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Original Article

Incidence of pancreatic exocrine insufficiency and efficacy of pancreatic enzyme replacement therapy in acute pancreatitis patients

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Abstract: Objectives: To evaluate the incidence and risk factors of pancreatic exocrine insufficiency (PEI) in patients with acute pancreatitis (AP) and to assess the clinical efficacy of pancreatic enzyme replacement therapy (PERT). Methods: A retrospective study was conducted with 371 patients with AP. Patients were classified into mild acute pancreatitis (MAP, n=88), moderately severe acute pancreatitis (MSAP, n=192), and severe acute pancreatitis (SAP, n=91). Risk factors for PEI were identified through logistic regression analysis. The therapeutic efficacy was assessed by comparing the group receiving PERT with the control group (n=72) receiving conventional treatment. Patients were assigned to the treatment and control groups based on the severity of their condition (mainly MSAP and SAP, n=55) and whether they met the diagnostic criteria for PEI (based on FE-1 levels). Results: The incidence of PEI was 39.9%. A higher proportion of patients with PEI had SAP (37.2%) and infected pancreatic necrosis (P<0.001). Compared to the control group, the Treatment Group demonstrated significantly lower rates of enteral nutrition intolerance, higher 24-hour relief rates, and improved bowel function on day 7 (all P<0.05). Subgroup analyses revealed that PERT significantly improved intolerance and bowel function in MSAP patients and reduced intolerance in SAP patients. Hospital stay was shorter in the Treatment Group (P=0.012), especially in MSAP patients (P=0.001), while no significant difference was observed in SAP patients (P=0.880). Treatment costs were similar between the groups. Conclusions: PEI is prevalent in AP, particularly in severe cases. PERT effectively alleviates enteral nutrition intolerance, enhances bowel function, and shortens hospital stays, especially in MSAP patients. The development of PEI is strongly associated with disease severity and infected necrosis, highlighting the clinical value of PERT.

Keywords: Acute pancreatitis, pancreatic exocrine insufficiency, pancreatic enzyme replacement therapy, enteral nutrition intolerance, length of stay, treatment cost

Introduction

Acute pancreatitis (AP) is one of the most common acute abdominal emergencies in clinical practice. It results from an acute inflammatory response in the pancreas, typically presenting with abdominal pain, vomiting, and fever [1]. The global prevalence of AP varies significantly across regions, influenced by lifestyle factors. Gallstones and alcohol consumption are the primary etiological factors, highlighting the importance of etiological research in AP management [2].

The severity of AP is categorized into three groups: mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP). SAP is the most critical form, often associated with pancreatic necrosis, infection, and multiple organ dysfunction syndrome, leading to high mortality and disability rates [3]. A systematic review by de la Iglesia et al. [4] demonstrated that severe pancreatic injury commonly results in long-term complications, including pancreatic exocrine insufficiency (PEI), emphasizing the strong correlation between disease severity and subsequent complications. Despite advances in therapy reducing mortality rates, complications, particularly PEI, continue to challenge clinical management.

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PEI develops when pathologic pancreatic damage impairs its secretory function, leading to insufficient pancreatic enzyme production and, consequently, compromised digestion and nutrient absorption [5]. Research by Piciucchi et al. [6] indicates that various etiologies, including AP, can trigger PEI by inflammatory destruction of pancreatic acinar cells. The incidence of PEI is significantly elevated in AP patients, especially those with severe forms [7]. PEI contributes to malnutrition and weight loss in these patients, significantly affecting quality of life and emphasizing its importance in post-AP management [8].

The treatment of AP remains challenging, particularly when it progresses to PEI. Current therapeutic approaches include pharmacologic treatment, nutritional support, pain management, and complication management. Studies suggest that PEI increases the risk of new-onset diabetes, necessitating comprehensive management for multi-system complications in post-AP patients [9]. However, optimal treatment for PEI remains debated.

Pancreatic enzyme replacement therapy (PERT) is a targeted treatment for PEI that has shown promise in improving nutrient absorption and relieving symptoms in clinical studies. Real-world research by Barkin et al. [10] revealed that PERT efficacy often suffers from inadequate patient education and improper dosing, underlining the need for optimized treatment protocols. Evidence suggests that PERT improves digestive function in AP-related PEI by supplementing pancreatic enzymes, providing essential clinical management support [11]. However, the mechanisms underlying PEI development and its relationship to AP severity remain incompletely understood.

A case-control study by Alexandre-Heymann et al. [12] showed that PERT could improve nutritional status in patients with both PEI and diabetes, indicating its potential value in complex cases. Significant differences in PEI incidence and associated factors likely exist among AP patients with varying severity (MAP, MSAP, SAP). Literature suggests that optimizing PERT dosage and enhancing patient adherence are crucial for improving effectiveness, especially in post-AP PEI patients [13]. Therefore, identifying high-risk populations for PEI in AP patients and providing effective treatment remains a critical clinical challenge.

This study aimed to investigate the incidence of PEI in AP patients, explore its relationship with disease severity, analyze clinical factors influencing PEI occurrence, and assess the clinical efficacy of pancreatic enzyme replacement therapy in patients diagnosed with PEI.

Materials and methods

Sample size calculation

The sample size was based on the incidence of PEI (36.19%) in AP patients, as reported by Guo et al. [14]. The single proportion formula, $N = Z^2 \times [P \times (1-P)]/E^2$, was applied. Using P=0.3619, Z=1.96 (95% confidence level), and E=0.05 (margin of error), the required sample size was calculated to be 354.85, which was rounded up to 355 cases.

Sample collection

This retrospective study included 371 patients diagnosed with AP at our hospital between February 2019 and February 2024. The study protocol was approved by the Medical Ethics Committee of Xianyang First People's Hospital.

Group classification

Patients diagnosed with AP were stratified based on the severity of their condition. The criteria were as follows: MAP included patients without organ failure and any local or systemic complications. MSAP consisted of patients who experienced transient organ failure lasting less than 48 hours or had local or systemic complications. SAP involved persistent organ failure for 48 hours or more, often associated with severe complications such as infected pancreatic necrosis and multi-organ dysfunction. 88 patients were classified with MAP, 192 patients with MSAP, and 91 patients with SAP. These classifications were based on clinical presentation and diagnostic criteria, and were used to assess the incidence of PEI and to evaluate therapeutic outcomes according to disease severity. Based on FE-1 levels, patients were classified into two groups: PEI group (patients with pancreatic exocrine insufficiency, FE-1 ≤200 μg/g, n=148) and N-PEI group (patients without pancreatic exocrine insufficiency, FE-1 >200 μg/g, n=223).

Inclusion and exclusion criteria

Inclusion criteria for AP patients: (1) Age ≥18 years; (2) Clinical diagnosis of AP confirmed by imaging studies [15]; (3) Symptom duration during hospitalization exceeding 24 hours; (4) Availability of complete clinical data.

Exclusion criteria for AP patients: (1) Readmission due to AP-related complications; (2) History of severe hepatic, renal, or cardiovascular diseases; (3) Uncontrolled diabetes or autoimmune disorders; (4) Pregnant or lactating women; (5) Patients on long-term medications affecting gastric emptying or bile secretion.

Inclusion criteria for treatment cohort: (1) Age ≥18 years; (2) Clinical diagnosis of MSAP or SAP [16]; (3) Diagnosis of mild to moderate PEI based on fecal elastase-1 (FE-1) levels.

Exclusion criteria for treatment cohort: (1) Other potential causes of PEI, including chronic pancreatitis, celiac disease, cystic fibrosis, diabetic gastroparesis, or pancreatic tumors; (2) History of gastrointestinal or pancreatic surgery.

Diagnostic criteria and definitions

Acute Pancreatitis Diagnostic Criteria: At least two of the following criteria must be met: (1) Persistent upper abdominal pain; (2) Serum amylase or lipase levels at least three times the upper normal limit; (3) Characteristic findings of AP on imaging studies.

Acute Pancreatitis Severity Classification: MAP: No organ failure and no local or systemic complications. MSAP: Transient organ failure (<48 hours) or presence of local or systemic complications. SAP: Persistent organ failure (≥48 hours).

Acute Pancreatitis Etiological Classification: Biliary AP: Confirmed gallstones or common bile duct dilatation >10 mm (or >14 mm in post-cholecystectomy patients) on ultrasound or CT; serum total bilirubin >40 μmol/L; elevation of alanine aminotransferase (ALT) > three times the upper normal limit. Hypertriglyceridemic AP: Serum triglycerides ≥11.3 mmol/L upon admission. Alcoholic AP: Alcohol consumption history >5 years, with average daily intake >50 grams.

PEI Diagnostic Criteria: Based on FE-1 levels from stool samples collected on day 7 of hospitalization: Severe PEI: FE-1 <100 μg/g. Mild-to moderate PEI: FE-1 between 100-200 μg/g. Normal function: FE-1 >200 μg/g [17].

Enteral Nutrition Intolerance Diagnostic Criteria: Diagnosis confirmed if one or more of the following occurred: (1) Gastrointestinal adverse reactions during enteral feeding, including vomiting, abdominal distension, diarrhea, or gastric residual volume ≥500 mL/24 h; (2) Failure to achieve target energy intake of 20 kcal/(kg·d) after 72 hours of enteral nutrition support [18].

Treatment protocols

Control Group: Standard conventional therapy, including fasting, fluid resuscitation, gastrointestinal decompression, gastric acid secretion suppression, oral rhubarb and Glauber's salt for laxative effects, topical thenardite application, and early enteral nutrition.

Treatment Group: Conventional therapy plus pancrelipase (Creon) tablets. The regimen consisted of 4 tablets per dose, three times daily, swallowed during meals or with enteral nutrition, or mixed into a nutrition formula for infusion. Other enzyme preparations and medications affecting gastric emptying or bile secretion were discontinued. Discontinuation of pancrelipase was based on a normal FE-1 result (>200 μg/g) at 1, 3, 6, or 12-month follow-up.

Clinical data collection

Clinical data were collected from patients' electronic medical records, including demographics (age, sex, BMI), medical history (diabetes, hypertension, smoking, alcohol consumption), and etiology (hyperlipidemic, biliary, alcoholic, etc.), AP severity, infected pancreatic necrosis, local complications, neutrophil count (NEUT), albumin (ALB), ALT, aspartate aminotransferase (AST), creatinine (Cr), blood urea nitrogen (BUN), blood glucose (BG), calcium (Ca), triglycerides (TG), cholesterol (CHOL), amylase (AMY), C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and Modified CT Severity Index (MCTSI).

Post-treatment outcomes: Enteral nutrition intolerance incidence, 24-hour relief rate, and day 7 bowel movement status. Hospital stay length and treatment costs were also recorded.

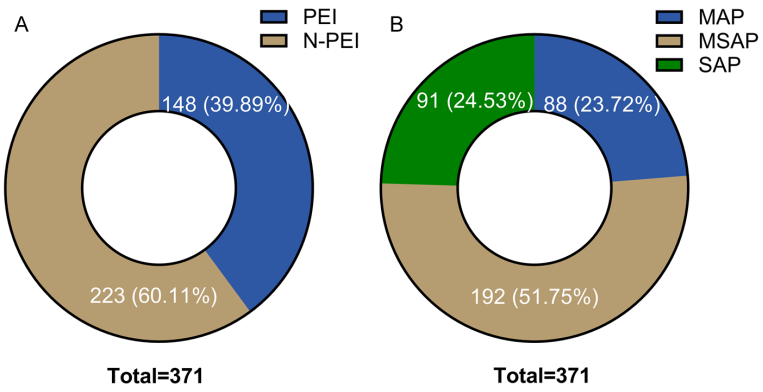

Figure 1. Incidence of PEI and Severity Distribution in Patients with AP. A. Incidence of PEI in patients with AP. B. Distribution of disease severity in patients with AP. Note: AP, Acute Pancreatitis; MAP, Mild Acute Pancreatitis; MSAP, Moderately Severe Acute Pancreatitis; SAP, Severe Acute Pancreatitis; PEI, Pancreatic Exocrine Insufficiency.

Outcome measures

Primary Outcome: Identification of independent risk factors for PEI development using logistic regression analysis.

Secondary Outcomes: Comparison of PERT versus conventional therapy effects on enteral nutrition intolerance incidence, 24-hour relief rate, and day 7 bowel movement status. Subgroup analyses were conducted based on independent risk factors (disease severity and infected pancreatic necrosis). Hospital stay length and treatment cost differences were also analyzed.

Statistical analysis

Data analysis was performed using SPSS version 26.0, R version 4.3.3, and GraphPad Prism version 10. Categorical variables expressed as counts and percentages, were compared using the Chi-square test, continuity-corrected Chi-square test, or Fisher's exact test as appropriate. Continuous variables were assessed for normality using the Kolmogorov-Smirnov (K-S) test. Normally distributed variables expressed as mean ± standard deviation, were compared using an independent samples t-test, while non-normally distributed variables used the Mann-Whitney U test. Logistic regression analysis evaluated the independent effects of various variables on PEI occurrence. Variance Inflation Factor (VIF) analysis was conducted to assess multicollinearity between predictor variables. Variables with VIF values greater than 10 were considered to exhibit significant multicollinearity and were excluded from the multivariate analysis. Interaction analysis and associated plots were generated using R 4.3.3, and doughnut charts were created with GraphPad Prism 10. All other statistical analyses and chart constructions used SPSS 26.0. *P*-values <0.05 were considered statistically significant.

Results

Overall PEI incidence

Among 371 AP patients, the overall PEI incidence was 39.89% (148/371) (**Figure 1A**). The distribution of AP severity was 88 patients (23.72%) with MAP, 192 patients (51.75%) with MSAP, and 91 patients (24.53%) with SAP (**Figure 1B**).

Comparison of baseline characteristics between PEI and N-PEI patients

Baseline characteristics were compared between the PEI and N-PEI groups. No significant differences were observed regarding age, sex, BMI, or histories of diabetes, hypertension, smoking, or alcohol consumption (all P>0.05). However, regarding etiology, the PEI group demonstrated a significantly higher proportion of hyperlipidemia-caused cases (P=0.004). AP severity and the incidence of infected pancreatic necrosis differed significantly between the groups, with the PEI group showing higher proportions of SAP and infected pancreatic necrosis (both P<0.001). Furthermore, the incidence of local complications was higher in the PEI group compared to the N-PEI group (P<0.001). Significant differences were also found in BUN, AMY, IL-6, and MCTSI levels between the groups (all P<0.05). No significant differences were observed for other variables, including ALB, AST, ALT, Cr, and blood glucose (all P>0.05) (**Table 1**).

Variable assignment and VIF analysis

For logistic regression analysis, variables were categorized. Categorical data were coded according to classifications, and continuous data were dichotomized using cutoff values. VIF analysis showed that the VIF values for BUN, AMY, IL-6, MCTSI, etiology, infected pancreatic

Table 1. Comparison of baseline characteristics between PEI and N-PEI patients

Variable	Total (n=371)	PEI (n=148)	N-PEI (n=223)	Statistic	*P*-value
Age				0.315	0.575
≥50 years	209 (56.33%)	86 (58.11%)	123 (55.16%)		
<50 years	162 (43.67%)	62 (41.89%)	100 (44.84%)		
Sex				0.328	0.567
Male	224 (60.38%)	92 (62.16%)	132 (59.19%)		
Female	147 (39.62%)	56 (37.84%)	91 (40.81%)		
BMI				0.520	0.471
≥24 kg/m^2	187 (50.40%)	78 (52.70%)	109 (48.88%)		
<24 kg/m^2	184 (49.60%)	70 (47.30%)	114 (51.12%)		
History of Diabetes				0.222	0.638
Yes	90 (24.26%)	34 (22.97%)	56 (25.11%)		
No	281 (75.74%)	114 (77.03%)	167 (74.89%)		
History of Hypertension				0.227	0.634
Yes	67 (18.06%)	25 (16.89%)	42 (18.83%)		
No	304 (81.94%)	123 (83.11%)	181 (81.17%)		
History of Smoking				0.885	0.347
Yes	152 (40.97%)	65 (43.92%)	87 (39.01%)		
No	219 (59.03%)	83 (56.08%)	136 (60.99%)		
History of Alcohol				0.603	0.437
Yes	62 (16.71%)	22 (14.86%)	40 (17.94%)		
No	309 (83.29%)	126 (85.14%)	183 (82.06%)		
Etiology				13.273	0.004
Hyperlipidemic	143 (38.54%)	66 (44.59%)	77 (34.53%)		
Biliary	129 (34.77%)	55 (37.16%)	74 (33.18%)		
Alcoholic	71 (19.14%)	15 (10.14%)	56 (25.11%)		
Other	28 (7.55%)	12 (8.11%)	16 (7.17%)		
AP Severity				65.219	<0.001
MAP	88 (23.72%)	4 (2.70%)	84 (37.67%)		
MSAP	192 (51.75%)	89 (60.14%)	103 (46.19%)		
SAP	91 (24.53%)	55 (37.16%)	36 (16.14%)		
Infected Pancreatic Necrosis				39.426	<0.001
Yes	179 (48.25%)	101 (68.24%)	78 (34.98%)		
No	192 (51.75%)	47 (31.76%)	145 (65.02%)		
Local Complications				27.042	<0.001
Yes	307 (82.75%)	141 (95.27%)	166 (74.44%)		
No	64 (17.25%)	7 (4.73%)	57 (25.56%)		
NEUT	77.15±13.58	77.16±12.63	77.13±14.21	0.020	0.984
ALB	31.67±6.38	31.01±5.62	32.12±6.82	1.640	0.102
ALT	18.00 [15.00, 21.00]	18.00 [15.00, 20.00]	18.00 [15.00, 22.00]	1.505	0.132
AST	25.00 [20.00, 30.00]	23.00 [19.00, 30.00]	26.00 [21.00, 31.00]	1.530	0.126
Cr	53.00 [40.50, 66.00]	53.00 [40.00, 66.00]	53.00 [41.50, 66.00]	0.291	0.771
BUN	4.56±1.83	5.53±1.89	3.91±1.47	9.253	<0.001
Blood Glucose	6.72±0.76	6.72±0.74	6.71±0.78	0.127	0.899
Ca	2.06±0.20	2.06±0.20	2.05±0.20	0.480	0.632
TG	1.30±0.50	1.28±0.54	1.31±0.48	0.447	0.655
CHOL	3.21±0.80	3.15±0.78	3.25±0.81	1.245	0.214
AMY	671.99±331.25	905.40±391.26	517.09±145.24	13.493	<0.001
CRP	83.34±30.38	84.32±31.18	82.70±29.89	0.503	0.615
PCT	0.32±0.12	0.34±0.12	0.31±0.12	1.733	0.084
IL-6	70.95±27.43	80.59±29.14	64.55±24.26	5.749	<0.001
MCTSI	6.00 [5.00, 7.00]	7.00 [5.00, 9.00]	5.00 [4.00, 6.50]	7.313	<0.001

Note: Data are presented as n (%), mean ± SD, or median [Interquartile Range]. PEI, Pancreatic Exocrine Insufficiency; N-PEI, Non-Pancreatic Exocrine Insufficiency; BMI, Body Mass Index; AP, Acute Pancreatitis; MAP, Mild Acute Pancreatitis; MSAP, Moderately Severe Acute Pancreatitis; SAP, Severe Acute Pancreatitis; NEUT, Neutrophils; ALB, Albumin; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; Cr, Creatinine; BUN, Blood Urea Nitrogen; TG, Triglycerides; CHOL, Cholesterol; AMY, Amylase; CRP, C-reactive Protein; PCT, Procalcitonin; IL-6, Interleukin-6; MCTSI, Modified CT Severity Index.

Table 2. Variable assignment and VIF values

Variable	Assignment	VIF
BUN		
≥5.325	1	Reference
<5.325	2	1.109
AMY		
≥789	1	Reference
<789	2	1.237
IL-6		
≥76.425	1	Reference
<76.425	2	1.049
MCTSI		
≥4.5	1	Reference
<4.5	2	1.263
Etiology		
Hyperlipidemic	1	Reference
Biliary	2	1.206
Alcoholic	3	1.163
Other	4	1.155
Infected pancreatic necrosis		
Yes	1	Reference
No	2	1.147
Local complications		
Yes	1	Reference
No	2	1.200
AP Severity		
MAP	1	Correlated with MCTSI, thus excluded
MSAP	2	
SAP	3	

Note: VIF, Variance Inflation Factor; BUN, Blood Urea Nitrogen; AMY, Amylase; IL-6, Interleukin-6; MCTSI, Modified CT Severity Index; AP, Acute Pancreatitis; MAP, Mild Acute Pancreatitis; MSAP, Moderately Severe Acute Pancreatitis; SAP, Severe Acute Pancreatitis.

necrosis, and local complications were all below 1.3. Due to high correlation between AP severity and MCTSI, AP severity was excluded from the multivariate model to avoid multicollinearity (**Table 2**).

Univariate and Multivariate Logistic Regression Analysis for PEI

Univariate analysis revealed that BUN, AMY, IL-6, MCTSI, infected pancreatic necrosis, and local complications were significantly associated with PEI presence (P<0.05). Specifically, odds ratios for BUN, AMY, IL-6, and MCTSI were all less than 1, indicating a negative association with PEI occurrence. The ORs for infected pancreatic necrosis and local complications were also less than 1, suggesting they were risk factors for PEI (**Table 3**).

Multivariate analysis confirmed that BUN, AMY, IL-6, MCTSI, and infected pancreatic necrosis were significant predictors of PEI (P<0.05). ORs for BUN, AMY, IL-6, and MCTSI remained below 1, confirming their negative association with PEI. The OR for infected pancreatic necrosis was 0.138, identifying it as a significant risk factor for PEI. Etiology and local complications showed no significance by multivariate analysis (P>0.05) (**Table 4**).

Independent risk factors interaction analysis for PEI

Logistic regression modeling, including interaction terms for BUN and AMY, showed that BUN, AMY, IL-6, MCTSI, and infected pancreatic necrosis were significant predictors of PEI (P<0.05). The coefficients for BUN, AMY, IL-6,

Table 3. Univariate logistic regression analysis for PEI

Variable	Estimate	Std Error	*P* Value	OR	Lower	Upper
BUN	-1.750	0.244	<0.001	0.174	0.108	0.280
AMY	-4.499	0.532	<0.001	0.011	0.004	0.032
IL-6	-1.179	0.221	<0.001	0.308	0.199	0.475
MCTSI	-3.080	0.525	<0.001	0.046	0.016	0.129
Etiology	-0.272	0.117	0.020	0.762	0.605	0.959
Infected pancreatic necrosis	-1.980	0.241	<0.001	0.138	0.086	0.221
Local complications	-1.934	0.417	<0.001	0.145	0.064	0.327

Note: PEI, Pancreatic Exocrine Insufficiency; N-PEI, Non-Pancreatic Exocrine Insufficiency; BUN, Blood Urea Nitrogen; AMY, Amylase; IL-6, Interleukin-6; MCTSI, Modified CT Severity Index; Local Complications; OR, Odds Ratio.

Table 4. Multivariate logistic regression analysis for PEI

Variable	Estimate	Std Error	*P* Value	OR	Lower	Upper
BUN	-1.796	0.388	<0.001	0.166	0.076	0.349
AMY	-4.730	0.687	<0.001	0.009	0.002	0.029
IL-6	-1.158	0.370	0.002	0.314	0.149	0.642
MCTSI	-3.475	0.883	<0.001	0.031	0.004	0.146
Etiology	-0.134	0.200	0.502	0.874	0.586	1.289
Infected pancreatic necrosis	-1.981	0.403	<0.001	0.138	0.060	0.296
Local complications	0.018	0.821	0.983	1.018	0.184	4.781

Note: PEI, Pancreatic Exocrine Insufficiency; N-PEI, Non-Pancreatic Exocrine Insufficiency; BUN, Blood Urea Nitrogen; AMY, Amylase; IL-6, Interleukin-6; MCTSI, Modified CT Severity Index; Local Complications; OR, Odds Ratio.

and MCTSI were positive, indicating that increases in these variables were associated with increased PEI risk. Conversely, the coefficient for infected pancreatic necrosis was negative, indicating a protective effect. Specifically, for each one-unit increase, PEI log-odds increased by 1.088 for BUN, 0.0095 for AMY, 0.02269 for IL-6, and 0.4359 for MCTSI. The presence of infected pancreatic necrosis decreased PEI log-odds by 1.267. The BUN*AMY interaction term had a coefficient of -0.0007315 (P=0.102), which was not statistically significant, suggesting weak predictive power for PEI and potential exclusion from the model (**Figure 2**).

Comparison of baseline characteristics between treatment and control groups

The therapeutic analysis included 127 patients, with 55 receiving PERT (treatment group) and 77 receiving conventional therapy (control group). Baseline characteristics were comparable between groups. No significant differences were found between groups in age, sex, BMI, diabetes history, hypertension, smoking, or alcohol consumption, as well as etiology, AP severity, infected pancreatic necrosis, or local complications (all P>0.05). Laboratory values, including NEUT, ALB, ALT, AST, TG, CHOL, AMY, and CRP, also showed no significant differences between groups (all P>0.05) (**Table 5**).

Treatment protocol effects on patient outcome

The incidence of enteral nutrition intolerance was significantly lower in the treatment group compared to the control group (P=0.007). At 24 hours post-treatment, the relief rate for enteral nutrition intolerance was significantly higher in the treatment group (P=0.022). On day 7 post-treatment, bowel function was significantly better in the treatment group than in the control group (P=0.006) (**Table 6**).

AP severity and infected pancreatic necrosis subgroup analysis

For MSAP patients, the treatment group showed significantly lower enteral nutrition intolerance incidence (P=0.026) and significantly better day 7 bowel function (P=0.017) compared to the control group. However, no significant difference was found in the 24-hour intolerance relief rate (P>0.999). For SAP patients, enteral nutrition intolerance incidence was also signifi-

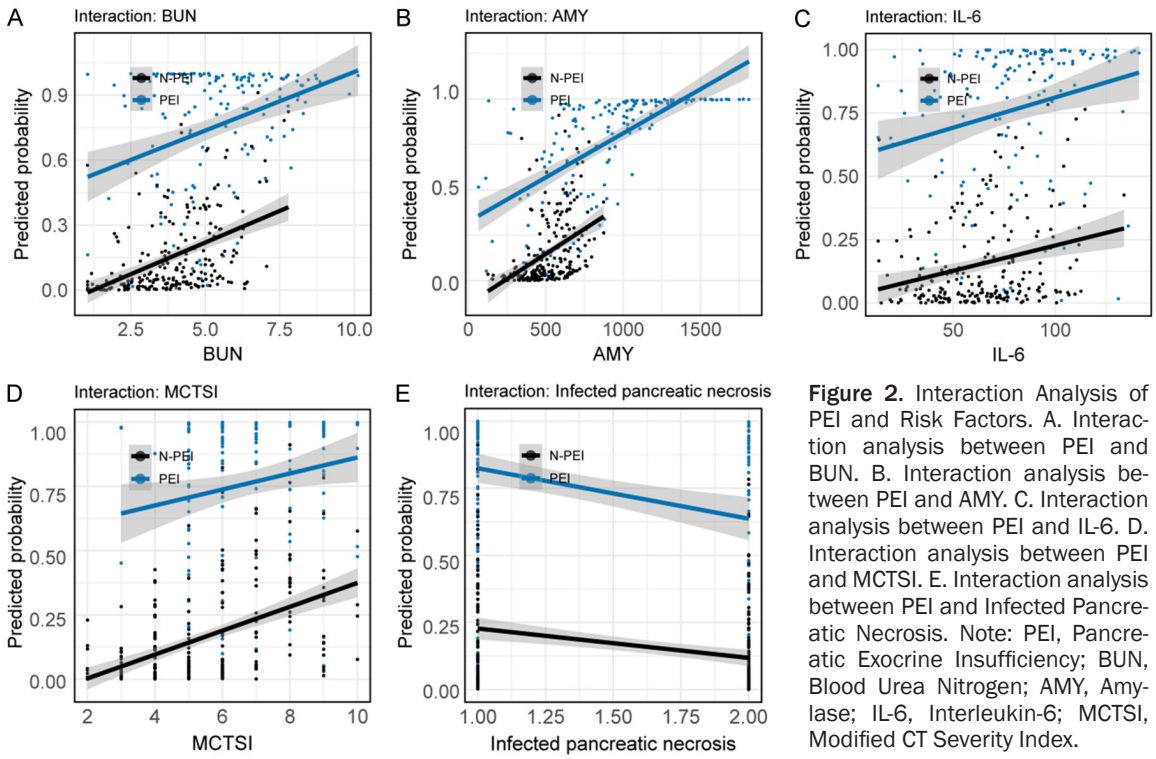

Figure 2. Interaction Analysis of PEI and Risk Factors. A. Interaction analysis between PEI and BUN. B. Interaction analysis between PEI and AMY. C. Interaction analysis between PEI and IL-6. D. Interaction analysis between PEI and MCTSI. E. Interaction analysis between PEI and Infected Pancreatic Necrosis. Note: PEI, Pancreatic Exocrine Insufficiency; BUN, Blood Urea Nitrogen; AMY, Amylase; IL-6, Interleukin-6; MCTSI, Modified CT Severity Index.

cantly lower in the treatment group (P=0.005). However, no significant differences were observed in the 24-hour relief rate (P=0.054) or day 7 bowel function (P=0.204) (**Table 7**).

Among patients with infected pancreatic necrosis, the treatment group had significantly lower enteral nutrition intolerance incidence (P=0.003), higher 24-hour relief rates (P=0.014), and better day 7 bowel function (P=0.030) compared to the control group. In contrast, no significant differences were found among patients without necrosis (all P>0.05) (**Table 8**).

Hospital stay and treatment cost analysis

Hospital stay was significantly shorter in the treatment group compared to the control group (P=0.012). However, treatment costs did not differ significantly between groups (P=0.081) (**Table 9**). Subgroup analysis revealed that the length of hospital stay was significantly shorter for MSAP patients in the treatment group (P=0.001), but no difference was observed for SAP patients (P=0.880). Treatment costs did not differ significantly in either the MSAP or SAP subgroups (both P>0.05) (**Table 10**). For patients with infected pancreatic necrosis, hospital stay was significantly shorter in the treatment group (P=0.015), whereas no difference was found among patients without necrosis (P=0.455). Treatment costs did not differ significantly in either subgroup (both P>0.05) (**Table 11**).

Discussion

Acute pancreatitis (AP) is a common acute abdominal emergency, and with rising incidence, a subset of patients develops PEI [10]. PEI impairs food digestion and nutrient absorption, particularly in SAP patients, leading to diminished quality of life, malnutrition, and prolonged hospital stays [19]. While PERT is considered promising for improving PEI, its efficacy lacks widespread validation. This study assessed PEI incidence and risk factors in AP patients and explored PERT's clinical efficacy, providing evidence for clinical practice.

Our study identified five independent factors significantly associated with PEI development: BUN, AMY, IL-6, MCTSI, and infected pancreatic necrosis. In regression analysis, odds ratios for BUN, AMY, IL-6, and MCTSI were all less than 1. However, this should not be interpreted as these markers being "protective". Instead, it reflects the way variables were categorized and dichotomized using specific cut-off values, with

Table 5. Comparison of baseline characteristics between the treatment and control groups

Variable	Total (n=127)	Treatment Group (n=55)	Control Group (n=72)	Statistic	*P*-value
Age				0.816	0.366
≥50 years	75 (59.06%)	30 (54.55%)	45 (62.50%)		
<50 years	52 (40.94%)	25 (45.45%)	27 (37.50%)		
Sex				0.963	0.326
Male	80 (62.99%)	32 (58.18%)	48 (66.67%)		
Female	47 (37.01%)	23 (41.82%)	24 (33.33%)		
BMI				0.947	0.331
≥24 kg/m^2	63 (49.61%)	30 (54.55%)	33 (45.83%)		
<24 kg/m^2	64 (50.39%)	25 (45.45%)	39 (54.17%)		
History of Diabetes				0.057	0.811
Yes	31 (24.41%)	14 (25.45%)	17 (23.61%)		
No	96 (75.59%)	41 (74.55%)	55 (76.39%)		
History of Hypertension				1.019	0.313
Yes	21 (16.54%)	7 (12.73%)	14 (19.44%)		
No	106 (83.46%)	48 (87.27%)	58 (80.56%)		
History of Smoking				0.271	0.603
Yes	59 (46.46%)	27 (49.09%)	32 (44.44%)		
No	68 (53.54%)	28 (50.91%)	40 (55.56%)		
History of Alcohol				0.001	0.969
Yes	16 (12.60%)	7 (12.73%)	9 (12.50%)		
No	111 (87.40%)	48 (87.27%)	63 (87.50%)		
Etiology				3.973	0.264
Hyperlipidemic	57 (44.88%)	29 (52.73%)	28 (38.89%)		
Biliary	49 (38.58%)	19 (34.55%)	30 (41.67%)		
Alcoholic	11 (8.66%)	5 (9.09%)	6 (8.33%)		
Other	10 (7.87%)	2 (3.64%)	8 (11.11%)		
AP Severity				0.373	0.542
MSAP	80 (62.99%)	33 (60.00%)	47 (65.28%)		
SAP	47 (37.01%)	22 (40.00%)	25 (34.72%)		
Infected Pancreatic Necrosis				0.694	0.405
Yes	85 (66.93%)	39 (70.91%)	46 (63.89%)		
No	42 (33.07%)	16 (29.09%)	26 (36.11%)		
Local Complications				0.135	0.713
Yes	120 (94.49%)	51 (92.73%)	69 (95.83%)		
No	7 (5.51%)	4 (7.27%)	3 (4.17%)		
NEUT	79.19 [69.26, 84.33]	78.93 [71.47, 86.02]	79.28 [67.75, 83.92]	0.552	0.581
ALB	30.96±5.50	31.13±5.85	30.83±5.25	0.309	0.758
ALT	18.00 [15.00, 20.00]	18.00 [15.00, 19.00]	18.00 [15.00, 21.00]	0.217	0.828
AST	23.00 [19.00, 30.00]	25.00 [16.00, 30.00]	23.00 [20.75, 30.00]	0.100	0.920
Cr	52.00 [39.50, 66.00]	48.00 [38.50, 62.00]	53.00 [41.00, 68.25]	1.047	0.295
BUN	5.52±1.87	5.51±1.90	5.53±1.86	-0.073	0.942
Blood Glucose	6.70 [6.22, 7.25]	6.46 [6.05, 7.22]	6.81 [6.29, 7.25]	1.691	0.091
Ca	2.07±0.20	2.08±0.21	2.06±0.20	0.576	0.566
TG	1.25±0.54	1.30±0.48	1.20±0.59	1.046	0.298
CHOL	3.15±0.77	3.26±0.86	3.07±0.69	1.355	0.178
AMY	899.10±386.93	898.25±367.20	899.75±403.90	-0.021	0.983
CRP	84.50±31.45	81.23±29.20	87.00±33.05	-1.025	0.307
PCT	0.33 [0.25, 0.42]	0.37 [0.28, 0.43]	0.30 [0.25, 0.41]	1.614	0.107
IL-6	80.12±29.23	83.38±32.02	77.63±26.88	1.099	0.274
MCTSI	7.00 [5.00, 8.50]	7.00 [6.00, 9.00]	6.00 [5.00, 8.00]	1.099	0.272

Note: Data are presented as n (%), mean ± SD, or median [Interquartile Range]. PEI, Pancreatic Exocrine Insufficiency; N-PEI, Non-Pancreatic Exocrine Insufficiency; BMI, Body Mass Index; AP, Acute Pancreatitis; MSAP, Moderately Severe Acute Pancreatitis; SAP, Severe Acute Pancreatitis; NEUT, Neutrophils; ALB, Albumin; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; Cr, Creatinine; BUN, Blood Urea Nitrogen; TG, Triglycerides; CHOL, Cholesterol; AMY, Amylase; CRP, C-reactive Protein; PCT, Procalcitonin; IL-6, Interleukin-6; MCTSI, Modified CT Severity Index.

Table 6. Comparison of the effects of treatment protocols on patient outcomes

Variable	Treatment Group (n=55)	Control Group (n=72)	Statistic	*P*-value
Incidence of enteral nutrition intolerance (Present/Absent)	13/42	35/37	7.244	0.007
Relief Rate of enteral nutrition intolerance at 24 h (Relieved/Not Relieved)	11/2	16/19	-	0.022
Bowel Movement Status on Day 7 (score, mean ± SD)	0.91±0.65	1.26±0.77	2.822	0.006

Table 7. Comparison of outcomes in subgroups by AP severity

Variable	MSAP				SAP			
	Treatment Group (n=33)	Control Group (n=47)	Statistic	*P*-value	Treatment Group (n=22)	Control Group (n=25)	Statistic	*P*-value
Incidence of enteral nutrition intolerance (Present/Absent)	3/30	14/33	4.962	0.026	10/12	21/4	7.743	0.005
Relief Rate of enteral nutrition intolerance at 24 h (Relieved/Not Relieved)	2/1	8/6	-	>0.999	8/2	8/13	-	0.054
Bowel Movement Status on Day 7 (score, mean ± SD)	1.00 [0.00, 1.00]	1.00 [1.00, 2.00]	2.388	0.017	1.00 [1.00, 1.00]	1.00 [1.00, 2.00]	1.271	0.204

Note: MSAP, Moderately Severe Acute Pancreatitis; SAP, Severe Acute Pancreatitis.

Table 8. Comparison of outcomes in subgroups by infected pancreatic necrosis

Variable	Necrosis Present				Necrosis Absent			
	Treatment Group (n=39)	Control Group (n=46)	Statistic	*P*-value	Treatment Group (n=16)	Control Group (n=26)	Statistic	*P*-value
Incidence of enteral nutrition intolerance (Present/Absent)	8/31	24/22	9.013	0.003	5/11	11/15	0.514	0.474
Relief Rate of enteral nutrition intolerance at 24 h (Relieved/Not Relieved)	8/0	11/13	-	0.014	2/3	5/6	-	>0.999
Bowel Movement Status on Day 7 (score, mean ± SD)	1.00 [0.00, 1.00]	1.00 [1.00, 2.00]	2.164	0.030	1.00 [1.00, 1.00]	1.00 [1.00, 2.00]	1.425	0.154

Table 9. Comparison of length of stay and treatment costs between treatment and control groups

Variable	Treatment Group (n=55)	Control Group (n=72)	Statistic	*P*-value
Length of Hospital Stay (days)	10.47±4.81	12.67±4.82	2.544	0.012
Treatment Cost (CNY)	21010.35±8653.95	23910.62±9586.40	1.761	0.081

Table 10. Comparison of length of stay and treatment costs in subgroups by AP severity

Length of Hospital Stay (days)	MSAP				SAP			
	Treatment Group (n=33)	Control Group (n=47)	Statistic	*P*-value	Treatment Group (n=22)	Control Group (n=25)	Statistic	*P*-value
Treatment Costs (CNY)	9.42±3.83	12.87±4.84	-3.407	0.001	12.05±5.73	12.28±4.85	-0.152	0.880
Length of Hospital Stay (days)	21370.79±9315.72	24469.87±9410.26	-1.456	0.149	20469.68±7734.71	22859.24±10018.86	-0.906	0.370

Table 11. Comparison of length of stay and treatment costs in subgroups by infected pancreatic necrosis

Length of Hospital Stay (days)	Necrosis Present				Necrosis Absent			
	Treatment Group (n=39)	Control Group (n=46)	Statistic	*P*-value	Treatment Group (n=16)	Control Group (n=26)	Statistic	*P*-value
Treatment Costs (CNY)	9.97±5.12	12.54±4.40	-2.489	0.015	11.69±3.82	12.88±5.58	-0.754	0.455
Length of Hospital Stay (days)	20473.97±7921.01	23147.76±9130.96	-1.429	0.157	22317.75±10396.55	25260.31±10390.10	-0.891	0.378

the "higher-value" group as the reference. Thus, an OR <1 indicates that the lower group had a reduced risk relative to the higher group, meaning higher levels of these markers were associated with greater PEI risk.

This interpretation aligns with existing evidence: lower BUN levels generally indicate better renal function and overall health [20]; lower AMY may reflect milder pancreatic inflammation [21]; lower IL-6 corresponds to a less severe inflammatory response [22]; and lower MCTSI suggests less radiological severity of pancreatic damage [23]. Literature indicates that MCTSI is an independent risk factor for post-AP PEI, with higher MCTSI scores associated with increased risk, aligning with the protective effect of lower MCTSI observed in our study and further emphasizing the importance of imaging in PEI risk stratification [14].

Conversely, ORs for infected pancreatic necrosis and local complications were both greater than 1, identifying them as significant PEI risk factors. A cross-sectional study by Wang et al. [24] found that PEI incidence in critically ill patients reached 52.2%, with shock and sepsis being significant risk factors. This supports the view that infected pancreatic necrosis is a major risk factor for post-AP PEI, highlighting the critical role of inflammation and tissue damage in its pathogenesis. A review by Bejjani et al. [7] noted that post-AP PEI development is closely linked to acinar cell destruction and the degree of inflammation. As a severe pancreatic injury marker, infected pancreatic necrosis significantly increases PEI risk, corroborating our findings.

Infected pancreatic necrosis typically associates with extensive tissue death and infection, leading to severe pancreatic dysfunction and exacerbating exocrine insufficiency risk [25]. Local complications, such as pancreatic cysts or pseudocysts, are common in severe AP and can intensify pancreatic damage, promoting PEI development. Therefore, the presence of infected pancreatic necrosis and local complications significantly increases PEI risk, suggesting that enhanced monitoring and management of these high-risk factors are warranted in clinical practice.

PERT efficacy evaluation in PEI patients revealed that the treatment group achieved significantly better outcomes than the control group regarding enteral nutrition intolerance incidence, 24-hour relief rate, and day 7 bowel function. Particularly in SAP patients, PERT significantly reduced enteral nutrition intolerance incidence and improved bowel function. A study by Barkin et al. [26] found that PERT significantly improved stool frequency and fat absorption in patients with chronic pancreatitis-related PEI. This is consistent with the bowel function improvement observed in our AP patients, suggesting PERT's broad-spectrum efficacy in pancreatic insufficiency.

Literature shows that post-AP PEI is closely related to pancreatic acinar cell destruction; PERT effectively alleviates indigestion and malabsorption by supplementing exogenous enzymes, aligning with our findings of improved nutritional tolerance and bowel function in SAP patients [27]. Although the 24-hour relief rate was not as pronounced in some patients compared to the control group, symptom improvement over 7 days and hospital stay reduction were highly significant. A meta-analysis has shown that standard-dose PERT significantly improves fat absorption and digestive symptoms, suggesting that the limited efficacy observed in our SAP patients might be due to insufficient dosage or disease complexity [28].

For patients with infected pancreatic necrosis, PERT also demonstrated a significant advantage in alleviating enteral nutrition intolerance and improving bowel function. PEI patients often suffer from indigestion and malabsorption, and PERT aids digestion by supplementing exogenous enzymes, thus reducing gastrointestinal adverse reactions. This is particularly crucial in SAP patients, where pancreatic necrosis and multi-organ damage create more urgent digestive support needs. A systematic review by Kadaj-Lipka et al. [29] indicated that guideline-compliant PERT not only relieves GI symptoms but also improves nutritional status, supporting our observation of more significant efficacy in MSAP patients and suggesting potential benefits from dose optimization for SAP patients.

While infection control and surgical intervention are key for infected pancreatic necrosis, PERT still plays a positive role in managing digestive symptoms, reflecting its value in com-

plex disease management. Research by Layer et al. [30] further noted that PERT improves malnutrition and weight maintenance in PEI patients, supporting the positive impact of PERT on digestive function in our patients with infected pancreatic necrosis.

This study found that PERT's impact on hospital stay length and treatment costs varied among patients with different AP severities and the presence of infected pancreatic necrosis. In MSAP patients, PERT significantly shortened hospital stay, reducing patient burden, while treatment costs showed no significant difference, possibly because cost savings from shorter stays were offset by medication costs. In contrast, for SAP patients, hospital stay changes were less pronounced, and costs were not significantly different, likely due to their condition complexity and severity. SAP patients often have persistent organ failure and multi-organ damage, requiring complex treatment regimens that may limit PERT's relative effect.

Research suggests that severe PEI requires definite PERT, whereas mild-to-moderate PEI may not, which could explain the limited efficacy observed in our SAP patients, whose disease severity might exceed PERT's primary intervention scope [31]. In patients with infected pancreatic necrosis, the treatment group had significantly shorter hospital stays, indicating a positive impact. However, in patients without necrosis, the effect was limited, possibly because other interventions (e.g., infection control, surgery) played dominant roles. Overall, PERT efficacy varies across different disease stages, and its impact on hospital stay and costs is less ideal in patients with SAP and infected pancreatic necrosis, where other therapeutic interventions are paramount.

Based on our findings, PERT demonstrates clear clinical advantages for AP patients, with particularly strong performance in those with MSAP and infected pancreatic necrosis. The treatment group showed significantly lower enteral nutrition intolerance incidence and improved bowel function compared to the control group, especially in these high-risk subgroups. However, in SAP patients, PERT's effect on alleviating enteral nutrition intolerance was more limited, and the 24-hour relief rate did not differ significantly from the control group. Furthermore, although the treatment group had a notable advantage in overall stay length, this difference was not significant for SAP patients, indicating a weaker effect in this cohort.

While this study provides preliminary clinical evidence for PERT, larger, multicenter, long-term follow-up studies are needed to further validate its long-term efficacy and safety. Future research should delve deeper into PEI pathogenesis and focus on optimizing PERT, potentially through personalized treatment approaches, to enhance therapeutic outcomes and minimize adverse effects.

In conclusion, this study revealed a high PEI incidence among acute pancreatitis patients, particularly in those with severe disease forms, posing a significant clinical risk. Pancreatic enzyme replacement therapy stands out as an effective treatment, capable of significantly alleviating enteral nutrition intolerance symptoms, improving bowel function, and effectively shortening hospital stay length for patients with PEI.

Disclosure of conflict of interest

None.

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