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Study on administration timing and combination therapy of NSAIDs for preventing post-ERCP pancreatitis

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ABSTRACT

Objective: To determine the optimal timing, dosage, and efficacy of combination NSAID therapy in preventing post-ERCP pancreatitis.

Methods: A total of 866 patients undergoing ERCP between December 2021 and December 2023 were enrolled and randomly assigned to an observation group or a control group, with further subgrouping into combination therapy or monotherapy groups. The observation group received NSAIDs such as indomethacin suppositories and/or diclofenac sodium before ERCP, while the control group received NSAIDs postoperatively. The combination therapy group received both diclofenac sodium and indomethacin suppositories, whereas the monotherapy group received only diclofenac sodium. Primary endpoints included the incidence and severity of pancreatitis, as well as the occurrence of post-procedural complications such as perforation, bleeding, cholangitis, and pain scores. These outcomes were compared between groups to evaluate differences in the incidence and severity of PEP.

Results: The group receiving pre-procedural NSAIDs had a significantly lower risk of adverse reactions compared with the post-procedural group. Combination therapy showed superior PEP risk reduction compared to monotherapy. Independent risk factors for PEP included female sex, age > 60 years, a history of gallstones or pancreatitis, hypertension, five cannulation attempts > 5, and non-dilated extrahepatic bile ducts.

Conclusion: Prophylactic combination therapy with indomethacin suppositories and diclofenac sodium before ERCP significantly reduces PEP incidence and severity, while concurrently decreasing risks of perforation, hemorrhage, cholangitis, and postoperative pain scores.

Introduction

Since its introduction in the 1960s, endoscopic retrograde cholangiopancreatography (ERCP) has become an important technique for diagnosing and treating biliary and pancreatic disorders.[1,2] However, post-ERCP pancreatitis (PEP) remains one of the most common and serious complications, with an incidence rate ranging from 3 % to 16 %.[3,4] PEP not only prolongs hospitalization and increases medical costs but also significantly affects patients' quality of life. Therefore, effective prevention of PEP has emerged as a major research focus in the field of ERCP.

Nonsteroidal anti-inflammatory drugs (NSAIDs), widely used for pain and inflammation management due to their anti-inflammatory and analgesic properties,[5,6] have recently demonstrated potential efficacy in PEP prophylaxis.[7,8] NSAIDs exert their analgesic effects primarily by inhibiting cyclooxygenase (COX) activity, thereby blocking the conversion of arachidonic acid to prostaglandins.[9,10] As a result, NSAIDs have become one of the main pharmacological options for preventing PEP. However, there are currently no studies comprehensively investigated the potential relationship between NSAIDs and PEP risk.

Both indomethacin and diclofenac sodium are NSAIDs that reduce prostaglandin synthesis by inhibiting COX-1 and COX-2, thereby

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mitigating inflammatory responses and pancreatic injury mitigating inflammatory responses and pancreatic injury. Emerging evidence suggests that combination therapy may enhance anti-inflammatory efficacy and further reduce risks of acute inflammatory reactions through targeting multiple pathways, offering complementary administration routes, and reducing adverse effects from high-dose monotherapy.[11]

This study aimed to evaluate the optimal timing, dosage, and administration routes of NSAIDs in the prevention of PEP and other common post-ERCP adverse events, with the goal of establishing evidence-based clinical applications. The findings are expected to not only provide scientific evidence for the use of NSAIDs in ERCP complication prevention, but also offer clinicians practical guidance on NSAID administration strategies to further reduce the incidence and severity of PEP and improve patient outcomes.

Materials and methods

Study subjects

A total of 866 patients who underwent ERCP in Handan Central Hospital between December 2021 and December 2023 were included in this study. The enrollment flowchart is shown in Fig. 1. Inclusion criteria: age > 18 years; meeting ERCP indications; no contraindications to NSAID use prior to ERCP; completion of routine baseline examinations, including abdominal ultrasonography, blood cell analysis, biochemical tests, before treatment; signed informed consent; full civil capacity. Exclusion criteria: known allergy or intolerance to NSAIDs; active upper gastrointestinal bleeding or bleeding tendency not adequately controlled; severe hepatic/renal dysfunction (e.g., acute liver/kidney failure, decompensated liver cirrhosis); pregnancy or lactation; severe cardiac disease, (e.g., unstable angina, recent myocardial infarction, severe heart failure); severe infection or sepsis; psychiatric disorders or cognitive impairment affecting compliance; incomplete clinical data; participation in other clinical trials within the past month; any other condition considered unsuitable for inclusion by the investigators.

Participants were randomly assigned in a 1:1 ratio using a computer-generated random number table. The randomization process was conducted by a designated researcher, and a single-blind approach was applied to minimize selection bias. The study was approved by the Medical Ethics Committee (Approval No.: [2024] Ethics Review Paper No. (020)).

ERCP procedure

ERCP was performed by senior physicians with over five years of experience. Standard ERCP enables the identification of the location and extent of biliary lesions and determination of appropriate sites for plastic stent placement. For patients with common bile duct obstruction, cholangiography was first performed to visualize biliary anatomy, a guidewire was then inserted through the stenotic segment. In cases of severe stricture, balloon dilation was performed before stent placement. When the guidewire was stabilized, the stent and its delivery system were advanced over the wire. Through fine adjustment of the endoscope's lens position and leveraging the mechanical advantage of the elevator, the stent was progressively deployed across the biliary stricture with its distal end secured at the duodenal papilla.

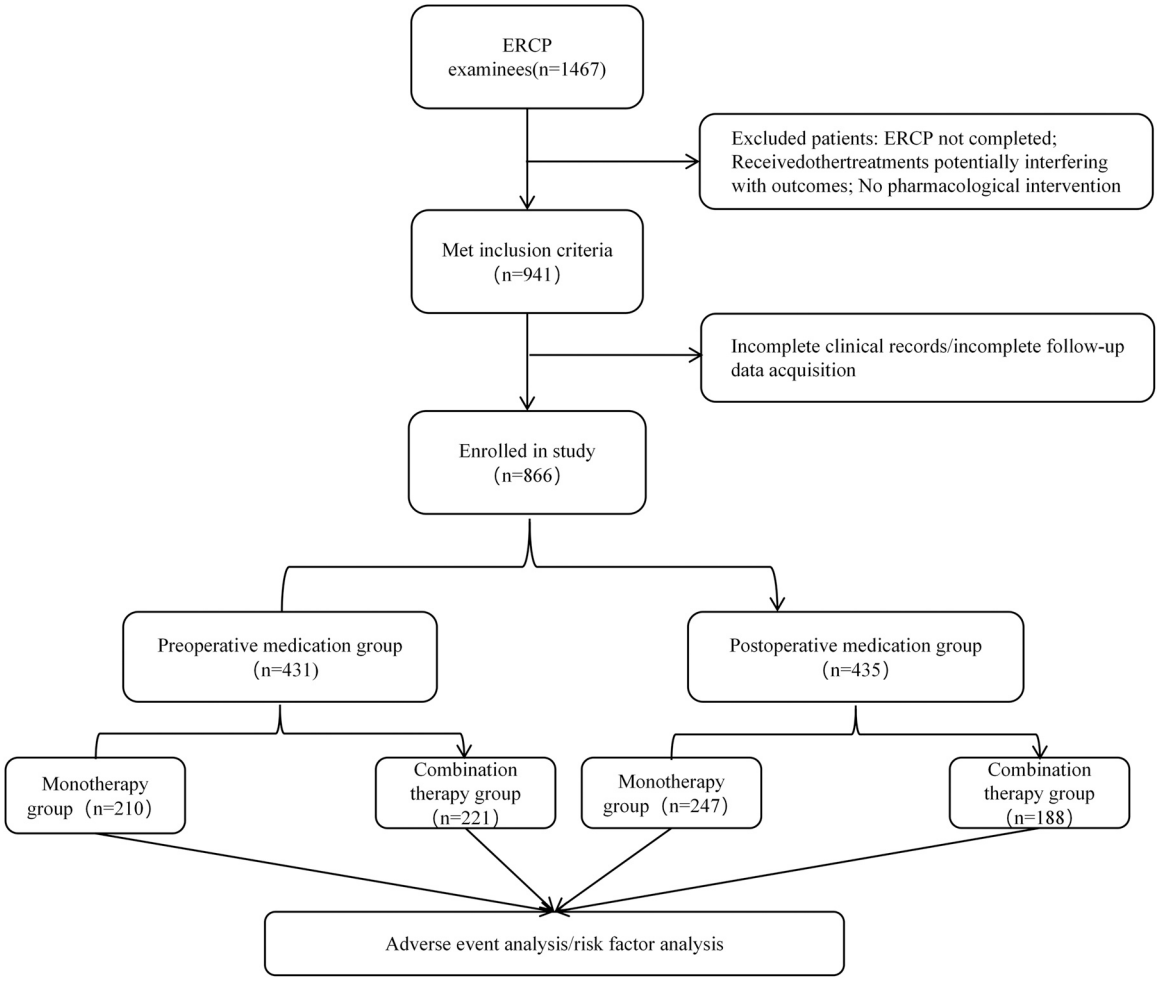

Fig. 1. Flowchart of the study.

Table 1
Comparison of demographic and clinical characteristics.

Characteristics	Total cases (n = 866)	Preoperative monotherapy (n = 210)	Preoperative combination therapy (n = 221)	Postoperative monotherapy (n = 247)	Postoperative combination therapy (n = 188)	χ^2 value	*P* value
Gender, n (%)						1.013	0.798
Male	442 (51.039)	107 (50.952)	118 (53.394)	126 (51.012)	91 (48.404)		
Female	424 (48.961)	103 (49.048)	103 (46.606)	121 (48.988)	97 (51.596)		
Liver cirrhosis, n (%)						3.921	0.270
No	422 (48.730)	112 (53.333)	112 (50.679)	112 (45.344)	86 (45.745)		
Yes	444 (51.270)	98 (46.667)	109 (49.321)	135 (54.656)	102 (54.255)		
BMI, n (%)						0.805	0.848
< 24	672 (77.598)	162 (77.143)	173 (78.281)	195 (78.947)	142 (75.532)		
≥ 24	194 (22.402)	48 (22.857)	48 (21.719)	52 (21.053)	46 (24.468)		
Smoke, n (%)						2.766	0.429
No	463 (53.464)	102 (48.571)	120 (54.299)	136 (55.061)	105 (55.851)		
Yes	403 (46.536)	108 (51.429)	101 (45.701)	111 (44.939)	83 (44.149)		
Drinking, n (%)						1.671	0.643
No	642 (74.134)	162 (77.143)	160 (72.398)	184 (74.494)	136 (72.340)		
Yes	224 (25.866)	48 (22.857)	61 (27.602)	63 (25.506)	52 (27.660)		
Diabetes, n (%)						0.803	0.849
No	630 (72.748)	151 (71.905)	164 (74.208)	182 (73.684)	133 (70.745)		
Yes	236 (27.252)	59 (28.095)	57 (25.792)	65 (26.316)	55 (29.255)		
Intubation duration > 10 min, n (%)						1.383	0.709
No	638 (73.672)	156 (74.286)	160 (72.398)	178 (72.065)	144 (76.596)		
Yes	228 (26.328)	54 (25.714)	61 (27.602)	69 (27.935)	44 (23.404)		
Age, n (%)						7.181	0.066
< 60	782 (90.300)	198 (94.286)	202 (91.403)	217 (87.854)	165 (87.766)		
≥ 60	84 (9.700)	12 (5.714)	19 (8.597)	30 (12.146)	23 (12.234)		
History of cholelithiasis, n (%)						0.821	0.845
No	838 (96.767)	204 (97.143)	214 (96.833)	237 (95.951)	183 (97.340)		
Yes	28 (3.233)	6 (2.857)	7 (3.167)	10 (4.049)	5 (2.660)		
History of pancreatitis n (%)						—	0.461
No	847 (97.806)	207 (98.571)	218 (98.643)	239 (96.761)	183 (97.340)		
Yes	19 (2.194)	3 (1.429)	3 (1.357)	8 (3.239)	5 (2.660)		
Hypertension, n (%)						0.278	0.964
No	625 (72.171)	154 (73.333)	158 (71.493)	179 (72.470)	134 (71.277)		
Yes	241 (27.829)	56 (26.667)	63 (28.507)	68 (27.530)	54 (28.723)		
ERCP cannulations > 5, n (%)						1.074	0.783
No	638 (73.672)	159 (75.714)	158 (71.493)	181 (73.279)	140 (74.468)		
Yes	228 (26.328)	51 (24.286)	63 (28.507)	66 (26.721)	48 (25.532)		
Double-guidewire technique, n (%)						5.06	0.168
No	673 (77.71)	673 (77.71)	673 (77.71)	673 (77.71)	673 (77.71)		
Yes	193 (22.29)	193 (22.29)	193 (22.29)	193 (22.29)	193 (22.29)		
Precut sphincterotomy, n (%)						3.74	0.291
No	750 (86.61)	750 (86.61)	750 (86.61)	750 (86.61)	750 (86.61)		
Yes	116 (13.39)	116 (13.39)	116 (13.39)	116 (13.39)	116 (13.39)		
Papillary balloon dilation, n (%)						3.55	0.315
No	725 (83.72)	725 (83.72)	725 (83.72)	725 (83.72)	725 (83.72)		
Yes	141 (16.28)	141 (16.28)	141 (16.28)	141 (16.28)	141 (16.28)		
Extrahepatic bile duct dilation on ultrasound, n (%)						1.215	0.749
No	468 (54.042)	110 (52.381)	119 (53.846)	131 (53.036)	108 (57.447)		
Yes	398 (45.958)	100 (47.619)	102 (46.154)	116 (46.964)	80 (42.553)		

Note: χ^2: chi-square test; —: Fisher exact.

The procedure was conducted using an Olympus TJF-240 electronic duodenoscope, zebra guidewires, and imported plastic biliary stents. To ensure comfort and procedural safety, patients received intramuscular injections of anisodamine (10 mg), diazepam (10 mg), and pethidine (1 mg/kg) 30 min before the operation. Patients scheduled for biliary stent placement also received prophylactic antibiotics preoperatively. During the procedure, the endoscope was advanced into the duodenum and the papilla was cannulated. After the guidewire successfully passed the stricture, contrast agent was injected to evaluate the biliary anatomy under fluoroscopy, which enables detection of pathological changes including calculi, strictures, or neoplastic lesions. The procedure ended with the withdrawal of the endoscope and catheter.

NSAIDs administration

The NSAIDs were administered as follows: diclofenac sodium (75 mg per ampule of Olfen) was injected intramuscularly either 30 min before ERCP or immediately after ERCP, while indomethacin suppository (100 mg) were given rectally either 30 min before or immediately after ERCP. Patients in the observation group received prophylactic NSAIDs prior to ERCP, whereas those in the control group received NSAIDs after the procedure. The treatment groups were further divided into monotherapy and combination therapy subgroups: the monotherapy subgroup received diclofenac sodium injection alone, while the combination therapy subgroup received both diclofenac sodium intramuscular injection and indomethacin suppository.

Post-ERCP observation indicators

Post-ERCP observation indicators included PEP, postoperative perforation, cholangitis, hemorrhage and pain score. (i) PEP was diagnosed when patients experienced new or worsened abdominal pain after ERCP, accompanied by serum amylase levels ≥ 3 times the upper normal limit within 24 h, or imaging evidence suggestive of pancreatitis.[12] PEP severity was graded as follows: mild cases presented with

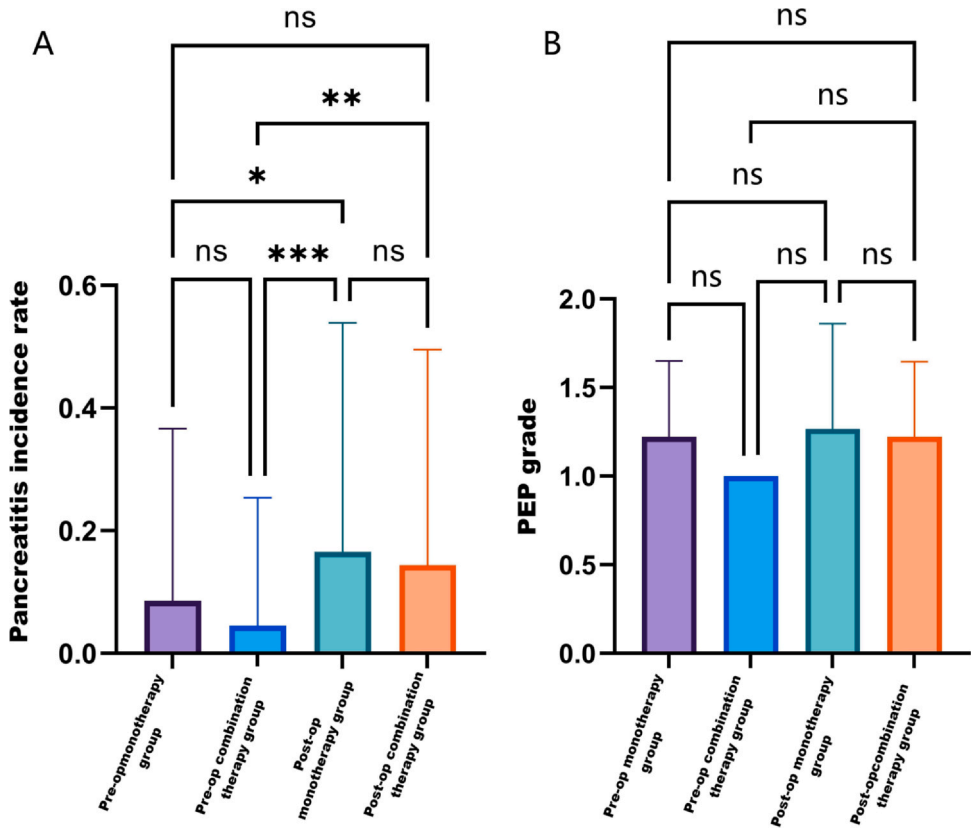

Fig. 2. Comparative analysis of post-ERCP PEP risk. Note: (A) Incidence of PEP among different groups after ERCP. (B) Severity of PEP among different groups after ERCP; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; ns = not significant ($p > 0.05$).

Table 2
Univariate logistic analysis of PEP risk after ERCP in each group.

Group	β	S.E	Z	*P*	OR (95 %CI)
Preoperative monotherapy (n = 210)					1.00 (Reference)
Preoperative combination therapy (n = 221)	− 17.071	723.393	− 0.024	0.981	0.000 (0.000–Inf)
Postoperative monotherapy (n = 247)	− 0.902	0.444	− 2.033	0.042	0.406 (0.170–0.968)
Postoperative combination therapy (n = 188)	2.018	0.300	6.722	< .001	7.526 (4.178–13.557)

Table 3
Comparison analysis of medication regimens and PEP severity.

Group/PEP severity	Mild (n, %)	Moderate (n, %)	Severe (n, %)
Preoperative monotherapy	14 (77.78 %)	4 (22.22 %)	0 (0 %)
Preoperative combination therapy	10 (100 %)	0 (0 %)	0 (0 %)
Postoperative monotherapy	33 (80.49 %)	5 (12.20 %)	3 (7.31 %)
Postoperative combination therapy	21 (77.78 %)	6 (22.22 %)	0(0 %)
χ^2 value	5.620		
P value	0.004		

transient abdominal pain accompanied by nausea and vomiting, typically resolving spontaneously within days without requiring specific treatment or needing only symptomatic management; moderate cases were characterized by abdominal pain persisting beyond 3 days, potentially with fever and gastrointestinal dysfunction such as abdominal distension or ileus; severe cases involved prolonged pain with marked inflammatory response, possible organ dysfunction (including respiratory failure, renal failure, or circulatory failure), and necessitated intensive care with aggressive interventions including fluid resuscitation, antibiotic therapy, and nutritional support. (ii) perforation: manifested by abdominal pain, fever, abdominal rigidity with rebound tenderness, and confirmed by free intraperitoneal air on X-ray or CT imaging. (iii) cholangitis: characterized by fever, chills, abdominal pain and jaundice, with pathogens identified through blood/bile cultures and biliary dilatation/fluid collections demonstrated on ultrasound or CT. (iv) hemorrhage: evidenced by hematemesis, melena, hematochezia or hypotension; (v) pain assessment: evaluated using the Visual Analog Scale (VAS, range 1–10) preoperatively and at 24 h post-ERCP, with higher scores indicating greater pain intensity.[13]

Risk factor analysis

The study population was randomly divided into a training set and a validation set in a 7:3 ratio. In the logistic regression model, input variables included clinical factors (such as age, sex, smoking history, and alcohol consumption history) and imaging characteristics (such as

Table 4
Analysis of adverse reactions after ERCP.

Adverse reactions	Total cases (n = 866)	Preoperative monotherapy (n = 210)	Preoperative combination therapy (n = 221)	Postoperative monotherapy (n = 247)	Postoperative combination therapy (n = 188)	χ^2 value	*P* value
Occurrence of PEP, n (%)						20.663	< **0.001**
No	770 (88.915)	192 (91.429)	211 (95.475)	206 (83.401)	161 (85.638)		
Yes	96 (11.085)	18 (8.571)	10 (4.525)	41 (16.599)	27 (14.362)		
Bleeding, n (%)						-	0.659
No	846 (97.691)	207 (98.571)	216 (97.738)	239 (96.761)	184 (97.872)		
Yes	20 (2.309)	3 (1.429)	5 (2.262)	8 (3.239)	4 (2.128)		
Perforation, n (%)− 0.088						-	0.088
No	857 (98.961)	209 (99.524)	221 (100.000)	242 (97.976)	185 (98.404)		
Yes	9 (1.039)	1 (0.476)	0 (0.00)	5 (2.024)	3 (1.596)		
Cholangitis, n (%)						-	0.180
No	855 (98.730)	210 (100.000)	218 (98.643)	243 (98.381)	184 (97.872)		
Yes	11 (1.270)	0 (0.00)	3 (1.357)	4 (1.619)	4 (2.128)		

Note: χ^2: chi-square test; -: Fisher exact.

the presence of extrahepatic bile duct dilation and liver cirrhosis). Univariate logistic regression analysis was first performed to assess the association between each risk factor and the clinical outcome. For each variable, the odds ratio (OR) and corresponding 95 % confidence interval (CI) were calculated. Variables that showed statistical significance in the univariate analysis were then included in a multivariate logistic regression model. A stepwise forward selection procedure was adopted, with an entry criterion of P = 0.05 and a removal criterion of P = 0.10. Adjusted odds ratios and 95 % confidence intervals were calculated to evaluate the independent association between each risk factor and the clinical outcome, and to construct a risk prediction model.

A receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated to assess the model's predictive performance. To enhance predictive capability, a nomogram-based weighted scoring system was applied. Each feature was assigned a weight based on its relative contribution to diagnostic accuracy, and the final diagnostic prediction score was derived by summing the individual scores. To validate the robustness and generalizability of the model, k-fold cross-validation was performed. The dataset was divided into k subsets; in each iteration, k-1 subsets were used for model training and the remaining one for testing. This process was repeated k times, with each subset serving once as the test set.

Statistical analysis

All statistical analyses were conducted using R version 4.3.0. For continuous variables with a normal distribution, data were expressed as mean ± standard deviation (Mean ± SD). Comparisons between two groups were made using the independent-sample *t*-test, and comparisons among multiple groups were performed using analysis of variance (ANOVA). For continuous variables, the *t*-test was used, while categorical variables were presented as n (%) and analyzed using the Chi-square test or Fisher's exact test. A P-value < 0.05 was considered to indicate statistical significance, and a P-value < 0.01 was considered to indicate high statistical significance.

Results

General clinical characteristics of enrolled patients

The 866 patients enrolled in this study comprise 442 males and 424 females. The age range was 41–71 years, with a mean age of 51.33 ± 7.119 years. Among them, 431 patients received preoperative NSAID administration, while 435 received postoperative administration. Detailed demographic data, clinical characteristics, and examination findings are presented in Table 1. The baseline clinical features between the two groups were comparable, with no statistically significant differences (P > 0.05), indicating good group comparability.

Incidence of PEP

A total of 96 patients developed PEP, including 28 patients (6.50 %) in the preoperative medication group and 68 patients (15.63 %) in the postoperative group. Within subgroups, 18 patients (8.57 %) in the preoperative monotherapy group developed PEP, compared with 10 patients (4.52 %) in the preoperative combination therapy group, 41 patients (16.60 %) in the postoperative monotherapy group, and 27 patients (14.36 %) in the postoperative combination group. Detailed data are shown in Fig. 2A. The mean PEP incidence across all groups was 0.11 ± 0.31. The differences in PEP incidence between different groups were statistically significant (P < 0.05). Results of univariate logistic regression analysis for key PEP risk factors are presented in Table 2.

Comparison of PEP severity

Among the 96 patients who developed PEP, the cases were further classified into mild, moderate, and severe categories. There were no statistically significant differences in the severity distribution among the four treatment groups (P > 0.05). Detailed data are shown in Fig. 2B and Table 3.

Analysis of other adverse events

Other adverse events associated with PEP are summarized in Table 4. A total of 20 patients (2.309 %) experienced gastrointestinal bleeding, 9 patients (1.039 %) had perforation, and 11 patients (1.270 %) developed cholangitis. No statistically significant differences were found among the four groups in terms of the incidence of the non-PEP adverse events (P > 0.05). Pain scores of patients are shown in Table 5.

Risk factor analysis and prediction model for PEP

As shown in Table 6, both univariate and multivariate logistic regression analyses identified the following as independent risk factors for developing PEP: female sex, age over 60 years, history of cholelithiasis, history of pancreatitis, hypertension, more than five cannulation attempts, and absence of extrahepatic bile duct dilation. Based on these findings, a PEP risk prediction model was developed. Variables with high correlation were incorporated into the model, and a nomogram was constructed (Fig. 3). The model's discrimination ability was

Table 5
Comparison of pain scores before and after ERCP.

Pain score(Mean ± SD)	Total cases (n = 866)	Preoperative monotherapy (n = 210)	Preoperative combination therapy (n = 221)	Postoperative monotherapy (n = 247)	Postoperative combination therapy (n = 188)	F value	*P* value
Before ERCP	4.193 ± 1.844	4.276 ± 1.683	4.281 ± 1.842	3.980 ± 1.833	4.277 ± 2.015	1.541	0.202
After ERCP	3.012 ± 1.361	3.071 ± 1.487	3.041 ± 1.266	3.012 ± 1.324	2.910 ± 1.375	0.520	0.668

Note: SD: standard deviation.

assessed by the ROC curve and AUC. Fig. 4 shows the ROC curves for both the training and validation cohorts, with AUCs of 0.90 and 0.91, respectively, and corresponding 95 % CI of 0.86–0.93 and 0.85–0.96. These results indicate excellent predictive performance. The confusion matrices for both models are shown in Table 7.

Discussion

This study aimed to investigate the timing, dosage, and administration route of NSAIDs in preventing PEP. By comparing the outcomes between pre- and post-procedural administration, as well as monotherapy versus combination therapy, our results indicate that the use of indomethacin suppositories and/or diclofenac sodium prior to ERCP significantly reduces the incidence of PEP. This finding supports the potential prophylactic role of NSAIDs in mitigating PEP. Notably, the incidence of adverse reactions was significantly lower in the preoperative group compared to the postoperative group, suggesting that the anti-inflammatory effects of NSAIDs may begin intraoperatively, thereby attenuating the postoperative inflammatory responses.

ERCP is a standard technique for the diagnosis and treatment of biliary and pancreatic diseases. It improves therapeutic outcomes in conditions such as choledocholithiasis and cholangitis and, due to its minimally invasive nature, reduces patient discomfort and recovery time. As such, it has become a key tool in the management of biliary and pancreatic disorders. However, post-ERCP complications, particularly pancreatitis, not only increase patient risks but may also lead to

Table 6
Analysis of risk factors for PEP after ERCP.

Variate	Univariate analysis					Multivariate analysis				
	β	S.E	Z	*P*	OR (95 %CI)	β	S.E	Z	*P*	OR (95 %CI)
Gender										
male					1.000 (Ref)					1.000 (Ref)
Female	1.98	0.35	5.61	< **0.01**	7.26 (3.63–14.50)	1.83	0.43	4.26	< **0.01**	6.21 (2.68–14.39)
Liver cirrhosis										
No					1.000 (Ref)					
Yes	0.01	0.26	0.03	0.98	1.01 (0.61–1.67)					
BMI										
< 24					1.000 (Ref)					1.000 (Ref)
≥ 24	0.59	0.29	2.05	**0.04**	1.80 (1.02–3.17)	0.40	0.39	1.01	0.31	1.49 (0.69–3.22)
Smoke										
No					1.000 (Ref)					
Yes	− 0.09	0.26	− 0.37	0.71	0.91 (0.55–1.51)					
Drinking										
No					1.000 (Ref)					1.000 (Ref)
Yes	1.27	0.26	4.83	< **0.01**	3.57 (2.13–5.97)	0.57	0.32	1.78	0.07	1.77 (0.94–3.32)
Diabetes										
No					1.000 (Ref)					1.000 (Ref)
Yes	1.26	0.26	4.80	< **0.01**	3.53 (2.11–5.91)	0.44	0.32	1.37	0.17	1.56 (0.83–2.95)
Age										
< 60					1.000 (Ref)					1.000 (Ref)
≥ 60	2.00	0.31	6.54	< **0.01**	7.39 (4.06–13.44)	1.74	0.40	4.35	< **0.01**	5.68 (2.60–12.40)
History of cholelithiasis										
No					1.000 (Ref)					1.000 (Ref)
Yes	1.85	0.48	3.83	< **0.01**	6.39 (2.47–16.50)	1.88	0.63	2.99	< **0.01**	6.57 (1.91–22.61)
History of pancreatitis										
No					1.000 (Ref)					1.000 (Ref)
Yes	2.16	0.55	3.92	< **0.01**	8.70 (2.95–25.65)	1.49	0.70	2.13	**0.03**	4.44 (1.13–17.47)
ERCP cannulations > 5										
No					1.000 (Ref)					1.000 (Ref)
Yes	1.32	0.26	4.99	< **0.01**	3.73 (2.23–6.26)	1.87	0.33	5.59	< **0.01**	6.50 (3.37–12.53)
Intubation duration > 10 min										
No					1.000 (Ref)					1.000 (Ref)
Yes	0.20	0.28	0.72	0.47	1.22 (0.71–2.12)					
Hypertension										
No					1.000 (Ref)					1.000 (Ref)
Yes	0.65	0.26	2.45	**0.01**	1.92 (1.14–3.22)	0.72	0.33	2.18	**0.03**	2.05 (1.07–3.92)
Extrahepatic bile duct dilation on ultrasound										
No					1.000 (Ref)					1.000 (Ref)
Yes	− 0.93	0.28	− 3.26	< **0.01**	0.40 (0.23–0.69)	− 0.79	0.33	− 2.38	**0.02**	0.45 (0.24–0.87)

Note: OR: odds ratio; CI: confidence interval; Ref: reference value; BMI: body mass index.

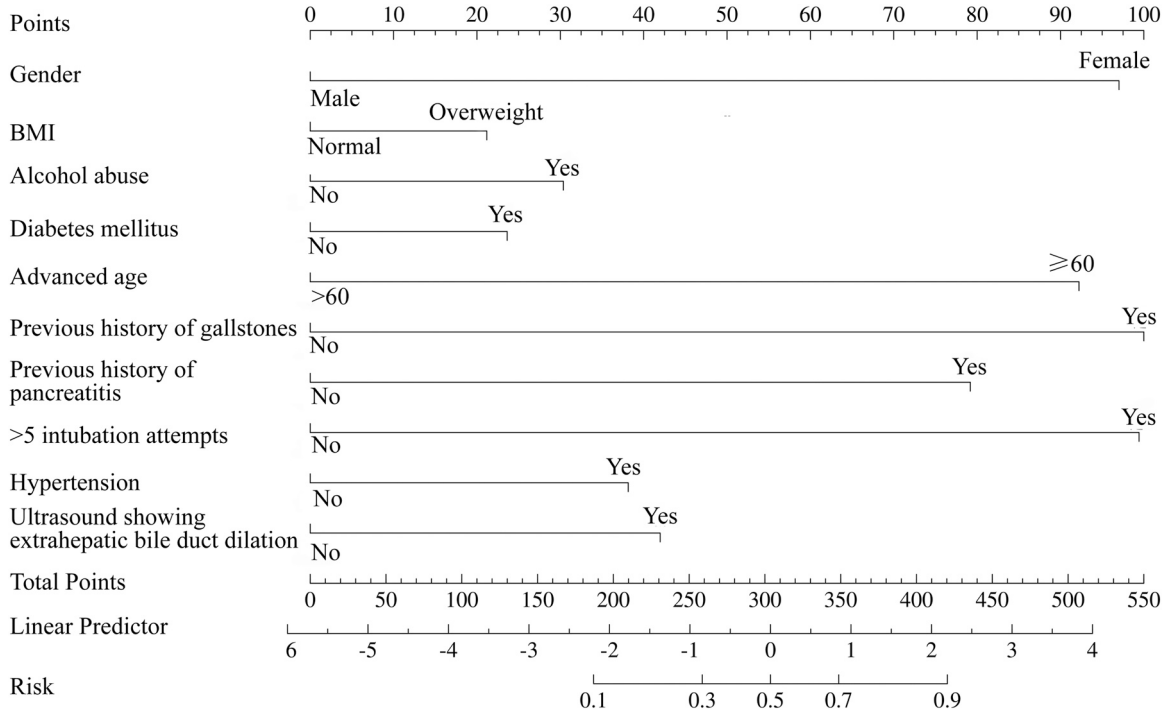

Fig. 3. Nomogram-based multidimensional PEP risk prediction model.

fatal outcomes. PEP is the most common complication of ERCP, with reported incidence rates of approximately 10 %, and even as high as 14.7 % in high-risk populations.[14–16] PEP exacerbates patient suffering and financial burden and may result in severe physiological risks, including severe pancreatitis, hemorrhage, infection, and multi-organ failure. These complications may necessitate intensive care and costly treatments, and in some cases, may result in death.[17] Consequently, the risk of PEP poses a major limitation to the broader implementation of ERCP by increasing healthcare resource consumption and patient safety risks. Moreover, the occurrence of PEP may hinder the further adoption of ERCP into clinical management of biliary and pancreatic diseases. While most PEP cases resolve with conservative treatment, a reported mortality rate exceeding 0.7 %,[18,19] indicating that while the majority of PEP patients recover, some faces life-threatening complications.

Previous studies have shown that the incidence of PEP is associated with multiple factors, including disease-related factors such as a history of acute pancreatitis or bile duct strictures, and procedure-related factors such as difficulty of cannulation, volume and speed of contrast injection into the pancreatic duct.[17,20] Therefore, preventing PEP is crucial for improving both the safety and feasibility of ERCP. Our findings suggest that prophylactic NSAIDs administration before ERCP significantly reduces PEP occurrence. Mechanical stimulation of the pancreatic duct and pancreatic cell injury during ERCP may induce local inflammatory responses, leading to activation and release of pancreatic enzymes and triggering PEP. Preoperative administration of NSAIDs can inhibit the synthesis of inflammatory mediators before the onset of mechanical stimulation, thereby attenuating local inflammation and reducing pancreatic tissue damage and enzyme activation.[21] This early intervention helps to lower the risk of post-ERCP acute pancreatitis and improve patient outcomes.

The weaker efficacy of NSAID administration after ERCP compared to pre-procedural use may be related to the timing of the inflammatory cascade and pharmacokinetic properties. The pathological progression of PEP begins with mechanical stimulation of the pancreatic duct and sphincter of Oddi, leading to early activation of trypsinogen, neutrophil recruitment, and rapid release of inflammatory mediators. NSAIDs inhibit cyclooxygenase (COX)-1/2 to block prostaglandin synthesis, requiring effective plasma concentrations before inflammation initiation to maximally suppress initial injury. Preoperative dosing ensures peak drug levels during the procedure that span the critical inflammatory window after pancreatic duct injury, which helps to reduce ductal epithelial permeability, neutrophil infiltration, and pancreatic enzyme activation. Reduction of prostaglandin E2 further stabilizes ductal epithelium and limits exudation. In contrast, post-procedural administration can only partially mitigate subsequent inflammatory responses due to the already initiated cascade and may not reverse early acinar cell apoptosis and microcirculatory dysfunction.

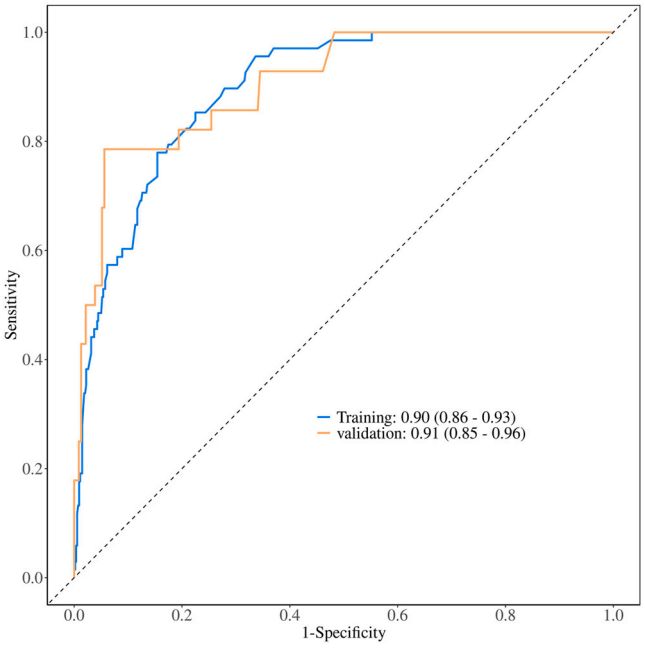

Fig. 4. ROC curves for validation of the multidimensional predictive model for PEP risk.

Table 7
Confusion matrix of multi-dimensional PEP prediction model.

Dataset	AUC (95 %CI)	Accuracy (95 %CI)	Sensitivity (95 %CI)	Specificity (95 %CI)	PPV (95 %CI)	NPV (95 %CI)	Cutoff value
Training set	0.90 (0.86–0.93)	0.78 (0.75–0.82)	0.78 (0.74–0.81)	0.85 (0.77–0.94)	0.98 (0.96–0.99)	0.32 (0.26–0.39)	0.101
Validation set	0.91 (0.85–0.96)	0.80 (0.75–0.85)	0.80 (0.75–0.85)	0.82 (0.68–0.96)	0.97 (0.95–1.00)	0.33 (0.22–0.44)	0.101

Note: AUC: area under the curve; CI: confidence interval; PPV: positive prediction value; NPV: negative prediction value.

Additionally, the synergistic advantage of combining diclofenac sodium injection with indomethacin suppositories stems from complementary pharmacokinetics and additive pharmacodynamics. Intravenous or intramuscular diclofenac achieves rapid onset within 15–30 min, suppressing acute inflammation during the procedure, while indomethacin suppositories provide sustained anti-inflammatory concentrations via rectal mucosal absorption, creating a dual effect of immediate blockade and prolonged suppression. Pharmacologically, diclofenac's high COX-2 selectivity reduces gastrointestinal side effects, while indomethacin's dual COX-1/2 inhibition more thoroughly suppresses prostaglandin synthesis. Their combination further suppresses phospholipase A2, reducing arachidonic acid release and synergistically lowering inflammatory mediator levels via multi-target inhibition.

In this study, the combination of diclofenac sodium injection and indomethacin suppositories significantly reduced PEP risk compared to diclofenac alone. This suggests that different NSAIDs may act synergistically through distinct mechanisms to enhance PEP prevention. These NSAIDs not only irreversibly inhibit COX enzymes and prostaglandin synthesis but also suppress neutrophil-endothelial adhesion and block the amplification of the inflammatory cascade. The observed PEP reduction (RR = 0.45) aligns with this mechanism. In contrast, combined NSAID administration after ERCP was less effective, likely because the inflammatory cascade had already been triggered, limiting the therapeutic window for anti-inflammatory intervention. Moreover, prophylactic NSAIDs did not significantly reduce other common post-ERCP complications, such as perforation, bleeding, or cholangitis.

This study also identified several independent risk factors for PEP, including female sex, age over 60 years, history of gallstones or pancreatitis, hypertension, > 5 cannulation attempts, and non-dilated extrahepatic bile duct. Higher sphincter of Oddi tone in females increases cannulation resistance, while hormonal influences could modulate inflammation responses or ductal permeability. Elderly patients exhibit reduced pancreatic duct elasticity, impaired microcirculation, and diminished repair capacity. Prior pancreatic and biliary diseases alter local anatomy, increasing tissue sensitivity to mechanical stimuli in these patients. Hypertension and reduced vascular compliance may exacerbate ischemic injury. Repeated cannulation directly damages the papilla and pancreatic duct orifice, causing outflow obstruction and ductal hypertension, while excessive contrast injection worsens acinar injury. Stone impaction or chronic biliary inflammation may cause papillary edema and anatomical distortion, complicating cannulation and increasing the risk of unintended contrast injection into the pancreatic duct. Bile reflux may further activate pancreatic enzymes. A narrow bile duct may indicate sphincter of Oddi dysfunction or stenosis, necessitating forceful wire-guided cannulation and increasing the likelihood of mechanical trauma. These findings can inform comprehensive pre-ERCP risk assessment and targeted prophylaxis. For high-risk individuals, clinicians may consider pre-procedural NSAIDs use and gentler cannulation strategies to minimize PEP risk.[22,23] Risk factor identification also supports more effective physician-patient communication, allowing improved compliance and better postoperative management. Focused monitoring and individualized prophylactic strategies for high-risk patients may further reduce PEP incidence and improve outcomes, underscoring the clinical significance of these factors in precision prevention in ERCP.

Compared with prior studies, this study is the first to highlight the potential roles of hypertension and diabetes in PEP risk. Intravascular pressure and vascular endothelial cell damage caused by hypertension and diabetes may increase the risk of PEP after ERCP through multiple pathophysiological mechanisms. Chronic hypertension induces endothelial dysfunction and impaired microvascular regulation, exacerbating ischemia-reperfusion injury during cannulation. Angiotensin II activates NF-κB, upregulating HMGB1 and interleukin production, which promotes local inflammation, aberrant enzyme activation, and acinar apoptosis. Diabetes-related oxidative stress, pancreatic fibrosis, and thickened ductal basement membranes increase mechanical resistance and outflow obstruction. Hyperglycemia amplifies inflammation via advanced glycation end-products while impairing anti-inflammatory repair. Autonomic neuropathy in diabetes may dysregulate sphincter of Oddi tone, increasing repeated ductal trauma. Moreover, the additive effect of chronic metabolic disease and microvascular dysfunction likely further elevates PEP risk, although further studies are needed to delineate independent contributions and molecular interactions.

This study offers several important implications for clinical practice. First, it highlights the importance of preoperative NSAIDs administration for effective PEP prevention. Second, the proposed combination therapy may serve as a more effective prophylactic strategy. Third, by identifying independent risk factors, clinicians can more precisely stratify patient risk and implement personalized prevention strategies. Despite these insights, the study has several limitations. The sample size, although substantial, may still limit generalizability. As a single-center study, selection bias may exist due to regional or demographic factors. Given the observational design, unmeasured confounders may remain. Future randomized controlled trials (RCTs) or Mendelian randomization studies are needed to strengthen causal inference. Although certain non-significant risk factors were excluded, the absolute risk reduction for rare but serious complications may still be underappreciated. While bleeding and perforation were recorded, the study may have lacked statistical power to detect rare adverse events. Delayed complications might also have been missed due to fixed follow-up periods or underreporting after discharge. Thus, future studies should adopt multicenter, large-scale designs to enhance representativeness and external validity. Such efforts would help confirm our findings and support evidence-based improvements in clinical practice.

Conclusion

In conclusion, the prophylactic combination of indomethacin suppositories and diclofenac sodium administered before ERCP effectively reduces the risk and severity of PEP, while also decreasing the incidence of related adverse events such as perforation, bleeding, cholangitis, and postoperative pain. This strategy may become a standard prophylactic approach. Future studies that optimize NSAID dosing, routes, and combination regimens to maximize PEP prevention are warranted.

Declarations

Not applicable.

Authors' contributions

X. Wu: Conceptualization, Methodology, Project Administration, Resources. W. Cui: Data Curation, Writing - Original Draft, Writing - Review & Editing. X. Wu: Formal Analysis, Supervision. E. Li: Investigation, Validation. H. Wang: Data Curation, Investigation. W. Qi: Data Curation, Formal Analysis. X. Li: Methodology, Formal Analysis, Validation. S. Hou: Supervision, Project Administration.

Ethics approval and consent to participate

The study was approved by the Medical Ethics Committee of Handan Central Hospital (Approval No.: [2024] Ethics Review Paper No. (020)). All procedures involving human participants were conducted in accordance with the ethical standards set by the institutional and national research committees and with the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards. Informed consent was obtained from all participants before participation in the study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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Authors' other information

Not applicable.

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