Value of Urinary Trypsinogen-2 Test in Early Diagnosis of Pancreatitis after Endoscopic Retrograde Cholangiopancreatography (ERCP)

Ahlam Mohammed Sabra[a], Hasan Sedeek Mahmoud[b], Esraa Abbass Abdallah Ahmed[c], Mustafa Ebead[a*], Mohamed Tag-Adeen Said[a]

[a]Internal Medicine Department, Faculty of Medicine, South Valley University, Qena , Egypt.
[b]Tropical Medicine Department, Faculty of Medicine, South Valley University, Qena, Egypt.
[c]Clinical Pathology Department, Faculty of Medicine, South Valley University, Qena, Egypt.

Abstract

Background: Acute pancreatitis is one of the most serious complications of ERCP. Early diagnosis of post-ERCP pancreatitis (PEP) helps physicians to provide intensive care and possible medical treatment as early as possible. Trypsinogen 2 has recently gained attention as a useful biomarker for diagnosing and assessing the severity of acute PEP.

Objectives: to evaluate the role of the urinary trypsinogen-2 test in early diagnosis of PEP and compare its diagnostic value with serum amylase and lipase levels.

Patients and methods: We tested the urinary trypsinogen-2 test and serum levels of amylase and lipase in a total of 70 patients with obstructive jaundice after ERCP.

Results: PEP was diagnosed in 16 (22.9%) of 70 patients. At cutoff level (>10.9 ng/ml) , the sensitivity, specificity, PPV, NPV, and accuracy of urinary trypsinogen-2 test as a predictor of Post-ERCP pancreatitis at 3 hours after ERCP were 93.75%, 94.4 %, 83.3%, 98.1%, and 94.2%, respectively. At the cutoff level (>87 U/L) for amylase, the sensitivity, specificity, PPV , NPV, and accuracy were 75%, 83.3%, 57.1%, 91.8%, and 81.4 % respectively. At the cutoff level (>83 U/L) for lipase, the sensitivity, specificity, PPV, NPV, and accuracy were 75%, 66.7%, 40%, 90%, and 68.57 %, respectively.

Conclusions: Urinary TRY-2 is an accurate early marker for diagnosing post-ERCP pancreatitis, with high sensitivity, specificity, and accuracy outperforming serum amylase and lipase, and its strong link to clinical outcomes makes it a valuable noninvasive tool.

Keywords: ERCP; Pancreatitis; Urinary trypsinogen-2 test.

***Correspondence**: mustafa.ebead@med .svu.edu.eg

DOI: 10.21608/SVUIJM.2024.334129.2011

Received: 16 November, 2024
Revised: 2 December, 2024.
Accepted: 5 December, 2024.
Published: 17 October, 2025

Cite this article as Ahmed Mamdouh AbdelAziz , Ahmed Ali Ibrahim, Zaki F. Aref, Aida A. Abdelmaksoud. (2025). Evaluation of Endoscopic Repair of Cerebrospinal Fluid (CSF) Rhinorrhea with Single Layer Graft versus Multilayers Graft. *SVU-International Journal of Medical Sciences*. Vol.8, Issue 2, pp: 645-656.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a more technically challenging procedure compared to standard gastrointestinal methods like esophagogastroduodenoscopy and colonoscopy. Because of its complications, ERCP requires more medical experience and a longer learning curve to attain competency. Furthermore, it presents a greater risk of challenges. Studies show that ERCP complications can occur in up to 9.7% of patients, with a mortality rate of 0.7% in the general population. The most common consequences include post-ERCP pancreatitis (PEP), bleeding, visceral perforations, and post-ERCP cholecystitis **(Solanki et al., 2022).**

Acute pancreatitis is the most dangerous complication of ERCP. This condition is characterized by pancreatic inflammation and can be diagnosed based on two of three criteria: sudden onset of severe epigastric pain, elevated serum amylase or lipase levels (three times above normal), and confirmation of pancreatitis through imaging such as CT, MRI, or ultrasound **(Bhatt, 2021).**

TRY-2 has recently emerged as a promising biomarker for identifying and evaluating the severity of acute PEP. A non-invasive bedside dipstick test can recognize the rapid rise in urine during acute PEP, making it an effective tool for early screening **(Yewale et al., 2022).**

This study aims to evaluate the role of the urinary TRY-2 test in early diagnosis of PEP and compare its diagnostic value with serum amylase and lipase levels.

Patients and methods

This cross-sectional study was conducted at Qena University Hospital and involved adult patient's ≥ 18 years of age who underwent ERCP for biliary obstruction between June 2022 and December 2023. Patients with end-stage renal disease, a history of pancreatitis, or alcohol use were excluded. Key clinical data, including age, sex, body mass index (BMI), tobacco and alcohol consumption, surgical history, and full clinical assessments, were collected.

Sample size calculation: the following formula was used to calculate an adequate sample size:

$$n = \frac{\left(\frac{z\alpha}{2}\sqrt{2\times\bar{P}(1-\bar{P})}+z\beta\sqrt{P1(1-P1)+P2\,(1-P2)}\right)^2}{(P1-P2)^2}$$ **(Dicker et al., 2006)**.

Where n: Sample size

$\bar{P}$: The average of P1 and P2 = 80%

P1: The expected sensitivity of the serum amylase or lipase levels =70%

P2: The expected sensitivity of the urinary TRY-2 tests = 90%

P1-P2: Significant difference = 20%

Zα/2: This depends on the level of significance, for 5% this is 1.96

Zβ: This depends on power, for 80% this is 0.84

So, $n= \frac{(1.96\times\sqrt{2\times0.80\times0.20}+0.84\sqrt{0.70\times0.30+0.90\times0.10})^2}{(0.20)^2} =$ 62

The study sample consisted of 70 adult patients with obstructive jaundice.

Laboratory investigations included a complete blood count (CBC), serum bilirubin (total and direct), liver enzyme, Alanine transaminase (ALT), Aspartate transaminase (AST),Alkaline phpsphatase (ALP) , prothrombin time (PT), prothrombin concentration (PC), international normalized ratio (INR), blood urea nitrogen(BUN) , serum creatinine, and serum amylase and serum lipase.

After obtaining informed consent, patients in the study underwent the following procedures:

1. **Imaging**: Abdominal ultrasonography, contrast-enhanced computed tomography (CECT), or magnetic resonance imaging (MRI) were performed on all patients to assess the pancreas and biliary system, confirming biliary obstruction and identifying its cause.
2. **ERCP**: This procedure was carried out by an experienced ERCP endoscopist.
3. **Specimen Collection**: Blood samples were collected from all participants under aseptic conditions. Total 7 ml blood was drawn into an EDTA tube for the analysis of CBC. Another 2 mL of blood was collected in a citrate tube for coagulation studies, including PT, PC, and INR. Additionally, 3 mL of blood was drawn into a plain tube, allowed to clot, and centrifuged to obtain serum. The serum was subsequently used for

the assessment of liver function tests and kidney function tests. Three hours following ERCP, samples of blood and urine were collected. Serum amylase and lipase levels were measured in a 5 ml fasting venous blood sample, and the urinary TRY-2 ELISA kit was used to quantify TRY-2 in a 5 ml urine sample. Samples of urine were either examined immediately or kept at -20°C **(Tseng et al., 2011).**

Test Principle: The biochemical analyses in this study were performed using the Architect series chemistry analyzer (Abbott Diagnostics, USA) utilizing advanced chemiluminescent micro particle immunoassay (CMIA) technology. The Architect analyzer was used for the measurement of liver function tests (ALT, AST, ALP, total bilirubin, and albumin), kidney function tests (urea and creatinine), and pancreatic enzymes (amylase and lipase). Standardized protocols were followed, and quality controls were run daily to ensure the accuracy and reproducibility of results.

Human Trypsinogen-2 (Try-II): Urinary TRY-2 was quantified through enzyme immunoassay (EIA) ELISA Kit Catalog No: SG-14417 (Sinogeneclon Co., Ltd, Hangzhou, China) was used for urinary TRY-2 determination (Detection range: 0.3ng/ml-20ng/ml , Intra-Assay: CV< 8% , Inter-Assay: CV< 10%) according to the manufactural instructions.

Two of the three criteria have to be met in order to diagnose acute pancreatitis: Serum amylase and/or lipase levels that are three times higher than the upper normal range, severe, acute epigastric pain that radiates to the back, and characteristic abdominal imaging findings **(Leppäniemi et al., 2019).**

Ethical consideration: Written informed consent was obtained from all patients or their close relatives and all were well informed regarding the procedure and that the results were confidential. This study was approved by the Institutional Review Board (IRB). Ethical approval code: SVU-MED-MED018-2-21-12-287.

Statistical analysis

Data was analyzed using SPSS version 25. Qualitative variables were reported as frequencies and percentages and compared using the chi-square test (X2), while quantitative data were presented as medians with interquartile range (IQR) and compared using Mann–Whitney U test (U). A probability value (P value) less than 0.05 was considered statistically significant. . Data normality was evaluated through Kolmogorov-Smirnov and Shapiro-Wilk test. Mann Whitney U test was used when comparing between two groups (for abnormally distributed data). Chi-square test was used when comparing between non-parametric categorical data. Kappa test was done for measurement of agreement. The validity of urinary TRY-2 was evaluated through sensitivity, specificity, positive and negative predictive values, and overall accuracy. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were calculated and compared to serum amylase and lipase results. Multivariate logistic regression predicts the likelihood of PEP using multiple predictors, with coefficients (B) showing effect sizes, p-values testing significance, odds ratios indicating association strength, and confidence intervals (CI) providing a range of values. Linear regression analyzes continuous variables' relationship with PEP, using coefficients (B) for effects, standard errors (SE) for precision, p-values for significance, and CIs for the range of true values.

Results

The study included 70 patients referred to the gastrointestinal endoscopy unit at Qena University Hospital to perform ERCP. The age of the patients ranged between 18 and 85 years, with a median age of 54 years (IQR = 35-67). Those patients were 22 males (31.4%) and 48 females (68.6%). 16 of them developed pancreatitis post-ERCP (22.9%) (3 males and 13 females), while 54 of them did not (77.1%).

Table 1. Demographic and laboratory data for all studied patients

Variables		Post-ERCP pancreatitis				Stat. test	P-value
		Yes (n = 16)		No (n = 54)			
Sex N (%)	Males	3	18.8%	19	35.2%	X^2= 1.5	0.21 NS
	Females	13	81.3%	35	64.8%		
Age (years)	Median (IQR)	47 (29 – 54)		59 (37 – 70)		U= 394	0.053 NS
Residence N(%)	Urban	11	68.8%	26	48.1%	X^2= 2.1	0.15 NS
	Rural	5	31.3%	28	51.9%		
OccupationN(%)	Not Employed	12	75.0%	34	63.0%	X^2= 0.79	0.37 NS
	Employed	4	25.0%	20	37.0%		
Marital status N (%)	Single	1	6.3%	4	7.4%	X^2= 0.025	0.88 NS
	Married	15	93.8%	50	92.6%		
Smoking N (%)		2	12.5%	15	27.8%	X^2= 1.6	0.21 NS
BMI (kg/m2)	Median (IQR)	29 (20 – 33)		26 (22 – 29)		U= 339	0.19 NS
DM N (%)		6	37.5%	16	29.6%	X^2= 0.36	0.55 NS
Hypertension N (%)		4	25.0%	13	24.1%	X^2= 0.006	0.94 NS
Causes of CBD obstruction	CBD stones	14	87.5%	28	51.9%	6.9	0.14 NS
	CBD stricture	1	6.3%	6	11.1%		
	Cholangiocarcinoma	0	0.0%	3	5.6%		
	Pancreatic mass	1	6.3%	13	24.1%		
	Periampullary mass	0	0.0%	4	7.4%		
HB (gm/dl)		12.4 (10.6 – 13)		12.2 (10.7 – 13.1)		U=390	0.62 NS
WBCs (× 10^9/L)		8.1 (6.7 – 10.2)		7.4 (6.2 – 8.5)		U=362	0.32 NS
PLT (× 10^9/L)		289 (221.3 – 316)		273 (211 – 352)		U=424	0.91 NS
T. Bilirubin (mg/dl)		7.8 (4.4 – 9.2)		7.6 (2.5 – 12.1)		U=419	0.85 NS
D. Bilirubin (mg/dl)		6.2 (3.3 – 7.1)		6 (1.6 – 10.4)		U=427	0.94 NS
ALP (IU/L)		612 (470 – 748)		402 (290 – 644)		U=238	**0.01 S**
ALT (U/L)		64 (55.5 – 140)		56.5 (41.3 – 102.3)		U=333	0.17 NS
AST (U/L)		71.5 (53 – 90)		67 (40.8 – 104.3)		U=383	0.49 NS
S. Albumin (mg/dl)		3.9 (3.4 – 4.3)		3.9 (3.5 – 4.1)		U=400	0.65 NS
PC (%)		97.5 (86.3 – 100)		87.5 (75.8 – 100)		U=298	0.06 NS
INR		1 (1 – 1.1)		1.1 (1 – 1.2)		U=295	**0.04 S**
BUN (mg/dl)		23 (16.5 – 31.3)		29 (19 – 41.3)		U=339	0.19 NS
S. creatinine (mg/dl)		0.7 (0.6 – 1)		0.7 (0.6 – 1)		U=405	0.70 NS
Urinary TRY-2 (ng/ml)		69 (49 – 79)		7.5 (6 – 9)		25	**< 0.001 HS**
Serum amylase (U/L)		101 (78 – 162)		65 (55 – 85)		139	**< 0.001 HS**
Serum lipase (U/L)		91 (80 – 128)		77 (58 – 88)		218	**0.003 S**

X^2: value of chi-square test; U: Mann–Whitney U test; NS: non-significant; S: significant.

As regard laboratory data: alkaline phosphatase (ALP) showed a significant increase in patients with PEP (P = 0.01). Additionally, the international normalized ratio (INR) was significantly higher in patients without PEP (P = 0.04). Otherwise: no significant difference was detected. As regard laboratory markers of pancreatitis three hours after ERCP, urinary TRY-2 was markedly elevated in patients with PEP, compared to those without PEP (P < 0.001).

Similarly, serum amylase levels were significantly higher in the PEP group versus the non-PEP group (P < 0.001). Additionally, serum lipase was significantly increased in patients with PEP, compared to those without PEP (P = 0.003). **(Table.1).**

Table 2. ERCP data for both patients' groups

Variables		Post-ERCP pancreatitis				Stat. test	P-value
		Yes (n = 16)		No (n = 54)			
Cannulation time (minutes)	**Median (IQR)**	23 (20 – 29)		10 (5 – 12)		28	**< 0.001 HS**
Cannulation attempts	**Median (IQR)**	6.5 (5.3 – 7)		4 (3 – 6)		157	**< 0.001 HS**
Cannulation technique	**TPF**	6	37.5%	10	18.5%	4.95	0.08 NS
	Standard WGC	8	50.0%	42	77.8%		
	DGC	2	12.5%	2	3.7%		
Endoscopic sphincterotomy (EST)		8	50.0%	24	44.4%	0.15	0.7 NS
Large balloon dilatation		0	0.0%	9	16.7%	3.1	0.08 NS
Cholangiogram	**CBD stones**	14	87.5%	28	51.9%	6.6	**0.037 S**
	Distal CBD stricture	2	12.5%	24	44.4%		
	Hilar CBD stricture	0	0.0%	2	3.7%		

X2: value of chi-square test; U: Mann–Whitney U test; HS: highly significant; NS: non-significant; S: significant.

Regarding the findings related to the ERCP procedure **(Table 2)**. We found that cannulation time was significantly higher in patients with PEP, with a median of 23 minutes (IQR = 20–29), compared to 10 minutes (IQR = 5–12) in those without pancreatitis (P < 0.001). Additionally, cannulation attempts were significantly increased in patients with PEP, with a median of 6.5 (IQR = 5.3–7) compared to 4 (IQR = 3–6) for those without pancreatitis (P < 0.001). There was a statistically significant difference in cholangiogram of ERCP results (P = 0.037); among patients with pancreatitis, 87.5% of the cases had CBD stones, while 51.9% of those without pancreatitis had CBD stones, alongside 44.4% with distal CBD stricture and 3.7% with hilar CBD stricture.

Table 3. Diagnostic performance of urinary trypsinogen 2 versus S. amylase and S. lipase (3 hours after ERCP) in the prediction of PEP

Variables	Urinary trypsinogen 2	S. Amylase	S. Lipase
Cutoff	(>10.9 ng/ml)	(>87 U/L)	(>83 U/L)
AUC	0.971	0.84	0.748
True positive	15	12	12
True negative	51	45	36
False positive	3	9	18
False negative	1	4	4
Total	70	70	70
Sensitivity	93.75	75	75
Specificity	94.44	83.33	66.7
PPV	83.33	57.14	40
NPV	98.1	91.84	90
Accuracy	94.29	81.43	68.57
Kappa Agreement	0.8448	0.5255	0.3186
P-Value	< 0.0001	< 0.0001	< 0.0001

PPV: positive predictive value; AUC: Area under curve; NPV: negative predictive value.

The ROC curve analysis **(Table 3)** indicates that urinary TRY-2 measured three hours after ERCP effectively discriminates between patients with and without PEP. A cutoff level of (>10.9 ng/ml) of urinary TRY-2 achieved a sensitivity of 93.7%, specificity of 94.4%, PPV of 83.3%, and NPV of 98.1%, with an AUC of 0.971 (P < 0.001) and accuracy reaching 94.29%. For serum amylase, a cutoff level of (>87 U/L) demonstrated a sensitivity of 75%, specificity of 83.3%, PPV of 57.1%, and NPV of 91.8%, yielding an AUC of 0.84 (P < 0.001) and accuracy reaching 81.43%. Serum lipase also distinguished between the two groups, with a cutoff level of (>83 U/L) resulting in a sensitivity of 75%, specificity of 66.7%, PPV of 40%, and NPV of 90%, along with an AUC of 0.748 (P < 0.001) and accuracy reaching 68.57% **(Fig.1)**.

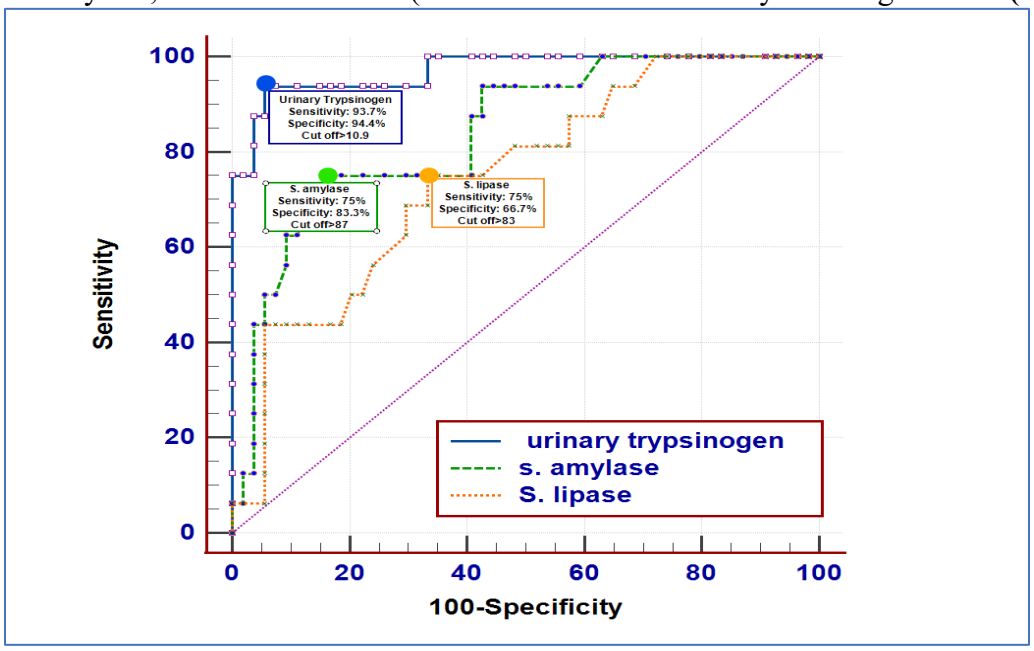

Fig.1. ROC curve of urinary TRY-2, S. amylase, and S. Lipase (3 hours after ERCP) in discrimination between patients with and without PEP in patients' group.

Table 4.Linear regression analysis of ERCP data for the prediction of PEP in patients' group

Variables	B	SE	p-value	95% CI	
CBD stones	0.262	0.099	**0.01***	0.064	0.46
CBD stricture	-0.179	0.193	0.361	-0.575	0.217
Cholangiocarcinoma	-0.485	0.366	0.196	-1.236	0.266
Pancreatic mass	-0.173	0.216	0.431	-0.617	0.271
Periampullary mass	-0.444	0.290	0.137	-1.039	0.151
CBD diameter	0.004	0.008	0.622	-0.012	0.020
Cannulation time	0.020	0.008	**0.026***	0.035	0.052
Cannulation attempts	0.119	0.027	**<0.001***	0.064	0.173
Cannulation technique	0.003	0.070	0.963	-0.140	0.146
EST	-0.066	0.072	0.369	-0.215	0.083
Large Ballon Dilatation	-0.070	0.091	0.452	-0.258	0.118
Cholangiogram					
CBD stones	0.262	0.099	**0.01***	0.064	0.46

CBD distal stricture	-0.121	0.051	**0.02***	-0.222	-0.02
CBD hilar stricture	0.221	0.144	0.136	-0.074	0.516
3 hours after ERCP lab. data					
Urinary trypsinogen	0.014	0.001	**<0.001***	0.011	0.016
Serum amylase	0.005	0.001	**<0.001***	0.003	0.007
Serum lipase	0.004	0.001	**0.004***	0.001	0.007
Pain score	0.146	0.013	**<0.001***	0.21	0.172

B: Regression coefficient; SE: Standard error; CI: Confidence interval; *: significant.

Linear regression analysis **(Table.4)** identified several predictive risk factors for PEP. CBD stones were positively associated with the outcome (B = 0.262, P = 0.01). Increased cannulation time (B = 0.02, P = 0.026) and attempts (B = 0.119, P < 0.001) also correlated significantly. In contrast, a distal CBD stricture had a negative association (B = -0.121, P = 0.02). Additionally, urinary TRY-2 levels measured three hours after ERCP showed a strong positive relationship (B = 0.014, P <0.001), as did S. amylase (B = 0.005, P < 0.001) and S. lipase (B = 0.004, P = 0.004) at the same time point. Pain scores after ERCP (B = 0.146, P < 0.001) were also significant.

Table 5. Multivariate logistic regression analysis for the prediction of PEP in patients' group

Variables	B	SE	p-value	Odds	95% CI	
Sex	0.855	0.701	0.222	2.35	0.60	9.29
Age	-0.027	0.016	0.084	0.97	0.94	1.00
Residence	-0.863	0.604	0.153	0.42	0.13	1.38
Occupation	-0.568	0.642	0.377	0.57	0.16	2.00
Marital status	0.182	1.156	0.875	1.20	0.12	11.57
Smoking	-0.990	0.815	0.224	0.37	0.08	1.83
BMI	0.080	0.061	0.190	1.08	0.96	1.22
DM	0.354	0.596	0.552	1.42	0.44	4.58
HTN	0.050	0.659	0.940	1.05	0.29	3.83
Main presentation (Jaundice)	-1.253	0.809	0.122	0.29	0.06	1.40
Duration of presentation	-0.026	0.033	0.431	0.97	0.91	1.04
HB	0.116	0.170	0.494	1.12	0.81	1.57
WBCs	0.087	0.114	0.443	1.09	0.87	1.36
PLT	-0.001	0.003	0.642	1.00	0.99	1.00
T. Bilirubin	-0.036	0.045	0.419	0.96	0.88	1.05
D. Bilirubin	-0.043	0.054	0.423	0.96	0.86	1.06
ALP	0.003	0.001	**0.015***	1.003	1.00	1.01
ALT	0.005	0.004	0.207	1.01	1.00	1.01
AST	0.004	0.004	0.315	1.00	1.00	1.01
S. Albumin	0.174	0.569	0.759	1.19	0.39	3.63
PC	0.057	0.029	0.054	1.06	1.00	1.12
INR	-9.091	4.598	**0.048***	0.0001	0.00	0.92
BUN	-0.016	0.019	0.404	0.98	0.95	1.02
S. creatinine	-0.939	1.064	0.378	0.39	0.05	3.15

B: Regression coefficient; SE: Standard error; CI: Confidence interval; *: significant.

Multivariate logistic regression analysis **(Table.5)** identified key predictive risk factors for PEP. Elevated ALP levels were associated with an increased risk, with a coefficient of B = 0.003, a standard error of SE = 0.001, and a P-value of 0.015, indicating that a one-unit increase in ALP

raises the odds of developing PEP by 0.3% (Odds = 1.003, 95% CI =1–1.01). Conversely, a higher INR was linked to a significantly reduced risk, with B=-9.091, SE=4.598, and P = 0.048, suggesting that a one-unit increase in INR decreases the odds of PEP by 99.9% (Odds = 0.0001, 95% CI = 0–0.92).

Table 6. Multivariate logistic regression analysis of ERCP data for the prediction of PEP in patients' group

Variables	B	SE	P-value	Odds	95% CI	
Causes of CBD obstruction						
CBD stones	1.872	0.803	**0.020***	6.50	1.35	31.39
CBD stricture	-0.629	1.120	0.575	0.53	0.06	4.79
Cholangiocarcinoma	-20.044	23205.422	0.999	0.00	0.00	0.00
Pancreatic mass	-1.559	1.081	0.149	0.21	0.03	1.75
Periampullary mass	-20.063	20096.485	0.999	0.00	0.00	0.00
CBD diameter	-0.089	0.083	0.283	0.91	0.78	1.08
Cannulation time	0.558	0.164	**0.001***	1.75	1.27	2.41
Cannulation attempts	0.881	0.262	**0.001***	2.41	1.45	4.03
Cannulation technique	-0.394	0.560	0.481	0.67	0.23	2.02
EST	0.223	0.570	0.695	1.25	0.41	3.82
Large Ballon Dilatation	-20.169	13397.657	0.999	0.000	0.000	0.000
Cholangiogram						
CBD stones	1.872	0.803	**0.020***	6.50	1.35	31.39
CBD distal stricture	-0.861	0.402	**0.032***	0.42	0.19	0.93
CBD hilar stricture	-6.675	9473.574	0.999	0.00	0.00	0.00
3 hours after ERCP lab. data						
Urinary trypsinogen	0.102	0.023	**<0.001***	1.11	1.06	1.16
Serum amylase	0.028	0.009	**0.001***	1.03	1.01	1.05
Serum lipase	0.023	0.009	**0.011***	1.02	1.01	1.04
Pain score	1.538	0.415	**<0.001***	4.66	2.06	10.51

B: Regression coefficient; SE: Standard error; CI: Confidence interval; *: significant.

Multivariate logistic regression analysis **(Table 6)** identified several predictive risk factors for PEP. Patients with CBD stones showed significantly higher odds of developing pancreatitis, with an odds ratio of 6.5 (B = 1.872, P = 0.02). Each additional minute of cannulation time increased the odds by 75% (Odds = 1.75, B = 0.558, P = 0.001). Similarly, for each additional cannulation attempt, the odds rose by 141% (Odds = 2.41, B = 0.881, P = 0.001).

Conversely, patients with CBD distal stricture had a 58% reduction in odds of pancreatitis (Odds = 0.42, B = -0.861, P = 0.032). Urinary TRY-2 levels three hours after ERCP were linked to an 11% increase in odds per unit increase (Odds = 1.11, B = 0.102, P < 0.001). Elevated S. amylase and S. lipase levels also correlated with increased odds, with 3% and 2% increases, respectively, per unit increase (S. amylase: Odds = 1.03, B = 0.028, P=0.001; S. lipase: Odd s= 1.02, B = 0.023, P = 0.011).

Additionally, a pain score increases of one-unit post-ERCP led to a 366% increase in odds of pancreatitis (Odds = 4.66, B = 1.538, P = 0).

Discussion

In the current study, patients who developed PEP experienced longer cannulation times (23 minutes) and more attempts (6.5), with significant differences observed (P < 0.001). The prevalence of PEP was notably higher in patients with CBD stones (87.5%) compared to prevalence of non-PEP patients (51.9%) (P = 0.037).

The results of our study suggest the correlation between longer cannulation times and more attempts in patients with PEP most likely results from technical challenges associated with the greater incidence of CBD stones in this group of patients. These stones' challenges increase the need for additional time and attempts to obtain effective CBD access and increase the risk of biliary tree trauma, which can trigger an inflammatory reaction and result in pancreatitis. Consequently, the pathophysiology of PEP heavily relies on the difficulties of navigating obstructive lesions during ERCP **(Noel, 2017; Dietrich et al., 2022a, 2022b).**

In agreement with our findings**, Maitin-Casalis et al. (2015)** reported significant differences in rates of PEP and unplanned hospital admissions across age groups, linking these rates to procedure duration and indication ($P < 0.01$). Similarly, **Kadokura et al. (2021)** indicated that asymptomatic common bile duct stones, endoscopic papillary balloon dilatation, and longer cannulation times than ten minutes were risk factors for PEP. According to their multivariate analysis, the odds ratio for cannulation duration exceeding 10 minutes was 6.67 ($P < 0.001$), whereas the hazard ratios for asymptomatic CBD stones and endoscopic papillary balloon dilatation were 5.70 ($P < 0.001$) and 5.49 ($P < 0.001$), respectively.

Leghari et al. (2013) identified There were significant correlations between the incidence of pancreatitis and difficult cannulation (9.8%, $P = 0.006$), longer cannulation duration (7.6 minutes, $P = 0.002$), pancreatic duct cannulation (13.7%, $P = 0.001$), and contrast injection into the pancreatic duct (13.4%, $P < 0.001$). In contrast, **Xiao et al. (2021)** found patients with asymptomatic CBD stones did not have a higher risk of ERCP-related complications than patients with symptomatic stones, which is in contrast to our study's emphasis on complications related to CBD stones.

Our study findings indicate that elevated urinary TRY-2 , serum amylase, and serum lipase levels in PEP patients resulted from pancreatic inflammation and damage induced by the ERCP procedure. Urinary TRY-2 , which has high sensitivity (93.7%) and specificity (94.4%) and accuracy of 94.2% for diagnosing PEP, serves as a more reliable biomarker for early detection compared to serum amylase and lipase, which may be influenced by other factors **(Banks, 2013; Staubli et al., 2015 ; Prakash, 2018).**

In line with our findings, **Yewale et al. (2022)** assessed the accuracy of 91.1%, specificity of 92.1%, and sensitivity of 66.7% for predicting PEP four hours after ERCP using a rapid urine TRY-2 dipstick test. Eleven of the 79 individuals in their study had increased serum lipase levels, with a median level of 864 U/L. Additionally, **Tseng et al. (2011)** reported that Three hours following ERCP, the fast urine TRY-2 test had a sensitivity of 84.6% and a specificity of 97.1%. Amylase and lipase had much lower positive predictive values than the urine TRY-2 test, although having similar negative predictive values.

Our study findings are consistent with **Kobayashi et al. (2011),** who assessed TRY-2 levels in order to detect pancreatitis early following ERCP. During their examination, they discovered that PEP was identified in 8 out of 68 cases. TRY-2 levels rose two hours after ERCP, but patients without PEP peaked four hours after ERCP, as were total and pancreatic amylase levels. In patients with PEP, there were sustained increases in total-amylase, pancreatic-amylase, and TRY-2 levels. In a different study, pancreatic amylase levels rose 4–6 hours after ERCP, whereas TRY-2 levels peaked 1 hour later, hence none of the 23 patients were identified as post-ERCP pancreatitis.

The ROC curve analysis showed that urinary TRY-2 measured 3 hours after ERCP effectively predicts PEP with a cutoff of (>10.9 ng/ml), achieving 93.7% sensitivity, 94.4% specificity, 83.3% PPV, 98.1 % NPV, AUC of 0.971, and 94.2% accuracy. Serum amylase with a cutoff of (>87 U/L) had 75% sensitivity, 83.3% specificity, 57.1% PPV, 91.8% NPV, AUC of 0.84, and 81.4% accuracy. Serum lipase with a cutoff of (>83 U/L) had 75% sensitivity, 66.7% specificity, 40% PPV, 90% NPV, AUC of 0.748, and 68.57% accuracy. Thus, our study revealed that urinary TRY-2 was the most accurate marker.

Our study findings are consistent with **Hama et al. (2024)**, who evaluated the rapid urine TRY-2 dipstick test for PEP diagnosis in

comparison to serum lipase and amylase. Their findings showed that the dipstick test's sensitivity, specificity, PPV, and NPV were 100%, 83.2%, 23.8%, and 100%, respectively. Although these findings were comparable to serum lipase and amylase levels assessed the morning following ERCP, false positives should be taken into considerations.

Additionally, **El-Garem et al. (2013)** The sensitivity, specificity, PPV, and NPV of the urine TRY-2 dipstick test were 100%, 97%, 86%, and 100% at 6 hours after ERCP, respectively, when it was assessed for the early identification of post-ERCP pancreatitis. Amylase at a cutoff of 122 U/L had PPV and NPV of 60% and 100%, respectively, whereas lipase had both PPV and NPV of 100% at a cutoff of 130 U/L. According to their findings, the urine TRY-2 dipstick test and serum lipase are the most accurate diagnostic methods for PEP.

Furthermore, greater ALP levels increase probabilities of pancreatitis by 0.3% per unit, while a higher INR reduces odds by 99.9%. The presence of CBD stones raises the likelihood of pancreatitis by 6.5 times, longer cannulation times increase probabilities by 75%, and more attempts raise it by 141%. Conversely, distal CBD strictures decrease the risk by 58%. Urinary TRY-2, serum amylase, and serum lipase increase probabilities by 11%, 3%, and 2% per unit, respectively. Pain ratings significantly raise probabilities by 4.66 times, and serum amylase levels measured 8–12 hours post-ERCP increase odds by 1% per unit. Key predictors include ALP, INR, CBD stones, cannulation time, attempts, and pain ratings.

The study limitations include a small sample size, lack of control for confounding factors like medical history and medication use, and its single-center design, which may limit the generalizability of the findings.

Conclusion

The study found urinary TRY-2 is considered an accurate and early marker for diagnosing post-ERCP pancreatitis, outperforming serum amylase and lipase. Its strong link to clinical outcomes, like prolonged cannulation and higher pain scores, makes it a valuable noninvasive tool for identifying at-risk patients.

List of Abbreviations:

ALP	Alkaline phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area under the curve
BMI	Body mass index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBD	Common bile duct
CECT	Contrast Enhanced Computed Tomography
CI	Confidence interval
CV	Coefficient of Variation
D. Bilirubin	Direct bilirubin
DGC	Double Gidewire Cannulation
DM	Diabetes mellitus
EIA	Enzyme Immunoassay
ELISA	Enzyme-linked immunosorbent assay
ERCP	Endoscopic retrograde cholangiopancreatography
EST	Endoscopic Sphinctrotomy
HB	Hemoglobin
INR	International normalized ratio
IQR	Interquartile range
MRI	Magnetic Resonant Imaging
NPV	Negative predictive value
PC	Prothrombin Concentration
PEP	Post-ERCP pancreatitis
PLT	Platelets
PPV	Positive predictive value
PT	Prothrombin Time
ROC	Receiver operating characteristic
S. Albumin	Serum Albumin
S. Amylase	Serum Amylase
S. Lipase	Serum Lipase
SE	Standard errors
SPSS	Statistical Package for the Social Sciences
T. Bilirubin	Total bilirubin
T. Bilirubin	Total bilirubin
TPF	Transpapillary Fistulotomy

TRY-2 Trypsinogen 2
WBCs White blood cells
WGC Wire Guided Cannulation

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