

# Association between type of major duodenal papilla and difficult biliary cannulation at first endoscopic retrograde cholangiopancreatography in adults: a cross-sectional study with bootstrap method

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## Abstract

**Background** The type of major duodenal papilla could be associated with difficult biliary cannulation at first endoscopic retrograde cholangiopancreatography (ERCP) in adults.

**Methods** This retrospective cross-sectional study included patients undergoing ERCP for the first time by an expert endoscopist. We defined the type of papilla according to the endoscopic classification of Haraldsson in type 1-4. The outcome of interest was difficult biliary cannulation, defined according to the European Society of Gastroenterology. To assess the association of interest, we calculated crude and adjusted prevalence ratios (PRc and PRa, respectively) and their respective 95% confidence intervals (CI) using Poisson regression with robust variance models, employing bootstrap methods. For the adjusted model we included the variables age, sex, and indication for ERCP, according to an epidemiological approach.

**Results** We included 230 patients. The most frequent type of papilla was type 1 (43.5%), and 101 (43.9%) of the patients presented difficult biliary cannulation. The results were consistent between the crude and adjusted analyses. After adjusting for age, sex, and ERCP indication, the prevalence of difficult biliary cannulation was highest in patients with papilla type 3 (PRa 3.66, 95%CI 2.49-5.84), followed by patients with papilla type 4 (PRa 3.21, 95%CI 1.82-5.75), and patients with papilla type 2 (PRa 1.95, 95%CI 1.15-3.20) compared to patients with papilla type 1.

**Conclusion** In adults undergoing ERCP for the first time, patients with papilla type 3 had a greater prevalence of difficult biliary cannulation than patients with papilla type 1.

**Keywords** Endoscopic retrograde cholangiopancreatography, ampulla of Vater, cannulation, biliary tract surgical procedures

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## Introduction

Endoscopic retrograde cholangiography (ERCP) is a useful and the preferred therapeutic endoscopic procedure for several biliary pathologies. Failure rates for cannulation of the main bile duct are described in the range of 18-20% [1], and in the hands of experienced endoscopists this can be reduced to 5-15% [2].

Although there is no global consensus to define difficult biliary cannulation, in 2016 the European Society of Gastroenterology defined difficult biliary cannulation according to the presence of at least one of the following criteria: a) more than 5 cannulation attempts; b) more than 5 min of cannulation time; or c) more than one unintended pancreatic duct cannulation or opacification [3]. It has been observed that the greater the time or the attempts at biliary cannulation, the greater the risk of complications, mainly post-ERCP pancreatitis [4-7]. For this

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reason, risk factors associated with difficult biliary cannulation have been determined, such as those related to the operator (especially the endoscopist's experience) and to patient factors (papilla morphology, anatomical and post-surgical alterations, among others) [3,6].

In 2017, Haraldsson *et al* published the first classification of the endoscopic appearance of the duodenal major papilla with interobserver and intraobserver validation. This study defined 4 types of papilla morphology: type 1 (regular), type 2 (small), type 3 (protruded or pendulous), and type 4 (creased or ridged) [8].

Previous studies explored the association between the type of papilla and a difficult biliary cannulation or a failed ERCP [9-11]; however, they had methodological limitations. These previous studies performed unadjusted analyses for other covariates, reported an inappropriate regression model, or included a small sample size. Therefore, the objective of this study was to assess the association between the type of papilla and a difficult biliary cannulation, using an adjusted regression model according to the study design and a bootstrap method for a robust statistical analysis.

## Materials and methods

We followed the "strengthening the reporting of observational studies in epidemiology" (STROBE) guidelines (Supplementary Table 1).

### Study design and setting

We performed a retrospective cross-sectional study in September 2022, using the data of patients who attended the gastroenterology service of the Hospital Nacional Arzobispo Loayza between April 2016 and December 2021. The Hospital Nacional Arzobispo Loayza is a specialized medical center in Lima (Peru) with an annual volume of more than 500 ERCP procedures.

### Study population

The participants were adults with an indication for ERCP. We included patients over 18 years undergoing ERCP for the first time (naïve papilla), performed by an expert endoscopist (over 1000 ERCP performed), whose target duct for cannulation was the common bile duct, and with images showing the full extent of the papilla before starting the procedure and after it.

We excluded patients who presented a papilla with macroscopic alteration of its shape or an anatomical variant, such as diverticulum or tumors, that would deform the papilla and make its classification difficult; incomplete recording of data in the ERCP report; altered anatomy due to surgical interventions; or an abnormal pancreaticobiliary junction.

We used a non-probabilistic sample. We included all the participants who attended in the mentioned period and who met the eligibility criteria.

### Procedures and variables

The database was populated with the records of the ERCP reports. For this purpose, we used a data collection form designed for this study. We extracted the patient demographic characteristics, ERCP indication, and characteristics of the ERCP procedure (common bile duct cannulation attempts, cannulation time, pancreatic duct cannulation or opacification, the need for an advanced cannulation technique, and failed procedures). In addition, 2 endoscopists (one expert and one fellow) used the preexisting photo documentation recorded in the video capture system to characterize the type of papilla.

The outcome of interest was difficult biliary cannulation, a dichotomous categorical variable, defined as the presence of at least one of the following criteria: a) more than 5 cannulation attempts; b) more than 5 min spent trying to cannulate after papilla visualization; or c) more than one unintended pancreatic duct cannulation or opacification [4].

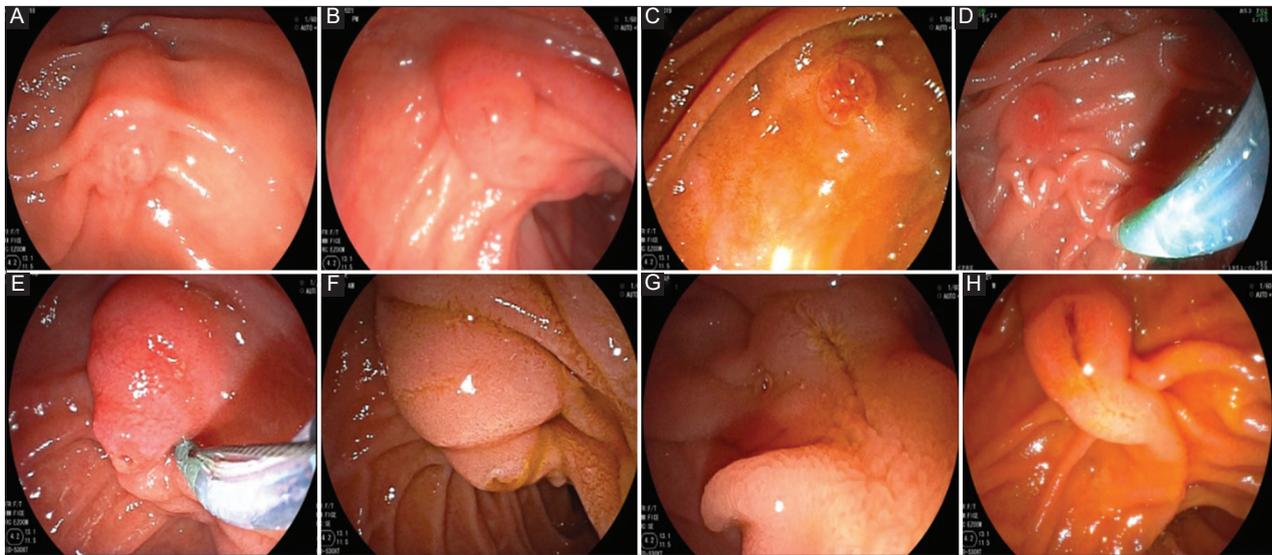
The independent variable was the type of major duodenal papilla morphology (type of papilla), a polytomous categorical variable, defined according to the endoscopic classification of Haraldsson *et al* as type 1 (regular: no distinguishing features), type 2 (small: often a flat papilla with a diameter  $\leq 3$  mm), type 3 (protruded or pendulous: the papilla protrudes into the duodenal lumen, or sometimes hangs downward, pendulous, with an orifice oriented caudally), or type 4 (creased or ridged: the ductal mucosa appears to extend distally, outside the papillary orifice, either ridged or in a fold) [8] (Fig. 1). The covariates were age (years), sex (female or male), and indications (common bile duct stones, tumors, other).

### ERCP procedure and cannulation process

No medication was used to prevent post-ERCP pancreatitis. All ERCP procedures were performed by an expert endoscopist. For this purpose, the endoscopist used a therapeutic duodenoscope with a triple-lumen sphincterotome and a 0.035" hydrophilic guidewire.

The endoscopist used guidewire-assisted cannulation as a standard method for biliary cannulation. First, the endoscopist positioned the duodenoscope and visualized the papilla. Then, the endoscopist oriented the instrument at 11 o'clock toward the common bile duct. Later, the endoscopist initiated cannulation using the sphincterotome and a 0.035-inch hydrophilic guidewire under fluoroscopic guidance [6].

The endoscopist used an advanced cannulation technique if entering the bile duct was not possible. In our institution, we performed a precut fistulotomy with a needle knife as an advanced cannulation technique [12]. The advanced cannulation technique consisted of making an incision near the papillary orifice to create a fistula between the duodenal lumen



**Figure 1** Classification of the endoscopic appearance of the major duodenal papilla according to Haraldsson *et al* in the included participants. (A, B) Regular (Type 1). (C, D) Small (Type 2). (E, F) Protruding or Pendular (Type 3). (G, H) Wrinkled or striated (Type 4)

and the common bile duct lumen [5,13]. For this purpose, the endoscopist used an ERBE VIO 200S as an electrosurgical unit. Finally, we defined cannulation as successful when fluoroscopy revealed the entry of the hydrophilic guidewire into the main bile duct.

### Statistical analysis

We used STATA v.17.0 software (Stata Corp LP, Texas, USA) for all the statistical analysis. For the descriptive analysis, we used absolute and relative frequencies for categorical variables and measures of central tendency and dispersion for quantitative variables, according to the distribution of the data (mean with standard deviation [SD] for a normal distribution; and median with interquartile range [IQR] for non-normal distribution). We used a histogram and the Shapiro-Wilk test to assess the type of distribution. To assess the association between the type of papilla and difficult biliary cannulation, we estimated crude and adjusted prevalence ratios (PRc and PRa, respectively) and their respective 95% confidence intervals (CI) using Poisson regression with robust variance models and employing bootstrap methods. We used 1000 bootstrap replications and reported the bias-corrected results. For the adjusted model we included the following variables according to an epidemiological approach: age, sex, and indication for ERCP.

### Ethical aspects

The protocol of this study was approved by the institutional committee of ethics in research of the Hospital Nacional Arzobispo Loayza (CONSTANCIA 039-2022). Data confidentiality was maintained.

## Results

### Patient characteristics

From April 2016 to December 2021, 7243 patients underwent ERCP in the gastroenterology service; 803 of these procedures were performed by an expert endoscopist. Of the 803 patients, 230 patients met the remaining eligibility criteria. Of the 230 patients included, 160 (69.6%) were female and the median age was 47 years (IQR: 31-66 years). The most frequent indication for ERCP was common bile duct stones (92.6%) followed by indications for other pathologies, such as benign stenosis of the extrahepatic bile duct and probable sphincter of Oddi dysfunction (4.8%). The most frequent type of papilla was type 1 (43.5%) and 101 (43.9%) of the patients presented difficult biliary cannulation (Table 1).

### ERCP procedure characteristics according to the type of papilla

During the ERCP procedure, 81 (35.2%) patients had more than 5 cannulation attempts, 88 (38.3%) patients had a cannulation time of more than 5 min, 37 (16.1%) patients had more than one unintended pancreatic duct cannulation or opacification, 71 (30.9%) patients needed a precut fistulotomy technique to achieve biliary cannulation, and 13 (5.7%) patients had a failed ERCP (Table 2).

According to the type of papilla, patients with papilla type 3 presented a higher frequency of difficult biliary cannulation (76.9%), more than 5 cannulation attempts (72.3%), cannulation time of more than 5 min (75.4%), and

precut fistulotomy technique to achieve biliary cannulation (66.2%), compared to patients with other types of papillae. In addition, patients with papilla type 4 presented a higher frequency of unintended pancreatic duct cannulation or opacification of more than one (35.3%) and failed ERCP (17.6%) in comparison to patients with other types of papillae (Table 2).

### Association between the type of papilla and difficult biliary cannulation

The results were consistent between the crude and adjusted analyses. After adjusting for age, sex and ERCP indication, the prevalence of difficult biliary cannulation was higher in patients with papilla type 3 (PRa 3.66, 95%CI 2.49-5.84), followed by patients with papilla type 4 (PRa 3.21, 95%CI 1.82-5.75), and patients with papilla type 2 (PRa 1.95, 95%CI 1.15-3.20), compared to patients with papilla type 1 (Table 3).

**Table 1** Characteristics of adults included in the study (n = 230), undergoing ERCP for the first time

Characteristics	N (%)
Age - years*	47 (31-66)
Sex	
Male	70 (30.4)
Female	160 (69.6)
Indication for ERCP	
Common bile duct stones	213 (92.6)
Tumor	6 (2.6)
Others	11 (4.8)
Type of papilla	
Type 1	100 (43.5)
Type 2	48 (20.9)
Type 3	65 (28.3)
Type 4	17 (7.4)
Difficult biliary cannulation	
No	129 (56.1)
Yes	101 (43.9)

\*Median (interquartile range)

ERCP, endoscopic retrograde cholangiography

### Discussion

ERCP is the treatment of choice for most diseases of the bile duct and pancreas. In our study, common bile duct stones were the most frequent indication for ERCP (92.6%). This is consistent with previous studies, in which this indication for ERCP ranged from 44-88.5% [9-11]. A possible explanation for this could be that common bile duct stones are more frequently associated with the female sex [14], who predominated in our study and previous studies [9,10].

We found that type 1 papilla was the most frequent (43.5%) in our study. This agrees with reports in the literature, in which type 1 papilla was found in 32-56% of participants [9-11]. In addition, the frequency of difficult biliary cannulation in our study was 43.9%, which agrees with Haraldsson *et al* (42%) [9] and Ismail *et al* (37.9%) [15] but differs from Gutierrez *et al* (29.8%) [10], a study conducted in a private tertiary center. This difference could be due to the variability between the time from the indication of ERCP to the procedure. The time to the procedure could be longer in a national reference health center than in a private health center. We hypothesize that a long time to procedure could increase the inflammation and fibrosis of the papilla via prolonged compression of the stone, making cannulation more difficult. Future studies could assess this hypothesis.

Regarding the association of interest, we found that the prevalence of difficult biliary cannulation was higher in patients with papilla types 3, 4, and 2 compared to patients with papilla type 1 (in that order, from largest to smallest magnitude). Our results are consistent with those of Gutierrez *et al* [10], a study that included 188 Peruvian patients who underwent ERCP for the first time between July 2019 and April 2021. It is plausible that papilla type 3 is the one with the highest prevalence of difficult biliary cannulation, since the intramural bile duct is longer and more unstable than for other types of papillae. Therefore, the axis of the bile duct could be more likely to become misaligned when inserting the cannulation catheter [6,16]. This hypothesis is consistent with a study that used another type of classification of the major duodenal papilla based on its degree of protrusion. The study published by Watanabe *et al* reported that, in the adjusted analysis, the large-type papilla (protrusion type L,

**Table 2** Characteristics of ERCP procedure according to the type of papilla (n=230)

Characteristics	Total	Type 1 (n=100)	Type 2 (n=48)	Type 3 (n=65)	Type 4 (n=17)
Difficult biliary cannulation - n (%)	101 (43.9)	21 (21)	19 (39.6)	50 (76.9)	11 (64.7)
Cannulation attempts >5	81 (35.2)	13 (13)	13 (27.1)	47 (72.3)	8 (47.1)
Cannulation time >5 min	88 (38.3)	17 (17)	13 (27.1)	49 (75.4)	9 (52.9)
Unintended pancreatic duct cannulation or opacification >1	37 (16.1)	7 (7)	10 (20.8)	14 (21.5)	6 (35.3)
Precut fistulotomy - n (%)*	71 (30.9)	13 (13)	7 (14.6)	43 (66.2)	8 (47.1)
Failed ERCP - n (%)	13 (5.7)	1 (1)	4 (8.3)	5 (7.7)	3 (17.6)

\*None of the participants received the double-wire technique

n (%), absolute frequency (relative frequency); ERCP, endoscopic retrograde cholangiography

**Table 3** Association between the type of papilla and difficult biliary cannulation in adults undergoing ERCP for the first time (n=230)

Variables	Outcome: Difficult biliary cannulation			
	No n (%)	Yes n (%)	PRc (95%CI)	PRa (95%CI)*
Type of papilla				
Type 1	79 (79)	21 (21)	Reference	Reference
Type 2	29 (60.4)	19 (39.6)	1.88 (1.10-3.14)	1.95 (1.15-3.20)
Type 3	15 (23.1)	50 (76.9)	3.66 (2.50-5.78)	3.66 (2.49-5.84)
Type 4	6 (35.3)	11 (64.7)	3.08 (1.77-5.39)	3.21 (1.82-5.75)
Age – years <sup>†</sup>	50 (29 - 70)	47 (34 - 63)	1.00 (0.99-1.00)	-
Sex				
Male	35 (50)	35 (50)	Reference	-
Female	94 (58.8)	66 (41.2)	0.82 (0.61-1.16)	-
Indication for ERCP				
Common bile duct stones	123 (57.8)	90 (42.2)	Reference	-
Tumor	2 (33.3)	4 (66.7)	1.58 (0.00-2.50)	-
Others	4 (36.4)	7 (63.6)	1.51 (0.75-2.23)	-

\*Model adjusted for age, sex, and indication for ERCP

<sup>†</sup>Median (interquartile range) for the no and yes columns

n (%), absolute frequency (relative frequency); ERCP, endoscopic retrograde cholangiography; PRc, crude prevalence ratio; PRa, adjusted prevalence ratio; CI, confidence interval

similar to the type 3 papilla of the Haraldsson classification) was the only one associated with a higher probability of difficult biliary cannulation [17].

Haraldsson *et al* also found an association between some types of papillae and difficult biliary cannulation [9]; however, in comparison to our results, the order and magnitude of the probability of difficult biliary cannulation between papilla types were different. Compared to patients with type 1 papilla and in order from largest to smallest, Haraldsson *et al* reported that the odds of difficult biliary cannulation were highest in patients with type 2 papillae (odds ratio [OR] 1.89, 95%CI 1.37-2.62), followed by type 3 (OR 1.61, 95%CI 1.24-2.10) [9]. In addition, the authors did not find a statistically significant association between papilla type 4 and difficult biliary cannulation [9], whereas in our study, papilla type 4 was associated with the second highest prevalence of difficult biliary cannulation.

The discrepancy between our study and that of Haraldsson *et al*, regarding the type of papilla associated with a higher probability of difficult biliary cannulation, could be due to differences in the endoscopists' experience and the lack of adjusted analyses. The investigators reported that the frequency of difficult biliary cannulation varied depending on the degree of experience of the endoscopist [9]. More specifically, in patients with papilla type 2, biliary cannulation was difficult in 83% when performed by endoscopists who had just begun their fellowship [9]. Therefore, the magnitude of the associations could be different if the regression model was adjusted for the experience of the endoscopist.

In our study, precut fistulotomy was used in 30.9% of our patients as an advanced cannulation technique. This was because our institution does not have the instruments to perform other types of advanced cannulation techniques; however,

the frequency of patients requiring advanced cannulation techniques was similar to that in other studies. Haraldsson *et al* used advanced cannulation techniques in 49% of their patients, including precut fistulotomy (9%), pancreatic sphincterotomy (15%), double-guide technique (15%), and a combination of techniques (10%) [9]. Gutierrez *et al* used advanced cannulation techniques in 33.5% of their patients, such as precut (26.6%) and the double-guide technique (6.9%) [10].

On the other hand, the prevalence of failed ERCP was 5.7% in our study, consistent with Chen *et al* (5.9%) [11]. Our study did not aim to assess the association between the papilla type and failed ERCP, but we found that failed ERCP tended to be higher in patients with papilla type 4. In contrast, Chen *et al* found an association between papilla types 3 (OR 7.44, 95%CI 1.45-38.28) and 2 (OR 7.18, 95%CI 1.05-49.19) and failed ERCP [11]; however, their results are too imprecise to be informative. Therefore, we consider that the association between the type of papilla and failed ERCP is still uncertain.

Regarding clinical implications, difficult biliary cannulation could lead to the development of complications related to ERCP [16,18], among which post-ERCP pancreatitis is the most frequent [15,19,20]. Post-ERCP pancreatitis is severe or fatal in 0.8% and 0.7% of patients, respectively [21]. In addition, post-ERCP pancreatitis is likely to prolong the hospital stay and increase the costs of medical care. In this sense, \$200 million are spent per year on the care of patients with post-ERCP pancreatitis in the United States [22]. Therefore, we recommend that endoscopists consider the early use of an advanced cannulation technique, such as precut fistulotomy [13,23-26], instead of persisting in repetitive attempts. Further manipulation of the papilla could make it swell, increasing the risk of ERCP failure.

The results of our study suggest that the endoscopist should adopt a cautious approach, especially when attempting to cannulate a type 3 papilla, to reduce the probability of difficult biliary cannulation. In consequence, in a training setting for endoscopists who just begin their fellowship, we suggest that an experienced endoscopist should guide the procedure. Nevertheless, this possibility will depend on each context.

Our study had several limitations. Because of its retrospective nature, the papilla was not photo-documented to classify it according to Haraldsson *et al* [8]; however, we included only the cases that had complete images of the papilla for proper classification, and this process was carried out by 2 endoscopists. In addition, the sample size of our study may not have had sufficient statistical power to detect minimal differences; however, we used a resampling method to estimate valid confidence intervals. Another limitation was the cross-sectional design, which does not allow the determination of a causal relationship between the type of papilla and difficult biliary cannulation; however, this direction of causality is plausible. Furthermore, we had no information on complications following difficult biliary cannulation, which limits any extrapolation of our results' clinical impact. Finally, given that this study was carried out with patients who attended a reference hospital center specialized in ERCP, the application of our results may be limited only to patients with similar characteristics.

Among the strengths of our study was our decision to standardize the definition of difficult biliary cannulation according to an evidence-based clinical practice guideline [3], since there is currently no consensus on its definition. In addition, we used the classification of the Scandinavian Association of Digestive Endoscopy (Haraldsson classification), since it is the only classification based on the endoscopic appearance of the major duodenal papilla that has been validated in terms of intra- and inter-observer variability and has been used in a multicenter prospective study that evaluated its implications in clinical complications [8,9,18]. Other strengths are that our study was developed in one of the health centers with the highest flow of patients nationwide and the cannulation procedure was carried out by an experienced endoscopist in all cases. Finally, in the statistical analysis, the bootstrap resampling method was used to estimate more precise and valid confidence intervals compared to previous studies.

In conclusion, in adults undergoing ERCP for the first time, compared to patients with papilla type 1, patients with papilla type 3 had a greater prevalence of difficult biliary cannulation, followed by patients with papilla types 4 and 2.

## Acknowledgment

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## Summary Box

### What is already known:

- Failure rates in cannulation of the main bile duct range from 18-20%, and are associated with the operator and patient-related factors such as papilla morphology, anatomical and post-surgical alterations
- Previous studies explored the association between the type of papilla and difficult biliary cannulation or a failed endoscopic retrograde cholangiopancreatography (ERCP)
- The methodological limitations of the previous studies included: unadjusted analyses of other covariates, such as endoscopists' experience; an inappropriate regression model; or a small sample size

### What the new findings are:

- In adults undergoing ERCP for the first time, compared to patients with papilla type 1, patients with papilla type 3 had the highest prevalence of difficult biliary cannulation, followed by patients with other types of papillae
- The endoscopist should adopt a cautious approach, especially when attempting to cannulate a type 3 papilla, to reduce the probability of difficult biliary cannulation
- Endoscopists should consider the early use of an advanced cannulation technique, such as precut fistulotomy, instead of persisting in repetitive attempts

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  25. Maharshi S, Sharma SS. Early precut versus primary precut sphincterotomy to reduce post-ERCP pancreatitis: randomized controlled trial (with videos). *Gastrointest Endosc* 2021;**93**:586-593.
  26. Wen J, Li T, Lu Y, Bie LK, Gong B. Comparison of efficacy and safety of transpancreatic septotomy, needle-knife fistulotomy or both based on biliary cannulation unintentional pancreatic access and papillary morphology. *Hepatobiliary Pancreat Dis Int* 2019;**18**:73-78.

## Supplementary material

Supplementary Table 1 STROBE checklist

	Item No	Recommendation	Page No.
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction	2	Explain the scientific background and rationale for the investigation being reported	4
Background/rationale			
Objectives	3	State specific objectives, including any prespecified hypotheses	4
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	-
		(c) Explain how missing data were addressed	-
		(d) If applicable, describe analytical methods taking account of sampling strategy	-
		(e) Describe any sensitivity analyses	-
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow up, and analyzed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(b) Report category boundaries when continuous variables were categorized	-
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	-
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-12
Generalizability	21	Discuss the generalizability (external validity) of the study results	12
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2