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Difficult biliary cannulation in patients with distal malignant biliary obstruction: An underestimated problem?

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ABSTRACT

Background: Failed biliary cannulation still poses a major challenge in patients undergoing Endoscopic Retrograde Cholangiopancreatography (ERCP). To date, there is a lack of data on rates of Difficult Biliary Cannulation (DBC) in patients with distal malignant biliary obstruction (DMBO).

Materials: This was a retrospective study (09/2015 to 02/2019) of consecutive patients with DMBO that underwent ERCP in four Italian centers. The primary outcome was to evaluate the rate of DBC. Secondary outcomes were: cannulation failure, rate of adverse events (AEs), the predictive factors for DBC as well as for AEs.

Results: A total of 622 patients with DMBO, were included in the study, with 351(56,4%) matching the definition of DBC.

One-hundred and two ERCP-related AEs occurred in 97 of 622 patients (15,6%). Subjects with DBC showed a higher risk for AEs ($p = 0.02$). The lack of pancreatitis prophylaxis ($p = 0.03$), diagnosis of cholangiocarcinoma ($p = 0.02$), the use of papillotomy (OR=1.98; 95%CI = 1.14–3.45) and the combination of two or more techniques for cannulation (OR = 2.88; 95%CI = 1.04–7.97) were associated with the occurrence of AEs.

Conclusions: According to the results of this study, patients with DMBO carries a higher rate of DBC thus requiring alternative techniques for biliary drainage. Furthermore, DBC carries a high risk for AEs. Further prospective multicentric studies are needed to confirm these data in this specific subgroup of patients.

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is the primary therapeutic procedure for many bilio-pancreatic diseases, and requires the first crucial step of the successful deep cannulation of the common bile duct (CBD) through the Vater's papilla [1,2]. Difficult biliary cannulation (DBC) is a well-recognized risk factor for adverse events (AEs) and cannulation failure, which has been reported in about 11% of ERCP regardless of their indication. Unfortunately, a relevant heterogeneity in definition of DBC has been observed in different studies [3]. More recently, DBC during ERCP has been precisely defined by the European Society of Gastrointestinal Endoscopy (ESGE) as follows: more than 5 contacts with the papilla whilst attempting to cannulate; more than 5 min spent attempting to cannulate after visualization of the papilla; more than one unintended pancreatic duct cannulation or opacification [4]. In such cases, alternative biliary cannu-

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lation techniques (e.g. pre-cut sphincterotomy, transpancreatic biliary sphincterotomy (TBS)) are often needed to achieve successful cannulation and to decrease the risks of AEs [4–7]. To date, the rate of DBC has not been calculated for specific sub-groups of ERCP indications. In particular, the rate of DBC in the setting of distal malignant biliary obstruction (DMBO), a frequent indication for ERCP, has not yet been reported. DMBO is generally secondary to pancreatic adenocarcinoma, distal cholangiocarcinoma, ampullary carcinomas or adenopathy/metastasis from other cancers, and could potentially increase the complexity of the procedure as the tumor compression or infiltration may alter the normal duodenal/papillary anatomy or determine duodenal rigidity [8–10]. Patients suffering from DMBO often require biliary drainage for jaundice management, and an unsuccessful endoscopic drainage may impair patients' outcome [8–10]. In this study, we aimed to investigate the rate and the outcome of DBC in patients undergoing ERCP for DMBO.

2. Methods

2.1. Study design

We conducted a retrospective analysis of data from a multicenter network that measured the outcome of ERCP, in order to investigate the incidence and outcomes of DBC in patients undergoing ERCP for DMBO due to pancreatico-biliary malignancies. We included patients who underwent ERCP in four Italian tertiary level centers from September 2015 to February 2019. All ERCP were performed by experienced operators (> 1000 ERCP as first operator in the previous 5 years). Informed consent to the procedure was obtained in all patients.

The enrolled cases were divided in two different groups: DBC group (defined as patients with DBMO who underwent ERCP and met the ESGE criteria for DBC) and non-DBC group (defined as patients with DBMO who underwent a successful biliary cannulation and did not meet ESGE criteria for DBC). Institutional review board approval was obtained for this study.

The study was performed in accordance with the Declaration of Helsinki (NCT04709666).

2.2. Endpoints

The primary endpoint of this study was to evaluate the incidence of DBC according to ESGE guidelines definition [4]. Secondary endpoints were to evaluate the overall rate of cannulation failure, the rate of AEs in DBC group compared with non-DBC group, predictive factors for DBC, predictive factors for cannulation failure, AEs and to analyze alternative cannulation techniques used. Technical success was defined as successful biliary cannulation and subsequent stent placement. AEs were defined as the occurrence of unintentional perforation, bleeding requiring hemostasis or transfusion, stent malposition or migration, cholecystitis, cholangitis, jaundice, pancreatitis, peritonitis, pneumoperitoneum, and procedure-related death. The severity of the AEs was defined according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon for endoscopic AEs [11]. Pancreatitis was defined according to Cotton's criteria, as abdominal pain is suggestive of pancreatitis and a serum amylase or lipase at least three times the upper limit of normal, 24 hours after the procedure [11].

2.3. Patients

We include all consecutive patients who performed ERCP for jaundice due to DMBO during the study period. Exclusion criteria were previous sphincterotomy, INR > 1.5, platelet count < 50.000 $10^3/mm^3$ and patients with middle-proximal malignant biliary obstruction. Data collection included patient demographics, characteristics of the CBD, papilla and duodenum, etiology of DMBO, procedure details such as alternative techniques used to achieve cannulation and AEs.

Dilation of CBD was defined as diameter > 8 mm in patient with gallbladder in situ and > 10 mm in patient with previous cholecystectomy. Vater's papilla morphology and duodenal abnormalities were recorded to analyze possible associations with relevant outcomes. A papilla with no peculiar features was defined "normal"; a papilla bulging into the duodenal lumen with the orifice oriented caudally was defined as "protruding"; a distorted papilla with irregular mucosa was defined "infiltrated". Furthermore, the presence of a periampullary diverticulum and the relation with the papilla were recorded. A duodenum with no peculiar features was defined "normal"; a duodenum with irregular mucosa, distorted lumen and/or rigidity was defined "infiltrated"; a duodenum with a narrowed lumen (but without complete obstruction and with the possibility to reach the major papilla) was defined "stenotic". Alternative biliary cannulation techniques included pre-cut biliary papillotomy (if the cut starts from the papillary orifice); pre-cut biliary fistulotomy (if the cut starts about 5 mm above the papillary orifice); double guide wire (DGW) technique, wire-guided cannulation over a pancreatic stent and TBS. In case of DBC, the choice of the alternative cannulation techniques was at discretion of the endoscopist. Rectal indomethacin (100 mg) and peri-procedural hydration with Ringer's lactate was administered in a high-risk patients for post-ERCP pancreatitis (PEP) prophylaxis, if not contraindicated. Data were collected and extracted into a dedicated database (Excel file, Microsoft Office).

2.4. Statistical analysis

We expressed continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR), according to the parameter distribution assessed by the Shapiro-Wilk test. We reported categorical variables as percentage. We created multivariable models for predicting difficult biliary cannulation and failure during difficult biliary cannulation, considering all plausible explanatory variables as potential predictive factors. First, we performed univariate analyses to assess the association between each explanatory variable and the selected outcome (i.e. difficult biliary cannulation or failure during difficult biliary cannulation). We fitted univariate logistic regression models to estimate unadjusted odds ratios (ORs) with 95% confidence intervals (95%CIs). We checked potential collinearity issues by fitting a linear regression model to the data, considering the presence of collinearity for type-II tolerance values <0.1. Then, we identified significant predictors using the backward multiple logistic regression analysis and expressed their association with the selected outcome using adjusted ORs with 95%CIs. We also estimated adjusted ORs with 95%CIs for the parameters not included in the final predictive models by adding one variable at a time to the multivariable logistic regression models. We calculated the sensitivity, specificity, and area under the curve of the predictive models, selecting the cut-off point based on the criterion that maximizes the Youden's J index.

We also investigated the association between difficult biliary cannulation and the occurrence of any procedure-related AEs. For this purpose, we estimated the effect of DBC and each covariate on the outcome (i.e. any procedural adverse events), creating univariate logistic regression models to calculate unadjusted ORs with 95%CIs. We included in the multivariable analysis the study factor and all covariates with a p value <0.25 at univariate analysis. We checked possible collinearity issues and used the backward method to evaluate the confounding effect of the selected covariates. In the multivariable model we retained the study factor and confound-

ing covariates, calculating adjusted ORs with 95%CIs for these variables. We also estimated and adjusted ORs with 95%CIs for the covariates not included in the final model by adding one variable at a time to the multivariable logistic regression model. We assessed the fit of the multivariable models using the Hosmer-Lemeshow goodness-of-fit test for calibration and the c statistic for discrimination. We carried out all statistical analyses using the Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 622 patients (301, 48.4% female), with mean age 74 (range 65–80 years) with DMBO were included in this retrospective analysis. The characteristics of the patients are summarized in Table 1. DBC occurred in 351 patients (56,4%). The univariate analysis indicated that there was a significant association of DBC with etiology of stenosis ($p = 0.04$), papilla morphology ($p = 0.002$) and duodenum morphology ($p = 0.002$). In particular, there was a higher risk of DBC in patients with infiltrated papilla compared to normal morphology (OR = 2.07; 95%CI = 1.26–3.40) and in subjects with duodenal infiltration (OR = 1.75; 95%CI = 1.15–2.65) or stenosis (OR = 2.82; 95%CI = 1.30–6.10) compared to regular morphology. Comparatively, there were lower odds of DBC in patients with ampullary carcinoma than pancreatic cancer (OR = 0.45; 95%CI = 0.22–0.93) (Table 2). The multivariate analysis confirmed the significant association of DBC with etiology of stenosis ($p = 0.01$) and papilla morphology ($p = 0.0003$) (Figure 1). In detail, there was a higher risk of DBC in patients with infiltrated (OR = 2.17; 95%CI = 1.31–3.59) or protruding (OR = 1.81; 95%CI = 1.17–2.80) papilla compared to normal morphology and a lower risk in ampullary carcinoma than pancreatic cancer (OR = 0.32; 95%CI = 0.15–0.70) (Table 2). The predictive model, including papilla morphology and etiology of stenosis showed sensitivity of 38% and specificity of 78% for predicting DBC. The area under the curve was 0.61, indicating acceptable discrimination (Fig. 1 suppl). In patients with DBC, technical success was achieved in 271(77,2%). Specifically, the techniques applied for biliary cannulation were associated with different rates of technical success summarized in Table 1 (Fig. 2).

Failure of biliary cannulation occurred in 80/351 (22.8%) patients in DBC group, corresponding to 12,9% (80/622) of the entire cohort of patients. In this group of patients different approaches have been used in order to achieve biliary drainage (Table 1).

At univariate analysis, no bile duct dilation (OR = 4.78; 95%CI = 1.72–13.28; $p = 0.003$), papilla morphology ($p < 0.0001$), duodenum morphology ($p < 0.0001$), and technique for biliary access ($p < 0.0001$) were significantly associated with cannulation failure in patients with DBC. There was a higher risk of cannulation failure in patients with infiltrated papilla compared to normal morphology (OR = 22.39; 95%CI = 10.85–46.20), in subjects with duodenal infiltration (OR = 4.24; 95%CI = 2.31–7.77) or stenosis (OR = 46.29; 95%CI = 14.96–143.19) compared to regular morphology (Table 3). Among endoscopic techniques for biliary access, multiple cannulation attempts were associated with a higher risk of failure compared to papillotomy (OR = 12.18; 95%CI = 4.48–33.09) (Table 3). The multivariate analysis confirmed the significant association of cannulation failure during DBC with no bile duct dilation (OR = 5.75; 95%CI = 1.65–20.03; $p = 0.007$), papilla morphology ($p < 0.0001$), and duodenum morphology ($p < 0.0001$). In detail, there was a higher risk of cannulation failure in patients with infiltrated papilla (OR = 14.18; 95%CI = 6.29–31.95), duodenal infiltration (OR = 2.62; 95%CI = 1.30–5.27) or duodenal stenosis (OR = 19.16; 95%CI = 5.48–66.96) compared to normal morphology (Table 3). Multiple cannulation attempts showed higher odds of cannulation failure compared to papillotomy at multivariate analysis (OR = 6.12; 95%CI = 1.66–22.60; $p = 0.0001$) (Table 3). The predictive model, which included the bile duct dilation, papilla morphology, and duodenum morphology had sensitivity of 65% and specificity of 90% for predicting failure during DBC. The area under the curve was 0.84, indicating excellent discrimination (Fig. 1 suppl.).

One-hundred and two ERCP-related AEs occurred in 97 of 622 patients (15,6%). These 97 cases included 102 AEs (5 patients with 2 AEs) consisting of 33 (5,3%) cases of cholangitis, 34 (5.5%) pancreatitis, 20 (3,2%) bleeding, 7 (1,1%) cholecystitis, 5(0,8%) stent migration, 3(0,5%) perforation (Table 1).

There was no difference in the risk of AEs occurrence between patients with and without DBC at univariate analysis (OR = 1.53; 95%CI 0.97–2.39; $p = 0.06$). However, after adjusting for etiology of stenosis and pancreatitis prophylaxis, subjects with DBC showed a higher risk of AEs (OR = 1.73; 95%CI = 1.08–2.77; $p = 0.02$) (Table 4). Among covariates, the lack of pancreatitis prophylaxis (OR = 1.94; 95%CI = 1.09–3.44; $p = 0.03$) and etiology of stenosis ($p = 0.02$) were significantly associated with a higher risk of AEs at multivariate analysis. In detail, patients with cholangiocarcinoma showed higher odds than those with pancreatic cancer (OR = 2.39; 95%CI = 1.29–4.41). Among alternative endoscopic techniques for biliary access, papillotomy (OR = 1.98; 95%CI = 1.14–3.45) and the combination of two or more techniques (OR = 2.88; 95%CI = 1.04–7.97) had a higher risk of complications compared to the index technique (sphincterotome plus guidewire). There was a higher rate of bleeding in patients with than in patients without DBC (4.8% vs. 1.1%; $p = 0.01$). The sub-analysis by bleeding grading, indicated that subjects with DBC had higher rates of moderate events (1.7% vs. 0%; $p = 0.038$). There was no difference in the comparison between the two groups for all other AE rates ($p > 0.05$) (Table 1 suppl).

4. Discussion

In this study we investigated the rate of DBC and the outcome of ERCP performed in patients with DMBO. To the best of our knowledge, this is the first study that evaluated DBC rate in this specific setting, when applying the definition proposed by ESGE [4]. Our results highlight the following key points: first, the rate of DBC in the specific setting of patients undergoing ERCP for DMBO was remarkably higher compared to the rate reported in the literature for any ERCP, regardless of the indication, reaching an overall rate of 56,4%. Moreover, cannulation failure rate in this setting was 22.8% that is much higher when compared with the cannulation failure of unselected patients (5-10%) [4]. Second, the etiology of the stenosis and specific features of the CBD, papilla or duodenum could predict DBC or cannulation failure in patients with DBMO. Third, DBC was associated with increased risk of AEs after adjusting for confounding factors.

These points should be evaluated with caution since they are based on data that may have been indirectly influenced by the retrospective nature of this study.

Nevertheless, it is important to note that previous studies provided several different definitions of “difficult” biliary access, with the common feature that, in these cases, alternative and/or advanced cannulation techniques were needed to achieve success. Differences were noticed in the cut-off of minutes spent attempting to cannulate (mainly ranging from 5 to 15), number of attempts (from 5 to 10) or number of unintentional pancreatic duct cannulations/injections (from 2 to 5) [3,12–25]. Such studies, which included ERCP performed for several different indications, reported a DBC rate generally below 15%, which is significantly lower to that reported in our cohort [3,12–25]. Of course, it could be speculated that the more stringent cut-off set by ESGE definition (i.e. 5 min, 5 attempts, 2 pancreatic duct cannulation) could have led to higher rate of DBC in our cohort. With this regard, a recent prospective

Table 1
Baseline parameters, endoscopic procedure characteristics and clinical outcomes of included patients.

Parameter	Value (n = 622)
Sex, no./total no.(%)	
Female	301/622 (48.4)
Male	321/622 (51.6)
Age, median (IQR), years	74 (65-80)
Bile duct dilation[§], no./total no.(%)	593/622 (95.3)
Papilla morphology, no./total no.(%)	
Normal	367/622 (59.0)
Protruding	140/622 (22.5)
Infiltrated	89/622 (14.3)
Intradiverticular	26/622 (4.2)
Duodenum morphology, no./total no.(%)	
Normal	465/622 (74.8)
Infiltrated	120/622 (19.3)
Stenosis	37/622 (5.9)
Previous ERCP, no./total no.(%)	22/622 (3.5)
Etiology of stenosis, no./total no.(%)	
Pancreatic cancer	508/622 (81.7)
Cholangiocarcinoma	62/622 (10.0)
Ampullary carcinoma	33/622 (5.3)
Others[*]	19/622 (3.0)
Pancreatitis prophylaxis, no./total no.(%)	533/622 (85.7)
Sphincterotomy, no./total no.(%)	357/622 (57.4)
Biliary stenting, no./total no.(%)	542/622 (87.1)
Type of biliary stent, no./total no.(%)	
Plastic	180/542 (33.2)
SEMS	362/542 (66.8)
Pancreatic stenting, no./total no.(%)	40/622 (6.4)
DBC group, no./total no.(%)	351/622 (56.4)
Reason for difficult biliary cannulation, no./total no.(%)	
>5 cannulation attempts	254/351 (72.4)
Wirsung cannulation	62/351 (17.6)
Contrast agent in Wirsung	7/351 (2.0)
>5 cannulation attempts and Wirsung cannulation	23/351 (6.6)
>5 cannulation attempts and contrast agent in Wirsung	1/351 (0.3)
Cannulation and contrast agent in Wirsung	4/351 (1.1)
Technique for biliary access in DBC group, no./total no.(%)	
Papillotomy	167/351 (47.6)
Fistulotomy	83/351 (23.6)
Transpancreatic	30/351 (8.5)
Double guidewire	21/351 (6.0)
Pancreatic stenting	3/351 (0.9)
Multiple attempts	24/351 (6.8)
≥2 techniques	23/351 (6.6)
Technical success in DBC group, no./total no.(%)	271/351 (77.2)
Technical success depending of the technique used, no./total no.(%)	
Papillotomy	134/167 (80.2)
Fistulotomy	63/83 (75.9)
Transpancreatic	27/30 (90.0)
Double guidewire	19/21 (90.5)
Pancreatic stenting + sphincterotome	3/3 (100)
Multiple attempts	6/24 (25.0)
≥2 techniques	19/23 (82.6)
Biliary cannulation failure, no./total no.(%)	80/622 (12.9)
Treatment of biliary cannulation failure, no./total no.(%)	
Second ERCP	6/80 (7.5)
EUS-CDS	48/80 (60.0)
EUS- RV	5/80 (6.2)
PTBD	18/80 (22.5)
Surgery	3/80 (3.8)
Adverse events, no. patients/total no. patients(%)[¶]	97/622 (15.6)
Cholangitis	33/622 (5.3)
Pancreatitis	34/622 (5.5)
Bleeding	20/622 (3.2)
Perforation	3/622 (0.5)
Stent migration	5/622 (0.8)
Cholecystitis	7/622 (1.1)

ERCP: Endoscopic Retrograde CholangioPancreatography; SEMS: Self Expandable Metal Stent; DBC: Difficult Biliary Cannulation; IQR, interquartile range; EUS-CDS: Endoscopic Ultrasound guided Choledochoduodenostomy; EUS- RV: Endoscopic Ultrasound Rendez-Vous; PTBD: Percutaneos Transhepatic Biliary Drainage.

[§] Defined as bile duct diameter ≥10 mm.

[*] Including 9 patients with metastasis, 9 with neuroendocrine tumor and 1 with duodenal cancer.

[¶] Five patients experienced two adverse events.

Table 2
Univariate and multivariate analysis results of the predictive model for difficult biliary cannulation.

Variable	Difficult biliary cannulation		Univariate analysis		Multivariate analysis	
	Yes (n = 351)	No (n = 271)	Unadjusted Odds Ratio (95%CI)	p value	Adjusted Odds Ratio (95%CI)[§]	p value
Sex						
Male[*]	176	145	1.00	0.41	1.00	0.46
Female	175	126	1.14 (0.83–1.57)		1.13 (0.82–1.57)	
Age, years[#]	74 (66-80)	73 (64-81)	1.01 (0.99–1.02)	0.44	1.01 (0.99-1.02)	0.32
Etiology						
Pancreatic cancer[*]	300	208	1.00	0.04	1.00	0.01
Cholangiocarcinoma	30	32	0.65 (0.38–1.10)		0.71 (0.42–1.22)	
Ampullary carcinoma	13	20	0.45 (0.22–0.93)		0.32 (0.15–0.70)	
Others[+]	8	11	0.50 (0.20–1.28)		0.49 (0.19-1.26)	
Bile duct dilation						
Yes[*]	335	258	1.00	0.89	1.00	0.83
No	16	13	0.95 (0.45–2.01)		1.09 (0.50–2.37)	
Papilla morphology						
Normal[*]	193	174	1.00	0.002	1.00	0.0003
Protruding	87	53	1.48 (0.99–2.20)		1.81 (1.17–2.80)	
Infiltrated	62	27	2.07 (1.26–3.40)		2.17 (1.31–3.59)	
Intradiverticular	9	17	0.48 (0.21–1.10)		0.52 (0.22–1.21)	
Duodenum morphology[¶]						
Normal[*]	244	221	1.00	0.002	1.00	0.08
Infiltrated	79	41	1.75 (1.15–2.65)		1.42 (0.91–2.21)	
Stenosis	28	9	2.82 (1.30–6.10)		2.11 (0.94–4.75)	

[§] Adjusted for papilla morphology and ERCP indication (i.e. the two variables included in the predictive model).
[*] Reference group.
[#] Expressed as median (IQR).
[+] Including 9 patients with metastasis, 9 with neuroendocrine tumor and 1 with duodenal cancer.

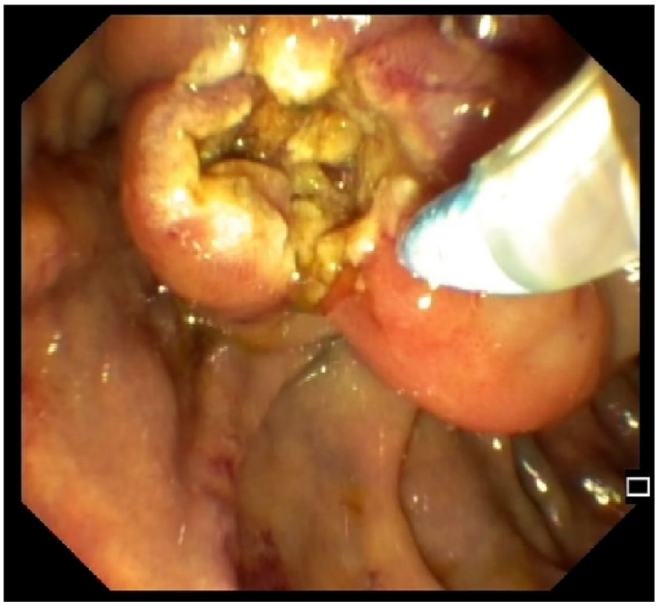

Fig. 1. Unsuccesfull pre-cut papillotomy in an infiltrated papilla.

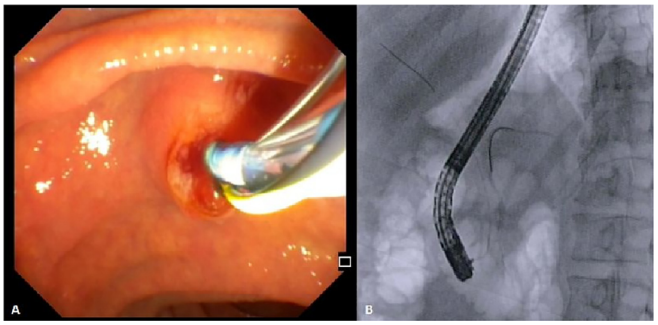

Fig. 2. A) Endoscopic and B) fluoroscopic appearance of double guide wire (DGW) technique.

study from Haraldsson and colleagues described outcomes of ERCP according to papilla morphology, and reported an overall rate of DBC of 42% by using the definition proposed by ESGE [26]. This rate is certainly higher compared with previous studies, thus suggesting that ESGE criteria could determine a lower threshold for defining DBC, but indeed, it is still lower compared to our cohort. Likewise, this could be also explained by the low frequency of DMBO (around 15–24%) in the Haraldsson's cohort in which bulky tumor of the papilla were excluded [26].

Our study also showed that specific factors can predict DBC and cannulation failure in the setting of DMBO. Indeed, ERCP indication and infiltrated or protruding papilla were associated with DBC in multivariate analysis while a non-dilated CBD, infiltrated papilla and infiltrated or stenotic duodenum were associated with cannulation failure. A predictive model for papilla morphology and etiology of stenosis showed a 78% specificity for DBC, while a predictive model for CBD dilation, papilla and duodenum morphology showed a 90% specificity for cannulation failure. In our opinion, this result could be clinically relevant as the ability to predict such complex situations is crucial for an effective management of these patients. Indeed, the high rate of DBC in our cohort corresponds to a very frequent need of advanced cannulation techniques (i.e. pre-cut papillotomy/fistulotomy, TBS, DGW technique). The availability of this information before starting the procedure (CBD diameter, etiology of stenosis) or before starting the attempts to cannulate (duodenal or papilla infiltration) could help to stratify patients according to the predicted difficulty of the procedure, and therefore to plan the best therapeutic strategy with the best operative setting. This may mean involving experienced endoscopists skilled also in advanced cannulation techniques and alternative biliary drainage methods (e.g. EUS biliary drainage (EUS-BD)), with the ultimate goal of improving patient's outcomes. The significant association between continuous attempts to cannulate with standard technique and cannulation failure in multivariate analysis further underlines the need of a timely switch to advanced alternative techniques. Importantly, prediction of increased technical difficulty

Table 3
Univariate and multivariate analysis results of the predictive model for failure during difficult biliary cannulation.

Variable	Failure		Univariate analysis		Multivariate analysis	
	Yes (n = 80)	No (n = 271)	Unadjusted Odds Ratio (95%CI)	p value	Adjusted Odds Ratio (95%CI)[§]	p value
Etiology of stenosis						
Pancreatic cancer[*]	77	223	1.00	0.72	1.00	0.67
Cholangiocarcinoma	0	30	n.e.		n.e.	
Ampullary carcinoma	2	11	0.53 (0.11–2.43)		0.78 (0.13–4.58)	
Others[+]	1	7	0.41 (0.05–3.42)		0.23 (0.02–2.40)	
Bile duct dilation						
Yes[*]	71	264	1.00	0.003	1.00	0.007
No	9	7	4.78 (1.72–13.28)		5.75 (1.65–20.03)	
Papilla morphology						
Normal[*]	19	174	1.00	<0.0001	1.00	<0.0001
Protruding	15	72	1.91 (0.92–3.96)		1.84 (0.83–4.07)	
Infiltrated	44	18	22.39 (10.85–46.20)		14.18 (6.29-31.95)	
Intradiverticular	2	7	2.62 (0.51–13.51)		2.40 (0.40–14.21)	
Duodenum morphology						
Normal[*]	28	216	1.00	<0.0001	1.00	<0.0001
Infiltrated	28	51	4.24 (2.31–7.77)		2.62 (1.30–5.27)	
Stenosis	24	4	46.29 (14.96–143.19)		19.16 (5.48–66.96)	
Technique for biliary access[⌘]						
Papillotomy[*]	33	134	1.00	<0.0001	1.00	0.06
Fistulotomy	20	63	1.29 (0.69–2.42)		1.23 (0.53–2.87)	
Transpancreatic	3	27	0.45 (0.13–1.58)		0.51 (0.12–2.18)	
Double guidewire	2	19	0.43 (0.10–1.93)		0.24 (0.04–1.38)	
Pancreatic stenting	0	3	n.e.		n.e.	
Multiple attempts	18	6	12.18 (4.48-33.09)		6.12 (1.66–22.60)	
≥2 techniques	4	19	0.86 (0.27–2.68)		0.87 (0.23–3.25)	

n.e., not estimable since there were no cannulation failure events in the variable category.
[§] Adjusted for bile duct dilation, papilla morphology, and duodenum morphology (i.e. the three variables included in the predictive model).
[*] Reference group.
[+] Including 2 patients with metastasis, 5 with neuroendocrine tumor and 1 with duodenal cancer.

could be useful especially in academic center where trainees are involved.

The most frequently used alternative cannulation technique in our cohort of patients was needle knife papillotomy (in near half of the DBC cases), followed by needle knife fistulotomy and TBS. All these techniques showed comparable efficacy (technical success rate of 80.2%, 75.9% and 90% respectively). Although randomized studies evaluating different pre-cut techniques are not available, a meta-analysis reported that TBS has higher success rate compared to needle-knife papillotomy, with similar safety [27]. Despite a trend toward a higher success rate for TBS was found also in our study, our results did not confirm a significant difference with regard to success rate, possibly because of the specific clinical setting analyzed. In general, the present data do not allow to favor any specific technique over another.

According to our study, DBC was associated with increased risk of AEs after adjusting for ERCP indication (i.e. cholangiocarcinoma) and prophylaxis for PEP. The overall rate of AEs in our cohort was 15,6% (97/622), which is slightly higher compared to the AE rate reported for ERCP for all indications from most cohorts, often below 10% [28–31]. Difficult biliary access represents itself a well-recognized risk factor for AEs, since long procedures with repeated cannulation attempts and inadvertent guide-wire passage in the pancreatic duct, increase the risk of PEP [32]. Nevertheless, the PEP rate was not different among groups (5,7% vs 4,8%, p = 0,72). On the other hand, it has been demonstrated that an “early” pre-cut sphincterotomy strategy is effective and safe in case of DBC when compared to the “late” strategy with prolonged cannulation attempts [33–36]. We can speculate that the progressive integration of such strategy in common daily practice could have reduced the differences in AEs rate between DBC and non-DBC group. Consistently, multiple attempts with standard cannulation technique were rarely adopted in DBC groups (24/351, 6,8%), and showed a very low technical success (25%). Furthermore, PEP rates were consistent with the general risk reported in literature [37]. The extensive use of rectal indomethacin and Ringer’s lactate hydration to prevent PEP could also account for a low rate of this AEs in both groups. Differently, DBC group showed a significant higher risk of bleeding compared non-DBC (4,8% vs 1,1%, p = 0,01). Several studies reported a bleeding rate after pre-cut sphincterotomy around 3-4%, which is higher compared to the general risk of bleeding after ERCP (0.3% to 2%) [27,38]. The frequent use of pre-cut in DBC group, that were performed on papilla with underlying malignant disease, could account for the increased risk of bleeding. Consistently, papillotomy is associated with increased risk of AEs in multivariate analysis. Taken together, data on AEs in our cohort emphasize once again the protective role of PEP prophylaxis, and the increased risk of AEs associated with pre-cut papillotomy, which should be performed only by experienced endoscopists.

With this regard, the efficacy and safety of ERCP as primary drainage technique in DMBO has been recently challenged by the widespread of EUS-BD techniques (i.e. EUS-guided choledochoduodenostomy and hepatogastrostomy), which have been tested as primary therapy for malignant jaundice in three randomized controlled trial showing good results [39–41]. Outside of experimental trials, this approach is currently recommended only after ERCP failure [42,43], and it has been the preferred alternative approach also in our cohort after cannulation failure. Previously, it has been also reported that a second attempt of ERCP after failed cannulation is effective in up to 75% of cases [44]. However, these data come from a small retrospective study which included mainly patients with benign diseases. In the setting of DBMO, the presence of infiltrated duodenum and/or papilla or a very tight biliary stricture is often responsible for failed deep cannulation, and such difficulties are not supposed to improve over time. The availability of interventional radiology and EUS in the centers involved in our study, together with the specific clinical setting of malignant disease and the need for prompt biliary drainage, could explain the low rate of second ERCP after failed cannulation in our cohort (6/80, 7.5%). It is conceivable that the growing experience in interventional EUS,

Table 4
Results of the univariate and multivariate analysis on the association between difficult biliary cannulation and adverse events.

Variable	Adverse events		Univariate analysis		Multivariate analysis	
	Yes (n = 97)	No (n = 525)	Unadjusted Odds Ratio (95%CI)	p value	Adjusted Odds Ratio (95%CI)[§]	p value
Difficult biliary cannulation						
No[*]	34	237	1.00	0.06	1.00	0.02
Yes	63	288	1.53 (0.97–2.39)		1.73 (1.08–2.77)	
Sex						0.16
Male[*]	42	279	1.00	0.08	1.00	
Female	55	246	1.49 (0.96–2.30)		1.38 (0.88–2.15)	
Age, years[#]	71 (64-79)	74 (66-81)	0.99 (0.97–1.01)	0.34	0.99 (0.97-1.01)	0.14
Etiology of stenosis						0.02
Pancreatic cancer[*]	74	434	1.00	0.02	1.00	
Cholangiocarcinoma	18	44	2.40 (1.32–4.38)		2.39 (1.29–4.41)	
Ampullary carcinoma	2	31	0.38 (0.09–1.62)		0.43 (0.10–1.85)	
Others[+]	3	16	1.10 (0.31–3.87)		1.34 (0.38-4.78)	
Bile duct dilation						
Yes[*]	92	501	1.00	0.80	1.00	0.69
No	5	24	1.14 (0.42–3.05)		0.81 (0.29–2.31)	
Papilla morphology						
Normal[*]	61	306	1.00	0.45	1.00	0.67
Protruding	18	122	0.74 (0.42–1.30)		0.85 (0.47–1.55)	
Infiltrated	16	73	1.10 (0.60–2.02)		1.13 (0.61–2.12)	
Intradiverticular	2	24	0.42 (0.10–1.82)		0.50 (0.11–2.20)	
Duodenum morphology						
Normal[*]	75	390	1.00	0.82	1.00	0.69
Infiltrated	17	103	0.86 (0.49–1.52)		0.82 (0.46–1.47)	
Stenosis	5	32	0.81 (0.31–2.15)		0.74 (0.27–1.99)	
Prophylaxis						
Yes[*]	76	457	1.00	0.02	1.00	0.03
No	21	68	1.86 (1.08–3.21)		1.94 (1.09–3.44)	
Sphincterotomy						
No[*]	44	221	1.00	0.55	1.00	0.40
Yes	53	304	0.88 (0.57–1.36)		0.82 (0.51–1.31)	
Technique for biliary access[⌘]						
Single guidewire/sphincterectome[*]	34	237	1.00	0.41	1.00	0.18
Papillotomy	33	134	1.72 (1.02–2.90)		1.98 (1.14–3.45)	
Fistulotomy	13	70	1.30 (0.65–2.59)		1.49 (0.74–3.04)	
Transpancreatic	6	24	1.74 (0.67–4.57)		1.94 (0.73–5.21)	
Double guidewire	3	18	1.16 (0.33–4.15)		1.15 (0.31–4.31)	
Pancreatic stenting	0	3	n.e.		n.e.	
Multiple attempts	2	22	0.63 (0.14–2.82)		0.79 (0.18–3.56)	
≥2 techniques	6	17	2.46 (0.91–6.67)		2.88 (1.04–7.97)	

n.e., not estimable since there were no adverse events in the variable category.
[§] Adjusted for difficult biliary cannulation, Etiology of stenosis, and prophylaxis.
[*] Reference group.
[#] Expressed as median (IQR).
[+] Including 9 patients with metastasis, 9 with neuroendocrine tumor and 1 with duodenal cancer.
[⌘] The results of the multivariate analysis for technique for biliary access were adjusted only for etiology of stenosis and prophylaxis, due to collinearity issues with the study factor (i.e. difficult biliary cannulation).

together with a better understanding of predictive factor of difficult/unsuccessful ERCP, will place EUS-BD in an earlier stage of the therapeutic algorithm of DMBO as also happened with pre-cut in the past. In our opinion indeed, EUS-BD could be considered as a different "pre-cut" approach with the potential benefit of not passing through the tumor and/or the pancreatic gland (thus reducing the risk of bleeding and PEP) and we should therefore start thinking about this as an alternative approach to be applied earlier in the therapeutic flow-chart of DBC in DMBO.

The main limitation of this study is indeed its retrospective design, with subsequent possible shortcomings in data collection and analysis. On the other hand, one of its strengths is the large number of patients included from different centers, and the precise, sharp and standardized criteria by which DBC rate and AEs have been analyzed. Data from this cohort highlight that ERCP in patients with DMBO is frequently complex and requires alternative cannulation techniques in more than half of cases. Moreover, endoscopists should be aware of the high rate of cannulation failure in case of DBC, and therefore they should be prepared to promptly switch to alternative strategies. Despite the need of further confirmatory studies, our model suggest that clinical data, radiological findings and endoscopic features could be used to predict procedural difficulty and eventually to refer selected patients with DMBO to tertiary centers with endoscopists skilled in advanced cannulation techniques and alternative drainage methods.

In conclusion, the presented data highlight that patients with DMBO carry a high risk for DBC with consequent high risk of occurrence of AEs. Further prospective randomized controlled trial hopefully will clarify which is the best therapeutic approach for biliary drainage in this setting of patients.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.07.010.

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