM staging, differentiation degree, lymph node metastasis and postoperative chemotherapy. Laboratory indexes included serum MMP-1, serum cancer antigen 199 (CA199), cancer antigen 125 (CA125), and carcinoembryonic antigen (CEA).

The patient's survival status was determined by reviewing their electronic medical records and outpatient follow-up records, with the cut-off time set to January 2023.

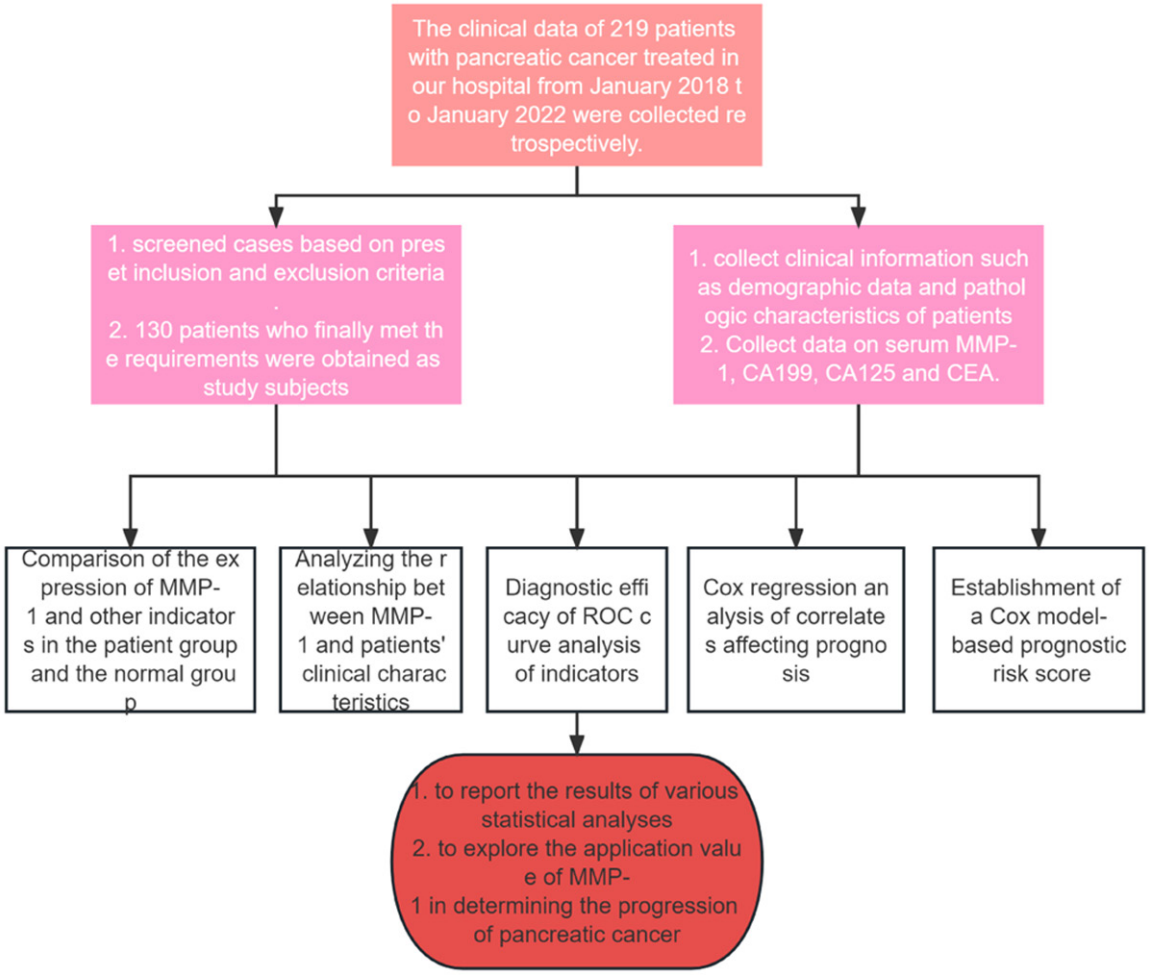

Figure 1. The flow chart.

Detection methods

Venous blood (5 ml) was collected from the patients, then centrifuged at a speed of 3000 r/min, and stored at -80°C for testing. ELISA was used to measure the MMP-1 levels in strict accordance with the instructions of the kit, which was provided by Shanghai enzyme-linked Biology. The batch number of the kit was ml038199. An automatic immune analyser (Jinan Qianshi Biotechnology Co., Ltd., BKI2200) was used to examine serum CA199 (KIP0311), CA125 (KIP0301), and CEA (KIP03105) levels, and the kits were from Beijing North Biotechnology Research Institute Co., Ltd.

Outcome measures

Primary outcome measures: The expressions of MMP-1, CA199, CA125, and CEA in the patients and the differences between them in diagnosing pancreatic carcinoma were compared. The risk factors affecting the prognosis of patients were analysed by Cox regression, and a risk prediction model was constructed based on Cox regression coefficient.

Secondary outcome measures: The relationship between MMP-1 and clinical data of patients was analysed. The value of MMP-1, CA199, CA125, and CEA in diagnosing TNM staging and lymph node metastasis was evaluated. The relationship between MMP-1 expression and survival in pancreatic carcinoma was analysed in online database.

Online tool analysis

Through the BEST database (https://rookieutopia.com/app_direct/BEST/), we analysed the expression of MMP-1 and overall survival (OS)

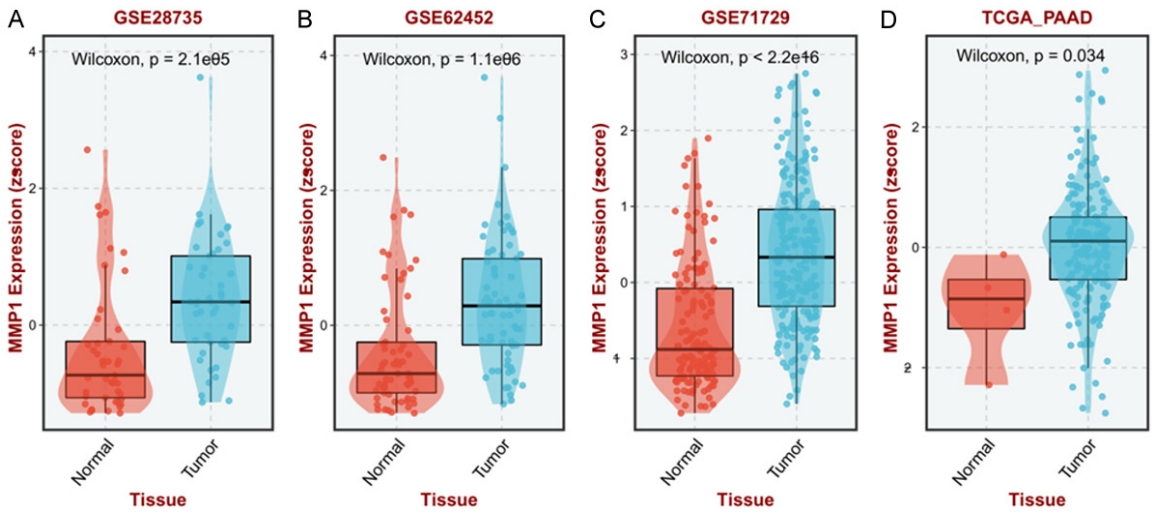

Figure 2. Expression level of MMP-1 in pancreatic carcinoma related database. A-C. Expression level of MMP-1 in GSE28735, GSE62452 and GSE71729 datasets. D. Expression level of MMP-1 in pancreatic carcinoma samples from TCGA database. Note: MMP-1: matrix metalloproteinase-1; TCGA: The Cancer Genome Atlas Program.

in patients with pancreatic carcinoma in various database.

Statistical analysis

SPSS 26.0 was applied for data analysis. Kolmogorov-Smirnov test was applied for normality analysis. Normally distributed data were expressed as mean ± standard deviation. The enumeration data were expressed by percentage and analysed by chi-squared test. In receiver operating characteristic (ROC) curve, sensitivity, specificity and other diagnostic indicators were applied to evaluate the clinical value of serum markers. DeLong test was applied to analyse the difference in areas under ROC curves (AUCs). Cox regression was applied to analyse the prognostic factors affecting the OS of patients, and a risk model was constructed through risk coefficient. The difference was statistically significant when $P<0.05$.

Results

Expression of MMP-1 in pancreatic carcinoma in online database

In order to determine the expression of MMP-1 in pancreatic carcinoma, we first analysed the expression of MMP-1 in pancreatic carcinoma-related datasets. Through the BEST database, we found that MMP-1 was highly expressed in pancreatic carcinoma samples in GSE28735, GSE62452, GSE71729, and The Cancer Genome Atlas Program (TCGA) (**Figure 2A-D**).

Expression and diagnostic value of MMP-1 and tumour markers in patients with pancreatic carcinoma

In this study, we further compared the levels of MMP-1, CA199, CA125, and CEA in pancreatic carcinoma and healthy people. Our results revealed that the expressions of MMP-1, CA199, CA125, and CEA in patients with pancreatic carcinoma were markedly higher than those in healthy people (**Figure 3A-D**) ($P< 0.0001$). In addition, ROC curve analysis revealed that the AUCs of MMP-1 and CA199 in diagnosing patients with pancreatic carcinoma were 1, while the AUCs of CA125 and CEA were 0.821 and 0.704, respectively (**Figure 3E**).

Relationship between MMP-1 and clinical data of patients with pancreatic carcinoma

In order to understand the relationship between MMP-1 and clinical data of patients with pancreatic carcinoma, the included patients were divided into a high expression group and a low expression group according to the median value of MMP-1 (36.54 pg/mL), and the relationship of clinical data between the two groups was further compared. The results showed that the proportion of patients with TNM staging (III), lymph node metastasis, and perineural inva-

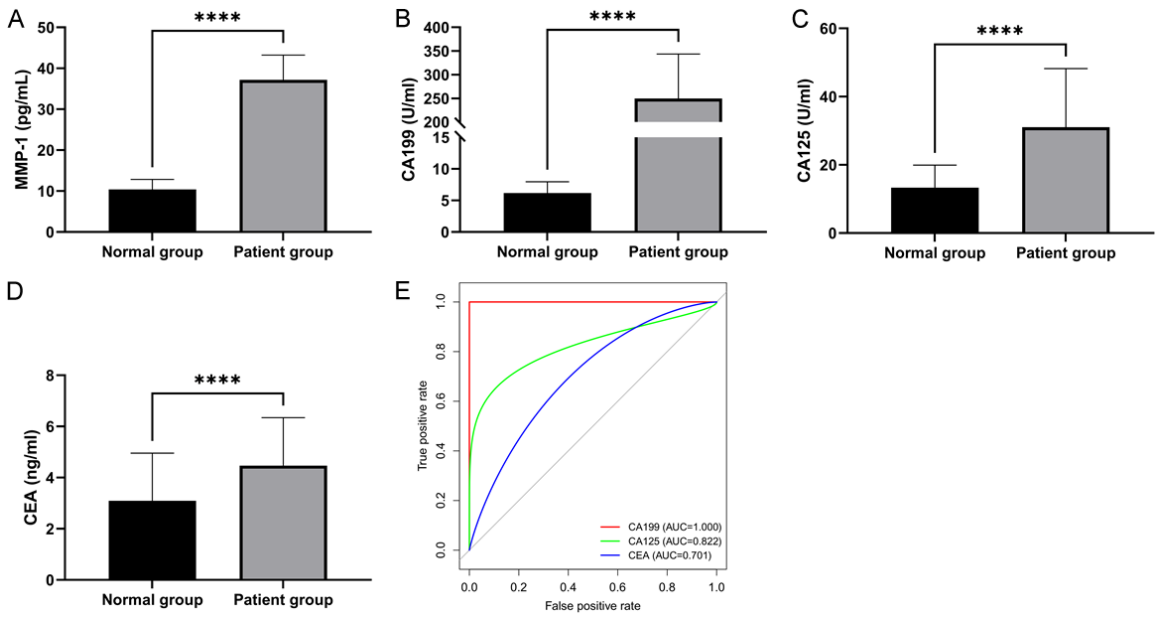

Figure 3. Difference in MMP-1 and tumour markers between healthy subjects and patients with pancreatic carcinoma. A-D. Differences in MMP-1, CA199, CA125 and CEA between healthy subjects and patients with pancreatic carcinoma. E. AUCs of MMP-1, CA199, CA125 and CEA in distinguishing healthy subjects from patients with pancreatic carcinoma. Note: MMP-1: matrix metalloproteinase-1; CA199: serum cancer antigen 19-9; CA125: cancer antigen 125; CEA: carcinoembryonic antigen; AUC: area under the curve; ****P<0.0001.

sion in the high expression group was markedly higher than that in the low expression group (**Table 1**) (P<0.001).

Comparison of the value of MMP-1 and tumour markers in distinguishing early pancreatic carcinoma

In the above analysis, we found that MMP-1 was related to TNM staging. To determine the diagnostic value of MMP-1 in early pancreatic carcinoma, we divided the patients into an early stage group (n=28) and a middle and late stage group (n=102). By drawing ROC curve, we found that the AUCs of MMP-1, CA199, CA125, and CEA in diagnosing early pancreatic carcinoma were 0.728, 0.706, 0.584, and 0.646, respectively (**Figure 4A**; **Table 2**). Through DeLong test, it was found that the clinical value of MMP-1 and CA199 showed no difference in diagnosing early pancreatic carcinoma, but their value was significantly higher than that of CA125 and CEA (**Table 3**) (P<0.01).

Comparison of the value of MMP-1 and tumour markers in diagnosing lymph node metastasis

In this study, we also found that MMP-1 was bound up with lymph node metastasis of patients. In order to determine the diagnostic value of MMP-1 in lymph node metastasis of patients with pancreatic carcinoma, we divided the patients into a metastatic group (n=63) and a non-metastatic group (n=67). By drawing ROC curves, we found that the AUCs of MMP-1, CA199, CA125, and CEA in the diagnosis of lymph node metastasis were 0.837, 0.723, 0.715, and 0.775, respectively (**Figure 4B**; **Table 4**). DeLong test revealed that the clinical value of MMP-1 in the diagnosis of lymph node metastasis was markedly higher than that of CA199, CA125, and CEA (**Table 5**) (P<0.001).

Comparison of the value of MMP-1 and tumour markers in distinguishing perineural invasion

In this study, we found that MMP-1 was bound up with perineural invasion of patients. In order to determine the diagnostic value of MMP-1 in perineural invasion of patients with pancreatic carcinoma, we divided the patients into a positive group (n=50) and a negative group (n=80) according to if they had perineural invasion or not. By drawing ROC curves, we found that the AUCs of MMP-1, CA199, CA125 and CEA in diagnosing perineural invasion were 0.859, 0.669, 0.550, and 0.621, respectively (**Figure 4C**; **Table 6**). Through DeLong test, we found

Table 1. Comparison between MMP-1 and baseline data of patients with pancreatic carcinoma

Factors	MMP-1		P
	High expression group (n=65)	Low expression group (n=65)	
Gender			0.522
Male	34	31	
Female	31	34	
Age			0.109
≥60 years old	37	28	
<60 years old	28	37	
BMI			0.690
≥25 kg/m^2	17	15	
<25 kg/m^2	48	50	
Lesion location			0.215
Pancreatic head	40	33	
Body and tail of pancreas	25	32	
Tumour diameter			0.356
≥2.5 cm	45	40	
<2.5 cm	20	25	
TNM staging			0.002
I	10	18	
II	20	32	
III	35	15	
Differentiation degree			0.520
Middle and well differentiated	27	23	
Poorly differentiated	38	42	
Lymph node metastasis			0.001
Metastasis	42	21	
Non-metastasis	23	44	
Postoperative chemotherapy			0.669
Yes	56	58	
No	20	17	
Perineural invasion			<0.001
Positive	35	15	
Negative	30	50	

Note: BMI: body mass index.

that the clinical value of MMP-1 in the diagnosis of perineural invasion was markedly higher than that of CA199, CA125 and CEA (**Table 7**) (P<0.001).

Risk factors affecting the OS of patients with pancreatic carcinoma

In this study, the OS of patients was collected from the electronic medical records, and the average OS of the 130 patients was 21.9 months. In order to understand the risk factors affecting the OS of patients, we regressed all the factors by Cox regression. Additionally, the data were initially assigned values (**Table 8**). Through univariate analysis, we found that TNM staging, differentiation degree, lymph node metastasis, postoperative chemotherapy, perineural invasion, MMP1, CA199, CA125 and CEA were significant factors affecting the prognosis of patients (**Table 9**) (P<0.01). Subsequently, multivariate Cox regression was performed on the significant indicators for backward likelihood ratio analysis. The results revealed that advanced TNM stage (stage III), poor differentiation/poorly differentiated subtype, positive perineural invasion, MMP1, and CA199 were independent risk factors affecting the OS of patients with pancreatic carcinoma (**Table 9**) (P<0.05).

Construction of prognostic risk model for patients with pancreatic carcinoma

At the end of the study, we constructed a risk model to predict the OS of patients based on Cox regression β coefficient of TNM staging, differentiation degree, perineural invasion, MMP1, and CA199. Patient risk score = 0.471 * TNM staging + 0.615 * differentiation degree + 0.678 * perineural invasion + 0.054 * MMP1 + 0.005 * CA199. By calculating the risk score of each patient, it was found that the risk score of patients in death group was markedly higher than that of patients in survival group (**Figure 5**) (P<0.0001). In addition, ROC curve showed that the AUC of the risk score in predicting the OS of patients was 0.878.

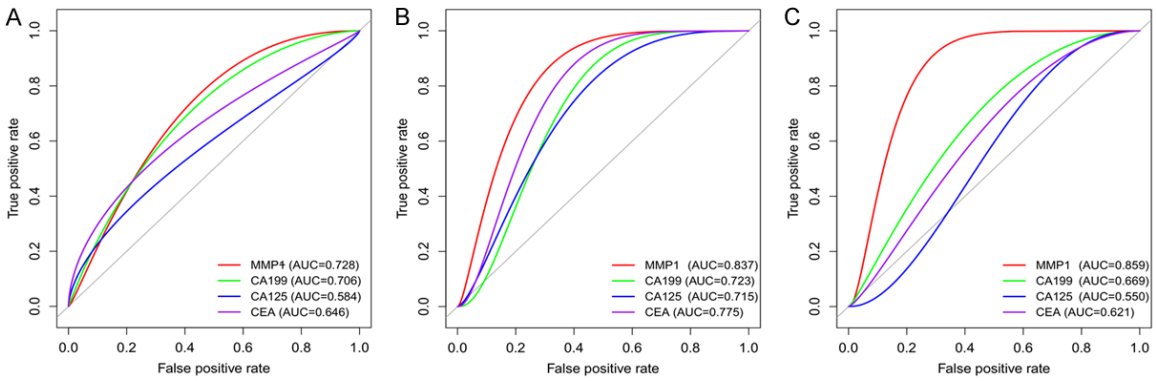

Figure 4. Diagnostic value of MMP-1, CA199, CA125 and CEA in TNM staging, lymph node metastasis and perineural invasion. A. Value of MMP-1 and tumour markers in differentiating TNM stages. B. Value of MMP-1 and tumour markers in differentiating lymph node metastasis. C. Value of MMP-1 and tumour markers in differentiating perineural invasion. Note: MMP-1: matrix metalloproteinase-1; CA199: serum cancer antigen 19-9; CA125: cancer antigen 125; CEA: carcinoembryonic antigen; ROC: receiver operating characteristic curve.

Table 2. ROC curve parameters

Predictor variable	AUC	Confidence interval	Cut-off	Sensitivity	Specificity	Youden index
MMP-1	0.728	0.615-0.841	33.89	84.31%	64.29%	48.60%
CA199	0.706	0.590-0.822	197.90	79.41%	64.29%	43.70%
CA125	0.584	0.477-0.692	46.02	24.51%	100.00%	24.51%
CEA	0.646	0.544-0.748	5.46	36.28%	96.43%	32.70%

Note: MMP-1: matrix metalloproteinase-1; CA199: serum cancer antigen 19-9; CA125: cancer antigen 125; CEA: carcinoembryonic antigen; AUC: area under the curve.

Table 3. Comparison of AUC

Test result *vs.*	Z	P	AUC difference value	Standard error value	95% confidence interval	
					Lower limit	Upper limit
MMP1 - CA199	1.634	0.102	0.022	0.332	-0.004	0.048
MMP1 - CA125	4.695	<0.001	0.143	0.327	0.084	0.203
MMP1 - CEA	2.729	0.006	0.082	0.323	0.023	0.14

Note: MMP-1: matrix metalloproteinase-1; CA199: serum cancer antigen 19-9; CA125: cancer antigen 125; CEA: carcinoembryonic antigen; AUC: area under the curve.

Table 4. ROC curve parameters

Predictor variable	AUC	Confidence interval	Cut-off	Sensitivity	Specificity	Youden index
MMP-1	0.837	0.766-0.908	35.755	67.16%	88.89%	56.05%
CA199	0.723	0.633-0.813	208.96	53.73%	90.48%	44.21%
CA125	0.715	0.627-0.804	17.95	43.28%	92.06%	35.35%
CEA	0.775	0.693-0.858	3.685	58.21%	95.24%	53.45%

Note: MMP-1: matrix metalloproteinase-1; CA199: serum cancer antigen 19-9; CA125: cancer antigen 125; CEA: carcinoembryonic antigen; AUC: area under the curve.

Discussion

Diagnosis at early clinical stages is the key factor affecting the cure possibility, posttreatment recurrence rate, and mortality of pancreatic carcinoma [8]. With the development of molecular marker research, increasing literatures [16-18] have revealed that some tumour-relat-

Table 5. Comparison of AUC

Test result *vs.*	Z	P	AUC difference value	Standard error value	95% confidence interval	
					Lower limit	Upper limit
MMP1 - CA199	5.049	<0.001	0.114	0.281	0.070	0.158
MMP1 - CA125	5.317	<0.001	0.122	0.280	0.077	0.167
MMP1 - CEA	2.759	0.006	0.062	0.275	0.018	0.106

Note: MMP-1: matrix metalloproteinase-1; CA199: serum cancer antigen 19-9; CA125: cancer antigen 125; CEA: carcinoembryonic antigen; AUC: area under the curve.

Table 6. ROC curve parameters

Predictor variable	AUC	Confidence interval	Cut-off	Sensitivity	Specificity	Youden index
MMP-1	0.859	0.795-0.923	36.17	70.00%	96.00%	66.00%
CA199	0.669	0.576-0.762	232.87	55.00%	74.00%	29.00%
CA125	0.550	0.452-0.649	14.795	26.25%	94.00%	20.25%
CEA	0.621	0.524-0.717	3.505	37.50%	86.00%	23.50%

Note: MMP-1: matrix metalloproteinase-1; CA199: serum cancer antigen 19-9; CA125: cancer antigen 125; CEA: carcinoembryonic antigen; AUC: area under the curve.

Table 7. Comparison of AUC

Test result *vs.*	Z	P	AUC difference value	Standard error value	95% confidence interval	
					Lower limit	Upper limit
MMP1 - CA199	-7.226	<0.001	-0.190	0.278	-0.242	-0.139
MMP1 - CA125	-9.318	<0.001	-0.309	0.284	-0.374	-0.244
MMP1 - CEA	-8.017	<0.001	-0.239	0.282	-0.297	-0.18

Note: MMP-1: matrix metalloproteinase-1; CA199: serum cancer antigen 19-9; CA125: cancer antigen 125; CEA: carcinoembryonic antigen; AUC: area under the curve.

Table 8. Assignment table

Factors	Assignment
Gender	Male =1, Female =0
Age	≥60 years old =1, <60 years old =0
BMI	≥25 kg/m^2 =1, <25 kg/m^2 =0
Lesion location	Pancreatic head =1, Body and tail of pancreas =0
Tumour diameter	≥2.5 cm =1, <2.5 cm =0
TNM staging	I =0, II-III =1
Differentiation degree	Middle and well differentiated =0, Poorly differentiated =1
Lymph node metastasis	Metastasis =1, Non-metastasis =0
Postoperative chemotherapy	Yes =1, No =0
perineural invasion	Positive =1, Negative =0
MMP1	≥36.46 pg/mL =1, <36.46 pg/mL =0
CA199	≥225.59 U/mL =1, <225.59 U/mL =0
CA125	≥24.40 U/mL =1, <24.40 U/mL =0
CEA	≥4.18 ng/mL =1, <4.18 ng/mL =0

ed antigens, such as CA19-9, CA125 and CEA, are usually released into peripheral blood during the development and progress of pancreatic tumours, presenting as abnormal expression of tumour-related antigens. However, studies [19, 20] have revealed that although tumour markers have high specificity and sensitivity in distinguishing cancer patients from normal

Table 9. Cox regression

Factors	Univariate analysis			Multivariate analysis		
	HR	P	95% CI	HR	P	95% CI
Gender	0.948	0.786	0.642-1.398			
Age	0.877	0.510	0.593-1.296			
BMI	0.804	0.352	0.508-1.273			
Lesion location	0.937	0.744	0.632-1.388			
Tumour diameter	0.886	0.564	0.588-1.336			
TNM staging	1.856	<0.001	1.396-2.468	1.602	0.002	1.182-2.171
Differentiation degree	2.195	<0.001	1.451-3.322	1.849	0.006	1.188-2.878
Lymph node metastasis	1.793	0.006	1.185-2.713	0.143	0.890	0.890-2.238
Postoperative chemotherapy	1.934	0.004	1.237-3.024	0.501	0.706	0.706-2.037
perineural invasion	1.786	0.006	1.179-2.706	1.971	0.004	1.249-3.109
MMP1	1.063	<0.001	1.030-1.098	1.056	0.003	1.018-1.095
CA199	1.003	0.002	1.001-1.005	1.004	0.001	1.002-1.006
CA125	1.014	0.006	1.004-1.024	0.966	0.283	0.907-1.029
CEA	1.149	0.005	1.042-1.266	1.002	0.987	0.762-1.319

Note: BMI: body mass index; MMP-1: matrix metalloproteinase-1; CA199: serum cancer antigen 19-9; CA125: cancer antigen 125; CEA: carcinoembryonic antigen.

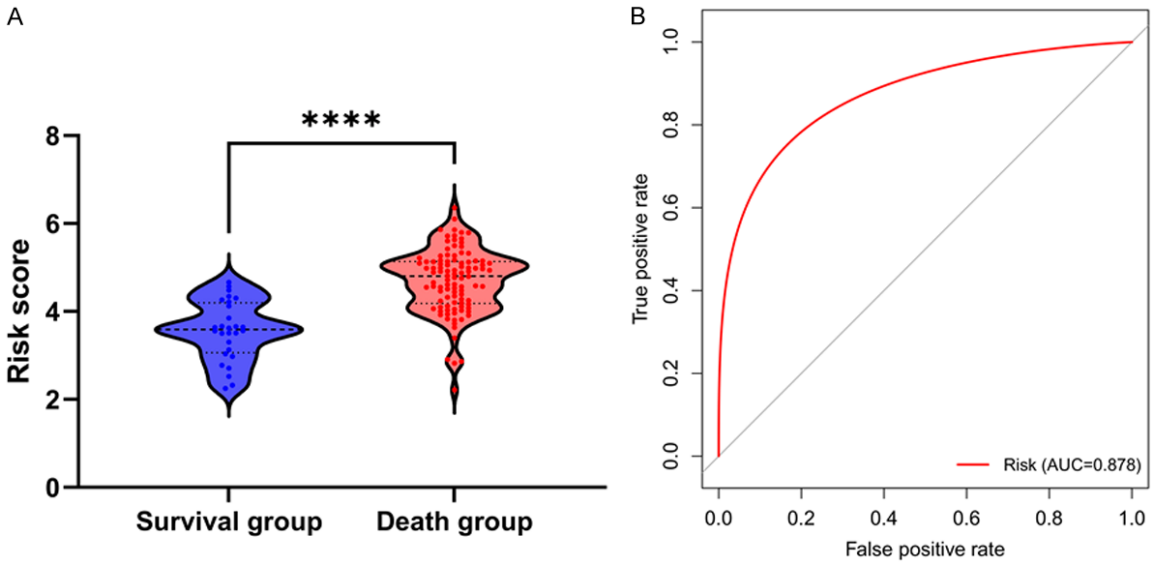

Figure 5. Value of risk model in predicting the OS of patients. A. Level of risk score for patients with pancreatic carcinoma in death and survival groups. B. ROC curve of risk score in predicting death of patients with pancreatic carcinoma. Note: **** P<0.0001; ROC: receiver operating characteristic curve.

people, their value in distinguishing clinical stages and lymph node metastasis is not ideal.

MMP-1, as an important matrix metalloproteinase, mainly degrades collagen and other components, and participates in the remodelling of extracellular matrix and cell migration [21]. The expression of MMP-1 is bound up with many diseases, such as tumour, arthritis, and cardiovascular diseases [22, 23]. Early studies [24] have revealed that MMP-1 is highly expressed in pancreatic carcinoma cells and has the ability to promote their metastasis. In this study, we first found that MMP-1 was highly expressed in pancreatic carcinoma through online database analysis. Subsequently, we found that the serum expression of MMP-1 in pancreatic carcinoma patients was higher than that of healthy

people through Elisa. This shows that MMP-1 participates in the progress of pancreatic carcinoma. Study of Xu et al. [25] found that the mRNA expression of MMP-1 in pancreatic carcinoma tissue was markedly higher than that in adjacent tissues, which is consistent with our research. Their study also revealed that the high expression of MMP-1 was bound up with histological grade, TNM staging, and lymph node metastasis, and our study also revealed that the high expression of MMP-1 was bound up with TNM staging and lymph node metastasis. This suggests that MMP-1 is expected to be an observation index of clinical staging and lymph node metastasis in patients with pancreatic carcinoma.

Because of the difficulty in early diagnosis, the prognosis of pancreatic carcinoma is usually poor, which leads to most patients being in a locally advanced stage or having metastasized at diagnosis [26]. Even for patients in earlier stages who can undergo potentially curative surgery, the 5-year survival rate remains low, at only about 30-40% [27]. In this study, it was found that only MMP-1 and CA199 exhibited an AUC greater than 0.7 for early diagnosis, while CA125 and CEA were not ideal for early diagnosis. Furthermore, the test results revealed that there was no difference in the ability of MMP-1 and CA199 for early diagnosis. CA199 is a glycoprotein produced by the human body and secreted by pancreatic tumour cells, and it only exists at very low levels in the blood of healthy adults [28]. CA199 is widely used as a tumour marker for diagnosing pancreatic carcinoma, which is the most commonly used gold-standard biological marker for pancreatic carcinoma and the only serum biomarker approved by the U.S. Food and Drug Administration for use in pancreatic carcinoma [29]. Many studies have reported that CA199 is related to clinicopathological staging [28]. This study revealed that the value of MMP-1 in diagnosing early pancreatic carcinoma was not different from that of CA199, indicating that MMP-1 can also be used as a diagnostic marker for clinicopathological staging of pancreatic carcinoma. The study of Xie et al. [30] revealed that the expression level of MMP-1 in early pancreatic carcinoma tissue was low, while the expression level of MMP-1 increased significantly in advanced pancreatic carcinoma. Combined with our research results, it is suggested that MMP-1 can be used as a potential diagnostic index to distinguish early pancreatic carcinoma from advanced pancreatic carcinoma.

Pancreatic carcinoma is a malignant tumour with easy metastasis, extremely high malignancy, and poor prognosis [31]. Lymph node metastasis is the primary route of pancreatic carcinoma metastasis, which develops early and has a high incidence rate. It is recognized as an independent factor affecting the prognosis of patients with pancreatic carcinoma [32]. Our study revealed that MMP-1 and CEA had high diagnostic value in diagnosing lymph node metastasis of patients with pancreatic carcinoma, but the diagnostic value of MMP-1 was higher than that of CEA. CEA is a nonspecific serum biomarker, which is mainly applied for the diagnosis of colorectal carcinoma. In the study by Jiang et al. [33] with a sample size of 56 pancreatic cancer patients, the AUCs of CA199 and CEA in diagnosing lymph node metastasis were reported to be 0.632 and 0.563, respectively. In comparison, our study included a larger sample of 130 patients, and found the AUCs of CA199 and CEA to be 0.723 and 0.775, respectively. The larger sample volume in our study may contribute to the higher AUC values compared to the study by Jiang et al. Besides, our results showed that the AUC of MMP-1 was markedly larger than that of the other three indexes, indicating that MMP-1 had high value in the diagnosis of lymph node metastasis. MMP-1 is involved in the invasiveness and metastasis of tumour cells, and the high expression of MMP-1 can promote the invasiveness and metastasis of pancreatic carcinoma cells to lymph nodes, thus further promoting the malignant progress of tumours [34].

Perineural invasion refers to the invasion of tumour cells into the tissues of peripheral nerve tracts, which is usually bound up with poor prognosis [35]. According to previous research [36], pancreatic carcinoma with peripheral nerve invasion is usually associated with high local invasion, lymph node metastasis rate, and distant metastasis rate, so pancreatic carcinoma patients with peripheral nerve invasion usually have a low 5-year survival rate and poor prognosis. In this study, we found that MMP-1 demonstrated high value in diagnosing perineural invasion of pancreatic carcinoma, and it was much higher than that of other tumour markers. A study [37] revealed that the expression level of MMP-1 in pancre-

atic carcinoma patients with positive peripheral invasion was markedly higher than that in patients with negative peripheral invasion. Moreover, MMP-1 may promote the peripheral invasion of pancreatic carcinoma by decomposing matrix components, such as collagen and fibrin, and regulate cell proliferation, apoptosis and metastasis by interacting with other signal pathways [38].

This study further analysed the factors affecting the OS of patients with pancreatic carcinoma. The results revealed that TNM staging, differentiation degree, perineural invasion, MMP1 and CA199 were independent risk factors affecting the OS of patients with pancreatic carcinoma. TNM staging, differentiation degree, and lymph node metastasis have been identified as independent factors affecting the survival of patients with pancreatic carcinoma by a number of studies [39-41]. The study of Wu et al. [42] revealed that preoperative serum CA199 level was closely bound up with the survival time of patients with pancreatic carcinoma, so CA199 can be used to evaluate their prognosis. This is the first time that MMP-1 was found to be an independent prognostic factor for the OS of pancreatic carcinoma. We believe that this is because MMP-1 can degrade matrix components such as collagen and fibronectin, thus promoting tumour cells to cross the basement membrane and enter blood vessels or lymphatic vessels, which eventually causes tumour metastasis and reduces the OS of patients. Finally, we constructed a risk prediction model based on Cox regression, and found that the risk score had high value in predicting the OS of patients.

In this study, we revealed the value of MMP-1 in pancreatic carcinoma. However, there are still some limitations. Firstly, we collected a relatively small number of samples that met the criteria, and the samples were collected from a single centre. Secondly, whether the risk model constructed in this study has generalizability still needs to be validated by collecting more samples. Lastly, we hope to carry out follow-up prospective research to obtain more samples and detection indicators, so as to further improve our research conclusions.

To sum up, MMP-1 is highly expressed in pancreatic carcinoma and is an independent prognostic factor affecting OS. MMP-1 also has high value in diagnosing pancreatic carcinoma staging and lymph node metastasis.

Disclosure of conflict of interest

None.

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