

Inhibition Effect of Pancreatic Exocrine Insufficiency on Immune Checkpoint Inhibitor Treatment in Pancreatic Cancer: A Retrospective Study

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Introduction: Chemotherapy combined with immune checkpoint inhibitors (ChIM) is used to treat advanced pancreatic ductal adenocarcinoma (PDAC). However, the efficacy of ChIM is similar to that of chemotherapy alone.

Methods: To assess potential factors affecting the effectiveness of ChIM, we analyzed the clinical data of 359 patients with PDAC who visited the hospital during June 2017 to December 2022.

Results: Surgical resection, diabetes, and ChIM were risk factors for pancreatic exocrine insufficiency (PEI). The adjusted odds ratio of ChIM was 2.63 (95% confidence interval (CI) 1.492–4.626) ($P = 0.001$). The incidence of PEI in the ChIM group (76.9%) was significantly higher than that of the chemotherapy group (60.2%) ($P = 0.004$). Survival analysis showed that ChIM did not improve the survival rate of patients with PDAC (hazard ratio (HR) 0.92, 0.707–1.197) ($P = 0.534$) in comparison with that of the chemotherapy group. However, in patients without PEI, those receiving ChIM showed a higher 1-year overall survival (OS) rate of 70.8% (two-sided, $P = 0.045$) and a median OS of 22.0 months (95% CI 11.5–32.5). Moreover, pancreatic enzyme replacement therapy significantly improved the OS of patients with PDAC (HR = 0.73, 95% CI = 0.561–0.956) ($P = 0.022$).

Conclusion: Immune checkpoint inhibitors (ICIs) increased the incidence of PEI in patients with PDAC. The OS was not different between patients receiving chemotherapy and ChIM due to irregular PERT treatment. The finding show that pancreatic enzyme replacement therapy may improve the response rate of patients with PDAC to ICIs.

Keywords: pancreatic cancer, pancreatic exocrine insufficiency, immune checkpoint inhibitors, pancreatic enzyme replacement therapy

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most challenging digestive tract malignancies. The 5-year survival rate of patients with the condition is less than 11%.¹ Surgical resection is the main technique for radical treatment of PDAC. However, more than 80% of patients cannot receive surgical resection due to local advancement and metastasis. Therefore, systemic treatments, especially chemotherapy, are the main strategies to improve survival in patients with PDAC. However, chemotherapy has a limited response in this patient population.²

In recent years, immune checkpoint inhibitors (ICIs) have produced noticeable improvements in the treatment of cancer patients.^{3,4} However, treatment with single-agent ICIs has shown disappointing results in PDAC.⁵ Researchers considered that the poor clinical outcomes may be attributed to the complex immunosuppressive tumor microenvironment and intrinsically non-immunogenetic features of PDAC.⁶ To this end, novel systemic treatments are urgently required. A few studies have reported that chemotherapy combined with immunotherapy (ChIM) increases the response rates of patients with PDAC,^{7,8}

while others showed similar efficacies between chemotherapy alone and ChIM treatment.^{9,10} Therefore, elucidating the factors that contribute to the poor response of patients with PDAC to ChIM is an urgent need.

Increasing evidence shows that ICIs have adverse effects on the pancreas and increase the morbidity of diabetes mellitus, pancreatitis, and pancreatic exocrine insufficiency (PEI),^{11,12} which results in poor quality of life and prognosis. Notably, PEI-induced malnutrition has been confirmed to have a significant effect on quality of life, overall survival (OS), and tumor progression in patients with PDAC.¹³ Pancreatic enzyme replacement therapy (PERT) is widely used in the clinical treatment of patients with PEI and plays an important role in the improvement of OS.¹⁴ However, there is no study reporting whether PEI affects the efficacy of ChIM in PDAC.

Here, we report clinical data from a retrospective cohort study of patients with PDAC receiving chemotherapy and ChIM treatment. This study aimed to evaluate the risk factors for PEI and the effects of PEI on the efficacy of ChIM treatment in patients with PDAC.

Materials and Methods

Study Design and Patients

This single-center, retrospective cohort study was approved by the Ethics Committee of Zhengzhou University People's Hospital (Approval No. 2021-69). The study complies with the Declaration of Helsinki. Written informed consent was obtained from all the participants prior to the enrollment of this study. From June 2017 to December 2022, 1088 patients with PDAC, diagnosed by surgical pathology or biopsy, were enrolled. None of the patients received any antitumor treatment before diagnosis. The exclusion criteria were OS of < 1 month, presence of other malignant tumors that affected life span, other potential causes of death, incomplete follow-up information, and other types of pancreatic tumors (Figure 1).

Data Collection and Definitions

General information of the participants that was recorded included their personal information, medical history, laboratory indicators, and medical imaging. Personal information included age, sex, smoking history, drinking history, weight, height, and family history of malignant tumors (Figure 1). Weight and height were used for body mass index (BMI) calculation. Medical history included diabetes, cardiovascular, and cerebrovascular diseases, and treatment history after diagnosis (surgical resection, chemotherapy, ICIs, and PERT). Laboratory indicators, including liver function and serum CA 19-9, were recorded. CA 19-9 was dichotomized as > 1000 U/mL or < 1000 U/mL at diagnosis. Enhanced pancreatic computed tomography (CT) was performed to evaluate tumor location.

Follow-Up and Endpoints

CA-19-9 and pancreatic CT were performed to evaluate tumor recurrence and metastasis. Patient information regarding chemotherapy, ChIM, and PERT was also recorded. The occurrence of PEI was evaluated based on PEI symptoms at the final follow-up, including post-treatment weight loss (> 10% weight loss at 3 months), diarrhea, other dyspepsia-related symptoms, and nutritional status.¹³ The primary endpoints were the 1-year survival rate and OS of each group. OS was defined as the time from the date of pathological diagnosis to death or the final follow-up.

Statistical Analysis

SPSS 22.0 and R version 4.2.3 were used for statistical analysis. Continuous variables were analyzed using the unpaired Student's *t*-test (normal distributions) (data are expressed as mean \pm SD) or the Mann-Whitney *U*-test (non-normal distributions) (data are expressed as median interquartile range). Qualitative variables were evaluated using the chi-squared test and data are expressed as percentages (%). Logistic regression analysis was used to assess risk factors for PEI. Risk ratios are presented as odds ratios (OR) and 95% confidence intervals (CI). Cox proportional hazards regression analysis was used to assess the risk factors for OS in patients with PDAC. Risk ratios are presented as hazard ratios (HR) and 95% CI. Forward selection Wald was used in multivariate analyses. The level of statistical significance for all statistical tests was set at $P < 0.05$.

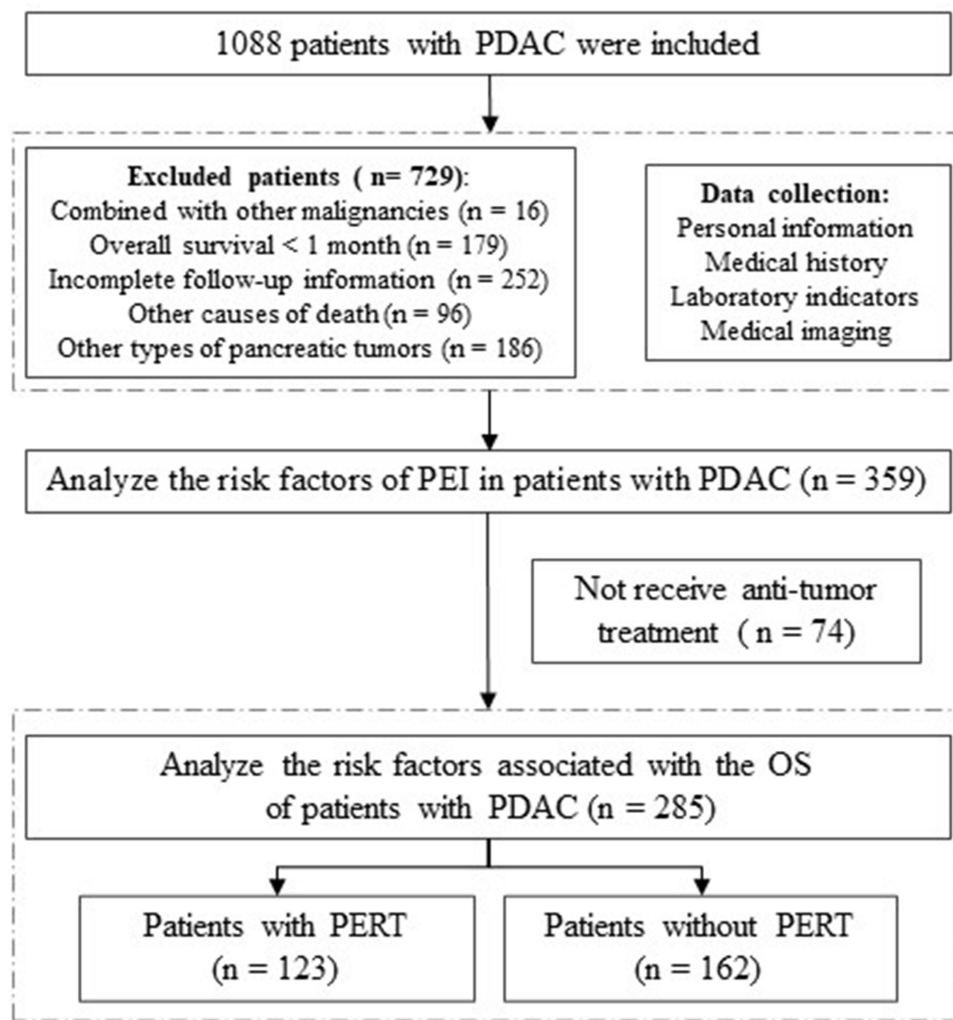


Figure 1 Flow diagram of patient selection.

Results

Baseline Characteristics of the Patients

A total of 359 patients with PDAC were enrolled in this study, with a non-normally distributed age of 63.0 (55.0–70.0) years and a BMI of 22.5 (20.5–24.7) kg/m². Among them, 205 (57.1%) were male, and 173 (48.2%) underwent radical surgical resection. Total PEI incidence was 67.7% (n = 243). There were 268 (74.7%) patients with tumors in the pancreatic head. However, only 149 patients (41.5%) underwent PERT. A total of 181 (50.4%) and 104 (29.0%) patients received chemotherapy alone and chemotherapy combined with immunotherapy (ChIM), respectively (Table 1).

Comparison of the Baseline Characteristics of Patients with or Without PEI

The clinical characteristics and therapeutic information of patients with PDAC and PEI are shown in Table 2. There were no statistically significant differences between patients with and without PEI in terms of age, sex, BMI, smoking status, alcohol consumption, or serum CA 19-9. Although the incidence of PEI in patients with tumors in the head of the pancreas (70.1%) was higher than that (60.4%) in patients with tumors in the body-tail of the pancreas, they were not significantly different ($P = 0.087$) (Table 2).

Consistent with that of previous studies, our results showed that surgical resection increased PEI incidence (72.8%) in patients with PDAC compared with that in patients who received palliative treatment (62.9%) ($P = 0.044$). The occurrence rate in patients with diabetes was significantly higher than that in patients without diabetes ($P = 0.013$).

Table 1 Characteristics of Cohorts (n = 359)

Demographics	
Age, years, median (IQR)	63.0 (55.0, 70.0)
Male, n (%)	205 (57.1)
BMI (kg/m ²), median (IQR)	22.5 (20.5, 24.7)
Smoking, n (%)	122 (34.0)
Alcohol drinking, n (%)	89 (24.8)
Tumor location, n (%)	
Head of pancreas	268 (74.7)
Body-tail of pancreas	91 (25.3)
Tumor stage (M0/M1)	271/88
CA 19–9 at diagnosis ≥ 1000 U/mL	85 (23.7)
PEI, n (%)	243 (67.7)
PERT, n (%)	149 (41.5)
Complicating diseases, n (%)	
Diabetes	102 (28.4)
Cardiovascular diseases	134 (37.3)
Treatment, n (%)	
Unresectable	186 (51.8)
Surgical resection	173 (48.2)
Anti-tumor therapy, n (%)	
None	74 (20.6)
Chemotherapy	181 (50.4)
Chemotherapy + Immunotherapy	104 (29.0)

Abbreviations: IQR, interquartile range; BMI, body mass index; PEI, pancreatic exocrine insufficiency; PERT, pancreatic enzyme replacement treatment.

Table 2 Clinical Characteristics of Patients with or Without PEI (n = 359)

Characteristic	PEI	Non-PEI	P value
Total No. of patients, n (%)	243 (67.7)	116 (32.3)	
Demographics			
Age, years, median (IQR)	63 (55.0, 70.0)	62 (54.0, 71.8)	0.974 ^a
Gender (male to female)	142/101	63/53	0.460 ^b
BMI (kg/m ²), median (IQR)	22.6 (20.5, 24.8)	22.3 (20.6, 24.6)	0.686 ^a
Smoking, n (%)	79 (64.8)	43 (35.2)	0.394 ^b
Alcohol drinking, n (%)	58 (65.2)	31 (34.8)	0.558 ^b
CA 19–9 at diagnosis			0.513 ^a
< 1000 U/mL, n (%)	183 (66.8)	91 (33.2)	
≥ 1000 U/mL, n (%)	60 (70.6)	25 (29.4)	
Tumor location, n (%)			0.087 ^b
Head of pancreas (n = 268)	188 (70.1)	80 (29.9)	
Body-tail of pancreas (n = 91)	55 (60.4)	36 (39.6)	
Surgical treatment, n (%)			0.044 ^{b*}
Unresectable (n = 186)	117 (62.9)	69 (37.1)	
Surgical resection (n = 173)	126 (72.8)	47 (27.2)	
Anti-tumor therapy, n (%)			0.004 ^{b***}
Chemotherapy	109 (60.2)	72 (39.8)	
Chemotherapy + Immunotherapy	80 (76.9)	24 (23.1)	
Comorbidities, n (%)			
Diabetes (n = 102)	79 (77.5)	23 (22.5)	0.013 ^{b*}
Cardiovascular diseases (n = 134)	90 (67.2)	44 (32.8)	0.870 ^b

Notes: ^aMann–Whitney U-test, ^bChi-Squared Test. *P < 0.05, **P < 0.01.

Moreover, the incidence of PEI in patients who received ChIM was significantly higher (76.9%) than that in patients who received chemotherapy only (60.2%) ($P = 0.004$) (Table 2).

Risk Factors of PEI in Patients with PDAC

To confirm the risk factors for PEI, univariate logistic regression analysis of the data of 285 patients who received chemotherapy ($n = 181$) and ChIM ($n = 104$) was performed. The results showed that surgical resection, diabetes, and ChIM increased the morbidity risk of PEI with ORs of 1.65 (95% CI 1.003–2.699) ($P = 0.048$), 2.08 (95% CI 1.155–3.726) ($P = 0.015$), and 2.20 (95% CI 1.277–3.796) ($P = 0.005$), respectively. The adjusted OR values of surgical resection, diabetes, and ChIM were 1.85 (95% CI 1.102–3.099) ($P = 0.020$), 2.32 (95% CI 1.268–4.227) ($P = 0.006$), and 2.63 (95% CI 1.492–4.626) ($P = 0.001$), respectively (Table 3). Thus, ChIM is an independent risk factor for PEI.

Baseline Characteristics of Patients Receiving Chemotherapy or ChIM

To assess the effect of ChIM on PDAC, we divided patients into two groups: chemotherapy alone and ChIM. The baseline characteristics of the two groups are shown in Table 4. There were no statistically significant differences in age, sex, BMI, serum

Table 3 Logistic Regression Variables Analysis of Risk Factors for PEI in PDAC ($n = 285$)

Characteristic	Univariate Analysis OR (95% CI)	P value	Multivariate Analysis OR (95% CI)	P value
Age at diagnosis	1.00 (0.980–1.027)	0.782		
BMI (kg/m²)	1.05 (0.966–1.134)	0.261		
CA 19–9 at diagnosis				
< 1000 U/mL, n (%)	1.00	0.591		
≥ 1000 U/mL, n (%)	0.85 (0.475–1.528)			
Comorbidities				
Diabetes	2.08 (1.155–3.726)	0.015*	2.32 (1.268–4.227)	0.006**
Surgical treatment				
Unresectable	1.00	0.048*	1.00	0.020*
Surgical resection	1.65 (1.003–2.699)		1.85 (1.102–3.099)	
Anti-tumor therapy				
Chemotherapy	1.00	0.005**	1.00	0.001**
Chemotherapy + Immunotherapy	2.20 (1.277–3.796)		2.63 (1.492–4.626)	

Notes: * $P < 0.05$, ** $P < 0.01$.

Table 4 Characteristics of Cohorts ($n = 285$)

Characteristic	Chemotherapy ($n = 181$)	Chemotherapy + Immunotherapy ($n = 104$)	P value
Demographics			
Age, years, median (IQR)	63 (55.0, 70.0)	60 (54.0, 67.0)	0.223 ^a
Gender (male to female)			
BMI (kg/m ²), median (IQR)	22.6 (20.5, 24.7)	22.2 (20.4, 25.0)	0.802 ^b
Smoking, n (%)	57 (62.0)	35 (38.0)	0.707 ^a
Drinking, n (%)	41 (59.4)	28 (40.6)	0.418 ^b
CA 19–9 at diagnosis			0.375 ^b
< 1000 U/mL, n (%)	138 (62.2)	84 (37.8)	
≥ 1000 U/mL, n (%)	43 (68.3)	20 (31.7)	
Tumor location, n (%)			0.898 ^b
Head of pancreas ($n = 207$)	131 (63.3)	76 (36.7)	
Body-tail of pancreas ($n = 78$)	50 (64.1)	28 (35.9)	

(Continued)

Table 4 (Continued).

Characteristic	Chemotherapy (n = 181)	Chemotherapy + Immunotherapy (n = 104)	P value
Surgical treatment, n (%)			0.043 ^{b,*}
Unresectable (n = 131)	75 (57.3)	56 (42.7)	
Surgical resection (n = 154)	106 (68.8)	48 (31.2)	
PEI incidence, n (%)	109 (60.2)	80 (76.9)	0.004 ^{b,**}
Comorbidities, n (%)			
Diabetes (n = 83)	59 (71.1)	24 (28.9)	0.089 ^b
Cardiovascular diseases (n = 134)	67 (63.8)	38 (36.2)	0.936 ^b
PERT, n (%)	71 (39.2)	52 (50.0)	0.077 ^b

Notes: ^aMann–Whitney U-test, ^bChi-Squared Test. * $P < 0.05$, ** $P < 0.01$.

CA 19–9, tumor location, diabetes incidence, and PERT application between the two groups. The rate of ChIM treatment in patients who underwent surgical resection (31.2%) was lower than that in patients with unresectable tumors (42.7%) ($P = 0.043$). This may be because patients with advanced tumors tend to receive ChIM treatment. In the chemotherapy and ChIM groups, PEI incidences were 60.2% and 76.9%, respectively ($P = 0.004$) (Table 4). This indicated that ChIM treatment had a promoting effect on PEI occurrence (contingency coefficient = 0.168, $P = 0.004$). A previous report has shown that ICIs increase the injury of pancreatic acinar cells and ductal cells by activating infiltrated immune cells in the pancreas, thereby inducing PEI.¹¹

Risk Factors Associated with the OS of Patients with PDAC

Age and serum CA 19–9 level increased the risk of death in patients with PDAC (HR of 1.02, 95% CI, 1.005–1.031) ($P = 0.006$) and 1.72 (95% CI 1.273–2.317) ($P = 0.006$). In contrast, surgical resection decreased the risk of death (HR 0.43, 95% CI 0.331–0.555) ($P < 0.001$). Moreover, ChIM did not improve the survival rate of patients with PDAC (HR 0.92, 0.707–1.197) ($P = 0.534$) (Table 5), similar to findings of a recent clinical study.⁹ The death risk in patients with PEI was increased, however, due to irregular PERT treatment, there was no statistical difference between patients with PEI and those without PEI ($P = 0.135$).

Table 5 Cox Proportional Hazard Regression Analysis of Risk Factors Associated with Overall Survival Among Patients with Pancreatic Cancer (n = 285)

Characteristic	Univariate Analysis HR (95% CI)	P value	Multivariate Analysis HR (95% CI)	P value
Age at diagnosis	1.02 (1.005–1.031)	0.006 ^{**}	1.01 (0.997–1.023)	0.148
BMI (kg/m²)	0.99 (0.953–1.035)	0.738		
PEI	1.228 (0.938–1.607)	0.135		
CA 19–9 at diagnosis				
< 1000 U/mL, n (%)	1.00	< 0.001 ^{***}	1.00	0.096
≥ 1000 U/mL, n (%)	1.72 (1.273–2.317)		1.30 (0.954–1.780)	
Anti-tumor therapy				
Chemotherapy	1.00	0.534		
Chemotherapy + Immunotherapy	0.92 (0.707–1.197)			
Surgical treatment				
Unresectable	1.00	< 0.001 ^{***}	1.00	< 0.001 ^{***}
Surgical resection	0.43 (0.331–0.555)		0.51 (0.383–0.669)	
PERT				
No	1.00	0.001 ^{**}	1.00	0.022 [*]
Yes	0.63 (0.487–0.818)		0.73 (0.561–0.956)	

Notes: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Interestingly, the association between ChIM treatment and OS was examined in the subgroups analyses according to age (> 63 or ≤ 63 years), (BMI (≥ 22.5 or < 22.5 kg/m²), surgical treatment (yes or no), CA 19-9 (≥ 1000 or < 1000 U/mL), diabetes (yes or no), and PERT (yes or no). The results showed that there was no statistically significant interaction between age, BMI, diabetes status, surgical treatment, serum CA 19-9 level, and PERT. The statistical significance was observed only among patients without PEI (HR = 0.53, 95% CI 0.306–0.905, $P = 0.020$) (Figure 2). Patients receiving ChIM had a lower risk of death.

In patients without PEI, the 1-year survival rate was 70.8% (two-side $P = 0.045$) and median OS was 22.0 months (95% CI 11.5–32.5) in the ChIM group, which was higher than those of the chemotherapy group (1-year survival rate = 47.2%, median OS = 11.0 months, 95% CI 8.0–14.0) (Figure 3A).

Moreover, Cox proportional hazard regression analysis showed that PERT was a significant protective factor for the OS of patients with PDAC in both univariate (HR 0.63, 95% CI 0.487–0.818) ($P = 0.001$) and multivariate analyses (HR 0.73, 95% CI 0.561–0.956) ($P = 0.022$) (Table 5). Kaplan-Meier survival analysis showed that the median OS of patients who received PERT ($n = 123$) was 16.0 months (95% CI 12.3–19.7), which was significantly longer than that of non-PERT patients ($n = 162$) (median OS = 11.0 months, 95% CI 9.6–12.4) ($P < 0.001$) (Figure 3B).

Discussion

ICIs, such as inhibitors of programmed cell death protein 1 (PD-1) or its ligand 1 (PD-L1), have been widely used in many solid tumor treatments and have achieved significant improvements in OS in many advanced cancers.¹⁵ However, PDAC is highly resistant to ICI therapy because of its complex tumor stroma and immune microenvironment.¹⁶ Chemotherapy with gemcitabine plus nab-paclitaxel and FOLFIRINOX can remodel the tumor stroma and immune

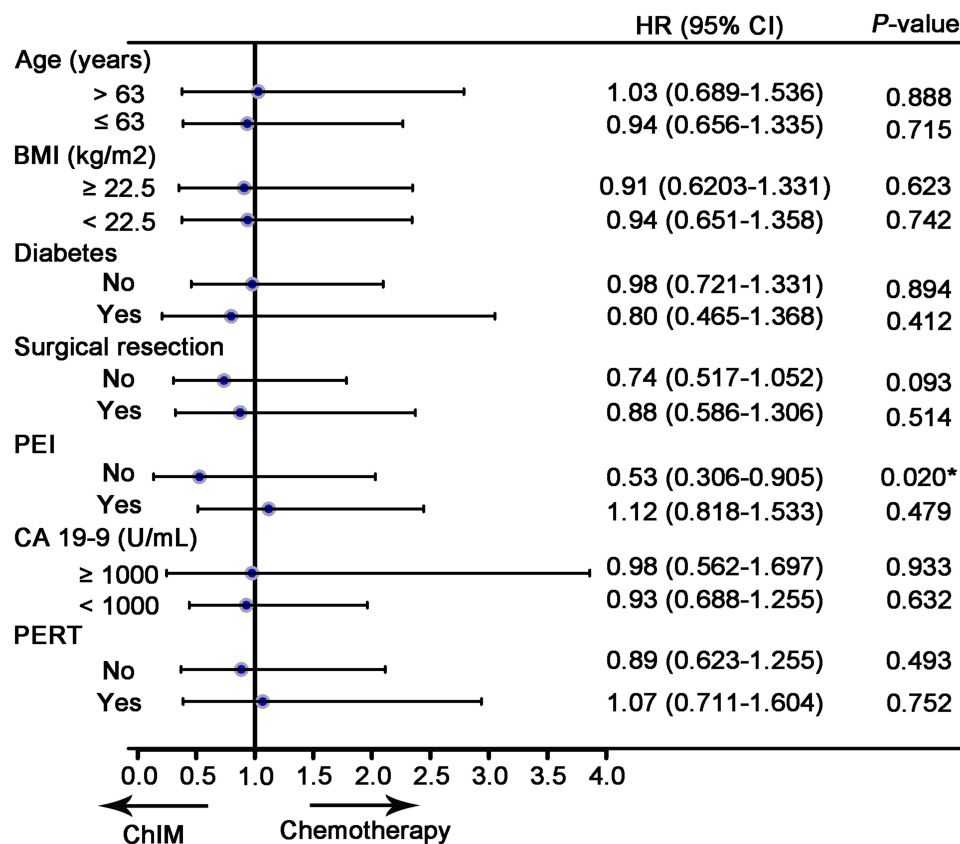


Figure 2 Cox proportional hazards analysis evaluating the association between chemotherapy plus immunotherapy (ChIM) treatment and risk factors of patients with PDAC. Hazard ratio (HR) was expressed as ChIM-to-chemotherapy risk ratio.

Abbreviations: BMI, body mass index; PEI, pancreatic exocrine insufficiency; PERT, pancreatic enzyme replacement therapy.

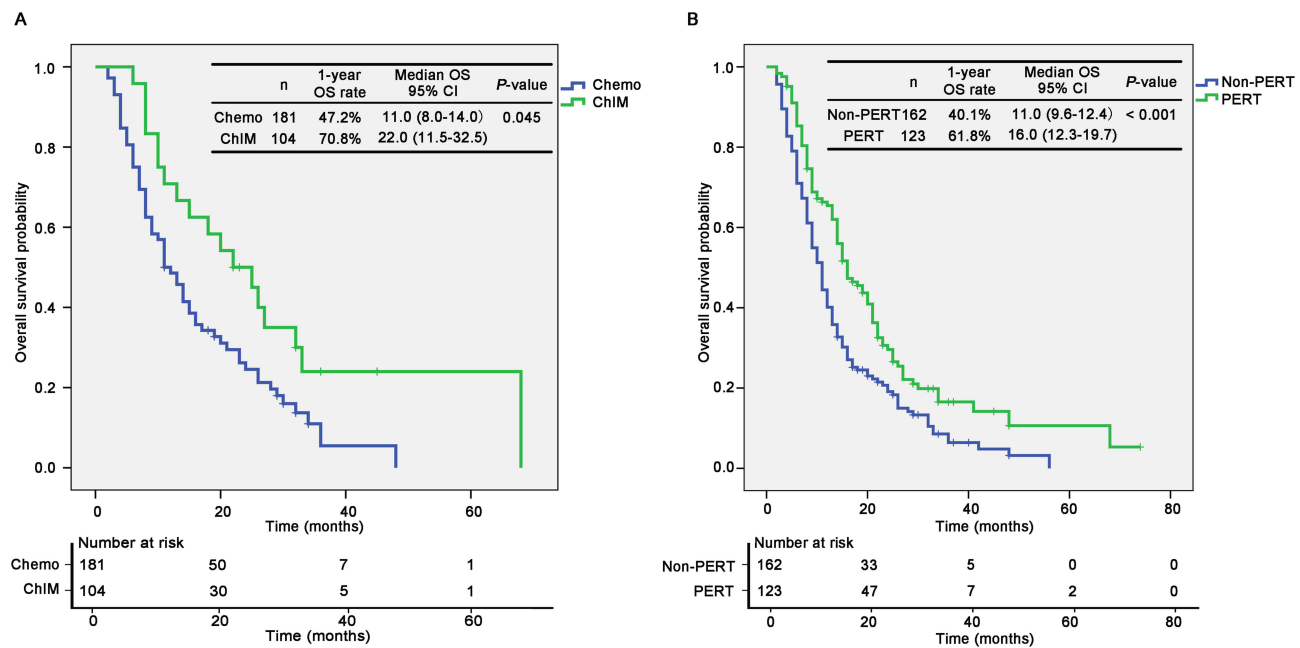


Figure 3 Kaplan–Meier survival analysis of patients with PDAC in different groups. **(A)** Kaplan–Meier curves of 1-year OS of patients receiving chemotherapy or ChIM. **(B)** Kaplan–Meier curves of 1-year OS of patients with or without PERT.

cell infiltration. Thus, its combination with chemotherapy is thought to be a potential way to improve the therapeutic efficacy of ICIs in PDAC.^{17,18}

In a mouse model of PDAC, PD-1 inhibitors combined with gemcitabine significantly inhibited the recurrence rate of resected PDAC compared to that with gemcitabine alone.¹⁹ In a clinical study, the PD-1 inhibitor nivolumab combined with nab-paclitaxel and gemcitabine achieved improved OS, progression-free survival (PFS), and manageable toxicity.²⁰ However, another Phase I study showed insufficient median PFS and OS in patients with advanced or metastatic PDAC who received nivolumab combined with gemcitabine and nab-paclitaxel.²¹ Therefore, it is necessary to elucidate the factors that affect ICI efficacy.

PEI is a common complication of PDAC, particularly in patients who have undergone surgical resection. A previous meta-analysis reported that the total prevalence of PEI was 72% in advanced PDAC.²² PEI is thought to be an important factor; however, it is often overlooked by surgeons, potentially impacting the prognosis of patients with PDAC.^{13,23} Studies have shown that ICIs are associated with pancreatic adverse events, including pancreatitis and diabetes. Moreover, ICIs may induce PEI.¹² Some studies have reported that the endocrine and exocrine pancreas may be destroyed by increased activated CD8+ T cell infiltration from ICIs treatment. To date, no studies have confirmed whether PEI affects the clinical effectiveness of ICIs.

Our clinical data showed that the total incidence of PEI was 72.8%, and tumors located at the head of the pancreas and surgical resection were risk factors for PEI. This is consistent with the results of a previous study.²⁴ We also found that patients with diabetes were more likely to develop PEI. Moreover, the data showed that chemotherapy combined with ICIs is an independent risk factor for PEI (OR 2.63, 95% CI 1.492–4.626) ($P = 0.001$). However, the PERT rate was only 41.5%, which is far below the PEI occurrence rate. This indicates that many patients with PEI do not receive PERT. PEI has been reported to be underdiagnosed and undertreated in many countries.^{25–27} Moreover, the role of PEI in the management of PDAC has not yet been elucidated.

Overall, age, surgical resection and CA 19–9 levels were key factors related to patient survival. ChIM did not improve patient OS. However, among patients without PEI, the 1-year survival rate and median OS of patients who received ChIM were superior to those of patients who received chemotherapy alone. Additionally, patients who received PERT had a longer OS and better prognosis than those who did not receive PERT, although the use of PERT may not be accurate. The findings of this study indicate that the OS of PDAC patients with PDAC was affected by a variety of

factors including age, chemotherapy, immunotherapy, surgical resection and PERT. More reliable global prospective studies still need to be developed to confirm the effect of PEI and ICI treatment on the prognosis of patients with PDAC.

In conclusion, our findings suggest that ICIs increase the incidence of PEI in patients with PDAC. ChIM may improve the OS of patients with PDAC without PEI. In the clinical management of PDAC, PEI and PERT should be seriously considered, as they may improve the response rate of PDAC to ICI therapy.

Data Sharing Statement

All the data in this study are available upon request from the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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