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ORIGINAL ARTICLE

The Influence of Challenging Biliary Cannulation Resulting from Duodenal Papillary Lesions on the Outcomes and Complications Associated with Endoscopic Retrograde Cholangio-Pancreatography.

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ABSTRACT

Background: The major duodenal papillary (MDP) lesions make biliary cannulation more difficult which has a significant impact on achievement and hazards of ERCP in adults. We aimed to assess difficult biliary cannulation (DBC) due to MDP lesions and evaluate the success and potential complications during and after ERCP.

Methods: A recruited 120 patients in a case control study who received ERCP for either diagnostic or therapeutic purposes and classified into 3 groups: Group A (N=40): Those with abnormal morphology of MDP (anatomical variant or pathological lesions) and DBC. Group B (N=40): patients with normal morphology of MDP and DBC. Group C (N=40): patients with type 1 and easy biliary cannulation as control group. All patients underwent detailed history, clinical evaluation, laboratory tests, radiological assessment and ERCP.

Results: Overall successful biliary cannulation was achieved in 104/120 (86.67%) patients, while in the other 16/120 (13.33%) patients, biliary cannulation failed and post-ERCP complications' rate has been (18.33%), pancreatitis (10.8 %) and hemorrhage (7.5%). In addition, the potential independent factor predicting DBC was pancreatic mass, history of cholecystectomy, intra-diverticular papilla, the presence of the main duodenal papilla and/or biliary stenosis on imaging. However, the risk factors predicting PEP were the duration of cannulation, number of trials of cannulation, morphological variation of papilla and duodenum, the use of precut and sphincterotomy.

Conclusion: Difficult biliary cannulation due to duodenal papillary lesions has an important effect on success and complications of ERCP.

Keywords: Post-ERCP pancreatitis (PEP), major duodenal papilla (MDP), difficult biliary cannulation (DBC).

INTRODUCTION

ERCP was initially developed as a diagnostic technique that included the cannulation of the pancreatic and bile ducts, along with biopsy or brush cytology. However, it has also evolved to serve therapeutic purposes, such as endoscopic sphincterotomy, stent placement, and stone extraction and others [1].

Selective biliary cannulation is recognized as crucial to the success of ERCP and its associated treatments. Various studies indicated that the failure rate of bile duct cannulation in patients ranges from 5% to 15% [2].

Difficult biliary cannulation (DBC) is characterized by attempts to achieve biliary access that exceed five minutes in duration, involve more than five attempts, or require at least two passages of a pancreatic guidewire. Patients presenting with a small duodenal papilla, a lax papilla, sclerosis at the papilla opening, peripapillary diverticula, or altered

surgical anatomy are at a higher risk of encountering unsuccessful biliary cannulation [3].

In cases where initial ERCP fails to achieve biliary cannulation, alternative approaches may include repeating the ERCP, utilizing percutaneous endoscopic or endoscopic ultrasound-guided rendezvous techniques, performing percutaneous transhepatic biliary drainage, or considering surgical options [4].

Complications associated with ERCP were characterized as adverse events or unforeseen clinical results arising from the procedure, including post ERCP pancreatitis (PEP), bleeding, cholangitis, and perforation [5]. Biliary endoscopic sphincterotomy (EST) presents multiple complications, both in the short and long term. These complications stem from the invasive nature of ERCP, which can vary among patients based on their health conditions and factors intrinsic to the procedure. Timely detection and appropriate management of these complications are crucial to reducing mortality and morbidity [6].

Post-ERCP pancreatitis (PEP) is severe or fatal in about 0.8% of patients. In addition, PEP is likely the main reason for prolongation of hospital stays and medical care costs. [7]. Moreover, post-ERCP bleeding is classified according to its severity as mild, moderate, or severe, considering different factors, such as the need for blood transfusion or the admission to a hospital or Intensive Care Unit [8].

The research conducted by Haraldsson et al. [9] highlights the significance of anatomical variations in the morphology and appearance of the major duodenal papilla, which can influence the outcomes of ERCP. This understanding aids in the decision-making process during the procedure.

Our study aims to assess DBC due to MDP lesions and evaluate the success and potential complications during and after ERCP.

METHODS

1. Study design

A case-control study was conducted within the Hepatology, Gastroenterology, and Endoscopy unit of the Internal Medicine Department at the Faculty of Medicine, Zagazig University Hospitals. Our study included 120 patients received diagnostic or therapeutic ERCP that had done on naïve MDP categorized into three groups: Group A (N=40): patients with abnormal morphology of MDP (anatomical variant or pathological lesions) and DBC. Group B (N=40): patients with normal morphology of MDP (type 1) and DBC. Group C (N=40): patients with type 1 and easy biliary cannulation as control group.

2. Patients selection and data collection

The included participants in our study should have a solid indication for ERCP with therapeutic intention. All participants in the study provided their consent. The study received approval from the institutional review board of Zagazig University (ZU-IRB#9707/22-8-2022).

We excluded uncooperative patients who did not consent for all or part of the expected procedures, or they had severe kyphoscoliosis, recent cerebrovascular stroke (≤ 8 weeks), or acute myocardial infarction, pregnancy, partial or complete obstructive lesions of the foregut expected to impede access to second part of the duodenum, decompensated cardiopulmonary diseases, Child-Pugh class C liver disease patients and uncorrectable major bleeding tendency. All included patients underwent comprehensive history taking, thorough physical examinations, and a series of laboratory and radiological investigations.

3. Laboratory evaluations and clinical examinations

Data were gathered for each patient who met the eligibility criteria for the study, including age, gender, body mass index (BMI), place of residence, smoking habits, hemoglobin A1C (HbA1C), complete blood count (CBC), international normalized ratio (INR), total bilirubin, direct bilirubin, aspartate transferase (AST), alanine transferase (ALT), albumin, total plasma protein, alkaline phosphatase, creatinine, blood urea nitrogen (BUN), and serum amylase and lipase. In addition, trans-abdominal ultrasound (TAUS) and ERCP by using upper GIT endoscopy (FUJI 2D127K093-ED-580XT) TECHNIX X-ray unit (55-16-002-532) were performed by experienced hands.

4. Assessment procedures

ERCP was done under general anesthesia in all 120 patients using Propofol intravenous infusion, with endotracheal intubation on mechanical ventilation, in the presence of an anesthesiologist. During the procedure, supplementary oxygen was given to each patient with monitoring of blood pressure, pulse rate, and oxygen saturation levels. Additionally, evaluation of the morphology and visual characteristics of the duodenal papilla, the time-intensive process of successful biliary cannulation, instances of challenging or unsuccessful biliary cannulation, effective drainage procedures, stone removal, stent insertion, and complications

associated with ERCP. All laboratory tests had been done before and after the procedure, including CBC, LFTs, KFTs, coagulation tests and serum amylase and lipase.

5. Statistical Analysis

The analysis of the collected data was conducted utilizing the SPSS software program, version 25.0 for Windows (SPSS; Chicago, IL, USA). Categorical variables were expressed in terms of frequency and percentage, whereas numerical variables were summarized as mean ± standard deviation (SD). Comparative analyses and inferential statistics were executed using either the parametric independent t-test or the Mann-Whitney U-test, depending on the Gaussian distribution of the variables. For categorical variables, the Chi-Square test was employed, or Fisher's exact test was applied when appropriate. A P-value of ≤ 0.05 was deemed statistically significant for all tests conducted. Univariate and multivariate logistic regression analyses were performed to identify predictor variables associated with post-ERCP pancreatitis, DBC, and post-ERCP bleeding.

RESULTS

The demographic distribution, baseline characteristics, and laboratory data of the three groups showed non-significant statistical difference concerning age & sex (52 males (43.33%), and 68 females (56.67%)) distribution, where their ages ranged from 20 to 65 years, & the mean ages in groups A, B, & C was (50.1±13.87, 49.9±8.18, 51.3±8.6 years respectively) as shown in **table 1**. Also, insignificant differences were noticed regarding associated co-morbidities and medical history among studied groups, such as, history of antiplatelets and/or anticoagulants, cholecystectomy and laboratorial results of CBC, LFTs, KFTs and pancreatic enzymes (P>0.05)**.**

There were four main shapes for the papilla in all groups; the most frequent type of papilla was type 1 (regular, normal) in 80/120 patients in groups B & C (66.67%), then type 4 papilla (wrinkled or striated) in 19 patients (15.83%), then type 3 papilla (protruding or pendulous) in 11 patients (9.17%) and type 2 papilla (small or flat) was the least frequent in 10 patients (8.33%). In another meaning the morphological varieties was only in group A in **table 2**, that showed, type 4 was more frequent in 19 patients (47.5%) followed by type 3 in 11 patients (27.5%) then type 2 in 10 patients (25%).

Successful papillary cannulation was achieved in 104 (86.67%) patients while, failed cannulation in 16 (13.33%) patients as shown in **table 3**. The most frequently causes of failure of biliary cannulation was abnormal variation of the major papilla 12 patients (75 %), the remainder 4 patients distributed one for each (variation of the duodenum 1 (6.25 %), or both 1 (6.25 %), CBD stone 1 (6.25 %) and CBD stricture 1 (6.25 %)).

Table 4 in multivariate analysis shows the potential factors predicting difficult cannulation such as pancreatic mass, history of cholecystectomy, intra-diverticular papilla, biliary stenosis on imaging, small papilla, papilla looking downwards, papilla in D3 and stenosis of undetermined origin have been found an independent risk factor ($p<0.01$)

The risk factors for post-ERCP pancreatitis among patients detected the age, number of trials of cannulation and use of precut and duration of cannulation have been found multivariate risk factors, while the use of precut and duration of cannulation were the only univariate risk factors as shown in **table 5**.

Difficult cannulation, CLD, use of anticoagulants or antiplatelets, thrombocytopenia, PT (seconds) and sphincterotomy were multivariate risk factors for intra -ERCP hemorrhage among studied patients as detected in **table 6**.

Regarding post ERCP complication, 13 cases with PEP (10.8%) (7 cases in group A and 6 cases in group B). Nine cases with post-ERCP bleeding (7.5%) (5 cases in group A and 4 cases in group B) as shown in **table 7**

Table (1): Descriptive data of demographic parameters and baseline characteristics in the different studied groups.

	Gr A (n=40)	Gr B (n=40)	Gr C (n=40)	Test	P value
Age (in years)	50.1±13.87	49.9±8.18	51.3±8.6	F=1.80	>0.05 N.S
Sex [n (%)] Male: Female:	 9 (25.5%) 31(77.5%)	 25(62.5%) 15(37.5%)	 18(45%) 22(55%)	X2=2.96	>0.05 N.S
Smoking [n (%)]	2 (5%)	5(12.5%)	3 (6.5%)	X2=5.78	>0.05 N.S
History of cholecystectomy [n (%)]	4 (10%)	8(20%)	4 (10%)	X2=5.78	>0.05 N.S
Hx of Antiplatelet and/or anticoagulation [n (%)]	6 (15%)	4(9%)	2 (5%)	X2=5.78	>0.05 N.S
DM / Yes DM /No	9(22.5) 31(77.5)	12(30) 28(70)	8(20) 32(80)	t=1.80	>0.05 N.S
HTN / Yes HTN / No	16(40) 24(60)	7(17.5) 33(82.5)	9(22.5) 31(77.5)	X2=2.96	>0.05 N.S
Chronic liver disease Child's class A Child's class B	 34(85) 6(15)	 12(30) 8(20)	 8(20) 3(1.2)	t=1.80	>0.05 N.S
Others diseases	7(17.5)	9(22.5%)	5 (12.5%)	X2=1.78	>0.05 N.S
Serum total bilirubin (mg/dl)	18.74 ± 5.3	17.75 ±7.19	19.85±2.58	t=1.30	>0.05 N.S
Serum direct bilirubin (mg/dl)	8.36 ± 4.7	12.8±7	13.05±6.07	t=1.40	>0.05 N.S
Prothrombin time (seconds)	18.12 ±2.86	16.34±0.32	17.86±0.193	X2=2.2	>0.05 N.S
INR (seconds)	1.3±.2	1.2±.3	1.1±.3	X2=1.4	>0.05 N.S
Serum alkaline phosphatase (IU/L)	633.87 ±185.3	765.57±110.12	654.89±123.1	t=1.10	>0.05 N.S
ALT (10- 40 U/L)	142.5±6.2	139±83	143.8±7.4	X2=1.9	>0.05 N.S
AST (10 – 40 U/L)	136.4±6.4	135±83	137.5±7.4	X2=1.1	>0.05 N.S
Alb (3.5-4.9 g/dl)	3.7 ± 0.1	3.9±0.3	4.1 ± 0.2	X2=1.5	>0.05 NS
Amylase (40 to 140 U/L)	135±90	132±85	125±60	X2=1.8	>0.05 N.S
Lipase (0 to 160 U/L)	155±120	150±110	110±45	X2=1.25	>0.05 NS
RBCs (1012\L)	5.2 ± 0.57	5.44 ± 0.58	5.19 ± 1.6	X2=1.24	>0.05 N.S
HB (12.5-17 g/dl)	9.6 ± 0.8	9.2 ± 0.9	9.8±0.65	X2=2.11	>0.05 N.S
WBC (4-11 103 /µL)	9.511±1.85	9.813 ±1.59	9.921 ± 1.2	X2=1.13	>0.05 N.S
PLT (x109L)	160.5±46.71	167.5±56.71	180.5±36.41	X2=2.19	>0.05 N.S
S.Cr (0.7 to 1.3 mg/dL)	1.04±.7	1.0±.3	1.01±.2	X2=3.2	>0.05 N.S
Urea (5 to 20 mg/dl)	9.5±0.27	11.2±0.37	15.15±0.49	X2=2.4	>0.05 N.S

t: ANOVA test X2: chi-square

Table 2: Morphological variation of the major duodenal papilla according to shape and size of the papilla among our patients in group A.

Clinical Signs [No. (%)]	**Group A n=40**
Type1	0 (0%)
Type2	10(25%)
Type3	11(27.5%)
Type 4	19(47.5%)

Table 3: Risk factors associated with failed cannulation among 16 patients in whom we initially failed

Factor		**Patients With failed cannulation n = 16**
Morphological variation	Variation of the papilla	12(75 %)
	Variation of the duodenum	1(6.25 %)
	Variation of both	1(6.25 %)
Pathologic condition	CBD stone	1(6.25 %)
	CBD stricture	1(6.25 %)

Table 4: Univariate and multivariate analysis of risk factors for factors predicting difficult biliary cannulation

	Univariate			**Multivariate**		
	Odds ratio	**95% CI**	***p*-value**	**Odds ratio**	**95% CI**	***p*-value**
Pancreatic mass	1.5	0.9-1.5	0.91	2.5	1.9-3.5	<0.001
History of cholecystectomy	1.2	0.2-0.7	0.71	1.6	1.2-2.1	<0.001
Intra-diverticular papilla	1.5	0.1-0.5	0.97	1.3	1.1-1.5	<0.001
Normal serum bilirubin	1.7	0. 1-0.2	0.68	1.3	1.01-1.7	0.03
Absence of acute cholangitis	1.4	1.1-1.5	0.69	1.3	1.00-1.7	0.049
Appearance of the major duodenal papilla	0.91	0.92-1.1	0.67	0.78	0.85-1.21	0.77
Biliary stenosis on imaging	0.52	0.87-1.5	0.81	2.95	2.3-3.5	<0.04
Small papilla	1.22	0.54-0.7	0.61	1.96	1.82-2.9	<0.03
Papilla looking downwards	1.95	0.3-0.5	0.67	1.73	1.71-1.9	<0.05
Stenosis of undetermined origin	1.74	0.1-1.2	0.89	1.33	2.00-3.7	<0.001

Table 5: Univariate and multivariate analysis of risk factors for post-ERCP pancreatitis among studied patients.

Factor		Univariate analysis			Multivariate analysis		
		OR	95% CI	P	OR	95% CI	P
Morphological variation (%)		1. 19	(1. 9-1. 30)	0.76	1.003	(0.989-1.018)	.643
Age (mean in years)		1.66	(1.23-3.18)	.087	1.901	(1.20-3.115)	.002
Sex: male % - female%		1.055	(1.03-1.08)	0.67	1.038	(1.23-1.95)	.036
Comorbidities (%)		1.001	(0.99-1.23)	.209	1.001	(0.89-1.013)	.109
S.bilirubin (mg/dl) (mean)		1.04	(1.31-1.90)	.049	1	(0.69-1.93)	.79
S.amylase (mg/dl) (mean)		1.43	(1.81-1.5)	.77	1.97	(0.93-1.32)	.882
S.alkaline phosphatase (IU/dl) (mean)		2.7	(1.9-4.457)	0.81	2.926	(0.9034.437)	0.91
Cannulation	No of trials (mean)	1.003	(1.71-1.55)	.01	1.037	(1.63-2.672)	<.001*
	Duration(min.) (mean)	2.706	(1.91-4.47)	<.00 1	2.926	(9.90-11.43)	<.001*
	Use of precut (%)	1.03	(1.01-1.05)	.01	1.037	(3.64-4.672)	<.001*
Sphincterotomy (%)		2.706	(1.93-4.47)	0.98	2.926	(1.94.437)	0.001
Other maneuvers (%)		1.003	(1.01-1.05)	0.76	1.037	(0.63-1.672)	0.92

NS = non-significant; p > 0.05 P<0.05: significant P<0.01: highly-significant

Table 6: Univariate and Multivariate analysis of risk factors for intra -ERCP hemorrhage among studied patients.

Factor		**Univariate analysis**			**Multivariate analysis**		
Morphological variation (%)		**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Age (mean in years)		1.86	(1. 9-3.2)	0.17	0.63	(0.17–1.03)	0.21
Sex: male %- female%		0.64	(0.12–1.2)	0.28	1.16	(0.70–12.1)	0.10
CLD; child's B (%)		2.12	(1.3–3.47)	042	2.39	(1.51–3.97)	0.001*
PT (seconds) (mean)		2.38	(1.63–3.5)	1.18	1.70	(1.19–2.30)	0.021*
Platelets(mean)(thousands/cmm)		1.28	(0.47–0.8)	0.41	0.29	(0.30–1.27)	0.001
Use of anticoagulation or antiplatelets		2.65	(1.9–3.9)	0.84	2.33	(1.51–3.97)	0.001
Cannulation	No of trials (mean)	0.38	(0.60-3. 7)	1.48	1.50	(1.09–1.70)	0.68
	Duration(min.) (mean)	0.62	(1.11–3. 7)	0.92	1.79	(1.11–1.37)	0.91
	Use of precut (%)	0.84	(1.1–1.83)	2.62	2.09	(0.35–3.60)	0.73
Sphincterotomy (%)		0.71	(1. 9–2.1)	0.84	2.50	(1.11–2.33)	0.001
Other maneuvers (%)		0.18	(0.21–0.3)	0.68	2.28	(1. 7–1.93)	0.97

PT = prothrombin time.

Table 7: Outcome of patients in studied groups

Variants		
Cannulation	**No of trials (mean)**	3.81 ± 2.6
	Duration (min.) mean	13.85 ± 3.6
	Initial success (N&%)	96(80)
	Use of precut (N&%)	72(60)
	Success rate (N&%)	104(86.6)
post-ERCP complications	**Pancreatitis (N&%)**	13(10.8)
	Hemorrhage (N&%)	9 (7.5)
	Total (N&%)	22 (18.33)
Failed CBD cannulation		16 (13.3)
Referral to PTD (%)		13 (10.8)
Referral to surgery (%)		٣(٢,٥)
post-ERCP mortality (%)		0 (0)
Mean hospital stay		5.86 ± 1.6

DISCUSSION

ERCP has emerged as the favored diagnostic and therapeutic modality for a variety of pancreaticobiliary disorders. Nevertheless, it may not succeed in certain instances, even when performed by skilled practitioners or in high-volume medical facilities. ERCP is employed to manage biliary stones, malignant obstructions, acute cholangitis, both malignant and benign biliary strictures, as well as post-operative biliary injuries [12].

Our study aimed to assess the difficult biliary cannulation due to major duodenal papillary lesions and evaluate the success and potential complications during and after ERCP.

A case control study that recruited 120 patients (52 males (43.33%), and 68 females (56.67%)) for either diagnostic or therapeutic ERCP that had done on naïve major duodenal papilla. The patients were divided equally into three groups (according to morphology of major duodenal papilla and selective biliary cannulation).

Regarding the demographic data of included patients, showed non-significant statistical difference concerning age & sex distribution, where their ages ranged from 20 to 65 years, & mean age in groups A, B, & C was (50.1±13.87, 49.9±8.18, 51.3±8.6 years respectively). This agreed with Tabak et al. [13], who reported that, in a study examining the correlation between age and challenging cannulation, no notable differences were observed between patients aged over 80 years and those under 80 years regarding the incidence of difficult cannulation. Also, non-significant difference among the studied groups regarding smoking (p>0.05).

Our results showed insignificant differences were noticed regarding associated co-morbidities and medical history such as, history of cholecystectomy, history of antiplatelet and/or anticoagulants, and laboratorial results of CBC, LFTs, KFTs and pancreatic enzymes (p>0.05).

Concerning indications for ERCP among the studied groups, showed insignificant statistical differences where choledocholithiasis in 66 patients, (55%), acute pancreatitis in 4 patients, (3.3%), malignant biliary stricture in 21 patients, (17.5%), benign biliary stricture in 19 patients, (15.83%), dilated CBD or intra and extra hepatic biliary radicals in 6 patients, (5%) and others in 5 patients, (4%) (p>0.05).

We have found four main types for the papilla based on Haraldsson et al. [9], endoscopic classification of papilla, the predominant variety of papilla observed was type 1 (regular, normal) in 80 patients (66.67%), followed by type 4 papilla (wrinkled or striated) in 19 patients (15.83%), then type 3 papilla (protruding or pendulous) in 11 patients (9.17%) and type 2 papilla (small or flat) was the least frequent in 10 patients (8.33%).

Type 1 papilla was the most frequent in 66.67% of patients, this was similar but rather higher than that reported by Chen et al. [14], in which type 1 papilla was found in 56% of participants. However, it differs in the arrangement of Quiroga-Purizaca et al. [12], who reported that, the predominant type of papilla was type 1, which was present in 81 patients (58.7%) of the total,

followed by type 3 papilla, found in 40 patients (28.9%). Type 2 papilla was identified in 11 patients (8.05%), while type 4 papilla was the least common, occurring in 6 patients, or 4.35%.

In our study, we have found that the commonest morphological variety of the major duodenal papilla in group A, these have had ridged or "creased" papilla (Type 4) in 19 patients (47.5%), followed by protruded, pendulous papilla (Type 3) in 11 patients (27.5%), followed by small or flat (Type2) in 10 patients (25%). In addition, the commonest location of the main duodenal papilla located in the second segment of the duodenum exactly, in posteromedial wall (95%) and the first part (5 %). In agreement with the result of Vickers et al. [15], who reported that approximately 75 % of their cases, the papilla is in the midportion of the second duodenal part, in these cases, the opening of the pancreatic duct is generally located anteriorly and inferiorly in relation to the terminal bile duct at the level of the ampulla.

The commonest duodenal anomalies are duodenal diverticula; with extraluminal diverticula are more frequent than intraluminal diverticula [16]. Periampullary diverticula (PAD) were divided into intra-diverticular papilla (IDP) and juxta-papillary diverticula (JPD) are categorized based on the Lobo classification system [17]. The identification of intra- and peri-diverticular papillae poses significant challenges, as they may be associated with conditions such as common bile duct obstruction, pancreatitis, perforation, hemorrhage, and, in rare instances, carcinoma. The presence of these papillae suggests that the process of cannulation will require additional time, the application of advanced techniques, and the involvement of a more skilled endoscopist [18].

our results showed that, PAD are risk factors predicting difficult biliary cannulation ($p<0.001$) and OR (1.3) and this agreed with Parlak et al. [19] and Cappell et al. [20] indicated that performing cannulation in cases of PAD may prove to be challenging, time-intensive, and frequently necessitates advanced endoscopic expertise. Moreover, Parlak et al. [19], reported that, PAD have been encountered in 5.9 - 18.5% of patients during all ERCP. In parallel with our results, that showed, the presence of JPD was in 11 patients of the entire patients' groups (9.16%), 2 cases with single type diverticula and 5 cases with double type in group A. Whereas, 2 cases with single type diverticula and 2 cases with double type in group B. All 11 cases have had choledocholithiasis. Also, we have found duodenal stenosis in 2 patients (1.66%), both of them were due to obstructing mass.

Our study was in bias with, a meta-analysis conducted by Mu, P et al. [21] revealed that the existence of PAD could elevate the likelihood of cannulation failure and may also correlate with an increased risk of adverse events following ERCP.

In the current study, common bile duct stones (CBDs) were the most frequent indication for ERCP (55%). This is consistent with studies by Chen et al. [14]) & Parras Castañera et al. [22], in that the indication for ERCP varied between 44% and 88.5% & choledocholithiasis was confirmed in an imaging test in 43.2 % of the cases. Our study showed that female cases were represented by (56.67%) & this could be possibly explained by Gutierrez-De Aranguren et al. [23], who reported that gallstone disease and CBDs are more often linked to the female gender (65%).

Our results showed that the sensitivity of TAUS in detection of CBDS was 71% and diagnostic accuracy 82.8%, this was similar to Qamar et al. [24], (sensitivity 82.69% & accuracy 88.89%) & Rickes et al. [25] (sensitivity 82% & accuracy 83%). Our results showed that TAUS correctly detect CBDS in 12 out of 18 cases having CBDS by ERCP. Our Positive predictive value (PPV) was 91.7%, similar to Tandon et al. [26] (PPV 90%) and lower than Rahim Khan et al. [27] (PPV 100%).

Finally, our current study detected that, ERCP is more sensitive procedure compared to TAUS as shown in table (6) $P<0.01$. This finding was supported by Upadhyaya et al. [28] & Karki et al. [29].

Godfrey et al. [30] indicated that certain instances of CBD may occur without the presence of CBDs as determined by ERCP. This dilatation can arise from various other factors, including CBD stricture, cholangiocarcinoma, periampullary diverticulum, pancreatic head mass, dysfunction of the sphincter of Oddi, and papillary stenosis.

The primary technical objective of ERCP is selective biliary cannulation (SBC), which is essential for performing sphincterotomy and other targeted therapeutic biliary interventions aimed at treating or alleviating disease while minimizing morbidity. Recent guidelines indicate that biliary cannulation success rates exceed 95%, with complication rates remaining below 5% [31]. The European Society of Gastrointestinal Endoscopy (ESGE) defines difficult biliary cannulation as a scenario where the procedure exceeds five minutes,

requires more than five attempts for success, or involves the guidewire inadvertently entering the pancreatic duct on two or more occasions. Consequently, alternative cannulation techniques are frequently necessary in challenging cases. Difficult cannulation is associated with an increased risk of adverse events, with the likelihood of unsuccessful biliary cannulation estimated to range from 5% to 18% of cases [32].

Our results showed that, the frequency of DBC was 66.6%, which came higher than Haraldsson et al. [33] (42%), Ismail et al. [34] (37.9%) and Gutierrez-De Aranguren et al. [35] (29.8%). The potential factors predicting difficult biliary cannulation in our multivariate analysis; Pancreatic mass (OR, 2.5; 95% CI, 1.9-3.5; p < 0.001), history of cholecystectomy (OR, 1.6; 95% CI, 1.2–2.1; p < 0.001), intra-diverticular papilla (OR, 1.3; 95% CI, 1.1–1.5; p < 0.001), normal serum bilirubin (OR, 1.3; 95% CI, 1.01–1.7; p 0.03), absence of acute cholangitis (OR, 1.6; 95% CI, 1.00-1.7; p 0.049), appearance of the major duodenal papilla (OR, 0.78; 95% CI, 0.85-1.21; p < 0.77), biliary stenosis on imaging (OR, 2.95; 95% CI, 2.3-3.5; p < <0.04), small papilla (OR, 1.96; 95% CI, 1.82-2.9; p < <0.03), papilla looking downwards (OR, 1.73; 95% CI, 1.71-1.9; p < <0.05), stenosis of undetermined origin (OR, 1.33; 95% CI, 2.00-3.7; p < <0.001).

The findings align with those of Cáceres-Escobar et al. [18], who demonstrated through multivariate analysis a direct and independent correlation between DBC and the acute care hospital environment (OR 2.92; 95% CI 1.70–5.01; P<0.001), as well as the presence of redundant papilla (OR 7.26; 95% CI 3.38–15.61; P<0.001) or peri-diverticular papilla (OR 2.45; 95% CI 1.38–4.36; P=0.002).

Conversely, Saito H et al. [36] indicated that univariate analysis identified six factors that significantly predicted difficult cannulation: ERCP conducted by non-expert endoscopists, low-volume centers, absence of acute cholangitis, normal serum bilirubin levels, intra-diverticular papilla, and the type of major duodenal papilla.

Our research was corroborated by Berry R et al. [37], who indicated that DBC complicates the ERCP procedure due to its extended duration and repetitive maneuvers. This complexity consequently elevates the risk of post-ERCP pancreatitis (PEP). Several factors contribute to the failure of biliary cannulation, including the positioning of the duodenum, the clarity of papilla visualization, the size of the papilla, variations in patient anatomy, and surgical factors, all of which can influence the success rate of cannulation. Furthermore, Cennamo V et al. [38] identified DBC as a prevalent risk factor for adverse events during ERCP, noting its close association with anatomical variations of the duodenal papilla.

In contrast, Quiroga-Purizaca et al. [12] found no significant correlation between the type of papilla and the difficulty of cannulation. They also reported no link between papilla type and the occurrence of PEP. Additionally, a multicenter study conducted by Canena et al. [51], which employed an alternative classification system, concluded that there was no significant difference in the rates of adverse events among the various types of papillae.

One of the critical elements influencing the success of sphincter of Oddi balloon dilation (SBC) is the operator's level of experience. Research indicates that the success rate of SBC improves significantly after an endoscopist has performed between 350 and 400 ERCP procedures [32]. According to Cáceres-Escobar et al. [18], an experience of over 200 procedures is deemed sufficient for an endoscopist to navigate the learning curve associated with ERCP. In our Endoscopy unit, the procedures were carried out by seasoned operators, each performing more than 120 ERCPs annually over a span of 10 years.

Saito H et al. [36] have noted that the presence of distal bile duct obstruction in patients with normal serum bilirubin levels, whether or not they exhibit acute cholangitis, may be linked to a tighter sphincter of Oddi. This condition potentially leads to a reduction in lower bile duct pressure compared to patients who have elevated serum bilirubin levels or those with acute cholangitis.

It has been proposed that elevated bilirubin levels correlate with an increased risk of DBC. DBC may arise from proximal lesions, malignant causes, or even in cases where bilirubin levels are within the normal range. However, the underlying mechanisms contributing to DBC are not fully elucidated, consequently, this study did not establish a link between high bilirubin levels and DBC [33].

Research conducted by Chen et al. [14], Berry R et al. [37], and Freeman and Guda [39] indicated that biliary obstruction related to malignancy is a significant risk factor for failure in cannulation. This complication may arise from tumor infiltration, which can distort and complicate the endoscopic approach to the ducts. Additionally, in patients with malignancies, the occurrence of papilla edema,

trauma, and bleeding during ERCP is more prevalent due to the fragility of the biliary tracts and associated vasculature, thereby complicating the cannulation process.

Our findings indicated that there were no statistically significant differences in the occurrence of PEP and other complications related to ERCP between patients with a history of cholecystectomy and those without, as noted by Kochar et al. [40]. In contrast, Seleem et al. [41], found that biliary cannulation was more challenging and that the overall duration of the procedure was significantly extended in patients with a history of complicated cholecystectomy.

In our study, we identified 13 cases (10.8%) of PEP, (7 cases in group A and 6 cases in group B). This aligns with the findings of Kochar et al. [40], who reported that the failure rate of ERCP remains between 5% and 20%, even among experienced practitioners. Furthermore, PEP has an incidence rate of 9.7% and a mortality rate of 0.7%. Additionally, research by Serrano et al. [42] and Matsubayashi et al. [43] indicated that pancreatitis is the most prevalent complication following ERCP, with an estimated overall incidence ranging from 4.8% to 11.9%. A recent meta-analysis conducted by Akshintala et al. [44] reported an incidence of PEP at 10.2%, while Dumonceau et al. [8] noted that the incidence of PEP varies between 3% and 10%.

In contrast, Kwak N, et al. [45] indicated that the incidence of pancreatitis was 1.7% when utilizing the widely recognized consensus definition for the condition. Additionally, the likelihood of PEP rises further in patients who experience challenging cannulation and are already at high risk for this complication. This is due to the fact that these risk factors have been demonstrated to be independent in multivariate analyses, suggesting a potential cumulative effect, as noted in the study conducted by Maharshi et al. [46].

Our results showed that, on multivariate analysis, the risk factors or the potential factors predicting PEP; duration of cannulation OR 2.9 95% CI (9.90-11.43) (p-value <.001), number of trials of cannulation OR 1.03 95% CI (1.63-2.67) (p-value <.001), morphological variation of papilla and duodenum OR 1.003 95% CI (0.989-1.018) (p-value .643), use of precut OR 1.037 95% CI (3.64-4.67) (p-value <.001) and sphincterotomy OR 2.926 95% CI (1.94-04.37) (p-value 0.001).

Our results were in agreement with Köseoğlu.H et al. [47], who found that, in multivariate analysis there were significant risk factors for PEP were as follows : female gender (OR:1.85, 95% CI:1.13-3.03, P=0.014), placing a biliary plastic stent during the procedure (OR:2.20, 95% CI:1.33-3.64, P=0.002), not having a prior endoscopic sphincterotomy (EST) history (OR:1.86, 95% CI:1.06-3.26, P=0.031) and having a CBD diameter less than 12 mm (OR:1.67, 95% CI:1.02-2.75, P=0.044).

Also, a study done by Pekgöz M, [48] stated that the risk factors associated with PEP can be categorized into those related to the patient and those related to the procedure. Patient-related risk factors encompass conditions such as female gender, younger age, a history of pancreatitis, dilation of the non-extrahepatic bile duct, non-chronic pancreatitis, dysfunction of the sphincter of Oddi and normal serum bilirubin levels. On the other hand, procedure-related risk factors include techniques such as precut sphincterotomy, injection into the pancreatic duct, five or more cannulations, pancreatic sphincterotomy, papillary balloon dilation, and endoscopic papillectomy.

Ding X et al. [49] & Wang P et al. [50], found that the increased risk of PEP in female patient was attributed to the higher frequency of biliary stones and SOD. However, Nakahar K et al. [51] and Zhou w et al. [52], have shown no increased risk of PEP in female gender. Performing EST during ERCP has increased risk for PEP development as in studies by Köseoğlu.H et al. [47] & Ding X et al. [49], meanwhile, formerly performed EST history showed no effect on PEP in studies by Sigounas d. et al. [53] & Freeman et al., [54].

The precise mechanism underlying PEP remains unclear; however, it may be attributed to thermal damage resulting from electro-cautery or elevated intra-ductal pressure within the pancreas, potentially caused by conditions such as papillary edema, dysfunction of the sphincter of Oddi, or chemical injury from contrast agents. Additionally, proteolytic damage due to instrumentation may contribute to the activation of the inflammatory response [31].

Post-ERCP bleeding is characterized by the presence of hematemesis and/or melena, or a reduction in hemoglobin levels exceeding 2 g/dl [33]. The European Society of Gastrointestinal Endoscopy (ESGE) classifies post-ERCP bleeding based on its severity into three categories: mild, moderate, or severe. Considering the necessity for blood transfusion or the requirement for

hospitalization or admission to an Intensive Care Unit [8].

Our study showed that, 9 cases (7.5%) with post-ERCP bleeding (5 cases in group A and 4 cases in group B). Our results showed ,in multivariate analysis, the potential factors predicting Post-ERCP bleeding; duration of cannulation OR 1.79 95% CI (1.11–1.37) (P=0.91), number of trials of cannulation OR 1.50 95% CI (1.09–1.70) (P=0.68), chronic liver disease (CLD) OR 2.39 95% CI (1.51–3.97) (P=0.001), use of anticoagulation or antiplatelets OR 2.33 95% CI (1.51–3.97) (P=0.001), thrombocytopenia OR 0.29 (0.30–1.27) (P=0.001), PT (seconds) OR 1.70 95% CI (1.19–2.30) (P=0.021) and Sphincterotomy OR 2.50 95% CI (1.11–2.33) (P=0.001).

In parallel with Parras Castañera et al. [22], who reported that, the percentage of post-ERCP bleeding was 4.6 % and Dumonceau et al. [8], who detected that, anticoagulation (OR 4.39), platelets less than 50000 (OR 35.30), cirrhosis (OR 2.05-2.85), intraprocedural bleeding (OR 4.28), low endoscopic experience (OR 1.44) and unsuccessful cannulation and use of pre-cut (OR 3.09) were independent risk factors associated with bleeding following ERCP. Also, Nakaji S et al. [55], found that Platelets <50.000/mm3 OR 35.30 (3.81-328.00) p value 0.002, Anticoagulants OR 4.39 (1.53-12.60] p value 0.006, Intraprocedural bleeding OR 4.28 (2.30-7.97) p value <0.001.

Bae et al. [56], evaluate the risk factors associated with hemorrhage following sphincterotomy in patients classified as medium risk. The observed bleeding rate was 9.6%. The independent risk factors identified for intra-procedure ERCP hemorrhage and post-ERCP bleeding included gender, age, cirrhosis, hemodialysis, the use of antiplatelet agents, thrombocytopenia, prolonged PT/aPTT, bilirubin levels, PAD, biliary stones, malignant strictures, and benign strictures. Also, Lee et al. [57], reported that, post-ERCP bleeding rate 11.8% with the abovementioned risk factors. However, in Austria, a retrospective study performed by Kienbauer et al. [58], reported that, 3.8 % of cases with bleeding as a complication in the total ERCP.

In addition, Kim JY et al. [59], assessed the safety of ERCP in patients with hepatic cirrhosis reported a global bleeding rate of 6.3 % in the total ERCP, with an incidence of 4.7 % for ERCP performed on non-cirrhotic patients (without risk factors) and 10.9 % for cirrhotic patients.

Our results came in line with Parras Castañera et al., [22], who revealed that a difficult and traumatic cannulation, a higher risk of bleeding may be expected. A similar finding was observed with the extraction of choledocholithiasis because the removal of the stones often causes damage in the sphincterotomy area, which promotes bleeding. Also, the history of cardiopathy p value 0.009, antiplatelets and/or anticoagulation with novel oral anticoagulants (NOACS) p value 0.02, pancreatic stent placement p value 0.026, biliary sphincterotomy p value < 0.001 and choledocholithiasis extraction p value 0.044. Also, a study by Alberca-de-las-Parras F et al. [60], showed that, anticoagulation is considered a risk factor for bleeding after ERCP with sphincterotomy. This agreed with our results supporting that, use of anticoagulation or antiplatelets OR 2.33 95% CI (1.51–3.97) p-value 0.001, risk factors for intra - procedure ERCP hemorrhage and post-ERCP bleeding among studied patients.

Successful papillary cannulation was achieved in 104 (86.67%) patients in the first session of ERCP and this came in agreement with Tabak et al. [13] reported that successful selective bile duct cannulation during ERCP can be accomplished after several attempts using standard guidewire-assisted techniques in approximately 80% of cases. In contrast, our findings were lower than those reported by Cankurtaran et al. [61], who noted a successful biliary cannulation rate of 93.6% during the initial ERCP session. The intervention was deemed effective if serum bilirubin levels decreased to below 3 g/dl within 30 days. Our patients underwent clinical follow-up and laboratory evaluations on days 1, 3, 7, and 30 post-procedure.

While, failed cannulation was in 16 (13.33%) patients. The most frequently causes of failure of biliary cannulation is abnormal variation of the major papilla 12 (75 %), variation of the duodenum 1 (6.25 %), variation of both 1 (6.25 %), CBD stone 1 (6.25 %) and CBD stricture 1 (6.25 %) as shown in table 3. This was consistent with Chen et al. [2], who reported that selective biliary access failure from 5%—15% of cases, even in expert high-volume centers. Our results were higher than obtained by E. León Estela et al., [22] & Chen et al. [14], who reported that failed ERCP was 5.7% & 5.9% respectively and in parallel with Hassany et al., [35], who found that, the abnormal variation in papilla (53.6%) and infiltrated papilla (28.6%) followed by altered anatomy with previous surgery in 4 (14.3%) patients and large JPD in one patient.

Our sixteen patients with failed biliary cannulation in the first ERCP session underwent alternative methods either percutaneous transhepatic biliary drainage (PTBD) then percutaneous-endoscopic rendezvous (PE-RV) (13 cases, 10 from group A and 3 from group B) or surgery (3 cases referred to surgery 2 from group A and 1 from group B). As Chen et al. [2], recommended that patients with failed biliary cannulation in the first session should undergo ERCP again a few days later in the second session. If cannulation is still not achieved, feasible alternative strategies such as surgery, PTBD, endoscopic ultrasound guided biliary drainage (EUSBD), PE-RV, and laparo-endoscopic rendezvous (LERV) should be applied.

PTBD is recognized as the standard alternative approach for patients who experience unsuccessful ERCP. Nevertheless, this method is linked to significant morbidity and may adversely affect the quality of life for patients. Its implementation can also be challenging in cases where the intrahepatic bile ducts are not sufficiently dilated. ERCP may fail for various reasons, including surgically altered anatomy, gastric outlet obstruction, periampullary diverticulum, the presence of an indwelling duodenal stent, and large tumors. Furthermore, unsuccessful ERCP procedures may elevate the risk of in-hospital mortality. Morbidity and mortality related to the procedure were defined as complications or fatalities directly associated with the ERCP within a one-month period [62].

Conclusion

Good evaluation and preparation of selected patients will minimize the potential risk factors predicting the post ERCP complications and improve the outcome. As we know, ERCP is not a routine tool and performed once indicated, because it is an invasive procedure & has many dangerous complications. Upon facing a morphological variant of the duodenum and/or major papilla and/or pathological lesions of major papilla, ERCP should be done by an experienced endoscopist to achieve a high success rate and to avoid post ERCP complications. Initially, difficult biliary cannulation has a significant impact on ERCP success and outcome. Finally, we hope our study will encourage the companies concerning with developing endoscopes and accessories to modify ERCP instruments that enable endoscopists to overcome the matter of difficult biliary cannulation. Consequently, ERCP related complications & hospital stay will be minimized.

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Authors' contributions: All authors shared in analyzing and interpreting the patient data and in writing the manuscript. All authors read and approved the final manuscript.

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