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Original Article

Clinical characteristics and prognostic value of serological markers in pancreatic neuroendocrine tumors: a single-center retrospective study

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Abstract: Objective: To investigate the clinical characteristics, diagnostic methods, treatment strategies and prognostic factors of pancreatic neuroendocrine tumors (pNETs). Methods: A retrospective analysis was conducted on 43 pNET patients treated at Huzhou Central Hospital from January 2003 to December 2023. The data included age, gender, function, tumor location, tumor size, pathological characteristics, lymph nodes, metastasis, and treatment. Association of these factors with pNET prognosis was proven by univariate analysis and multivariate analysis. Results: The incidence of G3 tumors in this group of advanced patients was relatively high (P=0.001). Meanwhile, elevated CA125 was commonly seen in the advanced stage (P=0.045), and surgeries occurred more frequently in the early stage (P=0.003). In addition, the positive expression of CD56 in low-grade tumors was relatively high (P=0.014). The incidence of non-functional tumors larger than 2 cm was high (P=0.015). Univariate Cox regression revealed that tumor size >2 cm, G3 grade, liver metastasis, advanced stage, lymph node metastasis and invasion were risk factors. Multivariate analysis revealed that G3 grade, liver metastasis and advanced stage were independent influencing factors for disease progression. Conclusion: pNETs are heterogeneous tumors. Pathological grade, metastatic status, and serological markers may assist in diagnosis and prognosis assessment, aiding individualized clinical management.

Keywords: Pancreatic neuroendocrine tumors, clinical and pathological features, diagnosis, treatment, prognostic analysis

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that originate from neuroendocrine cells, which are distributed throughout the body, including the gastrointestinal tract, lungs, and pancreas [1]. Pancreatic neuroendocrine tumors (pNETs) are the second most common type of pancreatic neoplasm, accounting for approximately 1%-2% of all pancreatic tumors. In recent years, advances in imaging technologies, serum biomarker detection, and improved disease recognition have led to an increased diagnosis rate of pNETs [2, 3].

Based on hormone secretion and clinical presentation, pNETs are classified as either functional or non-functional. Approximately 75% of pNETs are non-functional [4, 5]. Functional tumors secrete excessive amounts of peptide hormones such as insulin, gastrin, glucagon, and vasoactive intestinal peptide, resulting in characteristic clinical syndromes. In contrast, non-functional tumors typically do not cause hormone-related symptoms, although some patients may exhibit mild elevations in hormone levels without overt clinical manifestations.

pNETs exhibit marked heterogeneity in clinical and pathological features, treatment strate-

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gies, and prognostic outcomes, depending on their histologic grade and clinical stage. Surgical resection remains the preferred treatment for most pNETs. In functional tumors, debulking surgery is often necessary to relieve symptoms, even in the presence of distant metastases. For non-functional tumors larger than 2 cm, surgical intervention is generally recommended. In contrast, the management of tumors smaller than 2 cm depends on factors such as tumor location and individual patient characteristics, and may involve either surgery or active surveillance [6].

According to the latest American Joint Committee on Cancer (AJCC) staging system, pNETs are categorized into stages I-IV based on tumor size, invasion, and metastasis [7]. The most recent World Health Organization (WHO) classification system grades pNETs as G1, G2, or G3, or categorizes them as neuroendocrine carcinoma (NEC), based on mitotic count and the Ki-67 proliferation index [8].

Despite the increasing incidence of pNETs, limited studies have systematically investigated the associations between clinical characteristics, pathological features, prognosis, and clinical or pathological staging. This study aims to evaluate the relationships between clinicopathological features and prognosis, as well as to assess the diagnostic efficacy of serological markers.

Materials and methods

Patient selection

A retrospective analysis was conducted on patients diagnosed with pNETs at Huzhou Central Hospital between January 2003 and December 2023.

Inclusion criteria: (1) Pathologically confirmed diagnosis of pNET based on surgical resection or tumor biopsy; (2) Availability of complete clinical and follow-up data; (3) Completion of the full course of treatment at our hospital; (4) No prior treatment before hospital admission.

Exclusion criteria: Patients with other types of neuroendocrine tumors or coexisting malignancies were excluded.

This study adhered to the STROBE guidelines for observational research [9], complied with the Declaration of Helsinki (2013) [10], and was approved by the Ethics Committee of Huzhou Central Hospital (No. 202412035-01). All clinical data were retrieved from the hospital's electronic medical records and anonymized for analysis. According to the Clinical and Pathological grouping, the patients were divided into the Early to middle stage (n=32) and the Late to advanced stage (n=11); the Low-grade (n=37) and High-grade (n=6) groups. Additionally, baseline data from 50 healthy individuals undergoing routine physical examinations during the same period were collected as controls.

Data extraction

Clinical data from patients who met the inclusion criteria were collected, including: (1) demographic data (age, sex); (2) tumor characteristics (location, number of lesions, maximum diameter, invasion, metastasis); (3) immunohistochemical markers and tumor markers; (4) treatment modalities; (5) tumor function (functional vs. non-functional); (6) WHO pathological grade and AJCC stage; (7) microvascular and perineural invasion; (8) lymph node metastasis; (9) follow-up information.

Follow-up

The primary purpose was to assess survival duration, survival outcome, tumor recurrence, and distant organ metastasis. The observation period began at the time of pathological diagnosis and ended either at the patient's death from pNET or at the end of the follow-up period. Survival time was defined as the interval from diagnosis to death or censoring. All patients were followed up by telephone and review of medical records. The minimum follow-up duration was six months, with the cutoff date of follow-up set as June 30, 2024. A total of 43 cases were included in the study, all with complete follow-up data. No patients were lost to follow-up.

T grading and staging criteria

Tumor staging was performed according to the AJCC TNM classification system [7]: Stage I: T1N0M0; Stage II: T2/T3N0M0; Stage III: T4N0M0 or any T with N1M0; Stage IV: Any T, any N with M1.

Table 1. General information of patients

Variable	Parameter (n=43)	Percentage (%)
Age (year, median (range))	58 (26-80)	-
Gender (Female)	23	53.5
There are symptoms at the time of diagnosis		
Yes	20	46.5
No	23	53.5
Functional or not		
Yes	6	14.0
No	37	86.0
Tumor diameter (cm, median (range))	2.5 (0.6-11.0)	-
Tumor location		
neck	16	37.2
cauda	22	51.2
multiple	5	11.6
Synchronous liver metastasis	8	18.6
Treatment mode		
Surgical	36	83.7
Non-surgical	7	12.3
Surgical types		
Pancreaticoduodenectomy	6	16.7
Distal pancreatectomy	23	63.9
Middle segment pancreatectomy	3	8.3
Local pancreatectomy	4	11.1
Pathological grading		
G1	12	28.0
G2	25	58.1
G3	6	13.9
AJCC Clinical staging		
I	10	23.3
II	22	51.2
III	5	11.6
IV	6	13.9
Lymph node metastasis	7	16.3
Vascular invasion	6	4.0
Perineural invasion	9	20.9
Upper abdominal pain	7	16.3
Emaciation	3	6.9
Nausea and vomiting	2	4.6
Jaundice	1	2.4

For analytical purposes, stages I-II were grouped as early to intermediate stages, while stages III-IV were considered advanced stages.

According to the latest WHO grading system [8], pNETs were classified into G1, G2, G3, or NEC based on mitotic count and Ki-67 index. G1 and G2 tumors were defined as low-grade, while G3 and NEC were defined as high-grade.

Primary outcome measures

The correlations between age, gender, function, tumor location, tumor size, pathological features, lymph nodes, metastasis and treatment and the prognosis of PNEN were analyzed through univariate analysis and multivariate analysis.

Secondary outcome measures

The diagnostic value of serum biomarkers for pNETs was evaluated.

Statistical analysis

All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables not following a normal distribution were expressed as median (range) and compared using the Mann-Whitney U test. Measurement data following a normal distribution were presented as mean ± SEM. A t-test was used to analyze normally distributed data, and an independent samples t-test was performed for between-group comparisons.

Categorical variables were reported as frequency (percentage) and compared using the chi-square test or Fisher's exact test, as appropriate. Kaplan-Meier survival analysis was used to plot survival curves.

Univariate survival analysis was conducted using the log-rank test. Variables with significant differences in univariate analysis were

Table 2. Relationship between clinical pathological features of pancreatic neuroendocrine tumors and AJCC clinical staging

Variable	Early to middle stage (n=32)	Late to advanced stage (n=11)	χ^2	P
Age				
≥60	14 (43.8)	6 (54.5)	0.383	0.536
<60	18 (56.2)	5 (45.5)		
Gender				
Male	15 (46.9)	5 (45.5)	0.007	0.935
Female	17 (53.1)	6 (54.5)		
Functional or not				
Yes	5 (15.6)	1 (9.1)	-	1.0
No	27 (84.4)	10 (90.9)		
WHO Pathological Grading				
G1	12 (37.5)	0 (0)	13.101	0.001*
G2	19 (59.4)	6 (54.5)		
G3	1 (3.1)	5 (45.5)		
Immunohistochemical markers				
CgA	30 (93.8)	10 (90.9)	-	1.0
Syn	32 (100)	10 (90.9)	-	0.256
CD56	30 (93.8)	10 (90.9)	-	1.0
Tumor markers				
CA199	4 (12.5)	3 (27.3)	0.451	0.502
CA125	1 (3.1)	2 (27.3)	-	0.045*
AFP	1 (3.1)	0 (0)	-	1.00
CEA	3 (9.4)	2 (18.2)	-	0.589
NSE	6 (18.8)	3 (27.3)	0.029	0.865
Treatment mode				
surgical	31 (96.9)	6 (54.5)	-	0.003*
Non-surgical	1 (3.1)	5 (45.5)		
Tumor location				
neck	14 (43.8)	3 (27.3)	4.98	0.084
cauda	18 (56.2)	6 (54.5)		
multiple	0 (0)	2 (18.2)		

AJCC: American Joint Committee on Cancer; *$P<0.05$.

included in a multivariate Cox regression model, using the backward stepwise (likelihood ratio) method. A *p*-value <0.05 was considered statistically significant.

Result

Clinical and pathological features of pNET patients

This study included 43 patients with pNETs treated between January 2003 and December 2023. The median age was 58 years (range, 26-80), and 53.5% were female. At diagnosis, 46.5% presented with clinical symptoms, while 86% showed no hormone secretion syndromes. The median tumor size was 2.5 cm (range, 0.6-11.0 cm); 37.6% of tumors were located in the head and neck, and 51.2% in the body and tail of the pancreas. Multiple tumors were observed in 11.6% of patients, and 18.6% (8 cases) had liver metastasis. Surgical resection was performed in 83.7% of patients, with 63.9% undergoing distal pancreatectomy and 16.7% pancreatoduodenectomy. Most tumors were classified as WHO grade G2 (58.1%). According to the AJCC staging system, 74.5% were diagnosed at early to middle stages (stage I, 23.3%; stage II, 51.2%). Among all cases, 66.3% were non-functional tumors. The most common symptoms were upper abdominal pain (16.3%), nausea and vomiting (4.6%), and jaundice (2.4%) (**Table 1**).

Association between clinical/pathological features and AJCC stage and WHO grade

Advanced-stage patients had a significantly higher proportion of G3 tumors than those in the early-middle stage group (P<0.05). Elevated CA125 levels were also more common in advanced-stage patients, whereas early-middle stage patients were more likely to undergo surgery (both P<0.05). No significant differences were found in age, sex, or tumor location between groups (all P>0.05) (**Table 2**).

Regarding WHO grade, CD56 positivity was significantly higher in the low-grade group (G1/G2) compared to the high-grade group (G3/NEC) (P<0.05). No significant differences were observed in age, sex, surgical treatment, or tumor location (all P>0.05) (**Table 3**).

Table 3. Relationship between clinical pathological features of pancreatic neuroendocrine tumors and WHO pathological grading

Variable	Low-grade (n=37)	High-grade (n=6)	χ^2	P
Age				
≥60	15 (40.5)	5 (83.3)	-	0.081
<60	22 (59.5)	1 (16.7)		
Gender				
Male	16 (43.2)	4 (66.7)	-	0.393
Female	21 (56.8)	2 (33.3)		
Functional or not				
Yes	6 (16.2)	0 (0)	1.955	0.162
No	31 (83.8)	6 (100)		
Immunohistochemical markers				
CgA	35 (94.6)	5 (83.8)	-	0.370
Syn	36 (97.3)	6 (100)	1.72	0.190
CD56	35 (94.6)	3 (50.5)	-	0.014*
Tumor markers				
CA199	6 (16.2)	1 (16.6)	0.001	0.978
CA125	3 (8.1)	1 (16.6)	-	0.465
AFP	1 (2.70)	0 (0)	-	1.00
CEA	4 (10.8)	1 (16.6)	-	0.547
NSE	8 (21.6)	1 (16.6)	-	1.00
Treatment mode				
surgical	33 (89.2)	4 (66.7)	1.768	0.184
Non-surgical	4 (10.8)	2 (33.3)		
Tumor diameter				
≥2 cm	23 (62.2)	5 (83.8)	-	0.403
<2 cm	14 (37.8)	1 (16.2)		
Tumor location				
neck	13 (35.1)	3 (50)	0.750	0.751
cauda	22 (59.5)	3 (50)		
multiple	2 (5.4)	0 (0)		

CA199: Carbohydrate Antigen199; CA125: Carbohydrate Antigen125; AFP: alPhafetoProtein; CEA: carcinoembryonic antigen; CgA: Chromogranin A; Syn: Synaptophysin; CD56: Neural Cell Adhesion Molecule 56; *P<0.05.

Association between hormone secretion syndrome and clinical/pathological features

Patients were divided according to the presence or absence of hormone secretion syndrome. Non-functional tumors (>2 cm) were significantly more common in patients without hormone secretion syndromes (P<0.05). No significant differences were observed in age, sex, treatment modality, or tumor location (all P>0.05) (**Table 4**).

Prognostic factor analysis

The median follow-up duration was 52 months (range: 6-116 months), and the median relapse-free survival (RFS) was 44 months (range: 6-112 months). Univariate Cox regression analysis identified tumor size >2 cm, G3 grade, liver metastasis, advanced AJCC stage, lymph node metastasis, microvascular invasion, and perineural invasion as risk factors for disease progression. Surgical treatment was a protective factor. Multivariate Cox regression showed that G3 grade (HR=2.931), liver metastasis (HR=5.783), and advanced AJCC stage (HR=4.574) were independent predictors of progression (**Tables 5**, **6**).

Survival analysis

The median overall survival was 97 months (95% CI: 84.5-109.7 months). The 2-year and 5-year overall survival rates were 69.7% and 44.2%, respectively. The median RFS was 70 months (95% CI: 56.8-83.2 months), with 2-year and 5-year RFS rates of 67.4% and 37.2%, respectively (**Figure 1**).

Comparison of RFS by WHO grade

Patients with G3 tumors had a significantly higher risk of recurrence than those with G1 or G2 tumors (P<0.05). No significant difference in RFS was observed between G1 and G2 tumors (P>0.05) (**Figure 2A**).

Comparison of RFS by AJCC stage

Patients with advanced-stage disease had significantly lower RFS than those with early to middle-stage disease (P<0.05) (**Figure 2B**).

Comparison of baseline data between pNET patients and healthy controls

There were no significant differences in baseline characteristics (age, sex, hypertension, or diabetes) between pNET patients and healthy controls (all P>0.05). However, levels of CA19-9, CA125, AFP, CEA, and NSE were significantly higher in the pNET group (all P<0.05). These

Table 4. Relationship between clinical pathological features of pNETs and hormone secretion syndromes

Variable	Non-functional (n=37)	Functional (n=6)	χ^2	P
Age				
≥60	18 (48.6)	2 (33.3)	-	0.669
<60	19 (51.4)	4 (66.7)		
Gender				
Male	16 (43.2)	4 (66.7)	-	0.393
Female	21 (56.8)	2 (33.3)		
WHO Pathological Grading				
G1	11 (29.7)	1 (16.7)	1.345	0.564
G2	20 (54.1)	5 (83.3)		
G3	6 (16.2)	0 (0)		
Immunohistochemical markers				
CgA	35 (94.6)	5 (83.3)	-	0.370
Syn	36 (97.3)	6 (100)	-	1.00
CD56	35 (94.6)	5 (83.3)	-	0.370
Tumor markers				
CA199	7 (18.9)	0 (0)	2.314	0.128
CA125	3 (8.1)	1 (16.7)	-	0.465
AFP	1 (2.70)	0 (0)	-	1.00
CEA	4 (10.8)	1 (16.7)	-	0.547
NSE	7 (18.9)	2 (33.3)	-	0.589
Treatment mode				
Surgical	32 (86.5)	5 (83.3)	0.041	0.840
Non-surgical	5 (13.5)	1 (16.7)		
Tumor location				
neck	15 (40.5)	1 (16.7)	1.884	0.338
cauda	18 (48.7)	5 (83.3)		
multiple	4 (10.8)	0 (0)		
Tumor diameter				
≥2 cm	27 (73.0)	1 (16.7)	-	0.015*
<2 cm	10 (27.0)	5 (83.3)		

CA199: Carbohydrate Antigen199; CA125: Carbohydrate Antigen125; AFP: alPhafetoProtein; CEA: carcinoembryonic antigen; CgA: Chromogranin A; Syn: Synaptophysin; CD56: Neural Cell Adhesion Molecule 56; *P<0.05. pNETs: pancreatic neuroendocrine tumors.

markers demonstrated good diagnostic performance for pNETs (**Tables 7**, **8**; **Figure 3**).

Discussion

PNETs are relatively rare neoplasms, with an estimated incidence of approximately 1 per 100,000 individuals, accounting for 1%-2% of all pancreatic tumors. Data from the U.S. Surveillance, Epidemiology, and End Results program report an annual incidence of approximately 0.22 per 100,000, with a rising trend in recent years. Due to their rarity and often non-specific clinical symptoms, pNETs are prone to misdiagnosis or delayed diagnosis in clinical settings.

This study analyzed the clinical and pathological characteristics of pNETs in a single-center cohort over a 20-year period and explored their associations with patient prognosis. Consistent with previous literature, the majority of pNETs in this cohort were non-functional (86%), which aligns with findings by previous scholar, though the proportion observed here is higher than in some other reports. This discrepancy may be attributable to the small sample size or to increased detection of functional tumors due to improved diagnostic methods [12, 13].

Prior studies have confirmed that most pNETs are non-functional and asymptomatic, which underscores the importance of imaging in early detection. Computed tomography (CT) is typically the first-line imaging modality, with a reported sensitivity of 62%-83%. For lesions smaller than 2 cm, magnetic resonance imaging (MRI) is generally more sensitive than CT. Positron emission tomography (PET) can assess for metastatic disease, while endoscopic ultrasound (EUS) is particularly useful for detecting small tumors under 1 cm, with a sensitivity of 77%-95% [9].

Based on the findings from our 43-patient cohort, we recommend the routine use of high-resolution imaging such as CT and MRI in the preoperative evaluation of suspected pNETs. In addition, EUS and preoperative biopsy, when feasible, can increase the likelihood of early diagnosis and appropriate surgical planning. These approaches have improved the detection of non-functional tumors that were previ-

Table 5. Univariate and multivariate cox regression analysis of prognostic factors in pNETs patients

	Univariate Cox regression			Multivariate Cox regression		
	HR	95% CI	P	HR	95% CI	P
Tumor size (≥2 cm)	5.744	1.317-25.047	0.020*			
Pathological grade (G3)	17.435	3.287-92.476	0.001*	2.931	1.022-8.410	0.046*
Concomitant liver metastasis (yes)	6.737	2.211-20.529	0.001*	5.783	1.527-21.904	0.010*
Surgical treatment (yes)	0.010	0.032-0.317	0.000*			
Lymph node metastasis (yes)	6.364	2.204-18.378	0.001*			
Microvascular invasion (yes)	4.989	1.670-14.902	0.004*			
Nerve invasion (yes)	3.230	1.219-8.563	0.018*			
AJCC staging (late stage)	35.804	3.855-332.504	0.002*	4.574	2.121-9.865	0.000*

AJCC: American Joint Committee on Cancer; pNETs: pancreatic neuroendocrine tumors. *P<0.05.

Table 6. Logistic regression analysis variable assignment table

Variable	Assignment
Tumor size (≥2 cm)	0= Nothing, 1= Something
Pathological grade (G3)	Original value
Concomitant liver metastasis (yes)	0= Nothing, 1= Something
Surgical treatment (yes)	0= Nothing, 1= Something
Lymph node metastasis (yes)	0= Nothing, 1= Something
Microvascular invasion (yes)	0= Nothing, 1= Something
AJCC staging (late stage)	Original value

AJCC: American Joint Committee on Cancer.

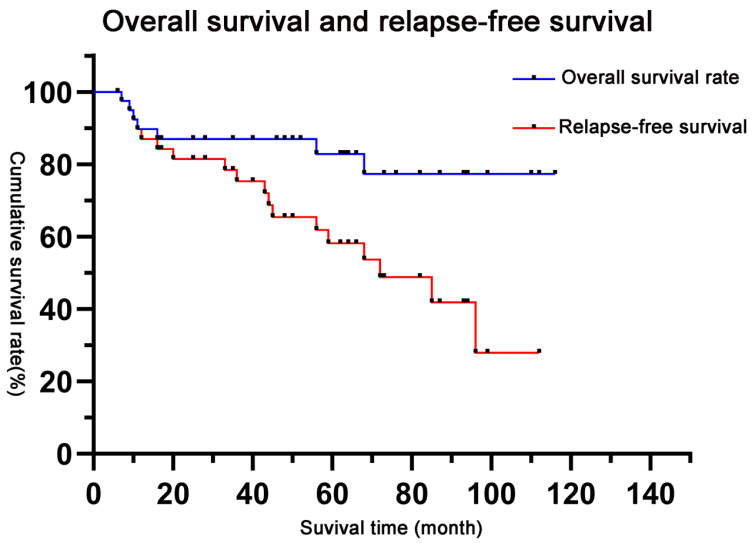

Figure 1. Overall survival and recurrence-free survival rates in the study cohort.

ously difficult to identify and are consistent with prior findings [14, 15].

In agreement with an Italian multicenter retrospective study [16], our analysis found no significant sex-based differences in pNET incidence. However, a large-scale U.S. database study reported a higher incidence in males [11]. Although our findings differ, this inconsistency may be related to racial or regional variations in gender-specific incidence, highlighting the need for multicenter studies in the Chinese population.

It is well established that functional tumors often produce symptoms early due to hormone hypersecretion, facilitating earlier diagnosis and generally smaller tumor size at detection [17]. In contrast, non-functional tumors are typically asymptomatic and are diagnosed later, usually at a larger size due to mass effect. Our findings support this pattern. However, in contrast to prior reports, we did not observe significant differences in WHO pathological grade distribution between functional and non-functional tumors. Previous studies have suggested that non-functional pNETs are more frequently classified as high-grade, while functional tumors are often G1 or G2 [18]. For example, Marini et al. reported that non-functional pNETs tend to have more insidious onset, poorer differentiation, and lower surgical resectability [19]. The inconsistency with our data may be due to improvements in

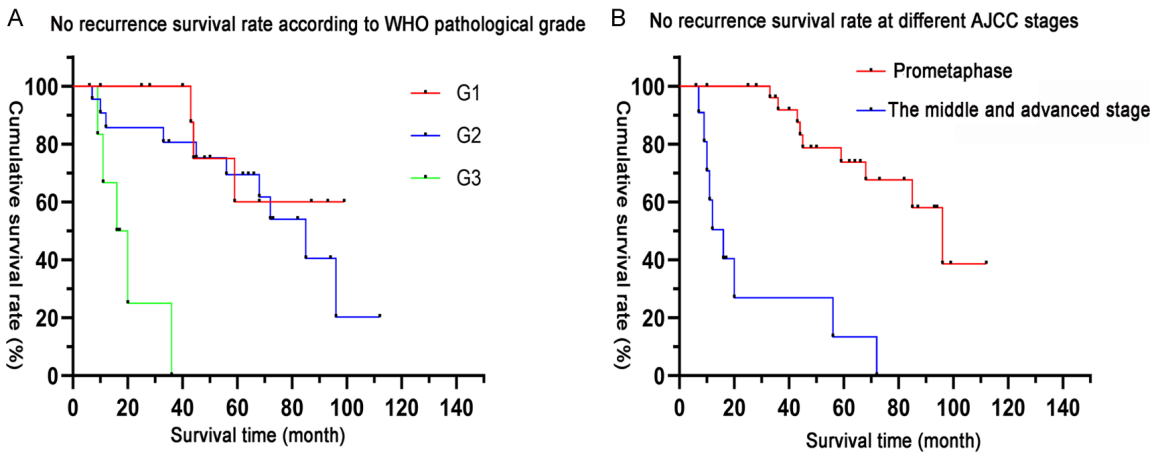

Figure 2. Comparison of recurrence-free survival rates among different pathological grades and clinical stages. A. Recurrence-free survival rates for different WHO pathological grades. B. Recurrence-free survival rates for different AJCC clinical stages.

Table 7. General information of pNETs and the control group

Variable	pNETs group (n=43)	Healthy individuals group (n=50)	*P*-value
Age (yr)	58.4±2.8	58.8±3.0	0.556
BMI	25.2±1.9	24.8±2.2	0.421
Male	23	27	0.224
Hypertension	8	10	0.775
Diabetes	5	5	0.557
CA199	12.44 (6.45, 22.08)	8.05 (4.8, 14.7)	0.646
CA125	9.15 (7.06, 14.66)	14.99 (9.57, 29.36)	0.810
AFP	14.3 (2.6, 16.3)	12.2 (2.2, 15.8)	0.267
CEA	2.92 (1.78, 5.59)	1.86 (1.31, 2.66)	0.344
NSE	22.30 (16.85, 24.74)	17.5 (14.53, 21.38)	0.486

pNETs: Pancreatic neuroendocrine tumors; CA199: Carbohydrate Antigen199; CA125: Carbohydrate Antigen125; AFP: alPhafetoProtein; CEA: carcinoembryonic antigen.

Table 8. Diagnostic efficacy of serum markers

Variable	Cut-off	AUC	AUC (95% CI)
AFP	15.5	0.658	0.537-0.779
CEA	3.08	0.685	0.572-0.798
NSE	23.5	0.810	0.725-0.985
CA199	13.29	0.993	0.983-0.995
CA125	10.74	0.883	0.812-0.954

CA199: Carbohydrate Antigen199; CA125: Carbohydrate Antigen125; AFP: alPhafetoProtein; CEA: carcinoembryonic antigen.

diagnostic imaging, which now allow for earlier detection of small, less aggressive non-functional tumors that were previously missed.

This study also found no significant differences in tumor location (head, body, or tail of the pancreas), AJCC stage distribution, or WHO grade distribution, findings that are consistent with previous reports [20, 21].

Previous studies have confirmed the diagnostic value of serological markers in pancreatic tumors. In this study, five markers - CA19-9, CEA, AFP, CA125, and NSE - demonstrated good diagnostic performance in pNETs, with underlying mechanisms discussed as follows:

CA19-9 is a widely used biomarker in digestive system malignancies, particularly pancreatic adenocarcinoma. Although less specific to pNETs, elevated CA19-9 levels have been observed in some pNET cases, likely due to its association with the secretory activity of tumor cells. Thus, CA19-9 may serve as an auxiliary diagnostic indicator, especially in patients with unexplained gastrointestinal symptoms.

CEA, a common tumor marker in colorectal and pancreatic cancers, shows limited sensitivity in pNETs. However, it may provide prognostic value during disease progression, as dynamic changes in CEA levels can reflect tumor biology and guide clinical decision-making.

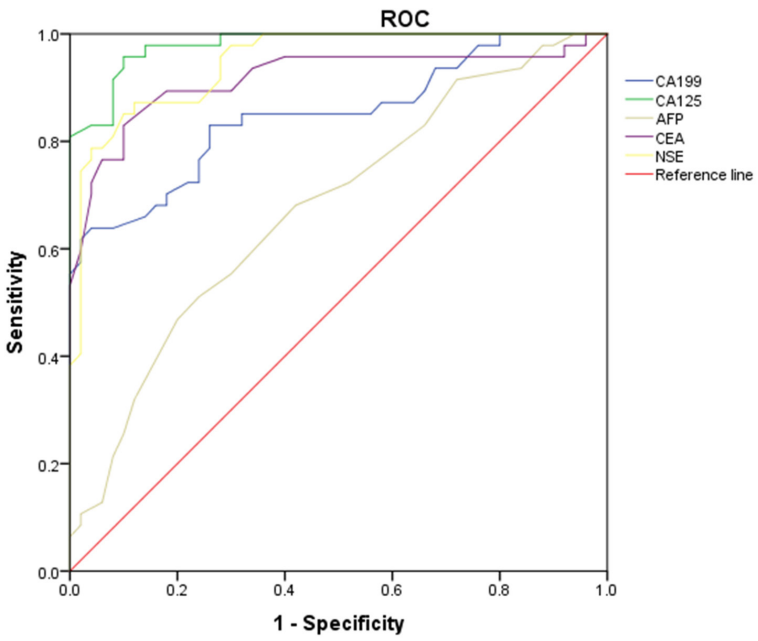

Figure 3. Receiver operating characteristic (ROC) curves illustrating the diagnostic performance of serum CA19-9, CA125, AFP, CEA, and NSE levels in patients with pancreatic neuroendocrine tumors. CA199: Carbohydrate Antigen199; CA125: Carbohydrate Antigen125; AFP: alPhafetoProtein; CEA: carcinoembryonic antigen.

AFP is primarily associated with hepatocellular carcinoma and germ cell tumors. However, rare cases of pNETs with elevated AFP levels have been reported, possibly due to atypical antigen expression. Although uncommon, AFP should not be disregarded when evaluating pNETs, especially in complex presentations.

CA125, typically used in ovarian cancer, has been found to be elevated in some pancreatic tumors, particularly those accompanied by ascites or inflammatory responses. While its specificity is low, its potential as a supplementary diagnostic tool in pNETs warrants further investigation.

NSE is closely associated with neuroendocrine tumors. Elevated NSE levels reflect neuroendocrine cell proliferation and tumor burden. Given its relatively high sensitivity and specificity in pNETs, NSE is a valuable clinical biomarker in diagnosis and monitoring [22-25].

In addition, analysis of tissue biomarkers showed significantly higher CD56 expression in low-grade tumors than in high-grade ones. This finding suggests that CD56 may be associated with tumor grade and, potentially, prognosis. As no prior studies have clearly addressed this relationship, further basic and clinical research is needed to validate these observations.

This study also found that early- and middle-stage pNET patients were more likely to have G1 or G2 tumors, while advanced-stage patients had a higher proportion of G2 and G3 tumors. These findings suggest a link between clinical stage and tumor aggressiveness. G3 tumors are typically more invasive and proliferative, limiting surgical options and leading to worse outcomes. Univariate analysis identified G3 tumors as significantly associated with poor prognosis, and survival analysis further supported the correlation between higher tumor grade and decreased survival. These results are consistent with previous findings by Shyr et al., who also reported tumor grade as an independent prognostic factor [25].

Univariate Cox regression analysis revealed that lymph node metastasis, microvascular invasion, and perineural invasion were significantly associated with poorer prognosis, indicating more advanced disease. For such patients, aggressive surgical strategies may improve survival, but further large-scale studies are needed. Multivariate analysis identified liver metastasis and advanced clinical stage as independent predictors of poor outcomes. These factors are associated with increased tumor proliferative and metastatic potential, emphasizing the need for close follow-up and early intervention to manage recurrence.

In our cohort, the 2-year and 5-year survival rates were significantly lower than those reported in earlier studies [26, 27]. This discrepancy may be due to the lower rate of early diagnosis and treatment in this region or the fact that many patients presented at advanced stages.

Enhancing early detection and intervention in the local healthcare system is critical to improving survival outcomes.

This study has several limitations. First, as a retrospective analysis, the data were derived from historical medical records, which may be incomplete or inaccurate, introducing potential bias. Second, the data span two decades during which diagnostic and treatment strategies have evolved, possibly affecting the consistency of findings. Third, the rarity of pNETs limited the sample size, which may reduce the statistical power of the analysis. Larger multicenter studies are necessary to confirm these results and improve the generalizability of the findings.

In conclusion, this study identified G3 grade, liver metastasis, and advanced AJCC stage as independent predictors of poor prognosis in pNETs. Non-functional tumors were more likely to be larger and asymptomatic. Elevated CA125, CA19-9, CEA, AFP, and NSE levels showed diagnostic value, and CD56 was associated with low-grade tumors. These findings provide valuable insights into the diagnosis and prognostic assessment of pNETs, supporting more precise clinical management.

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Disclosure of conflict of interest

None.

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References

[1] Panzuto F, Partelli S, Campana D, de Braud F, Spada F, Cives M, Tafuto S, Bertuzzi A, Gelsomino F, Bergamo F, Marcucci S, Mastrangelo L, Massironi S, Appetecchia M, Filice A, Badalamenti G, Bartolomei M, Amoroso V, Landoni L, Rodriquenz MG, Valente M, Colao A, Isidori A, Fanciulli G, Bollina R, Ciola M, Butturini G, Marconcini R, Arvat E, Cinieri S, Berardi R, Baldari S, Riccardi F, Spoto C, Giuffrida D, Gattuso D, Ferone D, Rinzivillo M, Bertani E, Versari A, Zerbi A, Lamberti G, Lauricella E, Pusceddu S, Fazio N, Dell'Unto E, Marini M and Falconi M. Epidemiology of gastroenteropancreatic neuroendocrine neoplasms: a review and protocol presentation for bridging tumor registry data with the Italian association for neuroendocrine tumors (Itanet) national database. Endocrine 2024; 84: 42-47.

[2] Kamboj S, Guerra-Bauman F, Mahmud H and Waheed A. Neuroendocrine neoplasms. Prim Care 2024; 51: 549-560.

[3] Kos-Kudła B, Castaño JP, Denecke T, Grande E, Kjaer A, Koumarianou A, de Mestier L, Partelli S, Perren A, Stättner S, Valle JW and Fazio N. European Neuroendocrine Tumour Society (ENETS) 2023 guidance paper for nonfunctioning pancreatic neuroendocrine tumours. J Neuroendocrinol 2023; 35: e13343.

[4] Tacelli M, Partelli S, Falconi M, Arcidiacono PG and Capurso G. Pancreatic neuroendocrine neoplasms: classification and novel role of endoscopic ultrasound in diagnosis and treatment personalization. United European Gastroenterol J 2025; 13: 34-43.

[5] Muller M, Hammel P, Couvelard A, Védie AL, Cros J, Burnichon N, Hercent A, Sauvanet A, Richard S and de Mestier L. Pancreatic neuroendocrine tumors in French VHL mutation carriers. J Clin Endocrinol Metab 2025; 110: e1160-e1166.

[6] Zhang XB, Fan YB, Jing R, Getu MA, Chen WY, Zhang W, Dong HX, Dakal TC, Hayat A, Cai HJ, Ashrafizadeh M, Abd El-Aty AM, Hacimuftuoglu A, Liu P, Li TF, Sethi G, Ahn KS, Ertas YN, Chen MJ, Ji JS, Ma L and Gong P. Gastroenteropancreatic neuroendocrine neoplasms: current development, challenges, and clinical perspectives. Mil Med Res 2024; 11: 35.

[7] Nagesh M, Gowtham S, Bharadwaj B, Ali M, Goud AK and Siddiqua S. Evolution of TNM classification for clinical staging of oral cancer: the past, present and the future. J Maxillofac Oral Surg 2023; 22: 710-719.

[8] Sanguedolce F, Zanelli M, Palicelli A, Cavazza A, DE Marco L, Zizzo M, Ascani S, Landriscina M, Giordano G, Sollitto F and Loizzi D. The classification of neuroendocrine neoplasms of the lung and digestive system according to WHO, 5th edition: similarities, differences, challenges, and unmet needs. Panminerva Med 2022; 64: 259-264.

[9] Kintu C, Soremekun O, Kamiza AB, Kalungi A, Mayanja R, Kalyesubula R, Bagaya S B, Jjingo

D, Fabian J, Gill D, Nyirenda M, Nitsch D, Chikowore T and Fatumo S. The causal effects of lipid traits on kidney function in Africans: bidirectional and multivariable Mendelian-randomization study. EBioMedicine 2023; 90: 104537.
[10] World Medical Association. World medical association declaration of helsinki: ethical principles for medical research involving human participants. JAMA 2025; 333: 71-74.
[11] Liu X, Chen B, Chen J, Su Z and Sun S. The incidence, prevalence, and survival analysis of pancreatic neuroendocrine tumors in the United States. J Endocrinol Invest 2023; 46: 1373-1384.
[12] Hofland J, Falconi M, Christ E, Castaño JP, Faggiano A, Lamarca A, Perren A, Petrucci S, Prasad V, Ruszniewski P, Thirlwell C, Vullierme MP, Welin S and Bartsch DK. European neuroendocrine tumor society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. J Neuroendocrinol 2023; 35: e13318.
[13] Alipour Z, Sweeney JR, Zhang Q and Yang Z. Neuroendocrine neoplasms of the pancreas: diagnostic challenges and practical approach. Adv Anat Pathol 2023; 30: 58-68.
[14] Sonbol MB, Mazza GL, Mi L, Oliver T, Starr J, Gudmundsdottir H, Cleary SP, Hobday T and Halfdanarson TR. Survival and incidence patterns of pancreatic neuroendocrine tumors over the last 2 decades: a SEER database analysis. Oncologist 2022; 27: 573-578.
[15] Chauhan A, Kohn E and Del Rivero J. Neuroendocrine tumors-less well known, often misunderstood, and rapidly growing in incidence. JAMA Oncol 2020; 6: 21-22.
[16] Muscogiuri G, Altieri B, Albertelli M, Dotto A, Modica R, Barrea L, Fanciulli G, Feola T, Baldelli R, Ruggeri RM, Gallo M, Guarnotta V, Malandrino P, Messina E, Venneri MA, Giannetta E, Ferone D, Colao A and Faggiano A; NIKE group. Epidemiology of pancreatic neuroendocrine neoplasms: a gender perspective. Endocrine 2020; 69: 441-450.
[17] Wang SE, Su CH, Kuo YJ, Shyr YM, Li AF, Chen TH, Wu CW and Lee CH. Comparison of functional and nonfunctional neuroendocrine tumors in the pancreas and peripancreatic region. Pancreas 2011; 40: 253-259.
[18] Ya L, Yan J, Yilin H, Jie W, Hanyue W and Yuxin S. Analysis of clinical features of pancreatic neuroendocrine tumors: a report of 111 cases. Chin J Gen Surg 2023; 32: 1305-1312.
[19] Marini F, Giusti F, Tonelli F and Brandi ML. Pancreatic neuroendocrine neoplasms in multiple endocrine neoplasia type 1. Int J Mol Sci 2021; 22: 4041.
[20] Wu WM, Chen J, Bai CM, Chi Y, Du YQ, Feng ST, Huo L, Jiang YX, Li JN, Lou WH, Luo J, Shao CH, Shen L, Wang F, Wang LW, Wang O, Wang Y, Wu HW, Xing XP, Xu JM, Xue HD, Xue L, Yang Y, Yu XJ, Yuan CH, Zhao H, Zhu XZ and Zhao YP; Chinese Pancreatic Surgery Association, Chinese Society of Surgery, Chinese Medical Association. The Chinese guidelines for the diagnosis and treatment of pancreatic neuroendocrine neoplasms (2020). Zhonghua Wai Ke Za Zhi 2021; 59: 401-421.
[21] Ma ZY, Gong YF, Zhuang HK, Zhou ZX, Huang SZ, Zou YP, Huang BW, Sun ZH, Zhang CZ, Tang YQ and Hou BH. Pancreatic neuroendocrine tumors: a review of serum biomarkers, staging, and management. World J Gastroenterol 2020; 26: 2305-2322.
[22] Jun W, Hang L, Guoliang L and Wei W. Expression of serum tumor markers in gastrointestinal and pancreatic neuroendocrine tumors. Chin J Prev Contr Chron Dis 2018; 26: 783-786.
[23] Ran CL, Shi HF, Ma CM, Hang YJ, Sun ZQ and Wang ZX. Diagnostic value of CEA, CA125 and CA199 in neuroendocrine tumors of digestive tract. Lab Med Clin 2023; 20: 3658-3661+3667.
[24] Wang SJ, Kidder W, Joseph NM, Le BK, Lindsay S, Moon F, Nakakura EK, Zhang L and Bergsland EK. Factors associated with grade progression in pancreatic neuroendocrine tumors. Endocr Relat Cancer 2025; 32: e240203.
[25] Rindi G and Inzani F. Differentiation versus grade for pancreatic neuroendocrine neoplasms. Arch Pathol Lab Med 2025; [Epub ahead of print].
[26] Bader A, Landau S, Hwang J, Passman J, Lee MK, Fraker D, Vollmer C and Wachtel H. Recurrence and treatment trends of pancreatic neuroendocrine tumors. Surgery 2025; 177: 108835.
[27] Giri S and Sahoo J. Advancements in medical treatment for pancreatic neuroendocrine tumors: a beacon of hope. World J Gastroenterol 2024; 30: 1670-1675.