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Real-world evidence comparing early and late pancreatic stent placement to prevent post-ERCP pancreatitis

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ABSTRACT

Background and study aims Pancreatic stenting effectively lowers the occurrence of post-ERCP pancreatitis (PEP) and reduces its severity. However, limited research has been conducted to determine the optimal timing for pancreatic stent placement. Our objective was to evaluate whether early pancreatic stent placement (EPSP) is more effective than late pancreatic stent placement (LPSP) in preventing PEP among patients with naive papilla.

Patients and methods We conducted a retrospective cohort study that analyzed 590 patients with difficult biliary cannulation using the pancreatic guidewire technique, who were divided into EPSP and LPSP groups. In the EPSP group, a pancreatic stent was placed immediately before/after endoscopic retrograde cholangiography (ERC) or endoscopic sphincterotomy (EST). Conversely, in the LPSP group, a pancreatic stent was placed after partial/all completion of major endoscopic procedures.

Results From November 2017 to May 2023, 385 patients were in the EPSP group and 205 in the LPSP group. EPSP was associated with a decreased PEP occurrence compared with LPSP (2.9% vs. 7.3%; $P = 0.012$). Similarly, hyperamylasemia was lower in the EPSP group (19.7% vs. 27.8%; $P = 0.026$). Furthermore, sensitivity analysis using multivariable analysis and propensity score–matched (PSM) analysis also validated these findings.

Conclusions Early pancreatic stent placement reduced the incidence of PEP and hyperamylasemia compared with late pancreatic stent placement. Our findings favor pancreatic stenting immediately before/after ERC or EST.

Introduction

With rapid advancement in endoscopic treatment techniques, endoscopic retrograde cholangiopancreatography (ERCP) has become established as the gold standard for managing cholangiopancreatic diseases [1, 2, 3]. As an invasive procedure, ERCP is associated with various complications that inevitably arise. Among these complications, post-ERCP pancreatitis (PEP) is the most common, with an overall occurrence rate ranging from 3% to 20% [4, 5, 6, 7, 8, 9, 10, 11, 12]. PEP not only leads to substantial morbidity but also poses occasional risks of mortality and places a significant economic burden on patients and healthcare systems. Furthermore, it represents the primary cause of malpractice lawsuits related to ERCP [13].

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PEP is associated with several factors related to ERCP, including difficult cannulation, inadvertent manipulation of the pancreatic duct (PD), and others [8, 14, 15]. Notably, deep placement of a guidewire in the main pancreatic access is a well-known independent risk factor for PEP [16]. Deep placement of pancreatic guidewire can cause edema and obstruction of the pancreatic outflow tract, leading to impaired flow of pancreatic secretions and subsequent development of PEP [17]. Furthermore, prolonged placement of the guidewire increases this risk [3]. To address these issues, pancreatic duct (PD) stenting is considered an effective measure for relieving PD hypertension and is recommended in multiple societal guidelines as a prophylactic measure against PEP [14, 15, 18, 19, 20].

A retrospective study [21] suggested that early PD stent placement (EPSP) during wire-guided cannulation (WGC) may potentially reduce incidence of PEP. However, this study was not specifically designed to assess the impact of EPSP on PEP prevention; rather, it was a comparative study examining the effectiveness of pancreatic stent placement after WGC compared with repeated WGC. Also, the outcomes were not statistically significant ($P = 0.08$).

Further investigation is warranted to identify the ideal timing of PD stenting in order to reduce the occurrence of PEP. We hypothesized that EPSP could potentially be a superior approach in preventing PEP. Therefore, we conducted a retrospective cohort study to evaluate the validity of our hypothesis.

Patients and methods

Study design

We conducted a retrospective cohort study at The First Affiliated Hospital of Anhui Medical University, approved by the Hospital Research Ethics Committee. Informed consent was not required for this study in accordance with the ethical guidelines outlined in the revised 2013 Declaration of Helsinki.

Patients

From November 2017 to May 2023, all consecutive patients who met the following criteria were enrolled in this study: naïve papilla, aged > 18 years, and underwent ERCP with pancreatic guidewire-assisted technique for biliary access.

Exclusion criteria were patients with unreachable main papillae, surgically altered gastrointestinal anatomy, no PD stenting, and inadvertent loss of PD guidewire after bile duct cannulation.

Design

The ERCP procedures in our study were performed by a team of seven experienced endoscopists, consisting of three expert endoscopists (completed over 1000 ERCPs) and four intermediate endoscopists (performed between 200 and 1000 ERCPs) [22]. We used standard duodenoscopes for ERCPs (JF-260V and TJF-260V; Olympus Co., Tokyo, Japan), with patients positioned in the prone position and sedated with diazepam, pethidine hydrochloride, midazolam, and/or propofol. Biliary cannulation was initially performed using a sphincterotome (Boston Scientific, Natick, Massachusetts, United States) preloaded with a 0.035-inch guidewire (Boston Scientific, Natick, Massachusetts, United States). If unsuccessful, the double-wire technique and precut sphincterotomy were applied as alternative methods for the bile duct approach. Administration of rectal nonsteroidal anti-inflammatory drugs (NSAIDs) (100 mg) for PEP prevention during the periprocedural period was at endoscopist discretion. All patients were administered Ringer's lactate infusion at a rate of 6 mL/kg/h throughout the procedure. Subsequently, a 20 mL/kg bolus was administered following ERCP, followed by a maintenance dose of 3 mL/kg for an additional 8 hours.

In the EPSP group, a single pigtail pancreatic stent with a flange (5F; Cook Corporation, Bloomington, Indiana, United States) was inserted instantly either before/after ERCP or endoscopic sphincterotomy (EST) (**Supplementary Fig. 1, Supplementary Fig. 3**). In contrast, in the LPSP group, while keeping the PD guidewire in place, a single pigtail PD stent with a flange (5F) was ultimately placed at the conclusion of partial/all major endoscopic procedures (**Supplementary Fig. 2, Supplementary Fig. 3**). Timing of stent positioning was assessed by reviewing the images captured during the procedures. The decision to remove the prosthesis depended on whether the disorder was benign or malignant. If benign, the pancreatic stent was typically removed endoscopically within 2 weeks after ERCP at our outpatient clinic. If malignant, it was usually not removed unless symptoms were present.

Following ERCP, all patients were hospitalized for monitoring potential adverse events (AEs) such as post-ERCP pancreatitis, cholangitis, perforation, bleeding, or any other AEs. All AEs, including PEP, were evaluated by experienced gastroenterologists. Serum amylase was measured at 3 and 24 hours after the operation. Thereafter, the decision to discharge patients was made by a senior physician based on their overall clinical condition.

Definitions and outcomes

The primary outcome of our research was incidence of post-ERCP pancreatitis, whereas secondary outcomes were hyperamylasemia, PEP severity, and other ERCP-related AEs.

Diagnosis and grading of post-ERCP pancreatitis were based on the revised Atlanta Classification [23]. Cholangitis was defined according to the 2018 Tokyo guidelines [24]. For other AEs, such as hemorrhage and perforation, we followed recommendations provided by the American Society for Gastrointestinal Endoscopy (ASGE) [25] (**Supplementary Table 1**).

In this study, difficult biliary cannulation was defined as occurring when accidental pancreatic cannulation happened at least twice. Major endoscopic procedures were defined as the process of biliary stone removal or drainage, involving endoscopic papillary balloon dilation, balloon or basket stone extraction, spyglass procedure, biliary biopsies, guidewire superselection, and biliary stenting.

Any AEs and readmissions within 30 days after surgery were documented. In addition, patients were counseled to connect with their doctor if they experienced ongoing or worsening symptoms. We assumed that absence of recorded AEs in patient records did not necessarily imply absence of AEs.

Statistical analysis

Differences in baseline characteristics between the EPSP and LPSP groups were analyzed using the Student *t*-test and Wilcoxon rank sum test for continuous variables and the chi-square test and Fisher's exact tests for categorical variables.

After ERCP, we compared patients in the EPSP cohort with those in the LPSP cohort and analyzed clinical and procedural factors associated with pancreatitis. The study employed univariate logistic regression analyses, with development of PEP as the dependent variable and the following independent variables considered: age, sex, coexisting disorders, indications, bile duct diameter, serum bilirubin levels, rectal NSAID prophylaxis, PD stent type, expert endoscopists, endoscopic appearance of papilla of Vater [26], history of pancreatitis, female aged < 50 years, normal bilirubin levels, non-biliary dilation, duodenal diverticulum, cannulation method, balloon dilatation of an intact biliary sphincter, failed PD stenting, and EPSP (Supplementary Table 2). Any independent variable ($P < 0.10$) was included in the final logistic regression model. A separate multivariable logistic regression model was developed specifically for classic post-ERCP pancreatitis risk factors and involved age < 50 years, sex, biliary stones, pancreatic carcinoma, cholangiocarcinoma, duodenal diverticulum, history of pancreatitis, rectal NSAID prophylaxis, normal bilirubin levels, non-biliary dilation, balloon dilatation of an intact biliary sphincter, and EPSP. The two models were also applied for hyperamylasemia exploration.

A propensity score-matched (PSM) analysis was conducted for 410 patients based on factors such as sex, biliary stones, cholangiocarcinoma, pancreatic carcinoma, serum bilirubin levels, and history of pancreatitis, which was achieved using the nearest neighbor method in a 1:1 ratio.

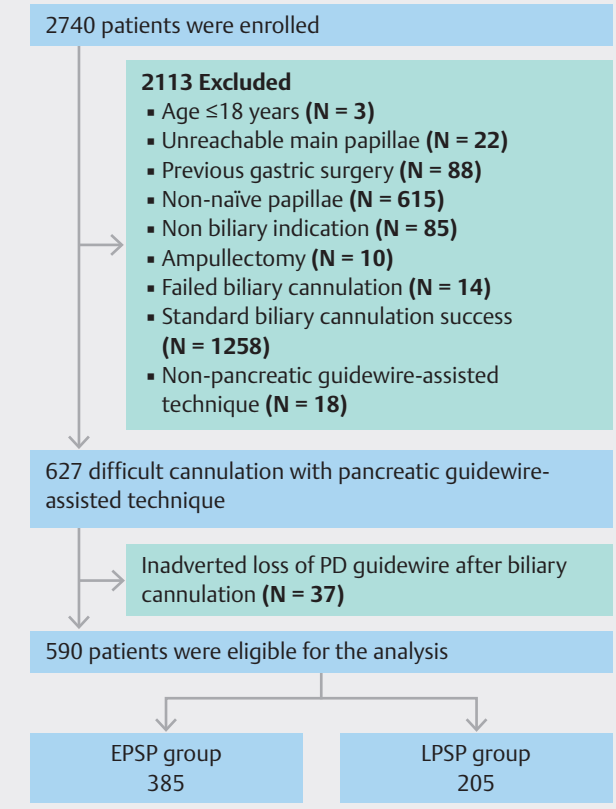
To clarify the impact of early and late PD stenting on different subgroups, subgroup analyses were performed to examine the association between EPSP and PEP occurrence, including age < 50 years, sex, etiology, duodenal diverticulum, history of pancreatitis, rectal NSAID prophylaxis, normal bilirubin levels, non-biliary dilation, and balloon dilatation of an intact biliary sphincter.

We assumed an occurrence rates for PEP in the EPSP group of approximately 8.5% and of 18% in the LPSP group, based on a previous study [21]. Approximately 199 patients were required in each cohort to explore a difference between the groups, with 80% power and a two-sided significance level of 0.05. All statistical analyses were performed using SPSS 23.0 (SPSS, Chicago, Illinois, United States) and R 4.3.1 (R Development Core Team).

Results

Baseline data

From November 2017 to May 2023, a total of 2,740 patients were referred to The First Affiliated Hospital of Anhui Medical University fortherapeutic ERCP. After screening based on exclusion criteria, 2,150 patients were excluded. 590 patients who fulfilled the inclusion criteria were divided into the EPSP group (n = 385) and the LPSP group (n = 205) (▶ **Fig. 1**).



▶ **Fig. 1** Patient flow diagram. The study flow diagram depicts the allocation of cases to the study groups in this retrospective study. PD, pancreatic duct; EPSP, early pancreatic stent placement; LPSP: late pancreatic stent placement.

Baseline characteristics of the two cohorts are presented in ▶ **Table 1**. Among the two cohorts, differences were observed in sex (male 209 [54.3%] vs 93 [45.1%]; female 176 [45.7%] vs 113 [54.9%]; $P = 0.030$), biliary stones (183 [47.5%] vs 166 [81.0%]; $P < 0.001$), pancreatic carcinoma (64 [16.6%] vs 6 [2.9%]; $P < 0.001$), cholangiocarcinoma (88 [22.9%] vs 15 [7.3%]; $P < 0.001$), history of pancreatitis (43 [11.2%] vs 36 [17.6%]; $P = 0.030$), normal bilirubin levels (79 [20.5%] vs 71 [34.6%]; $P < 0.001$), serum bilirubin levels (107.75 [200.25] vs 28.06 [65.90]; $P < 0.001$), EST (254 [66.0%] vs 163 [79.5%]; $P = 0.001$), mental stent placement (39 [10.1%] vs 7 [3.4%]; $P = 0.004$), 5F-7 cm pancreatic stent (41 [10.6%] vs 11 [5.4%]; $P = 0.031$), and other stent types (16 [4.2%] vs 2 [0.1%]; $P = 0.032$). The main indication for therapeutic ERCP was choledocholithiasis (349 of 590; 59.2%) and the first advanced technique was double guidewire technique (DGT) (476 of 590; 80.7%) to approach the common bile duct in patients in whom the pancreatic guidewire-assisted technique was used. In addition, the majority of patients who underwent EPSP had a pancreatic stent placed immediately followed by ERCP/EST (362 of 385; 94.0%) (**Supplementary Fig. 4**) and most patients (169 of 205; 82.4%) who underwent LPSP had a pancreatic stent placed after completing all major endoscopic procedures (**Supplementary Fig. 5**).

▶ **Table 1** Baseline characteristics.

	EPSP (N = 385)	LPSP (N = 205)	*P* value
Age, years	65 (22)	65(23)	0.612
Sex			**0.030**
Male	209 (54.3%)	93 (45.1%)	
Female	176 (45.7%)	113 (54.9%)	
Female aged < 50 years	32(8.3%)	20(9.8%)	0.556
Coexisting disorders			
▪ Hypertension	109 (28.3%)	65 (31.7%)	0.389
▪ Diabetes	47 (12.2%)	23 (11.2%)	0.724
Coronary heart disease	25 (6.5%)	22 (10.7%)	0.070
Chronic pulmonary disease	23 (6.0%)	11 (5.4%)	0.763
Liver cirrhosis	27 (7.0%)	10 (4.9%)	0.308
History of pancreatitis	43 (11.2%)	36 (17.6%)	**0.030**
Indications			
Biliary stones	183 (47.5%)	166 (81.0%)	< 0.001
Pancreatic carcinoma	64 (16.6%)	6 (2.9%)	< 0.001
Cholangiocarcinoma	88 (22.9%)	15 (7.3%)	< 0.001
Benign stricture	26 (6.8%)	9 (4.4%)	0.247
Biliary leak	13 (3.4%)	3 (1.5%)	0.173
Ampulloma	10 (2.6%)	3 (1.5%)	0.549
Others	4 (1.0%)	3 (1.5%)	0.957
Bile duct diameter, cm	1.20 (0.7)	1.20 (0.6)	0.634
Non-biliary dilation	150 (39.0%)	77 (37.6%)	0.739
Serum bilirubin levels, U/L	107.75 (200.25)	28.06 (65.90)	**< 0.001**
Normal bilirubin levels	79 (20.5%)	71 (34.6%)	**< 0.001**
Duodenal diverticulum	89 (23.1%)	56 (27.3%)	0.259
Endoscopic appearance of papilla of Vater*			
▪ Type 1	91 (24.6%)	54 (27.3%)	0.485
▪ Type 2	94 (25.4%)	51 (25.8%)	0.927
▪ Type 3	140 (37.8%)	67 (33.8%)	0.345
▪ Type 4	45 (12.2%)	26 (13.1%)	0.739
Rectal NSAID prophylaxis	95 (24.7%)	43 (21.0%)	0.312
Expert endoscopists			0.876
▪ Yes	323 (83.9%)	173 (84.4%)	
▪ No	62 (16.1%)	32 (15.6%)	
Cannulation method			
DGT success	304 (79.0%)	172 (83.9%)	0.148
TPS success	17 (4.4%)	6 (2.9%)	0.374
Sequential technique success	64 (16.6%)	27 (13.2%)	0.269
EST	254 (66.0%)	163 (79.5%)	**0.001**
Balloon dilatation of an intact biliary sphincter	24 (6.2%)	19 (9.3%)	0.177

▶ **Table 1** (Continuation)

	EPSP (N = 385)	LPSP (N = 205)	*P* value
PD stent type			
▪ 5F-3 cm	39 (10.1%)	24 (11.7%)	0.555
▪ 5F-5 cm	289 (75.1%)	168 (82.0%)	0.057
▪ 5F-7 cm	41 (10.6%)	11 (5.4%)	**0.031**
▪ others	16 (4.2%)	2 (0.1%)	**0.032**
Mental stent placement	39 (10.1%)	7 (3.4%)	**0.004**
Failed PD stenting			–

Data are n (%) or median (IQR).
Haraldsson classification: Type 1 regular papilla, Type 2 small papilla, Type 3 protruding or pendulous papilla, Type 4 creased or ridged papilla.
*Data about appearance of papilla of Vater were unavailable for 22 patients without endoscopic images.
EPSP, early pancreatic stent placement; LPSP, late pancreatic stent placement; ERCP, endoscopic retrograde cholangiopancreatography; PD, pancreatic duct; NSAID, nonsteroidal anti-inflammatory drug; DGT, double guidewire technique; TPS, transpancreatic sphincterotomy; EST, endoscopic sphincterotomy; CI, confidence interval.

▶ **Table 2** Incidence of primary, secondary, and safety outcomes.

	EPSP (N = 385)	LPSP (N = 205)	Odds ratio (95% CI)	*P* value
PEP	11 (2.9%)	15 (7.3%)	0.37 (0.17–0.83)	**0.012**
▪ Mild	2.9%	7.3%	0.37 (0.17–0.83)	**0.012**
▪ Moderate to severe	0	0	–	–
Hyperamylasemia	76 (19.7%)	57 (27.8%)	0.64 (0.43–0.95)	0.026
Elevated amylase levels, U/L	525.00 (433.00)	597.00 (626.00)	–	0.488
Gastrointestinal bleeding	14 (3.6%)	11 (5.4%)	0.67 (0.30–1.49)	0.321
Cholangitis	17 (4.4%)	2 (1.0%)	4.69 (1.07–20.50)	**0.024**
Gastrointestinal perforation	0 (0%)	3 (1.5%)	0.00 (0.00-Inf)	0.076
PD perforation	0	0	–	–
Postoperative hospital stay	6 (6)	5 (4)	–	**0.001**

Data are n (%) or median (IQR).
EPSP, early pancreatic stent placement; LPSP, late pancreatic stent placement; ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis; PD, pancreatic duct; CI, confidence interval.

Post-ERCP pancreatitis

PEP occurred in 2.9% of patients (11 of 385) in the EPSP group compared with 7.3% of patients (15 of 205) in the LPSP group (odds ratio [OR] 37, 95% confidence interval [CI] 0.37 (0.17–0.83), *P* = 0.012) and all cases were mild (▶ **Table 2**). After adjusting for likely confounders, the results remained consistent in two multivariable-adjusted models (multivariable-adjusted model 1 OR 0.41, 95% CI 0.18–0.92, *P* = 0.032; model 2 OR 0.42, 95% CI 0.17–0.99, *P* = 0.048) (▶ **Table 3**), thus verifying preliminary interpretation. All patients received conservative treatment for PEP and none died due to PEP.
EPSP showed a positive trend toward reducing PEP incidence in each subgroup analysis, and some of the results were statistically significant (▶ **Fig. 2**).

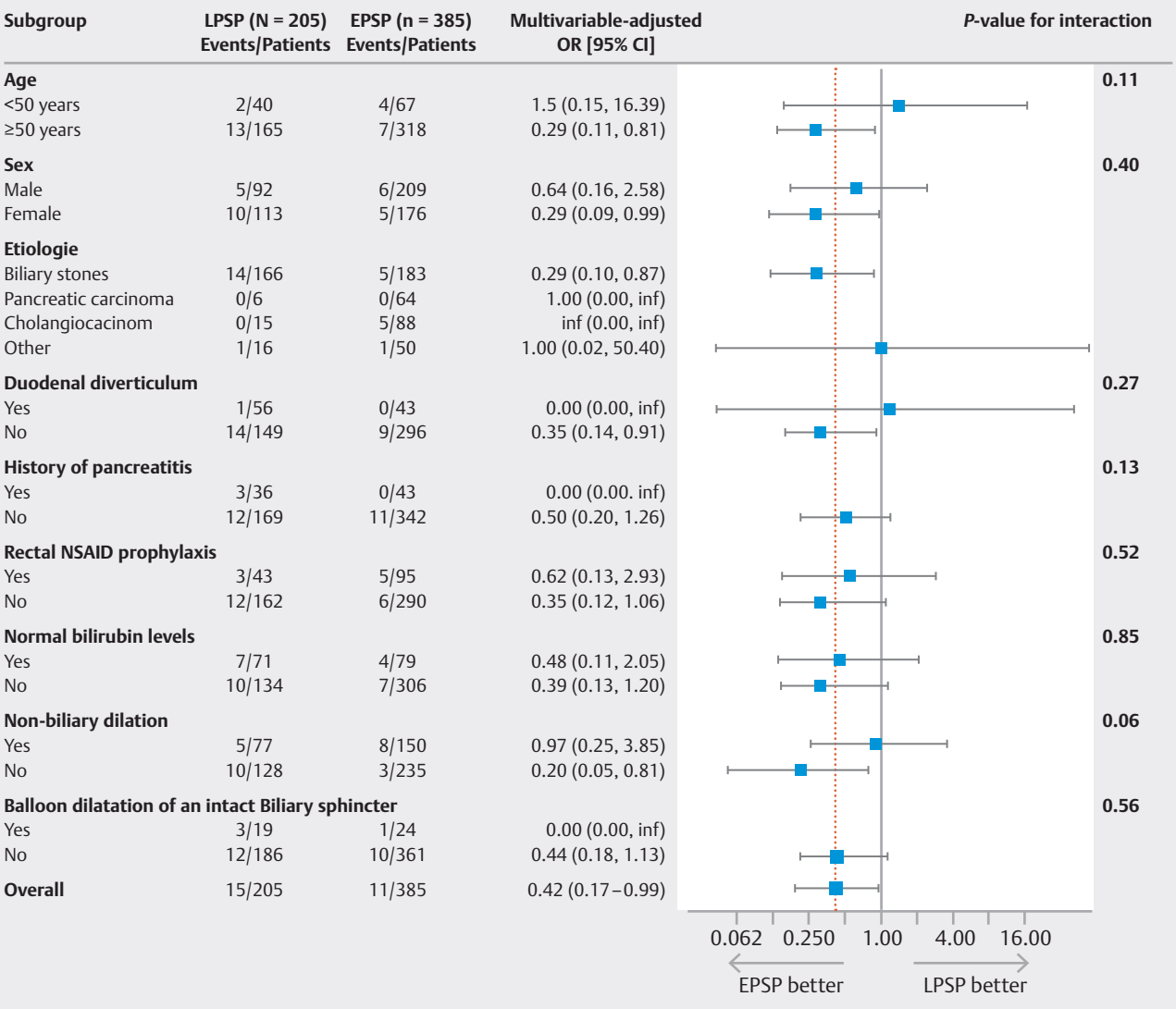
Hyperamylasemia

Of the 385 patients in the EPSP cohort, 76 (19.7%) developed hyperamylasemia compared with 57 of the 205 patients (27.8%) in the LPSP cohort (OR 0.64, 95% CI 0.43–0.95, *P* = 0.026) (▶ **Table 2**). After adjusting for the same two multivariable-adjusted models, asymptomatic hyperamylasemia was lower in the EPSP group than in the LPSP group (multivariable-adjusted model 1 OR 0.67, 95% CI 0.45–0.99, *P* = 0.046; model 2 OR 0.67, 95% CI 0.47–1.04, P = 0.073) (▶ **Table 3**). Meanwhile, median levels of amylase between the groups showed no significant difference in hyperamylasemia among the patients (525.00 [433.00 U/L] vs 597.00 [626 U/L], P = 0.488) (▶ **Table 2**).

▶ **Table 3** Primary analysis: multivariable-adjusted analysis for association between EPSP and incidence of PEP/hyperamylasemia.

	LPSP	EPSP (PEP)		EPSP (hyperamylasemia)	
		OR (95%CI)	*P* value	OR (95%CI)	*P* value
Model 1	1 (Ref)	0.41 (0.18–0.92)	0.032	0.67 (0.45–0.99)	0.046
Model 2	1 (Ref)	0.42 (0.17–0.99)	0.048	0.67 (0.44–1.04)	0.073

Model 1: Early PD stenting and normal bilirubin levels.
Model 2: Age < 50 years, sex, biliary stones, pancreatic carcinoma, cholangiocarcinoma, duodenal diverticulum, history of pancreatitis, normal bilirubin levels, rectal NSAID prophylaxis, non-biliary dilation, balloon dilatation of an intact biliary sphincter, and early PD stenting.
EPSP, early pancreatic stent placement; LPSP, late pancreatic stent placement; OR, odds ratio; CI, confidence interval.



▶ **Fig. 2** Subgroup analysis. Early pancreatic stent placement showed a positive trend toward reducing PEP incidence in each subgroup analysis, and some of the results were statistically significant. There were no significant interactions in any subgroup (P > 0.05 for all comparisons). EPSP, early pancreatic stent placement; LPSP, late pancreatic stent placement; NSAID, nonsteroidal anti-inflammatory drug; PD, pancreatic duct; OR, odds ratio; CI, confidence interval.

Other adverse events

During the 30-day follow-up period, occurrences of other AEs were similar in EPSP and LPSP groups, where the frequency of biliary infection was increased, the rate of AEs was 3.6% vs 5.4% (OR 0.67, 95% CI, 0.30–1.49, $P = 0.321$) for gastrointestinal bleeding, 0% vs 1.5% (OR 0.00, 95% CI 0.00-Inf), $P = 0.076$) for gastrointestinal perforation, and 4.4% vs 1.0% (OR 4.69, 95% CI 1.07–20.50, $P = 0.024$) for cholangitis (▶ **Table 2**). No patients developed PD perforation. Five patients died of primary disease progression, whereas the remaining patients received conservative treatments.

Propensity-matched analysis

To reduce the impact of selection bias between the two groups, we conducted a PSM analysis. This analysis considered the following factors: sex, biliary stones, cholangiocarcinoma, pancreatic carcinoma, serum bilirubin levels, and history of pancreatitis. We selected 205 matched cases in each group, maintaining a 1:1 ratio.

Changes in baseline characteristics after matching the two PSM groups are shown in **Supplementary Table 3**. The two groups did not differ significantly in measured characteristics in the PSM cohort, except for pancreatic carcinoma (0 [0.0%] vs 6 [2.9%], $P = 0.040$), cholangiocarcinoma (0 [0.0%] vs 15 [7.3%], $P < 0.001$), biliary leak (11 [5.4%] vs 3 [1.5%], $P = 0.030$), and rectal NSAID prophylaxis (74 [36.1%] vs 43 [21.0%], $P = 0.001$).

The matched EPSP group had a significantly lower incidence of PEP compared with the LPSP group (2.9% vs 7.3%; OR 0.38, 95% CI 0.15–1.01, $P = 0.044$). Moreover, incidence of hyperamylasemia was also lower in the EPSP group than in the LPSP group (20.5% vs 27.8%; OR 0.67, 95% CI 0.42–1.06, $P = 0.083$). Notably, there was no significant difference in incidence of other complications between the two groups (**Supplementary Table 4**).

Clinical outcomes after inadvertent PD guidewire loss post biliary cannulation in 37 patients

During the study period, prophylactic PD stenting was performed in 13 patients. One patient developed moderate to severe pancreatitis, whereas hyperamylasemia occurred in two patients.

Discussion

Currently, PD stenting is commonly employed as a prophylactic measure for PEP. However, there is limited research regarding ideal timing for pancreatic stent placement. To the best of our knowledge, our study is the first to compare the effectiveness of early and late PD stenting in preventing post-ERCP pancreatitis.

According to our study findings, EPSP significantly reduces the risk of PEP by 58% when compared with late PD stenting. Differences between the two groups were observed in a few baseline characteristics, which were confirmed in the subgroup and PSM analyses. Interestingly, delayed PD stent placement was associated with increased incidence of PEP (**Supplementary Table 5**). Furthermore, EPSP also led to a decrease in incidence of hyperamylasemia. This suggests that EPSP can prevent irritation and injury to the pancreatic duct and parenchyma which may occur during PD guidewire placement. In addition, it theoretically could help to prevent inadvertent insertion of instruments and biliary microlithiasis into the PD during subsequent procedures, while reducing transient high pressure during balloon dilation, balloon lithotomy, and extraction of large biliary stones.

Although fewer than 25% of the patients in our study received rectal NSAID prophylaxis, NSAID use was equally distributed among cohorts. Certain patients did not receive rectal NSAIDs, due to the endoscopist deeming them unnecessary or because of NSAID allergy/contraindication. Among patients who did not receive rectal NSAID prophylaxis, EPSP reduced risk of post-ERCP pancreatitis from 7.4% to 2.1% ($P = 0.005$). EPSP was associated with a positive trend in patients who received rectal NSAID prophylaxis, reducing risk of post-ERCP pancreatitis from 7.0% to 5.3% ($P = 0.995$) (**Supplementary Table 6**).

In our research, the overall incidence of PEP was 4.4% (26 of 590 patients), which appears to be lower than the findings reported in other studies [4, 8, 15, 27]. Notably, none of the patients in our research developed moderate to severe PEP, which is consistent with results from other studies[21, 28]. This favorable outcome can be attributed to several factors: First, we have implemented a systematic practice of placing a PD stent when the guidewire is unintendedly inserted into the PD. Numerous meta-analyses have demonstrated that pancreatic stenting significantly reduces risk of PEP to 5% [17, 28, 29]. Strong recommendations from both the ASGE [19] and the European Society of Gastrointestinal Endoscopy [20] support prophylactic placement of a PD stent in all patients undergoing pancreatic guidewire-assisted cannulation. Second, when biliary cannulation is challenging, we timely transitioned from the single-guidewire technique to advanced ERCP methods at our center. Recent publications have emphasized the effectiveness of early salvage techniques in reducing incidence of PEP [1, 30]. Third, we used the standard Atlanta Classification definitions for pancreatitis following ERCP in our research. Compared with The Cotton consensus criteria, the Atlanta Classification was more sensitive and objective [15, 31].

Incidence of bile duct infection was found to be higher in the EPSP cohort compared with the LPSP cohort. There are two potential explanations for that difference. First, it is possible that the proportion of patients with malignancy, who typically have compromised immunity, was higher in the EPSP cohort. Second, another contributing factor could be the higher levels of serum bilirubin observed in the EPSP group. These two factors have been demonstrated to be crucial risk factors for post-ERCP cholangitis [32, 33, 34], and they resulted in significantly longer postoperative hospital stays in the EPSP group. Nonetheless, it is important to note that after PSM, these results were not statistically significant.

There may be some concerns about using pancreatic stents, such as that they may potentially interfere with subsequent surgical procedures, result in failure of PD stenting, or lead to

PD perforation [29, 35]. However, it is worth noting that none of these events occurred in our study, which can be attributed to use of a single pigtail PD stent with a flange, as well as the expertise of the endoscopists who performed ERCP at a tertiary care center.

Our research study had several limitations that should be addressed. First, it was an observational and retrospective study, which has inherent biases. We endeavored to mitigate this possibility by conducting multivariable logistic regression analysis, considering a wide array of potentially confounding factors. Simultaneously, we meticulously delineated categorization of EPSP and LPSP by thoroughly profiling their distribution and comprehensively assessing AEs (**Supplementary Table 5**). Moreover, retrospective research may more accurately reflect real-world clinical settings. Second, decisions regarding timing of PD stenting were made by the performing endoscopists, which introduces the possibility of selection bias. Nevertheless, the two groups were well matched for most baseline data. Finally, despite being a single-center study, inclusion of a large sample size in this cohort study enhances the reproducibility of our findings.

Conclusions

In conclusion, our retrospective cohort study provides evidence that EPSP is a superior strategy compared with late PD stenting in reducing the risk of post-ERCP pancreatitis and additional randomized controlled trials are necessary to confirm our results.

Conflict of Interest

The authors declare that they have no conflict of interest.

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