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Serum Lipid Level in Evaluating Chinese Pancreatic Neuroendocrine Neoplasms: A Retrospective Study

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ABSTRACT

Background Pancreatic neuroendocrine neoplasms (p-NENs) are relatively rare and highly heterogeneous. Dyslipidemia may be related to the risk of developing p-NENs, although dyslipidemia in patients with p-NENs is rarely reported. In this study, the clinical characteristics of p-NENs patients with different lipid levels and their prognostic value in p-NENs patients were evaluated.

Methods Patients (n = 211) with p-NENs hospitalized at Jiangsu Neuroendocrine Tumor Centre of Jiangsu Province Hospital from December 2018 to December 2022 were enrolled. Clinical data related to p-NENs were collected. Based on the EGA database, the related lipoprotein, low-density lipoprotein receptor (LDLR) and high-density lipoprotein binding protein (HDLBP) mRNA in p-NENs and paratumoral tissues and the follow-up information of p-NENs were evaluated.

Results A total of 175 p-NENs patients ultimately met the inclusion criteria. The ki67 index was higher in p-NENs patients with elevated lipid with the proportion of ≥ 5, and in those with AJCC stage III and stage IV than p-NENs patients with low-level lipid. In p-NENs patients, the expression of HDLBP mRNA was downregulated in p-NENs tissues compared to the paratumoral tissues. Survival analysis showed that serum lipids had no effect on the prognosis of p-NENs; however, high LDLR level p-NENs were at the risk of poor survival.

Conclusion Serum lipid level in p-NENs can affect the grading and staging, but the correlation with the prognosis of p-NENs is not significant. However, dyslipidemia may be a potential predictor of p-NENs.

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Introduction

Pancreatic neuroendocrine neoplasms (p-NENs) are considered relatively rare tumors, accounting for only 1–2 % of all pancreatic tumors [1]. According to the Surveillance, Epidemiology, and End Results database, the incidence of p-NENs is 0.48–0.7/100 000 [2, 3]. Broadly, p-NENs can be divided into functional (F-p-NENs) and non-functional (NF-p-NENs) tumors according to clinical manifestations. NF-p-NENs account for 43–90 % of p-NENs, and it is not associated with hormone secretion syndrome. The characteristics of F-p-NENs are that tumor tissues secrete one or multiple hormones, including insulin, gastrin, glucagon, somatostatin, and vasoactive intestinal peptides. Most p-NENs are malignant, with metastases happening in more than 60 % of patients at the time of diagnosis. Despite the high rate of metastasis, the prognosis for p-NENs patients is still good [4–6].

In recent years, metabolic reprogramming has become an important marker of tumors. In particular, lipid metabolism plays a crucial role in bioenergetics and biomass formation of tumor cells [7]. More studies show that lipid metabolism is one of the targets for the treatment of tumors [8]. As a malignant tumor, lipid metabolism has an important effect on the occurrence and development of p-NENs. In recent years, several clinical and basic studies have focused on lipids and neuroendocrine tumors (NET); some clinical studies have pointed out that blood lipids are correlated with NET in the stomach, small intestine, rectum, etc. Meanwhile, some basic studies have shown that the lipid metabolism of NET may be related to neutrophil-mediated angiogenesis, inflammation, and oxidative stress [9]. In this work, we compared the clinical features of patients with high lipid level p-NENs with those having normal lipid level p-NENs and examined the diagnostic utility of lipid levels in p-NENs. For a better understanding of the role of lipid metabolism in the occurrence and development of pNENs, we utilized the European Genome-phenome Archive (EGA) data to identify differential lipid metabolism-related targets between p-NENs and non-p-NENs and assessed their prognostic value in p-NENs. Our study provides a new perspective for the study of lipid metabolism in p-NENs.

Materials and Methods

Patients and data collection

We collected data from 211 patients hospitalized at Jiangsu Neuroendocrine Tumor Centre of Jiangsu Province Hospital from December 2018 to December 2022. Among these, 161 patients were pathologically diagnosed with p-NENs, 14 were clinically confirmed as p-NENs, and 36 patients without follow-up data were excluded. General clinical features, laboratory data, serum lipid levels, pathological data, treatment modalities, and prognosis were collected through electronic inpatient case system. Patient prognoses were followed up by telephone calls. The follow-up time ended on March 15, 2023.

European Genome-phenome Archive data

The gene expressions dataset used in this study was downloaded from the EGA database(http://ega-archive.org) and derived from microarray studies comparing the mRNA expression profiling between p-NENs tissues and paratumoral tissues. The mRNA expression data of Validation and Discovery were acquired to identify differential target genes of related lipoprotein in p-NENs. Follow-up information on p-NENs was obtained from EGA database. Based on the expression of related lipoprotein, 84 p-NENs patients with follow-up data were selected for survival analysis.

Statistical analysis

SPSS 23.0 statistical software and GraphPad Prism 9 were used for statistical analysis. Continuous variables and categorical variables were expressed as mean ± standard deviation and frequency respectively. T-test was used for the comparison of continuous variables with normal distribution, and the Chi-square test or Fisher exact test was used for the differential analysis of categorical variables. Pearson correlation analysis was performed to analyze the correlation between serum lipid levels and clinical characteristics of p-NENs. A linear regression analysis model was used to identify risk factors of p-NENs. Overall survival (OS) was calculated by the Kaplan-Meier method. P-value < 0.05 was considered a statistically significant difference.

Results

Clinical features, laboratory data, pathological data, treatment modalities, and prognosis between different serum lipid level in patients with p-NENs

(1) High cholesterol (CHOL) versus normal CHOL levels: This study summarized the demographic data, clinical characteristics, pathological characteristics, tumor grading, and staging of p-NENs with different cholesterol levels. Compared to p-NENs patients with normal cholesterol levels, those with high cholesterol levels showed significant differences in total metastasis rate (P = 0.022) (▶ **Table 1**).

(2) High triglyceride (TG) versus normal TG levels: There were no significant differences in age of onset, metastasis rate, and treatment among p-NENs patients with different TG levels (P > 0.05); however, compared with p-NENs patients with normal TG level, those with high TG levels showed significant differences in whether the tumor is functional (P = 0.047), Ki67 index (P = 0.001), and AJCC staging (P = 0.001) (▶ **Table 1**).

(3) Normal high-density lipoprotein (HDL) versus high HDL levels: Unlike CHOL and TG, HDL plays a different role in p-NENs; compared to p-NENs patients with high HDL levels, those with normal levels showed a significant difference in only maximum tumor diameter (P = 0.023) and ki67 index (P = 0.004) (▶ **Table 1**).

(4) High low-density lipoprotein (LDL) versus normal LDL levels: Based on different TG and HDL levels in p-NENs patients, the ki67 index was significantly different in those with different levels of LDL (P = 0.004) (▶ **Table 1**).

(5) High lipoprotein (Lip) versus normal Lip levels: In p-NENs patients with different levels of Lip, there were significant variations in the tumor functional status (P = 0.046), Ki67 index (P = 0.031), Syn (P = 0.049), and AJCC staging (P = 0.020) (▶ **Table 1**).

▶ **Table 1** Clinicopathological and follow-up information of p-NENs patients in different lipid level.

	High CHOL	Low CHOL	x^2 or F value	*P value*	High TG	Low TG	x^2 or F value	*P value*	Low HDL	High HDL	x^2 or F value	*P value*	High HDL	Low HDL	x^2 or F value	*P value*	High Lip	Low Lip	x^2 or F value	*P value*
Sex																				
Female	10	81	1.414	0.286	16	75	0.353	0.681	81	10	3.495	0.084	17	74	0.316	0.689	25	66	2.935	0.103
Male	5	79			12	72			81	3			13	71			14	70		
Age of onset (years)	57.20±9 74	55.24±1 3.04	0.843	0.360	54.86±1 2.74	55.58±1 2.82	0.174	0.677	55.5±1 2.69	54.23±1 4.29	0.344	0.732	55.93±1 0.08	55.29±1 3.3	0.248	0.805	57.64±1 4.53	54.76±12 22	1.212	0.216
Tumor classification																				
Func-tional	3	24	0.263	0.706	8	19	4.413	**0.047**	26	1	0.644	0.492	4	23	0.122	0.792	2	25	4.081	**0.046**
Non-func-tional	12	136			20	128			136	12			26	122			37	111		
Maximum tumor diameter (cm)																				
< 2	4	52			13	44			26	3			9	55			12	46		
2–4	4	59	1.552	0.496	8	61	2.932	0.234	52	8	7.053	**0.023**	9	53	**2.468**	0.303	16	55	0.199	0.947
> 4	7	49			7	42			84	2			12	37			11	35		
Neuroaggression																				
No	11	125	0.182	0.746	22	114	0.014	1	124	12	1.727	0.302	21	115	1.244	0.334	29	107	0.326	0.663
Yes	4	35			6	33			38	1			9	30			10	29		
Vascular invasion																				
No	11	122	0.064	1.000	21	112	0.018	1.000	119	12	2.272	0.189	20	113	1.729		28	105	0.487	0.526
Yes	4	38			7	35			43	1			10	32			11	31		
Pathological grading																				
G1	2	42			6	38			41	3			5	39			14	33		
G2	11	89	1.512	0.462	16	84	0.517	0.78	91	9	0.888	0.624	19	81	1.384	0.533	16	80	4.055	0.13
G3	2	29			6	25			30	1			6	25			9	23		
ki67 index (%)																				
<5	6	72			12	70			50	10			12	70			23	61		
5–20	6	63	0.448	0.887	11	22	9.103	**0.011**	85	2	10.007	**0.004**	5	52	10.940	**0.004**	7	54	6.778	**0.031**
>20	3	25			5	55			27	1			13	23			9	21		
Syn																				
-	0	2	0.190	1.000	0	2	0.385	1.000	1	1	5.332	0.143	0	2	0.419	1.000	2	0	7.055	**0.049**
+	15	158			28	145			161	12			30	143			37	136		
CgA																				
-	0	4			0	9			8	1			1	8			3	6		
+	15	156	0.384	1.000	28	138	1.807	0.358	154	12	0.187	1.000	29	137	0.243	0.708	36	130	0.669	0.686

▶ **Table 1** Continued.

	High CHOL	Low CHOL	x^2 or F value	*P value*	High TG	Low TG	x^2 or F value	*P value*	Low HDL	High HDL	x^2 or F value	*P value*	High HDL	Low HDL	x^2 or F value	*P value*	High Lip	Low Lip	x^2 or F value	*P value*
Metastasis																				
No	5	106	6.406	**0.014**	19	96	0.068	0.832	106	11	2.072	0.224	17	98	1.315	0.292	21	94	3.137	0.087
Yes	10	54			9	51			57	2			13	47			18	42		
Lymph node																				
metastasis																				
No	10	119	0.421	0.544	19	96	0.068	0.832	120	11	0.710	0.521	20	109	0.928	0.365	25	104	2.393	0.149
Yes	5	41			9	51			42	2			10	36			14	32		
Peripheral organ metastasis																				
No	12	136	0.263	0.706	23	126	0.237	0.772	135	13	2.562	0.136	23	126	2.056	0.163	32	117	0.379	0.610
Yes	3	24			5	21			27	0			7	19			7	19		
Distant metastasis																				
No	12	133	0.094	1.000	25	120	0.970	0.420	133	12	0.883	0.472	22	123	2.312	0.180	34	103	2.335	0.185
Yes	3	27			3	27			29	1			8	22			5	33		
AJCC stage																				
I	4	49	0.965	0.845	13	40	15.918	**0.001**	50	3	4.132	0.217	9	44	2.567	0.459	10	43	9.643	**0.02**
II	5	62			6	61			60	7			9	58			12	55		
III	3	22			6	19			23	2			4	21			12	13		
IV	3	27			3	27			29	1			8	22			5	25		
Operation or not																				
No	1	14	0.076	1.000	11	46	0.684	0.510	54	3	0.576	0.551	7	48	1.101	0.389	10	47	1.097	0.337
Yes	14	146			17	101			108	10			23	97			29	89		
Prognosis																				
Sur-vival	11	137	1.588	0.25	24	124	0.033	1.000	135	13	2.562	0.136	22	126	3.505	0.091	34	114	0.262	0.663
Death	4	23		5	4	23			27	0			8	19			5	22		

Statistical method: Chi-square test or Fisher exact test. CHOL, cholesterol; TG, triglyceride; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; Lip, lipoprotein; p-NENs, pancreatic neuroendocrine neoplasms; CgA, chromogranin A.

▶ **Table 2** Correlation analysis between blood lipid level and clinical indexes of p-NENs patients (r(*P*)/F(*P*).

Serum lipid	CHOL	TG	HDLC	LDLC	Lip
Age of onset (years)	0.006 (0.933)	0.052 (0.498)	−0.035 (0.641)	−0.030 (0.695)	0.064 (0.398)
Tumor classification	1.105 (0.391)	0.940 (0.615)	1.078 (0.363)	0.759 (0.892)	0.776 (0.836)
Maximum tumor diameter (cm)	−0.021 (0.787)	−0.011 (0.884)	−0.098 (0.195)	−0.028 (0.716)	0.065 (0.396)
Neuro aggression	0.902 (0.665)	1.194 (0.245)	0.872 (0.736)	0.998 (0.515)	1.034 (0.478)
Vascular invasion	0.961 (0.581)	1.277 (0.168)	0.841 (0.789)	1.075 (0.389)	0.885 (0.691)
Pathological grading	0.680 (0.928)	0.930 (0.663)	0.720 (0.936)	0.908 (0.672)	1.150 (0.337)
Ki67 index/ %	−0.038 (0.618)	0.107 (0.161)	−0.086 (0.259)	−0.037 (0.630)	−0.024 (0.752)
Syn	0.591 (0.977)	0.749 (0.897)	**3.093 (0.0000014)**	0.313 (1.000)	1.356 (0.186)
CgA	0.776 (0.834)	0.506 (0.999)	0.723 (0.933)	1.196 (0.232)	1.316 (0.191)
Metastasis	1.302 (0.205)	1123 (0.329)	0.915 (0.659)	0.951 (0.579)	0.669 (0.938)
Lymph node metastasis	1.495 (0.102)	0.955 (0.590)	1.031 (0.442)	1.039 (0.447)	0.777 (0.834)
Peripheral organ metastasis	1.065 (0.439)	1.251 (0.190)	0.998 (0.503)	1.008 (0.498)	0.656 (0.946)
Distant metastasis	1.126 (0.367)	1.134 (0.315)	0.728 (0.930)	0.978 (0.550)	0.964 (0.576)
AJCC stage	1.241 (0.253)	0.851 (0.762)	0.859 (0.759)	0.826 (0.805)	1.270 (0.225)
Prognosis	0.731 (0.899)	1.359 (0.114)	0.814 (0.830)	0.905 (0.678)	1.471 (0.108)

Statistical method: Pearson correlation analysis. CHOL, cholesterol; TG, triglyceride; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; Lip, lipoprotein; p-NENs, pancreatic neuroendocrine neoplasms.

Pearson correlation analysis to assess the relationship between lipid levels in p-NENs and clinical characteristics of p-NENs

We analyzed the relationship of demographic data, clinical characteristics, pathological characteristics, tumor grading and staging and tumor prognosis with serum lipid level of p-NENs. The results showed no significant differences in demographic data, clinical characteristics, tumor grading and staging, tumor prognosis with serum lipid level ($P > 0.05$). However, only one pathological characteristic, Syn, differed significantly from HDL ($P < 0.0001$) (▶ **Table 2**).

Linear regression analysis of risk factors for p-NENs

CHOL, TG, HDL, LDL, and Lip levels of patients with p-NENs were used as independent variables, and age of onset, tumor function, maximum tumor diameter, tumor grade, neurovascular invasion, ki67 % index, positive Syn and chromogranin A, metastasis, and prognosis were used as dependent variables. Multiple linear regression analysis revealed that TG is an influential factor of tumor function ($P = 0.04$) and HDL is an influential factor of tumor metastasis ($P = 0.002$). Finally, Lip is an influential factor in determining whether Syn is positive in specific tumor pathology ($P = 0.011$). (▶ **Table 3**).

The Kaplan-Meier survival analysis for p-NENs

The Kaplan-Meier survival analysis showed that different serum lipid levels in p-NENs patients had no significant correlation with OS (▶ **Fig. 1**).

Differential expression of low-density lipoprotein receptor (LDLR) and high-density lipoprotein binding protein (HDLBP) mRNAs and their prognostic value in p-NENs

Analysis of the levels of LDLR and HDLBP mRNAs using Validation and Discovery cohorts from the EGA database showed that HDLPB mRNA expressions were significantly downregulated in p-NENs tissue compared with the paired adjacent noncancerous tissues ($P < 0.0001$) (▶ **Fig. 2**). Meanwhile, using the data of 84 patients with p-NENs from the EGA database, the clinical characteristics of patients with different LDLR and HDLBP gene expression levels were compared. The clinical data and follow-up information are presented in ▶ **Table 4**. Patients with p-NENs with a high LDLR expression had poor prognosis ($P = 0.1781$) (▶ **Fig. 3**), and those with a high LDLR ($P = 0.03$) expression had a longer follow-up period (▶ **Table 5**).

Discussion

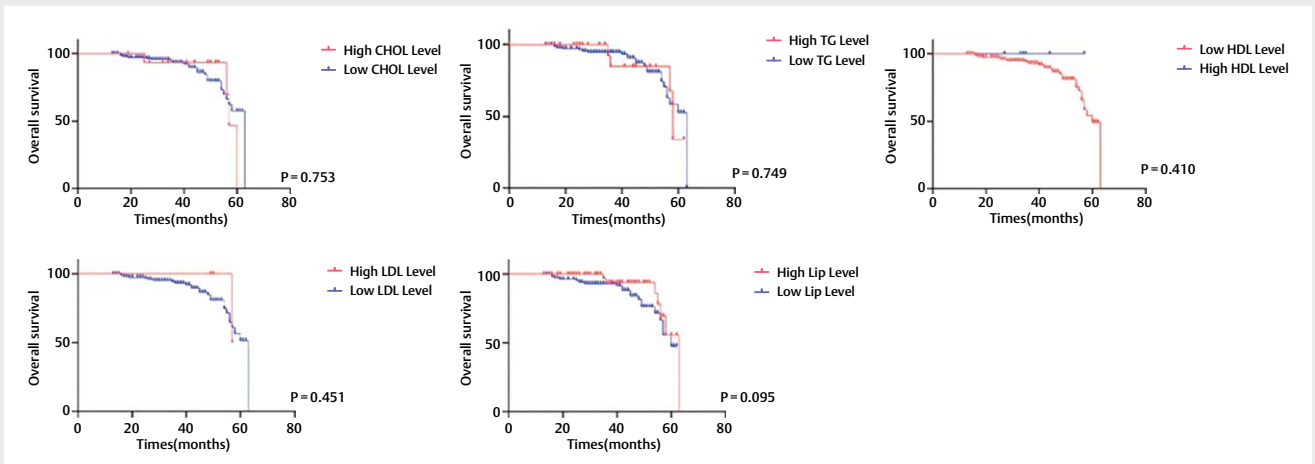
Tumor cells have unique metabolic characteristics, and lipid metabolism affects many biological behaviors of tumor cells. At present, more studies have revealed that lipid metabolism can affect tumor progression [10]. However, the role of lipid metabolism in the occurrence and development of neuroendocrine tumors, including p-NENs, is rarely noticed. Through the collection of clinical cases and data related to serum lipid levels and clinical characteristics of p-NENs patients, this study illustrates the influence of different serum lipid levels on the clinical characteristics of p-NENs patients.

In our study, compared with p-NENs patients with low serum lipid levels, those with high serum lipid levels had a higher transfer rate and high TG levels, the proportion of ki67 index (≥ 5), and AJCC stage III and stage IV were higher. The pathologic grade of neuroendocrine tumors is based on the Ki67 index, and the grading and staging of p-NENs greatly influence the choice of treatment and prognosis [11]. In general, according to the statistics of our study, p-NENs patients with high lipid levels may have higher tumor grade and stage and relatively poor prognosis. Lipid metabolism is now recognized as an important pathway in cancer development. Lipid metabolism can provide additional sources of energy required for

▶ **Table 3** Multiple linear regression analysis of clinical features of p-NENs patients (1) whether the tumor is functional; (2) whether the tumor has metastases; (3) whether Syn was positive.

(1)	Variable	Regression coefficient	Regression coefficient	Regression coefficient (after adjustment)	t value	*P-value*
	Constant	0.065	0.128	–	−0.504	0.615
	CHOL	−0.001	0.001	−0.039	−0.513	0.609
	TG	0.063	0.03	0.157	2.065	**0.04**
	HDLC	0.118	0.099	0.09	1.187	0.237
	LDLC	−0.001	0.002	−0.034	−0.444	0.658
	Lip	0.000	0.000	−0.063	−0.816	0.416
(2)	**Variable**	**Regression coefficient**	**Regression coefficient**	**Regression coefficient (after adjustment)**	**t value**	***P-value***
	Constant	0.555	0.151	–	3.672	0.0003
	CHOL	−0.001	−0.001	−0.047	−0.626	0.532
	TG	−0.001	0.036	−0.002	−0.028	0.978
	HDLC	−0.271	0.117	−0.176	−2.318	**0.002**
	LDLC	0.001	0.002	−0.047	−0.620	0.536
	Lip	0.000	0.000	−0.080	−1.052	0.294
(3)	**Variable**	**Regression coefficient**	**Regression coefficient**	**Regression coefficient (afteradjustment)**	**t value**	***P-value***
	Constant	0.993	0.039	–	25.780	0.000
	CHOL	0.000	0.000	−0.002	−0.022	0.983
	TG	0.006	0.009	0.049	0.644	0.520
	HDLC	0.005	0.029	0.014	0.185	0.853
	LDLC	0.000	0.000	0.005	0.072	0.943
	Lip	0.000	0.000	−0.197	−2.581	**0.011**

Statistical method: A liner regression analysis. CHOL, cholesterol; TG, triglyceride; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; Lip, lipoprotein; p-NENs, pancreatic neuroendocrine neoplasms.

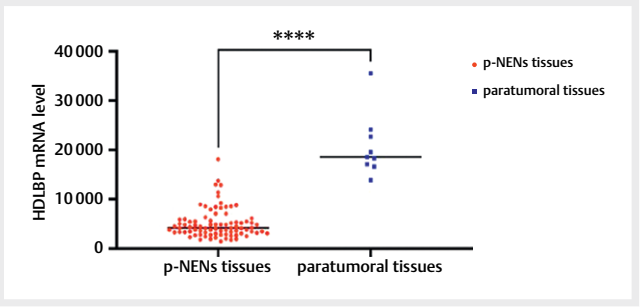


▶ **Fig. 1** Survival analysis of p-NENs according to different lipid level in our cohort. Statistical method: Kaplan-Meier method. p-NENs, pancreatic neuroendocrine neoplasms.

metastasis and assembly blocks for proliferation, and act as secondary messengers in various signaling pathways. In recent years, numerous studies have unraveled that lipid metabolism can promote tumor survival, metastasis, and disease progression [12].

LDLR is a cell surface receptor that removes cholesterol-rich LDL from blood plasma and maintains circulating cholesterol levels [13]. The HDLBP protein is specifically bound to HDL molecules and facilitates the removal of cholesterol from excess cells [14]. Therefore, LDLR and HDLBP are indispensable in the study of blood lipids and tumors. Considering the data we collected in the EGA database, HDLBP exhibited a higher expression in p-NENs tissue compared with paracancerous normal tissue. However, only a few stud-

ies have been reported on the relationship between HDLBP and p-NENs. In other types of tumors, such as hepatocellular carcinoma, HDLBP exhibited an anti-apoptotic effect on promoting cell proliferation and tumor growth [15]. In addition, survival analysis showed that patients with high LDLR levels had a poorer prognosis. LDLR is the transcriptional target of sterol regulatory element-binding protein-2. LDLR silencing can reduce the proliferation of pancreatic cancer, and high LDLR expression is associated with an increased risk of tumor recurrence [16].



▶ **Fig. 2** The expression level of HDLBP in p-NENs tissue and paratumoral tissues from EGA database, ****P < 0.001. Statistical method: T-test. HDLBP, high-density lipoprotein binding protein; p-NENs, pancreatic neuroendocrine neoplasms; EGA, European Genome-phenome Archive.

▶ **Table 4** Clinicopathological and follow up information of p-NENs. patients in EGA database.

Characteristic	No	84
Sex, female		48
Tissue differentiation		
well		78
poor		6
Pathological grading		
G1		37
G2		41
G3		6
AJCC stage		
I		24
II		17
III		24
IV		19
Follow-up time (months)		69.88 ± 40.62
Prognosis, death		22

Statistical method: Descriptive statistics. p-NENs, Pancreatic neuroendocrine neoplasms; EGA, European Genome-phenome Archive.

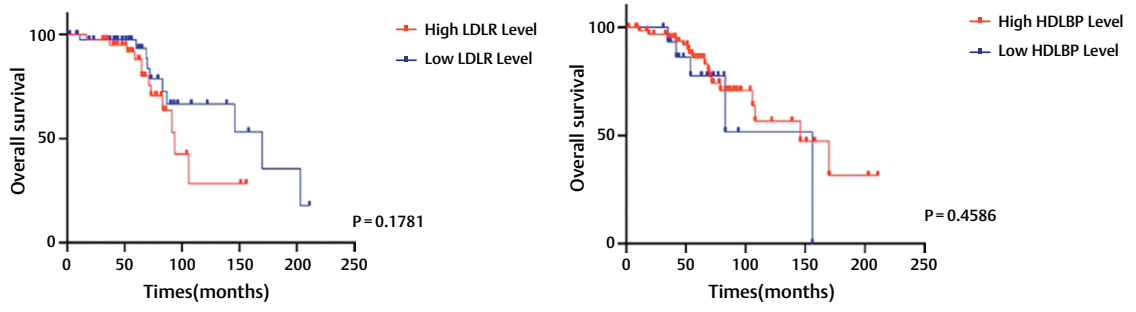
In brief, our study illustrates the differences in clinical features among p-NENs patients with different serum lipid levels; however, the underlying mechanism needs further study. The roles of specific lipoproteins in p-NENs and their diagnostic and prognostic values have not been fully demonstrated. However, the expression of lipid metabolism-related proteins, such as HDLBP, was significantly reduced in p-NENs, and LDLR had certain predictive value in the prognosis of p-NENs. In addition, lipid metabolism provides a new idea for the potential therapy of p-NENs.

Conclusion

This study highlights clinical differences in patients with different lipid levels of p-NENs, but there is no significant correlation between differentially expressed lipid levels and outcomes in patients with p-NENs. Among related lipoproteins, the expression of HDLBP is lower in p-NENs tissues. This study lays a foundation for the study of lipid metabolism and lipid-regulating drugs in p-NENs. This study still has several limitations. As a retrospective study, dyslipidemia in patients with p-NENs requires prospective studies; how dyslipidemia affects the occurrence and development of p-NENs still requires further research. The negative results of these lipid indexes in the diagnosis and survival analysis of p-NENs may be due to two reasons. First is the short follow-up period; second, p-NENs are relatively rare and the number of cases collected was small. The role of HDLBP and LDLR in p-NENs needs to be further verified through basic experiments. However, this retrospective study, with some reliability, provides new clues for the study of lipid metabolism in patients with p-NENs.

Ethics approval and consent to participate

This study was approved by the Jiangsu Province Hospital ethics board. Patients included in this study provided their consent for the use of their medical records for analysis.



▶ **Fig. 3** EGA database was searched to analyze overall survival of p-NENs in different LDLR and HDLBP level. Statistical method: Kaplan-Meier method. HDLBP, high-density lipoprotein binding protein; p-NENs, pancreatic neuroendocrine neoplasms; LDLR, low-density lipoprotein receptor.

▶ **Table 5** Clinicopathological and follow up information of p-NENs patients in different lipoprotein expression level from EGA database.

	High LDLR	Low LDLR	x^2 or F value	P value	Low HDLBP	High HDLBP	x^2 or F value	P value
Sex								
female	21	27	1.752	0.27	39	9	0.006	1.000
male	21	15			29	7		
Tumor classification								
Functional	7	3	1.816	0.313	8	2	0.007	1.000
Nonfunctional	35	39			60	14		
Tissue differentiation								
well	37	41	2.872	0.202	63	15	0.024	1.000
poor	5	1			5	1		
Pathological grading								
G1	18	23	2.188	0.493	31	10	1.221	0.476
G2	20	17			32	5		
G3	4	2			5	1		
Metastasis								
Yes	24	19	1.191	0.383	35	6	1.012	0.408
No	18	23			33	10		
AJCC stage								
I	11	13	5.975	0.14	18	8	4.423	0.409
II	7	10			15	2		
III	10	14			20	4		
IV	14	5			15	2		
Follow-up time(months)	65.80 ± 30.32	73.77 ± 48.51	4.098	**0.03**	70.74 ± 41.75	66.35 ± 30.78	0.626	0.300
Prognosis								
Survival	30	32	0.246	0.804	51	11	0.262	0.753
Death	12	10			17	5		

Statistical method: Chi-square test or Fisher exact test. LDLR, low-density lipoprotein receptor; HDLBP, high-density lipoprotein binding protein; p-NENs, Pancreatic neuroendocrine neoplasms; EGA, European Genome-phenome Archive.

Authors' contributions

Danyang Gu, Bingyan Xue, Guoqin Zhu, and Yanling Xu designed the study; Bingyan Xue and Guoqin Zhu collected data and searched for articles; Danyang Gu and Lijun Yan analyzed the data; Danyang Gu wrote the main manuscript text; Qiyun Tang and Chun Lu reviewed the article. All authors have read and approved the manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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