Analysis of the quality indicators, advanced biliary cannulation techniques and difficulty of endoscopic retrograde cholangiopancreatography (ERCP)

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LIST OF ABBREVIATIONS

ABP: acute biliary pancreatitis

AC: acute cholangitis

ASA score: American Society of Anesthesiologists score

ASGE: American Society of Gastrointestinal Endoscopy

B-ERCP: Benchmarking ERCP

BMI: body mass index

CBD: common bile duct

CI: confidence interval

DGW: double guidewire method

EBM: evidence-based medicine

ERCP: endoscopic retrograde cholangiopancreatography

ERCPQN: ERCP Quality Network

ESGE: European Society of Gastrointestinal Endoscopy

EUS: endoscopic ultrasonography

H-ERCP: Hungarian ERCP Registry

IND: indomethacin suppository

IQR: interquartile range

JED: Japanese Endoscopy Database

JPD: juxtapapillary diverticulum

MRCP: magnetic resonance cholangiopancreatography

N.A.: not applicable

NKPP: needle knife precut papillotomy

NKF: needle knife fistulotomy

NOS: Newcastle–Ottawa scale

NSAID: non-steroidal anti-inflammatory drug

OR: odds ratio

PGW: pancreatic guidewire technique

PEP: post-ERCP pancreatitis

PPS: prophylactic pancreatic stent

RAF-E: Rotterdam Assessment Form-ERCP

RCT: randomized controlled trial

RD: risk difference

RevMan: Review Manager

RR: risk ratio

SD: standard deviation

TPS: transpancreatic sphincterotomy

UK: United Kingdom

1. INTRODUCTION

1.1.History, current applications, and quality indicators of ERCP

Endoscopic retrograde cholangiopancreatography (ERCP) is an essential minimal invasive procedure in the treatment of several biliary and pancreatic disorders. We see a trend that with the advancement of technology, gastrointestinal endoscopy might obviate the need for more invasive surgical interventions (1,2). The first real challenge was to safely cannulate the biliary and pancreatic ducts to obtain a cholangiogram or pancreatogram. The first case of endoscopic cannulation of the papilla of Vater in a patient was carried out by William McCune and his colleagues in 1968 and published as a preliminary report (3). New devices and techniques were developed in the following years, American and Japanese research groups worked on this topic simultaneously. The side-viewing duodenoscope with a lever was a major leap forward among these efforts. Case series demonstrated high cannulation success rates with these devices (4,5). The next step was the therapeutic application of ERCP, at the beginning endoscopic sphincterotomy was developed in 1973 (6). After that, balloons were designed to extract biliary duct stones and stents were placed to achieve drainage in cases of strictures (7,8). Thanks to these advancements, ERCP stepped up as a reasonable alternative to surgery in the 1980s. Common bile duct stones were managed easily with ERCP and obstructive jaundice patients did not need an open operation to achieve biliary drainage anymore. Videoendoscopy changed the whole practice of endoscopy and ERCP in this decade (9). ERCP got gradually accepted by the medical community. Later on, in the 1990s, several new advancements helped to achieve better results with ERCP. Sphincterotomy became safer with monofilament wires and computer-regulated blended current and self-expandable metal stents provided longer patency with less need for repeat ERCP in patients with pancreatobiliary malignancies (10). In the 2000s, safety of ERCP became one of the main topics. The application of prophylactic pancreatic stents (11) and non-steroidal anti-inflammatory drug (NSAID) suppositories could lower the chance of pancreatitis after ERCP (12). Advanced cannulation methods became widely used and investigated to find the optimal cannulation strategy. New endoscopic technology and imaging methods were developed to complement ERCP. Endoscopic ultrasonography

(EUS) and magnetic resonance cholangiopancreatography (MRCP) are invaluable methods today (13). They could ensure the optimal and safe practice of ERCP which is not a risk-free procedure. Unfortunately, even now 4-10% of patients after ERCP develop post-ERCP pancreatitis (PEP) which could be a serious adverse event (14).

These days, the key questions of ERCP are still to find the best strategies to ensure a safe procedure, to minimize the risk for PEP, bleeding and perforations. NSAIDs (e.g. indomethacin, diclofenac) administered rectally with optimal hydration, and in case of pancreatic cannulation, the insertion of a pancreatic stent could significantly lower the chance of developing PEP (15). Additionally, finding the best cannulation strategy could improve the outcomes of ERCP, e.g. selective stepwise application of advanced cannulation methods according to the actual situation (16).

The European and American Society of Gastrointestinal Endoscopy (ESGE and ASGE) developed their quality indicators for ERCP practice. These measures include pre-, intra, and post-procedural elements to ensure safe and effective practice world-wide (17,18).

This short historical review of ERCP shows the various challenges during the procedure and the need for further research in the field. This field also offer great opportunities to gain further knowledge and improve our current practice for the benefit of the patients.

1.2.ERCP Registries

Clinical patient registries are getting essential tools of healthcare in the 21st century. These databases enable us to gather easily analyzable data on diseases, procedures related to healthcare, which could potentially lead to better, more efficient and cost-effective patient care (19). The widespread use of evidence-based medicine (EBM) made the demand for measuring and monitoring as much detail of healthcare as possible. Registries can help to ensure guideline adherence and give accurate feedback to clinicians and organizations and consequently can lower patient morbidity, mortality, and costs of care (20,21).

First, we must mention the most active countries in the development of quality patient registry systems. Sweden (22), Australia (23), UK (24) and Denmark (25) should be highlighted. With implementing these registries, we had gained several insights on how these systems should be managed and what approaches could prove effective. Data quality and completeness of reporting are key quality issues with these registries, which are still difficult tasks to manage. These publications mention the significance of the opt-out approach to reach higher inclusion rates, and they also highlight the need for complete follow-up to detect adverse events (26,27).

Besides their expected great quality improvement effects, these registries serve us also as scientific tools. Providing a vast quantity of invaluable "real-world data" which best mirrors the practice and gives us a picture of the actual applicability of certain methods and therapies. However, these structured data collecting systems require a high level of coordination between and also inside hospitals. By achieving that, they could make further collaborative efforts easier. For example, these registries could prove invaluable in the management of randomized clinical trials and prospective observational studies (28).

In gastrointestinal endoscopy, which includes potentially dangerous procedures to the patients, the need for monitoring quality indicators and provide the best possible outcomes for patients made the use of clinical registries essential (29). One good example is the colorectal screening programs, where continuous quality monitoring must be applied. Nevertheless, ERCP is the other good example for demonstrating the need for registries, because an ERCP might be 100 times more dangerous than a routine colonoscopy (2). With the application of the best possible approach, by the properly trained endoscopists should we only expect to reach the best possible outcome.

Several initiatives are known to the public in ERCP registries. In Northern Europe, two extensive and successful projects are running currently. The Swedish Gallriks (30) and the Norwegian Gastronet (31) initiatives collecting vast amounts of data, with unprecedented coverage of all procedures carried out in their countries. The Austrian

Benchmarking ERCP (B-ERCP) project reported a 5-year data collection period, and a major update on their system in 2012 (32,33). In the United States and several other countries, the ERCP Quality Network (ERCPQN) is known as an important quality project, providing international data of ERCPs, sadly that project had been ended with no successor so far (2,34).

Luckily, we could mention other relatively new nation-wide initiatives such as the Japanese Endoscopy Database (JED) project (35), the Dutch Rotterdam Assessment Form-ERCP (RAF-E) (36), and the Hungarian ERCP Registry (H-ERCP) (37). By the examination of the potential for cooperation between national project, collaborative efforts to further our knowledge in endoscopy could be invaluable (Figure 1, Table 1.)

The Clinical Outcomes Research Initiative providing a standardized reporting system in gastrointestinal endoscopy serves as a great example of how endoscopic reports could be standardized and utilized as research projects later on (38).

Country	ERCP number	Program name	Therapy	Indication	AE	Medication	Comorbidities	Success rate	30-day follow up
UK	40668	-	-	✓	✓	-	-	-	✓
UK	5264	-	✓	✓	✓	✓	✓	-	-
USA	11497	GI Trac	✓	✓	✓		✓		-
Norway	2808	Gastronet	✓	✓	✓	✓	✓	-	-
Netherlands	8575	RAF-E	✓	✓			✓	✓	-
Sweden	37860	GallRiks	✓	✓	✓	✓	✓	✓	✓
Austria	3132	B.-ERCP	✓	✓	✓		-	✓	-
Japan	1176	JED	✓	✓	✓	✓	✓	-	✓
Europe	1042	GASTER	✓	✓	-	-	-	-	-

Table 1: Data types collected in ERCP registries and data collection initiatives world-wide (B-ERCP: Benchmarking ERCP, GI: gastrointestinal, JED: Japanese Endoscopy Database, RAF-E: Rotterdam Assessment Form-ERCP, UK: United Kingdom, USA: United States of America)

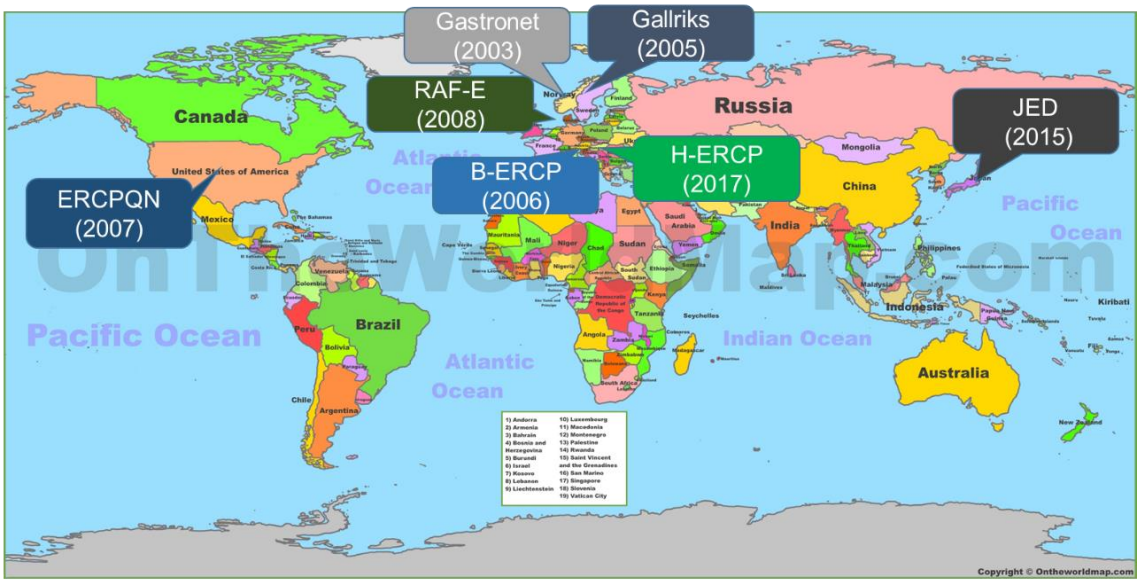


Figure 1: ERCP registries worldwide (ERCPQN: ERCP Quality Network, B-ERCP: Benchmarking ERCP, RAF-E: Rotterdam Assessment Form-ERCP, H-ERCP: Hungarian ERCP Registry, JED: Japanese Endoscopy Database), adapted from: http://ontheworldmap.com/world/world-political-map-with-countries.jpg

Another key aspect of quality is the training process of ERCP which is complicated and difficult to standardize (39). To determine competency in this field is still a matter of research and debate. More appropriate programs could be designed to register the performance of each trainee, and a standard licensing, credentialling system could be developed (40).

The ESGE (29,41) and the ASGE (17,42) started quality improvement projects to standardize and raise the quality of the endoscopic procedures and patient care worldwide. They report standardized quality measures in the field of upper, lower gastrointestinal endoscopy and ERCP, too. They support any effort that could potentially advance quality endoscopy by grants and by furthering collaboration. A great emphasis is put on the electronic, integrated, standardized reporting systems, as are the ERCP registries reported here (29).

1.3. Difficult biliary cannulation, advanced cannulation methods and ERCP in acute biliary pancreatitis cases

In about 20-30% of ERCPs, biliary access is difficult and the risk for adverse events increases, therefore the choice of proper cannulation technique is essential (43). In these situations, an advanced cannulation method should be used to access the bile ducts. If the pancreatic duct is cannulated more than once, a pancreatic guidewire-assisted technique could be used more easily. The double guidewire method, transpancreatic sphincterotomy and prophylactic pancreatic stent-assisted methods are the most widely used techniques to choose from. When the pancreatic duct is not accessed then a precut method, e.g., traditional needle knife precut papillotomy or fistulotomy could be used. Figure2 shows an algorithm for cannulation methods developed by the ESGE (16). However, there is great variability in the choice of cannulation methods between endoscopists.

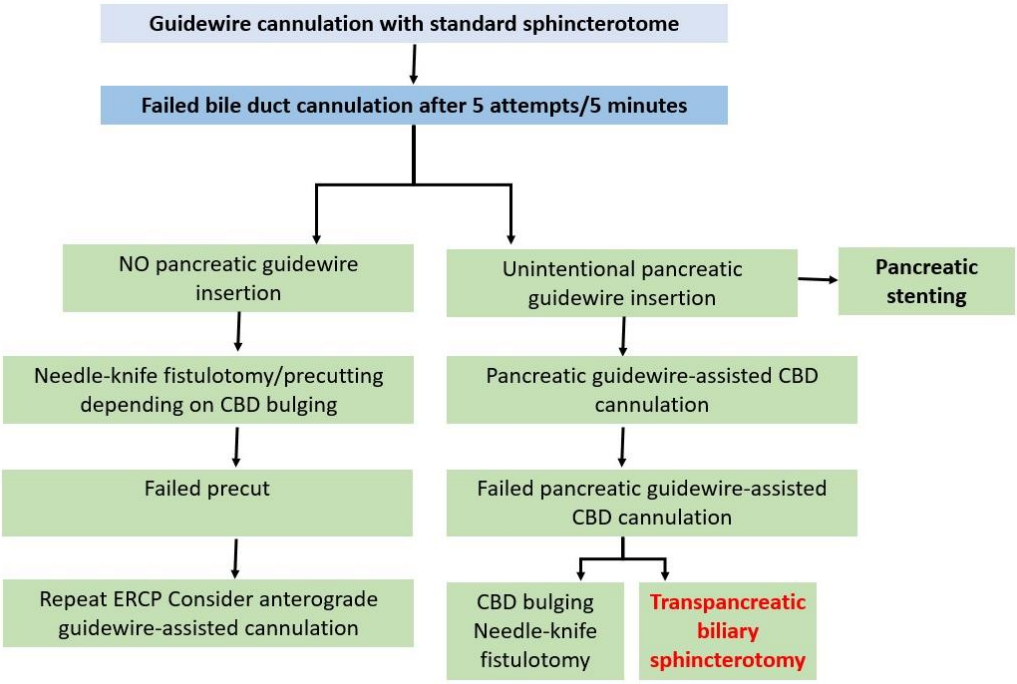


Figure 2: European Society of Gastrointestinal Endoscopy suggested algorithm for difficult biliary cannulation (CBD: common bile duct)

ERCP is a frequently indicated minimal invasive therapeutic modality and might be a lifesaving procedure in several pancreato-biliary disorders (44). In acute cholangitis (AC), early achievement of biliary drainage is associated with better outcomes, especially in the severe, septic cases as stated in the new 2018 Tokyo guideline for acute cholangitis (45). In acute biliary pancreatitis (ABP), the role of ERCP is more ambiguous, when AC is also present early intervention is indicated, however, in cases with temporary biliary obstruction only, the need for an early ERCP is questionable. The recent Dutch randomized controlled APEC trial concluded that in patients with predicted severe acute biliary pancreatitis, early (<72 hours) ERCP did not reduce the rate of death and major complications (46). Nevertheless, ERCP plays a significant role in the management of AC and ABP (47). It is a common experience that in cases of ABP, duodenal edema might result in more difficult cannulation. There are some attempts to objectively grade the difficulty of ERCP, e.g., in the consensus-based ASGE grading system cases of acute pancreatitis get a higher, 3 out of 4 points. However, no supporting data was found to this classification claim besides the consensus (48). A retrospective study validated the grading system based on their center's data and found that procedural success and complications correlate well with the ASGE grades (49). The previously widely used Schutz (50) and the newer H.O.U.S.E. classification does not contain ABP as a factor for more complicated procedures (51).

2. AIMS

1. The first aim was to develop a useable ERCP Registry System in Hungary since no structured data collecting systems were used in our country for this purpose. First single-center (37), then multicenter monitoring of quality indicators was planned.
2. Difficult biliary cannulation is a major challenge in ERCP, to achieve biliary access, advanced cannulation methods are used. We aimed to compare the cannulation success rate, adverse events rate of different advanced cannulation techniques by systematic literature review and meta-analytical methods (52,53).
3. We intended to analyze data from the H-ERCP to quantify the difficulty of ABP cases compared to AC cases without pancreatitis (54).

3. METHODS

3.1.Methods for AIM 1 (ERCP Registry)

3.1.1. General considerations

Center for Translational Medicine, University of Pécs and the Hungarian Endoscopy Study Group initiated the H-ERCP in 2016. The development of the registry was a major development in the monitoring of ERCP practice in Hungary. The development of the system is portrayed in Figure 3.

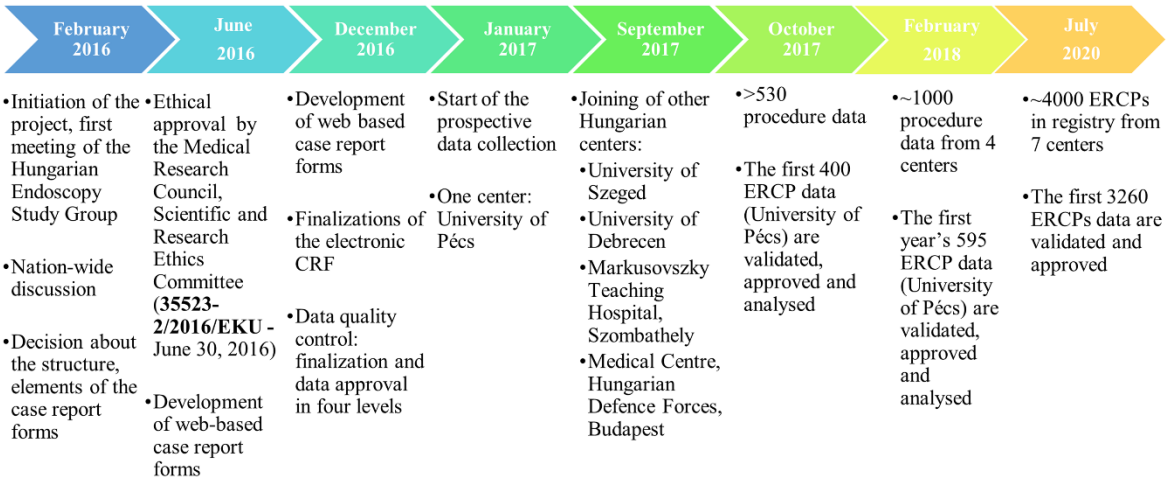


Figure 3: Development of the Hungarian ERCP Registry (ERCP: endoscopic retrograde cholangiopancreatography)

Data from the H-ERCP database was extracted to be analyzed in this study. At the point of analysis, 7 tertiary referral centers and 18 endoscopists uploaded data into the Registry. Consecutive patient enrollment was expected from all participating endoscopists. Cases from 09/2016 till 04/2019 were included in this study. A follow-up call after 30 days was carried out to discover late adverse events. In our registry, a 4-step checking system is used to ensure data quality: (1: local check from an administrator, 2: endoscopist, 3: central check by the chief administrator, 4: registry coordinator /ÁV/) (more information can be found at https://tm-centre.org/en/registries/ercp-registry/). The Scientific and Research Ethics Committee of the Medical Research Council approved the H-ERCP (TUKEB-35523/2016/EKU).

3.1.2. Inclusion and exclusion criteria

All available and quality checked, 3260 ERCP cases in the registry at the point of analysis were included. Subgroup analysis, according to e.g., native papillary status, advanced cannulation cases were executed.

3.1.3. Definitions

All definitions were made according to international guidelines. Accepted indications of procedure were based on ASGE and ESGE guidelines (15,17,55). The basis of the cannulation algorithm was provided in the ESGE cannulation guidelines (16). Complications were graded based on the 1991 consensus (14) and the new ESGE guidelines (15). Expected performance measures from ASGE (17) and ESGE were implemented (18).

3.1.4. Analyzed dataset

All available demographic data were analyzed (gender, age, ASA status /American Society of Anesthesiologists score/, body mass index /BMI/, anticoagulation/antiplatelet medication use). Indications of ERCP, cannulation techniques, cannulation and fluoroscopy times and complication rates were analyzed. The use of PEP prophylaxis measures (NSAID suppositories, prophylactic pancreatic stent placement) was also evaluated. The objective difficulty of ERCP was also investigated. This cohort study conforms with the STROBE guidelines (56).

3.1.5. Statistical analysis

Continuous measures are summarized and presented as means and standard deviations (SD) or as median and interquartile ranges (IQR). Categorical data are presented as observed and as percentages. To determine differences between continuous parameters, depending on the distribution of the data, we used the independent Student's t-test or the Mann–Whitney U test for two groups. We used the Chi-square test or Fisher's exact test to analyze the relations between the factors under examination and odds ratios were also calculated. All analyses were performed with SPSS 25 statistical software (IBM Corporation, Armonk, NY).

3.2.Methods for AIM 2 (Comparison of advanced cannulation techniques)

3.2.1. Search Strategy

A systematic literature search was conducted to find all relevant articles containing data on transpancreatic sphincterotomy(TPS)following the PRISMA guideline (57). The search strategy included the following terms: “transpancreatic septotomy” or “transpancreatic sphincterotomy” or “transpancreatic septostomy” or “transpancreatic precut sphincterotomy” or “pancreatic sphincterotomy” or “transpancreatic papillary septotomy” or “transpancreatic sphincter precut” or “transpancreatic duct precut” or “pancreatic sphincter precutting” or “pancreatic precut sphincterotomy” or “transpancreatic precut septotomy” or “transpancreatic precut septostomy” or “pancreatic septotomy” or “pancreatic septostomy” or “pancreatic precut” or “transpancreatic precut” or “transpancreatic.” EMBASE, PubMed, Scopus, Web of Science, ProQuest, and Cochrane Library databases were searched from their inception till February 8, 2018.

3.2.2. Inclusion Criteria

To compare TPS to double guidewire method (DGW) and needle knife precut papillotomy (NKPP), only prospective studies were included. However, only retrospective data were available in the comparison of TPS–needle knife fistulotomy (NKF), and these were also included in our analysis. Appropriate conference abstracts were also analyzed to minimize publication bias, and additional subgroup analyses excluding them were carried out to show their effects on outcomes. Comparative and also non-comparative prospective and retrospective studies were included in the calculation of overall success and complications rate of TPS. Randomized controlled trials (RCT) and prospective and retrospective observational studies were analyzed separately.

3.2.3. Study Selection and Data Collection

Titles and abstracts of studies identified were screened by two authors (D.P. and Á.V.) independently, and then, the full-text articles were searched to identify eligible studies. Data extraction and risk of bias assessment were done independently by the authors. Peer-

reviewed works and conference abstracts were included. Unpublished data were not requested by the authors. Any disagreement was resolved by discussion in plenum. Prophylactic measures to prevent PEP; furthermore, the length and results of follow-up were also collected and analyzed.

3.2.4. Risk of Bias Assessment

The Newcastle–Ottawa scale (NOS) was used for prospective and retrospective studies to assess the risk of bias within the individual studies (58) (Table 11). RCTs were assessed by the Cochrane Risk of Bias Tool (59) (Table 12).

3.2.5. Statistical Methods

Pooled odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to compare the biliary cannulation success and PEP rates among the different cannulation techniques. Risk difference (RD) was calculated to compare the bleeding and perforation rates to avoid overestimation since OR or risk ratio (RR) calculations would exclude those studies where zero events were reported. The random-effect model of DerSimonian and Laird(60) was used in meta-analysis. Subgroup analyses excluding studies with sequential designs and that reported only in an abstract format were also carried out. Sensitivity analyses were carried out using four types of summary statistics (RR vs. OR vs. RD vs. Peto's OR) and two types of meta-analytical models(fixed vs. random effects) to test the robustness of our findings (61). Heterogeneity was tested with two methods, namely the Cochrane's Q and the I^2 statistics. The Q test was computed by summing the squared deviations of each study's estimate from the overall meta-analysis estimate; P values were obtained by comparing the statistical results with a χ^2 distribution with $k-1$ degree of freedom (where k was the number of studies). A P value of less than 0.1 was considered suggestive of significant heterogeneity. The I^2 statistic represents the percentage of the total variability across studies that is due to heterogeneity, i.e., I^2 value between 0 and 40% indicates low, 30–60% moderate, 50–90% substantial, and 75–100% considerable heterogeneity, based on Cochrane Handbook for Systematic Reviews of

Interventions (61). Publication bias was planned to be examined by visual inspection of funnel plots and the Egger's method (62). Meta-analytical calculations were done with Review Manager (RevMan) computer program (version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3.3.Methods for AIM 3 (Difficulty of ERCP in ABP and AC)

3.3.1. General cohort from the Hungarian ERCP Registry

Prospectively collected data from the H-ERCP were analyzed in this cohort study comparing ABP and AC cases. The Hungarian Endoscopy Study Group initiated the project of the H-ERCP in 2016 (37) and the number of participating centers growing gradually since then. Cases from 7 tertiary referral centers and 15 endoscopists were uploaded into the Registry (Table 2). Quality indicators laid down by ESGE and ASGE were mostly met by our centers showing general good practice of ERCP (17,18), only NSAID suppository usage was significantly lower, while bleeding and perforation were somewhat higher than expected (Table 3). All participating endoscopists uploaded all ERCP cases which were done by them consecutively, no trainee participation was recorded. Recruitment period lasted from 09/2016 till 04/2019. A 30-day telephone follow-up, data quality check and ethical approval was carried out as detailed in Section 3.1.1. The same electronic data management system was used for data upload that Hungarian Pancreatic Study Group has used successfully for the past ten years (63–74).

Participating centers	Case numbers
Markusovszky University Teaching Hospital, Szombathely	7
Szent György University Teaching Hospital of County Fejér, Székesfehérvár	5
First Department of Medicine, University of Szeged, Szeged	103
First Department of Medicine, University of Pécs	270
Medical Centre HungarianDefenceForces, Budapest	59

Second Department of Medicine, University of Debrecen, Debrecen	33
Bács-Kiskun County University Teaching Hospital, Kecskemét	13
All cases	490

Table 2: Case numbers of participating centers

		Expected level by ESGE	**Expected level by ASGE**
Mean age (SD)	male: 67.53 (13.79) female:68.09 (16.94)	-	-
Sex ratio (female/all)	0.56	-	-
Native papilla cases	1479/2734 (54.1%)	-	-
Successful biliary cannulation rate (%)	All cases: 2512/2734 (91.9%) Native papilla cases: 1409/1479 (95.3%)	>90%	>90%
CBD stone removal rate (< 1 cm stone)	490/514 (95.3%)	≥90%	≥90%
Indomethacin suppository use rate (%)	All cases: 1399/2734 (51.2%) Native papilla cases: 909/1479 (61.5%)	~100%	N.A.
Post-ERCP pancreatitis rate (%)	All cases: 40/2734 (1.1%) Native papilla cases: 32/1479 (2.2%)	<10%	N.A.
Significant bleeding rate (%)	All cases: 30/2734 (1.1%) Native papilla cases: 20/1479 (1.4%)	N.A.	<1%
Perforation rate (%)	All cases 16/2734 (0.6%) Native papilla cases: 15/1479 (1.0%)	N.A.	<0.2%

Table 3: General characteristics of the whole cohort compared to expected quality parameters laid down by ESGE and ASGE (ESGE: European Society of Gastrointestinal Endoscopy; ASGE: American Society of Gastrointestinal Endoscopy, ERCP: endoscopic retrograde cholangiopancreatography, SD: standard deviation, CBD: common bile duct, N.A.: not applicable)

3.3.2. Inclusion and exclusion criteria

Subjects with previous papillotomy, altered gastroduodenal anatomy (surgery, gastro-duodenal obstruction), and biliary strictures were excluded to reach a more homogenous

patient population with biliary stones or sludge as main etiology. Based on these exclusion criteria from the total of 2734 cases, finally, 240 ABP and 250 AC cases without ABP were available for analysis (Figure 4). Diagnosis of AC was established by the Tokyo guidelines, while the diagnosis of ABP was based on imaging and laboratory parameters, and other etiologies of pancreatitis were excluded.

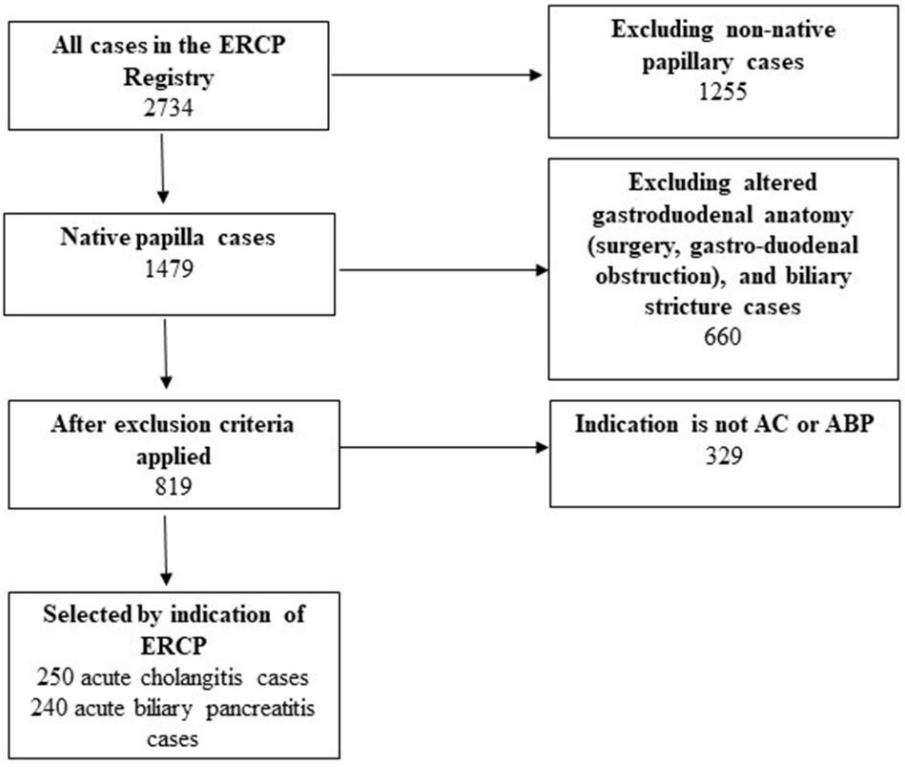


Figure 4: Flow chart of case selection to the cohort (ERCP: endoscopic retrograde cholangiopancreatography, AC: acute cholangitis, ABP: acute biliary pancreatitis)

3.3.3. Definitions

Indications of ERCP were defined in the Registry protocol according to international guidelines (17,45,47). Presence of sludge or stone in the common bile duct and/or increase of bilirubin and/or increase of transaminase levels and/or inflammatory parameters during repeated testing in 12-24 h intervals were the indications of ERCP in both groups. Guidewire-assisted simple cannulation technique was first attempted at

initial cannulation, in case of failure advanced cannulation methods (needle-knife precut, PGW-assisted techniques) were tried. PPS insertion was carried out in some cases of difficult biliary access, after unintentional PGW insertion (16).

Adverse events such as bleeding, perforation, PEP were defined as in the consensus paper from Cotton et al. (14).

3.3.4. Analyzed dataset

Besides the baseline, demographic data (gender, age, ASA status), the presence of juxtapapillary diverticulum (JPD), anticoagulation/antiplatelet medication use, the rate of successful biliary access, the use of advanced cannulation methods, PEP prophylactic measures (NSAID suppositories, prophylactic pancreatic stent placement), adverse event rates (bleeding, perforation, PEP), cannulation and fluoroscopy times were compared in the two groups. This cohort study conforms with the STROBE guidelines (56).

3.3.5. Statistical analysis

Basic statistical methods were used as detailed in Section 3.1.5. Binary logistic regression with stepwise forward elimination was used to observe independent prognostic factors from the followings: age, gender, study groups (ABP vs AC), JPD and ASA score for the main outcomes (advanced cannulation rate, pancreatic cannulation, pancreatic stent placement) where significant differences were detected, and enough data was available. All analyses were performed with SPSS 25 statistical software (IBM Corporation, Armonk, NY).

We performed a sample size calculation before the study was initiated which was based on the assumption that in the control group (AC) 20% advanced cannulation rate could be expected and we estimated the effect of ABP could increase the rate of advanced cannulation by an odds ratio of 2 (33%). Calculating by a two-sided significance level of 95%, 80% power, and the assumption mentioned above, at least 187 ABP and 187 AC

cases would be needed to detect a significant difference. OpenEpi online calculator was used to estimate the sample size (https://www.openepi.com/SampleSize/SSCohort.htm).

4. RESULTS

4.1.Results for AIM 1 (ERCP Registry)

4.1.1. General characteristics of the cohort

First, a single-center pilot study was carried out in our hospital analyzing data from the first year of the Registry. This showed the general usability of the registry system (37). In our multicenter cohort, 3260 ERCP procedures were done on 2573 patients and 1909 ERCPs (58.6%) were carried out on native papilla patients. Most patient had only 1 ERCP in the database while there were also patients with 5-9 registered procedures. From all ERCPs, 1434 (44.0%) were done on males and 1826 (56.0%) on female patients. Mean age of patients was 68.2 years (range: 2 – 103 years, SD: 15.5 years, mean of male patients: 68.0 vs. female: 68.4 years). The age distribution is shown on Figure 5.

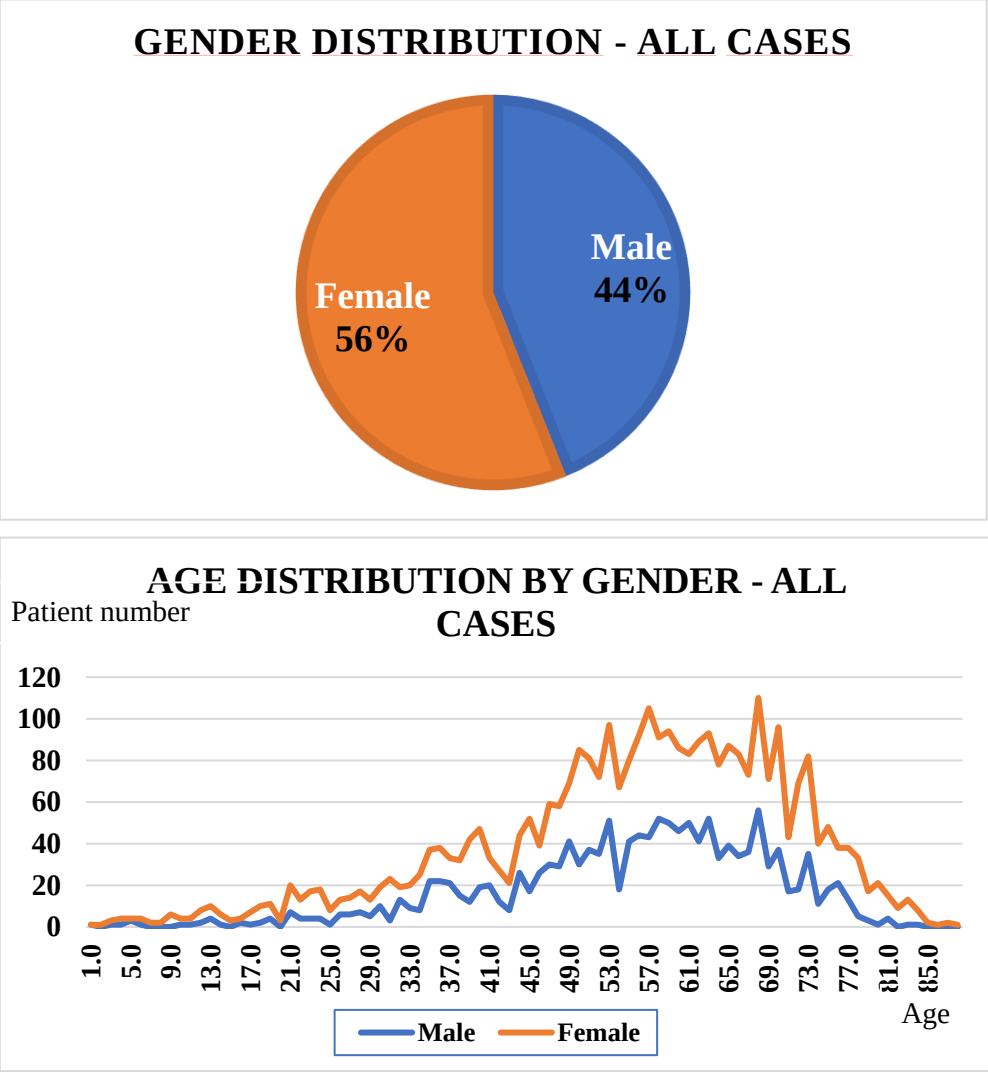


Figure 5: Gender and age distribution of cases

Mean bodyweight of the male patients was 82.9 kg vs. 70.6 kg of females. Mean height was 172.6 cm in man while 161.2 cm in females. Mean BMI was 27.8 kg/m^2 in males and 27.2 kg/m^2 in females. Most of the patients were ASA class 1 and 2 (2532/3260, 77.7%). ASA 1 class patients were significantly younger than ASA 2, 3 or 4 patients. Anticoagulation or antiplatelet medication use was more common in ASA 2, 3 and 4 patients compared to ASA 1 (Figure 6).

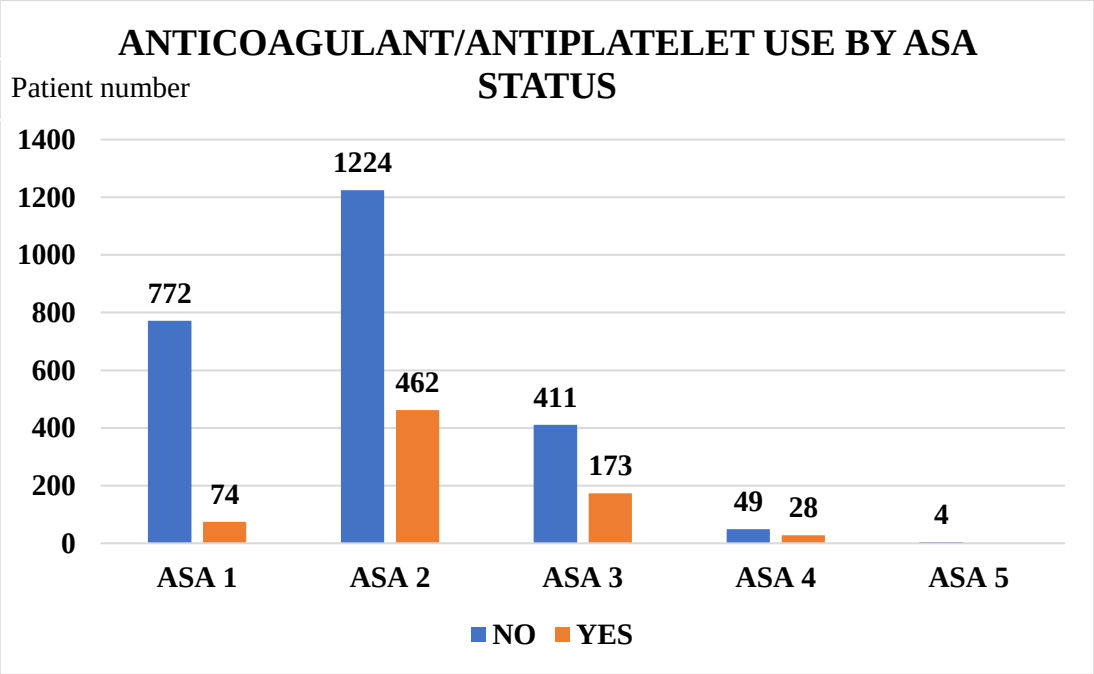


Figure 6: Distribution of anticoagulation and antiplatelet medication use by ASA (American Society of Anesthesiologists) classification groups

Patients with juxtapapillary diverticula were older (77.4 vs. 66.9 years), but gender distribution was similar (14.9% in males vs. 14.7% in females) (Figure7).

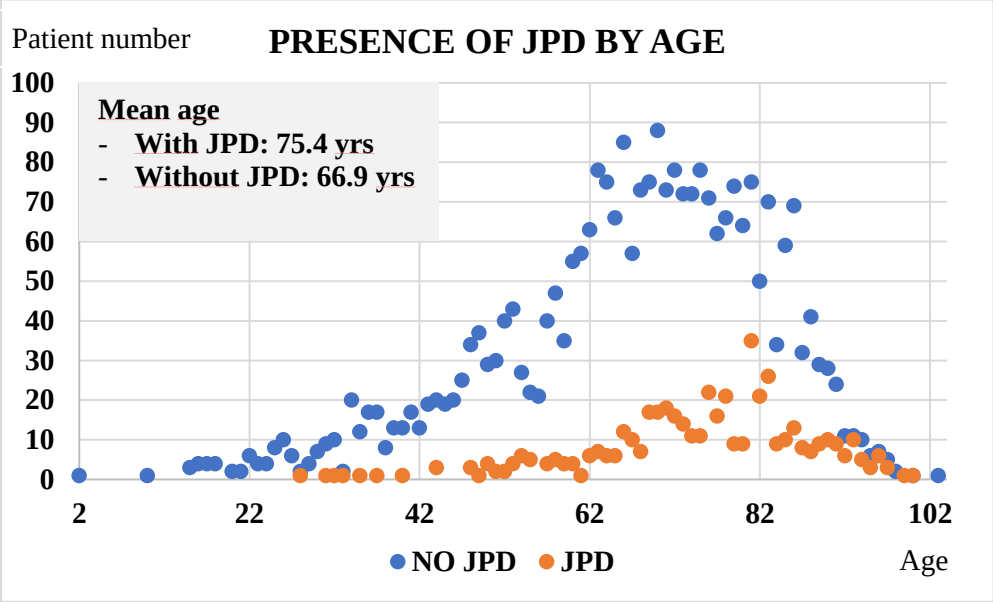


Figure 7: Presence of juxtapapillary diverticula by age (JPD: juxtapapillary diverticula)

4.1.2. Indications of ERCP

Most of ERCPs were carried out for biliary indications (3179/3260, 97.5%), pancreatic indications were rare (81/3260, 2.5%). Obstructive jaundice (31.0%), diseases of the bile ducts (32.2%) and acute cholangitis (25.9%) were the most common biliary indications. No significant differences could be observed in the distribution by gender or age.

Pancreatic indications were done for pancreatic duct disease (0.6%), for suspicion of pancreatic malignancy (0.7%) and for the evaluation of chronic pancreatitis or pseudocysts (1.1%).

4.1.3. Objective grading of ERCP difficulty

More than half of all ERCP cases were grade 2 (51%, n=1663), 31% were grade 3 (n=1018) and only 15% were grade 1 procedure according to the ASGE grading of ERCP complexity (Figure 8). The most difficult procedures with grade 4 were rare with only 3% (n=81) of all cases.

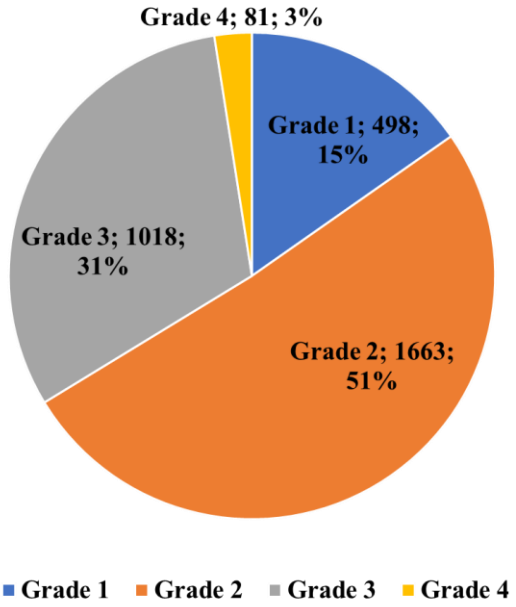


Figure 8: Distribution of ERCP difficulty grades by ASGE (ASGE: American Society of Gastrointestinal Endoscopy, ERCP: endoscopic retrograde cholangiopancreatography)

In grade 1 procedures biliary cannulation was unsuccessful in 1.4% of cases, while it was significantly higher in grade 2 (8.2%) and in grade 3 cases (7.0%), but the number of unsuccessful cannulation cases stayed below 10%. A significantly higher number of unsuccessful cannulation cases could be seen in the grade 4 ERCPs with 35.5% of all cases (Figure 9). PEP rate was not higher in the more complex grades; however, bleeding (3.7%) and perforation (1.2%) were more common in grade 4 cases.

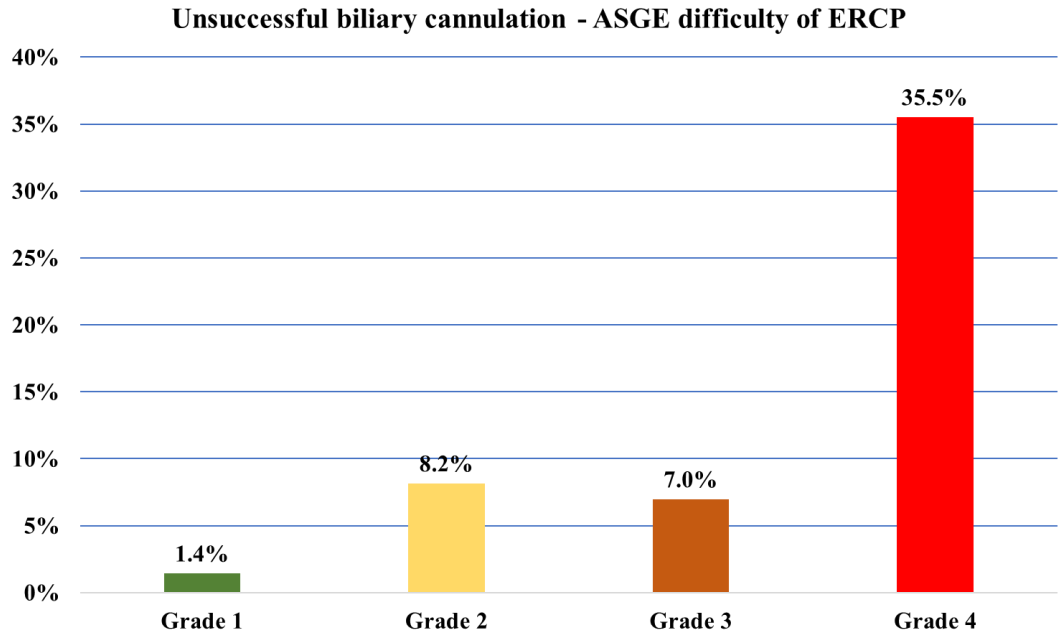


Figure 9: Distribution of ERCP difficulty grades by ASGE (ASGE: American Society of Gastrointestinal Endoscopy, ERCP: endoscopic retrograde cholangiopancreatography)

4.1.4. Biliary cannulation success rates

Biliary cannulation was successful in 92.6% (2943/3179) of all cases with biliary indication while 91.3% (1710/1872) in native papilla cases, while the success rate reduced to 88.1% (897/1018) in difficult biliary cannulation cases. After the use of advanced cannulation methods in 85.8% (738/860) of the cases successful biliary access was achieved. The overall cannulation rate was above 90% in all centers, but there were some variations in the cannulation success of native papilla cases and even more in cases of difficult biliary access (Figure 10).

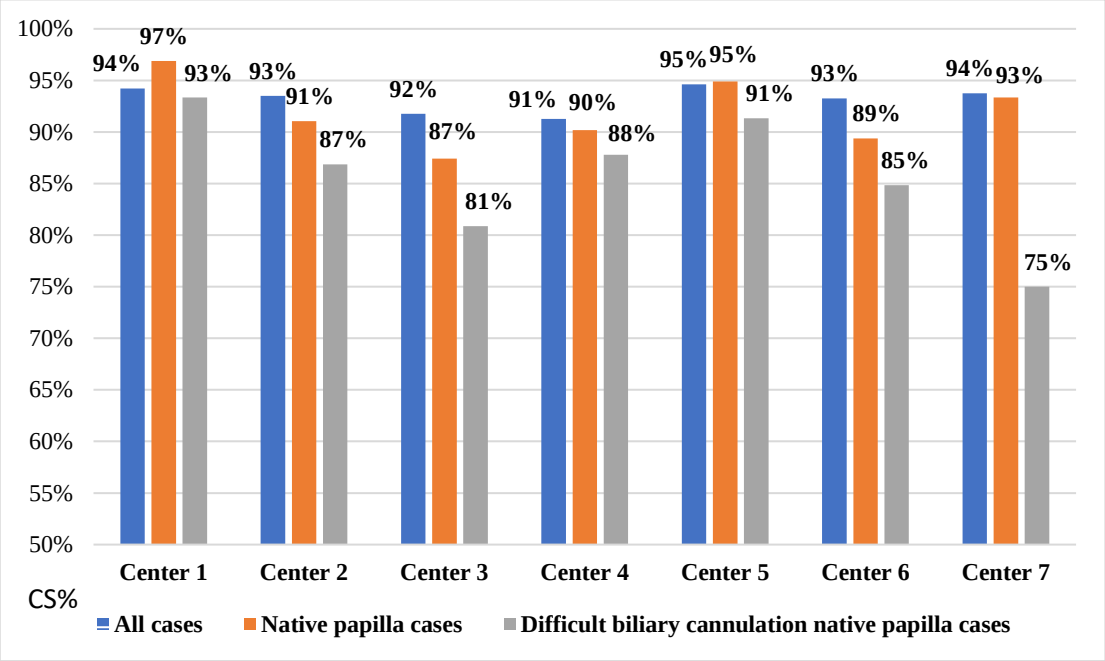


Figure 10: Cannulation success rates by centers (CS%: cannulation success rate)

4.1.5. Advanced cannulation methods

In 759 cases at least one advanced cannulation method was used. The cannulation algorithm and distribution of primary advanced cannulation techniques are displayed on Figure 11. In 40.2% (305/759) of advanced cannulation cases successful biliary access was achieved in less than 5 minutes from the beginning of the cannulation.

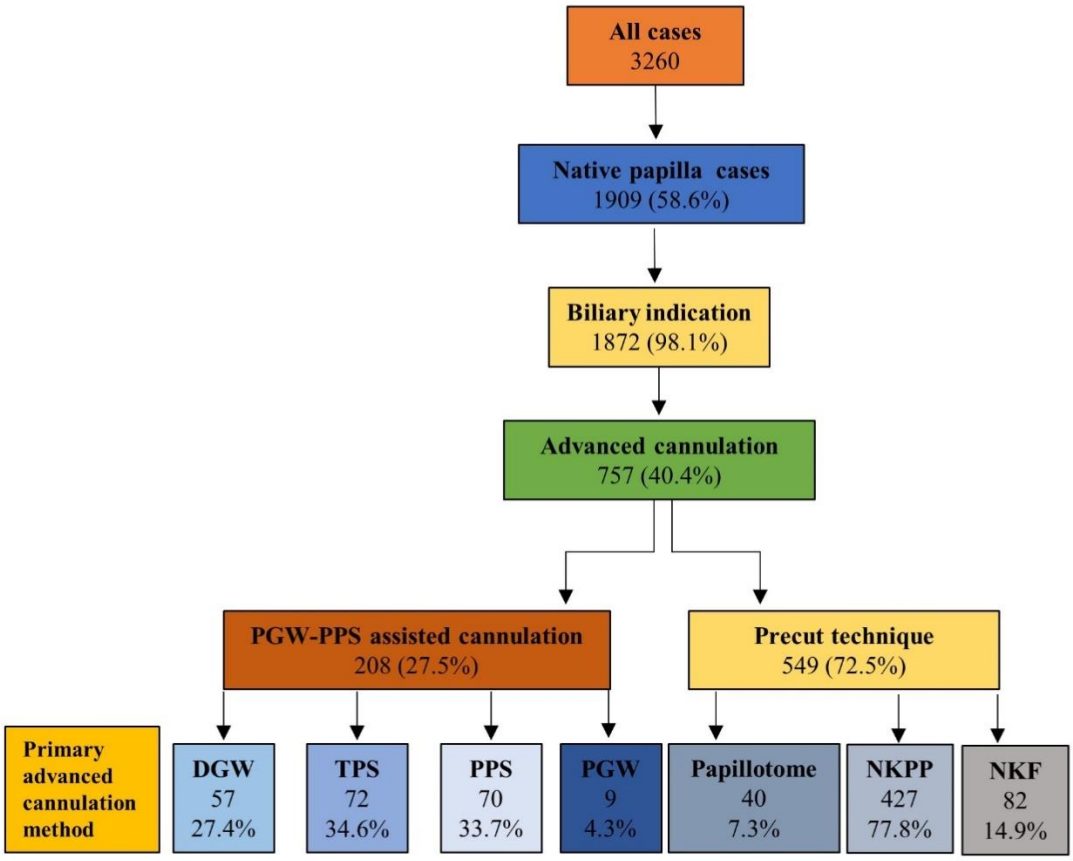


Figure 11: The use of advanced cannulation techniques (DGW: double guidewire method, TPS: transpancreatic sphincterotomy, PPS: prophylactic pancreatic stent, PGW: pancreatic guidewire technique, papillotome: papillotome precut, NKPP: needle knife precut papillotomy, NKF: needle knife fistulotomy)

4.1.6. Adverse event rates

PEP rate of all cases was 1.6% (53/3260), while in cases with native papilla was 2.5% (48/1909) and it was 3.1% (32/1045) in difficult biliary cannulation cases. The severity of PEP was mild in the majority of cases (n=38, 71.7%), moderate in 22.6%, while severe in 5.7%.

Clinically significant bleeding occurred in 0.9% (30/3260) of all cases, in native papilla cases it was 1.1% (21/1909), while in difficult cannulation cases it was 1.4% (15/1045).

50% of all significant bleeding events were mild, 43.3% were moderate severity and only 2 cases required 2 or more units of blood transfusions and classified as severe bleeding complications.

Perforations occurred in 0.6% (19/3260) of all ERCPs, mostly developed in native papilla patients (0.9%, 17/1909). Ten perforations were registered in difficult cannulation cases (1.0%, 10/1045). Out of all perforation cases 9 were mild, not requiring prolonged hospitalization (47.4%), however 10 cases (52.6%) required longer hospital stay (4-10 days) (14). Only one case required surgical operation due to perforation by the tip of the endoscope. Guidewire caused perforation (Stapfer type III) in six cases, in 11 cases periampullary perforation (Stapfer type II) occurred during sphincterotomy, one perforation occurred after ampullectomy and in one case distant perforation (Stapfer type I) was recorded (75).

Post-ERCP cholangitis developed in 74 patients (2.3%). 83.8% of them were mild and only required antibiotics, while re-ERCP was needed to resolve cholangitis in 16.2% of the cases.

Hypoxia were observed in 2.3% (75/3260) of all ERCPs and hypotension during procedure was recorded only in 2 patients.

The use of advanced cannulation techniques did not increase the PEP, clinically significant late bleeding and perforation rates compared to simple cannulation native papilla cases, while intraprocedural bleeding was significantly higher in the advanced cannulation group (Table 4).

	Native papilla simple cannulation cases (n=1140)		All advanced cannulation cases (n=860)		p-value
Post-ERCP pancreatitis	25	2.2%	24	2.8%	0.39
Intraprocedural bleeding	73	6.4%	121	14.1%	**<0.001**
Clinically significant late bleeding	9	0.8%	13	1.5%	0.13
Perforation	8	0.7%	9	1.0%	0.41

Table 4: Adverse events in advanced and simple cannulation cases

4.1.7. Post-ERCP pancreatitis prophylaxis

Indomethacin suppositories (IND) were administered in 47.4% (1546/3260) of all cases, while in cases with native papilla the use of NSAID increased to 57.2% (1092/1909), and it was similar to the latter in difficult cannulation cases (57.4%, 600/1045). 24 PEP developed in cases where no NSAID suppository was given, out of them unfortunately 1 was severe and 5 PEP was moderately severe. 9 PEP developed in the 243 ERCPs with multiple pancreatic cannulations (3.7%). Only 44% of these cases was a PPS placed, 6 PEP developed in patients without PPS (6/135, 4.4%), while with PPS only 3 PEP was registered (3/108, 2.8%) (Table 5).

	Case number	PEP	PEP%
All multiple pancreatic cannulation cases	243	9	**3.7%**
PPS+IND	74	2	**2.7%**
Only PPS	34	1	**2.9%**
Only IND	79	5	**6.3%**
No prophylaxis	56	1	**1.8%**

Table 5: PEP rate and prophylaxis methods in patients with multiple pancreatic cannulation (IND: indomethacin suppository, PEP: post-ERCP pancreatitis, PPS: prophylactic pancreatic stent)

4.1.8. Cannulation times

Mean cannulation time was 184 sec if all cases are included, cannulation time increased to 249 sec in native papilla cases, and in patients with difficult biliary cannulation it was 439 sec, above the 5-minute margin. Cannulation was achieved after 5 minutes in 470 cases, 15 PEP developed (3.2%) in these cases.

An increasing trend of PEP (Figure 12) and procedural bleeding (Figure 13) rates could be seen with prolonged cannulation times in simple cannulation cases. PEP rate increased from 0.6% in the <120 sec cannulation group to 2.1% in the 120-300 sec group (p=0.002), while clinically significant bleeding is 0.5% in the <120 sec groups and 1.7% in the groups >120-300 sec (p=0.01).

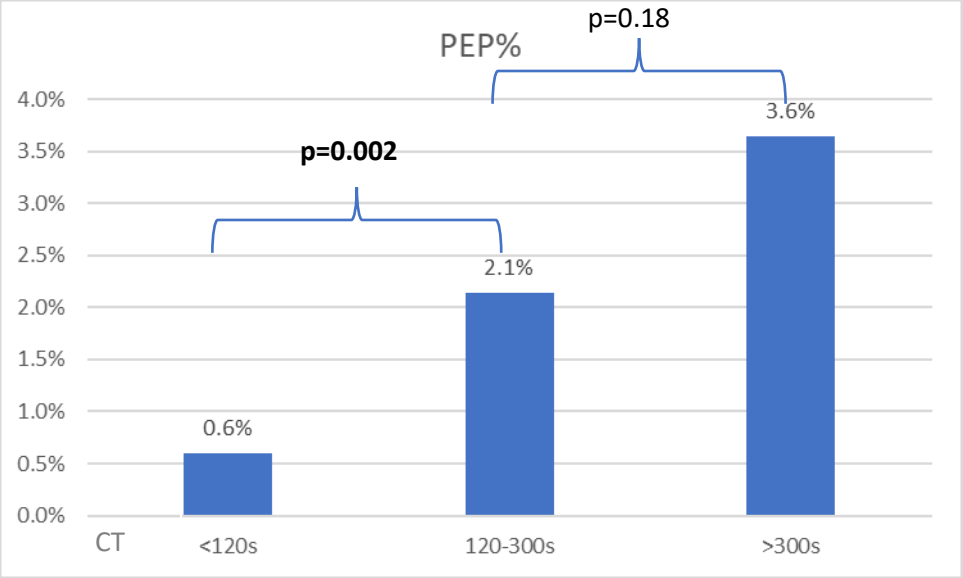


Figure 12: Post-ERCP pancreatitis rates and cannulation time (PEP: post-ERCP pancreatitis; CT: cannulation time)

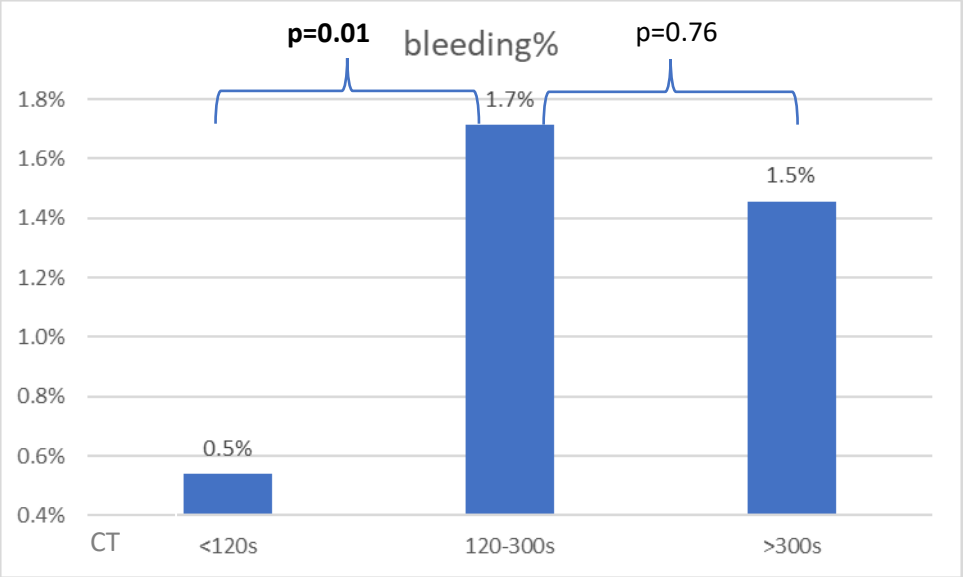


Figure 13: Procedural bleeding and cannulation time (CT: cannulation time)

4.1.9. Fluoroscopy times

Mean fluoroscopy time was 126 sec. In most centers, fluoroscopy time was in the 90-130 sec range. However, in 2 centers mean fluoroscopy time was considerably longer, 166 sec and 284 sec (Figure 14).

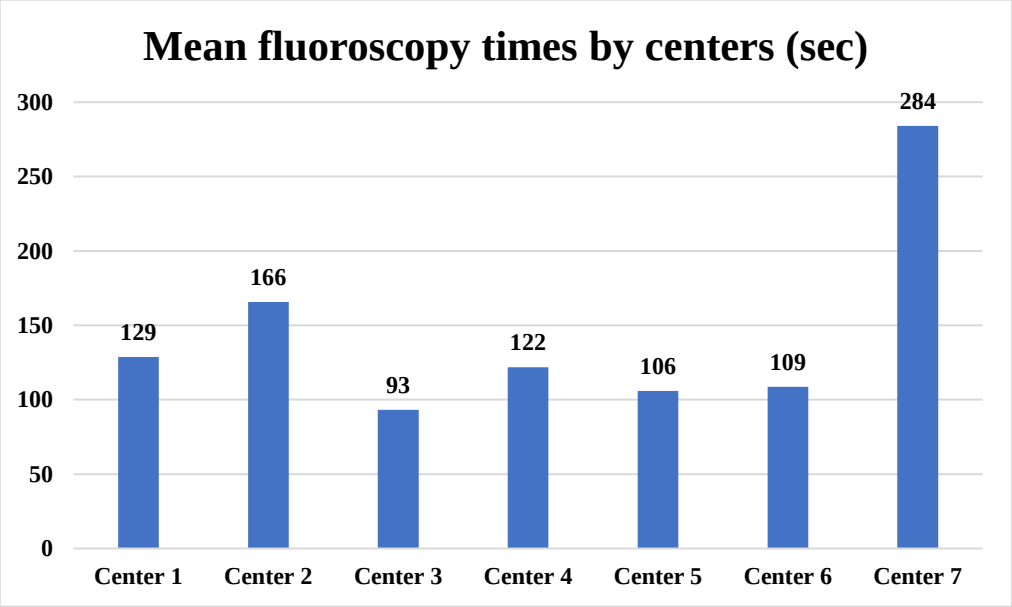


Figure 14: Mean fluoroscopy times by centers (in seconds)

4.1.10. Quality indicators of ERCP practice

Most quality indicators were met; however, perforations and bleeding complications rate were higher than the expected target. Follow up was only successful in 71.6% of cases, which should be improved to detect delayed adverse events.

There was a high variability in the use of INDs among centers (1.7-91.7% of all cases). In one center PEP rate was unexpectedly high, 20.4%.

In two centers, the rate of successful cannulation in native papilla cases were 0.6-2.6% lower than the 90% threshold (Table 6).

Quality indicators (ASGE 2015)	Grade of recomm.	Perfor-mance target	Measured rate All cases	Measured rate Pilot study (37)
Documented appropriate indication	1C+	>90%	**100%**	**100%**
Informed consent is obtained / documented	1C	>98%	**99.3%**	**99.0%**
Patient monitoring during sedation is performed	3	>98%	**98.4%**	**98.3%**
Doses and routes of medications are documented	3	>98%	**100%**	**99.0%**
Immediate adverse events are documented	3	>98%	**100%**	**100%**
Deep cannulation of the ducts of interest inpatients with native papilla and unaltered anatomy	1C	>90%	**92.0%**	**93.8%**
CBD stones <1 cm without stricture are extracted	1C	>90%	**95.7%**	**94.2%**
Stent placement for biliary obstruction below bifurcation	1C	>90%	**95.9%**	**90.4%**
Rate of post-ERCP pancreatitis	1C	(>10%)*	**2.5%**	**2.2%**
Rate of perforations	2C	≤0.2%	**0.6%**	**1.3%**
Rate of clinically significant bleeding after sphincterotomy	1C	≤1%	**1.1%**	**0.3%**
Frequency with which patients are contacted at or greater than 14 days to detect adverse events	3	>90%	**71.6%**	**75.5%**

Table 6: Quality indicators of ERCP practice laid down by ASGE (17) and ESGE* (15) (ASGE: American and European Society of Gastrointestinal Endoscopy, ESGE: European Society of Gastrointestinal Endoscopy, ERCP: endoscopic retrograde cholangiopancreatography, CBD: common bile duct)

4.2.Results for AIM 2 (Comparison of advanced cannulation techniques)

4.2.1. Study selection

Altogether, 2787 records identified during database searching: 510 in EMBASE, 339 in PubMed, 968 in Scopus, 255 in Web of Science, 544 in ProQuest and 171 in Cochrane Library, respectively. The latest search was run on February 8, 2018, and finally 33 relevant studies were included in the qualitative synthesis, while data from 14 studies were extracted for the meta-analysis (Figure 15).

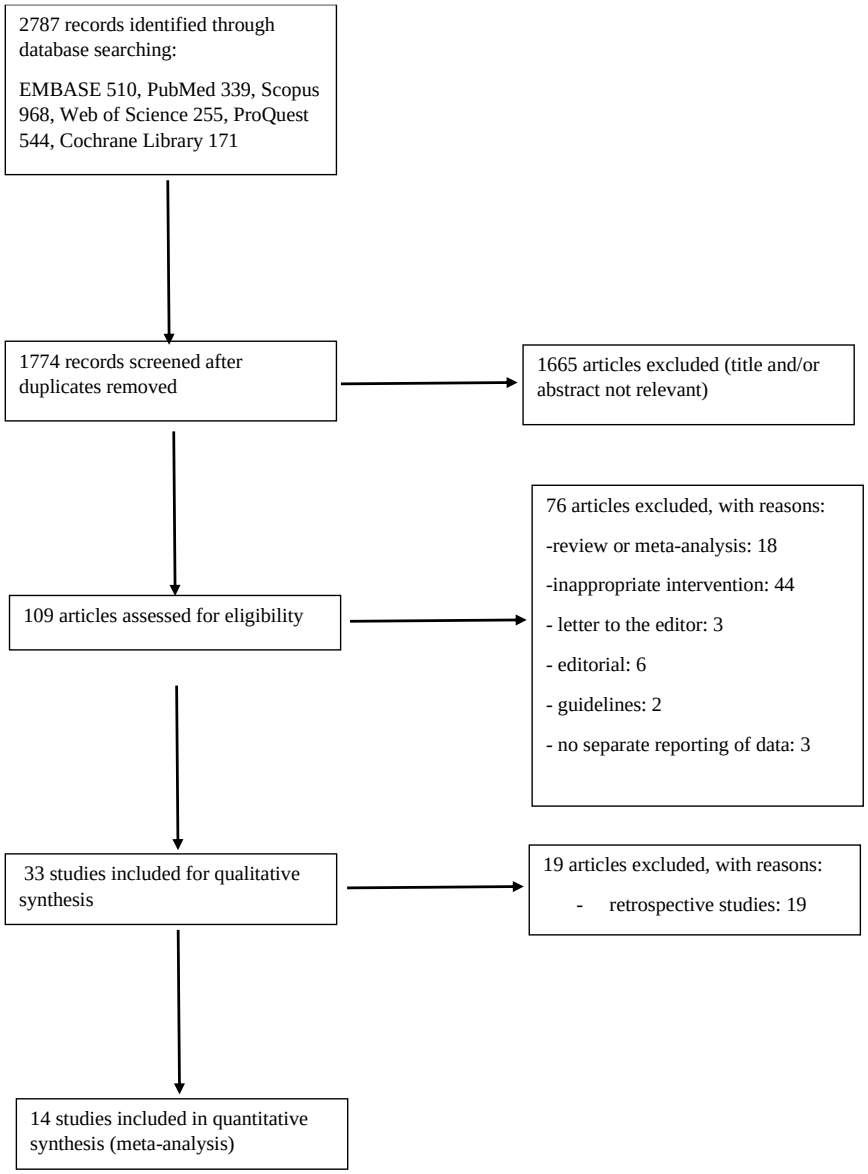


Figure 15: Flow diagram of literature search

4.2.2. Characteristics of studies included

Characteristics of the included studies with the applied PEP prophylaxis, the definitions of difficult biliary access and the endoscopists / centers experiences and the late adverse events are summarized in Table 7-9, respectively.

Three RCTs (76–78) and two prospective observational studies (79,80) reported comparable data about TPS vs. DGW. One of them was only available in abstract form (76). Two of them used a sequential design (79,80), applying TPS only after DGW, as a rescue technique.

Two RCTs (81,82) and three prospective, observational studies (79,80,83) provided data on the comparison of TPS vs. NKPP, two of them with sequential design (79,80), no new prospective studies were identified compared to our previous meta-analysis, however, additionally, we conducted further sensitivity and subgroup analyses in this comparison (53).

Comparison of TPS and NKF was not found in any prospective studies, in this estimation four retrospective studies (two of them only in abstract form) were analyzed to synthesize available comparative evidence (84–86).

Two prospective case series of TPS without relevant comparisons to other advanced cannulation methods (87,88) and, additionally, 23 retrospective observational studies with reported outcome data were included in the pooled analyses of overall outcomes of TPS (84,84–86,89–107) (Table 10).

Study	Study design	Comparison	Sequential design	Form of publication	PPS use	NSAID suppository
Cha, 2012	RCT	DGW vs. TPS	no	abstract	NR	NR
Sugiyama, 2017	RCT	DGW vs. TPS	no	full text	in all cases	no (nafamostate)
Yoo, 2013	RCT	DGW vs. TPS	no	full text	no	no
Kim, 2015	prospective	DGW vs. TPS vs. NKPP	yes	full text	2/27 (7%) in DGW group, 25/38 (66%) in TPS group, p<0.001	no
Zou, 2015	prospective	DGW vs. TPS vs. NKPP	yes	full text	14/63 in all patients compared, not reported separately in DGW/TPS groups	no
Catalano, 2004	RCT	NKPP vs. TPS	no	full text	PPS in some patients	no
Zang, 2014	RCT	NKPP vs. TPS	no	full text	no	no
Espinel-Diez, 2013	prospective	NKPP vs. TPS	no	full text	no	no
Horiuchi, 2007	retrospective	NKF vs. TPS	no	full text	no	no
Katsinelos, 2012	retrospective	NKF vs. TPS	no	full text	no	no (pentoxifylline)
Lee, 2015	retrospective	NKF vs. TPS	no	full text	no	no (protease inhibitor)
Wen, 2017	retrospective	NKF vs. TPS	no	abstract	NR	NR
Kahaleh, 2004	prospective	no	no	full text	25% (29/116) of all cases	NR
Weber, 2008	prospective	no	no	full text	no	NR

Table 7: Characteristics of the studies included in the meta-analysis with the prophylactic measures to prevent post-ERCP pancreatitis (PEP). (PPS prophylactic pancreatic stent, RCT randomized controlled trial, DGW double-guidewire cannulation, TPS transpancreatic biliary sphincterotomy, NKPP needle-knife precut papillotomy, NKF needle-knife fistulotomy, NR not reported)

Study	Definitions of difficult biliary access	Endoscopist's experience	Centers
Cha, 2012	Randomization when PGW inserted unintentionally	NR	Multicenter study, possibly high-volume university centers
Sugiyama, 2017	Unsuccessful biliary cannulation after 15 minutes or unintentional pancreatic duct cannulation more than three times	7 endoscopists who had at least 3 years' experience in the pancreaticobiliary team at the tertiary referral center, had performed over 300 ERCP-related procedures per year, and was able to achieve selective deep cannulation in more than 90% of cases using standard techniques	2052 ERCP in 3 years (1 high volume center)
Yoo, 2013	Unsuccessful biliary cannulation after 10 attempts or failure of biliary access after 10 min	1 experienced endoscopist	1 center, between January 2005 and September 2010, a total of 1893 ERCPs
Kim, 2015	Unsuccessful biliary cannulation after 10 attempts	Two similarly experienced endoscopists performed all procedures (> 1000 ERCPs in the past)	> 150 ERCPs/year in the study period for patients with a naïve papilla
Zou, 2015	Unsuccessful biliary cannulation by more than two experts; failure of biliary access after 30 minutes or unintentional pancreatic duct cannulation more than five times	Four experienced endoscopists performed all procedures (> 200 ERCPs/year during previous 3 years)	High volume center (> 1000 ERCPs/year during the previous 2 years)
Catalano, 2004	Unsuccessful biliary cannulation after 30 minutes and/or the pancreatic duct had been opacified multiple times	NR	High volume center (> 1000 ERCPs/year)
Zang, 2014	Unsuccessful biliary cannulation after 10 minutes and/or unintentional pancreatic duct cannulation more than five times	One experienced endoscopist performed all procedures (> 350 ERCPs/year)	No data on ERCP volume, high volume center can be assumed from number of included patients
Espinel-Diez, 2013	Unsuccessful biliary cannulation after 5 attempts	One experienced endoscopist performed all procedures (> 200 ERCPs/year)	High volume of therapeutic ERCPs, numbers not specified
Horiuchi, 2007	Unsuccessful biliary cannulation after 15 minutes and/or the pancreatic duct had been opacified multiple times	Two endoscopists, experience not reported	Approximately 200 ERCPs/year

Katsinelos, 2012	Unsuccessful biliary cannulation after 10 attempts	One experienced endoscopist performed all procedures (>300 ERCPs/year)	>300 ERCPs/year in the study period for patients with a naïve papilla
Lee, 2015	Repeated unintentional pancreatic duct cannulation within 5 minutes and/or unintentional pancreatic duct cannulation more than three times	One experienced endoscopist (>150 therapeutic ERCPs/year)	1 center
Wen, 2017	NR	One experienced endoscopist	1 center
Kahaleh, 2004	Unintentional pancreatic duct opacification more than three times	All ERCPs were performed by 2 dedicated pancreaticobiliary endoscopists, both performs more than 500 ERCPs annually.	High-volume center
Weber, 2008	Not defined	NR	High-volume center

Table 8: Summary of the definitions of difficult biliary access, endoscopists' experience, and centers' case load in the studies included in the meta-analysis. (NR not reported, PGW pancreatic guidewire, ERCP endoscopic retrograde cholangiopancreatography)

Study	Study design	Length of follow-up	Type	Complications	PD-stricture
Kim, 2015	Prospective, observational	NR	NR	no	No chronic pancreatitis or ductitis from PD stenting
Catalano, 2004	RCT	NR	Telephone contact and office visits	no	no
Kahaleh, 2004	Prospective, observational	Median follow-up was 5 months (2-35)	Clinic visit and/or telephone interview by a nurse	no	no

Table 9: Late adverse events in the prospective studies, where longer-term follow-ups were reported (Studies without follow-up data are not shown, RCT randomized controlled trial, PD pancreatic duct, NR not reported)

Studies	Design	Number of patients in TPS group	Successful biliary cannulation	%	PEP	%	Bleeding	%	Perfo-ration	%
Catalano, 2004	RCT	31	29	93.5%	1	3.2%	0	0.0%	0	0.0%
Cha, 2012 (abstract)	RCT	42	39	92.9%	5	11.9%	NA	NA	NA	NA
Sugiyama, 2017	RCT	34	32	94.1%	1	2.9%	0	0.0%	0	0.0%
Yoo, 2013	RCT	37	29	78.4%	4	10.8%	2	5.4%	0	0.0%
Zang, 2014	RCT	73	70	95.9%	5	6.8%	1	1.4%	0	0.0%
Sum RCT		**217**	**199**	**91.7%**	**16**	**7.4%**	**3**	**1.7%***	**0**	**0.0%***
Espinel-Díez, 2013	prospective	125	117	93.6%	4	3.2%	6	4.8%	1	0.8%
Kahaleh, 2004	prospective	116	99	85.3%	9	7.8%	3	2.6%	2	1.7%
Kim, 2015	prospective, sequential	38	28	73.7%	14	36.8%	1	2.6%	0	0.0%
Weber, 2008	prospective	108	103	95.4%	6	5.6%	6	5.6%	0	0.0%
Zou, 2015	prospective, sequential	25	18	72.0%	NA	NA	NA	NA	NA	NA
Sum prospective		**629**	**564**	**89.7%**	**49**	**8.1%***	**19**	**3.4%***	**3**	**0.5%***
Akashi, 2004	retrospective	172	163	94.8%	10	5.8%	2	1.2%	0	0.0%
Barakat, 2017 (abstract)	retrospective	368	321	87.2%	4	1.1%	1	0.3%	0	0.0%
Chan, 2012	retrospective	53	36	67.9%	2	3.8%	1	1.9%	0	0.0%
de-la-Morena-Madrigal, 2013	retrospective	50	35	70.0%	2	4.0%	1	2.0%	0	0.0%
de-la-Morena-Madrigal, 2017	retrospective	78	75	96.2%	5	6.4%	4	5.1%	4	5.1%
Esmaily, 2017 (abstract)	retrospective	105	81	77.1%	6	5.7%	1	1.0%	1	1.0%
Goff, 1995	retrospective	32	29	90.6%	4	12.5%	0	0.0%	0	0.0%
Goff, 1999	retrospective	51	50	98.0%	0	0.0%	0	0.0%	1	2.0%
Halttunen, 2009	retrospective	262	255	97.3%	23	8.8%	4	1.5%	0	0.0%

Studies	Design	Number of patients in TPS group	Successful biliary cannulation	%	PEP	%	Bleeding	%	Perfo-ration	%
Horiuchi, 2007	retrospective	48	46	95.8%	1	2.1%	0	0.0%	0	0.0%
Huang, 2016	retrospective	60	51	85.0%	2	3.3%	0	0.0%	0	0.0%
Javia, 2016 (abstract)	retrospective	20	15	75.0%	1	5.0%	0	0.0%	0	0.0%
Kapetanos, 2007	retrospective	34	29	85.3%	1	2.9%	1	2.9%	0	0.0%
Katsinelos, 2012	retrospective	67	67	100.0%	15	22.4%	0	0.0%	0	0.0%
Lee, 2015	retrospective	67	58	86.6%	7	10.4%	5	7.5%	0	0.0%
Liao, 2011 (abstract)	retrospective	108	99	91.7%	4	3.7%	2	1.9%	0	0.0%
Lin, 2014	retrospective	20	18	90.0%	3	15.0%	1	5.0%	0	0.0%
McGonigle, 2014 (abstract)	retrospective	31	25	80.6%	2	6.5%	1	3.2%	1	3.2%
Miao, 2015	retrospective	36	35	97.2%	2	5.6%	0	0.0%	0	0.0%
Miyatani, 2009	retrospective	20	17	85.0%	6	30.0%	1	5.0%	0	0.0%
Wang, 2010	retrospective	140	116	82.9%	16	11.4%	2	1.4%	0	0.0%
Wen, 2017 (abstract)	retrospective	113	111	98.2%	11	9.7%	2	1.8%	1	0.9%
Zhong, 2018	retrospective	77	73	94.8%	8	10.4%	2	2.6%	0	0.0%
Sum all		**2615**	**2343**	**89.6%**	**183**	**7.1%***	**50**	**2.0%***	**11**	**0.4%***

Table 10: Summary of adverse events and success rates of all studies containing data about TPS. (NA: not applicable, RCT: randomized controlled trial, TPS: transpancreatic sphincterotomy, *calculated from those studies where the rate of this adverse event was available)

4.2.3. Methodological quality and risk of bias assessment

The risk of bias in the prospective (not RCTs) and the four retrospective studies included in the meta-analyses were analyzed with the NOS (Table 11). In most of the full-text studies baseline characteristics of cohorts were reported with comparable, homogeneous groups. Technical details of interventions were thoroughly reported, all full-text studies defined precut methods appropriately. On the other hand, definitions of adverse outcomes were not the same in all the studies. However, most of them used the consensus definitions (14). The appropriate length of follow-up is questionable in the cases of late adverse events, only one prospective study reported the length of follow-up as longer than 30 days (87). All abstracts lacked information about most of the above- mentioned details, therefore they are of high risk of bias.

	Selection		Comparison		Exposure		
	S/1	S/2	C/1	C/2	E/1	E/2	E/3
Espinel Diez, 2013	+	+	?	?	−	−	+
Horiuchi, 2007	+	+	+	+	−	?	?
Kahaleh, 2004*	−	+	−	−	−	+	+
Katsinelos, 2012	+	+	+	+	−	+	+
Kim, 2015	+	+	+	+	−	?	+
Lee (abstract), 2015	?	?	?	?	−	+	+
Weber, 2008*	−	+	−	−	−	?	?
Wen (abstract), 2017	?	?	?	?	−	?	?
Zou, 2015	+	+	+	+	−	?	?

Table 11: Risk of bias assessment of prospective, non-randomized, and retrospective studies with the Newcastle–Ottawa scale (S/1: Representativeness of the exposed cohort /transpancreatic sphincterotomy group compared to advanced cannulation technique group/; S/2: Selection of the non-exposed cohort /advanced cannulation technique group/; C/1: Comparability of cohorts on the basis of similar indications of procedure; C/2: Comparability of cohorts on the basis of age; E/1: Assessment of outcome /were blinded assessment executed?/; E/2: Was follow-up long enough? /longer than 14 days/; E/3: Adequacy of follow-up of cohorts /is any attrition of patients present?/ Two studies are not comparing TPS to another advanced cannulation technique and are marked with an asterisk)

RCTs	1	2	3	4	5	6	7
Cha (abstract), 2012	?	?	−	−	−	−	−
Catalano, 2004	?	?	−	−	−	−	+
Sugiyama, 2017	?	?	−	−	+	+	+
Yoo, 2013	+	+	−	−	+	+	+
Zang, 2014	?	?	−	−	−	−	+

Table 12: Risk of bias assessment of RCTs with the Cochrane Collaboration risk of bias tool (1: Random sequence generation; 2: allocation concealment; 3: blinding of participants and personnel; 4: blinding of outcome assessment; 5: incomplete outcome data; 6: selective reporting; 7: other bias; RCT: randomized controlled trial)

In case of RCTs, the Cochrane Risk of Bias Tool was used (Table 12). Only one study (78) reported the method of randomization and the method of ensuring allocation concealment. Blinding in studies of endoscopic interventions at participant and personnel level is difficult to execute, and therefore could not be expected. However, blinded late outcome assessment (PEP, late bleeding, perforation) could be arranged more easily. Nevertheless, none of the studies reported blinding (masking) of any kind. Three out of 5 RCTs did not report the rate of cholangitis, therefore this outcome could not be analyzed (76,82,108). One RCT was published only in abstract form which makes the data quality questionable, consequently, this study was of high risk of bias (76).

Publication bias could not be reliably assessed based on funnel plots or by the Egger's method because of the small number of included studies. According to the Cochrane Handbook funnel plots and other statistical tests are not advised to assess small study effect and publication bias under ten studies per analysis (61,62,109).

4.2.4. Endoscopists' experience and centers' case volumes in the prospective studies

Most of the prospective studies reported endoscopists' experience in yearly case numbers, some also described lifetime ERCP numbers. Based on the reported numbers, all endoscopists performed more than 200 ERCPs/year. In one study, the case load of the endoscopists exceeded 500 ERCPs annually (87). Trainee participation was not reported in any of the studies (Table 8). Most of the centers reported high-volume ERCPs (even above 1000 procedures/year (80,85), only one study (84) reported lower numbers (<300 ERCPs/year), while no information was found about center or endoscopist case load in one studies (91) (Table 8).

4.2.5. Biliary cannulation success rate

TPS showed superiority in success rate compared to DGW (OR 2.72; 95% CI 1.30-5.69; 176 and 235 patients, respectively; I^2 =50%) (Figure 16A) and NKPP (OR 2.32; 95% CI 1.37-3.93; 292 and 260 patients, respectively; I^2 =7%) (Figure 16B). The success rate of TPS and NKF did not differ (OR 1.38; 95% CI 0.32-5.96; 295 and 141 patients, respectively; I^2 =22%) (Figure 16C).

In the TPS vs. DGW comparison of cannulation success rates, no significant difference was detected between the two methods (OR 3.02; 95% CI 0.73-12.59; 113 and 107 patients, respectively; I^2 =69%), if only RCTs were included, probably because of the greater confidence intervals of the results. On the other hand, subgroup analysis of full-text studies found the superiority of TPS over DGW with regard cannulation success rate.

The overall success rate of TPS in prospective studies was 89.7% (564/629). The success rate was the same if all studies were analyzed (89.6%, 2343/2615), as well as the separate analysis of RCTs were resulted similarly high value (91.7%, 199/217) (Table 10).

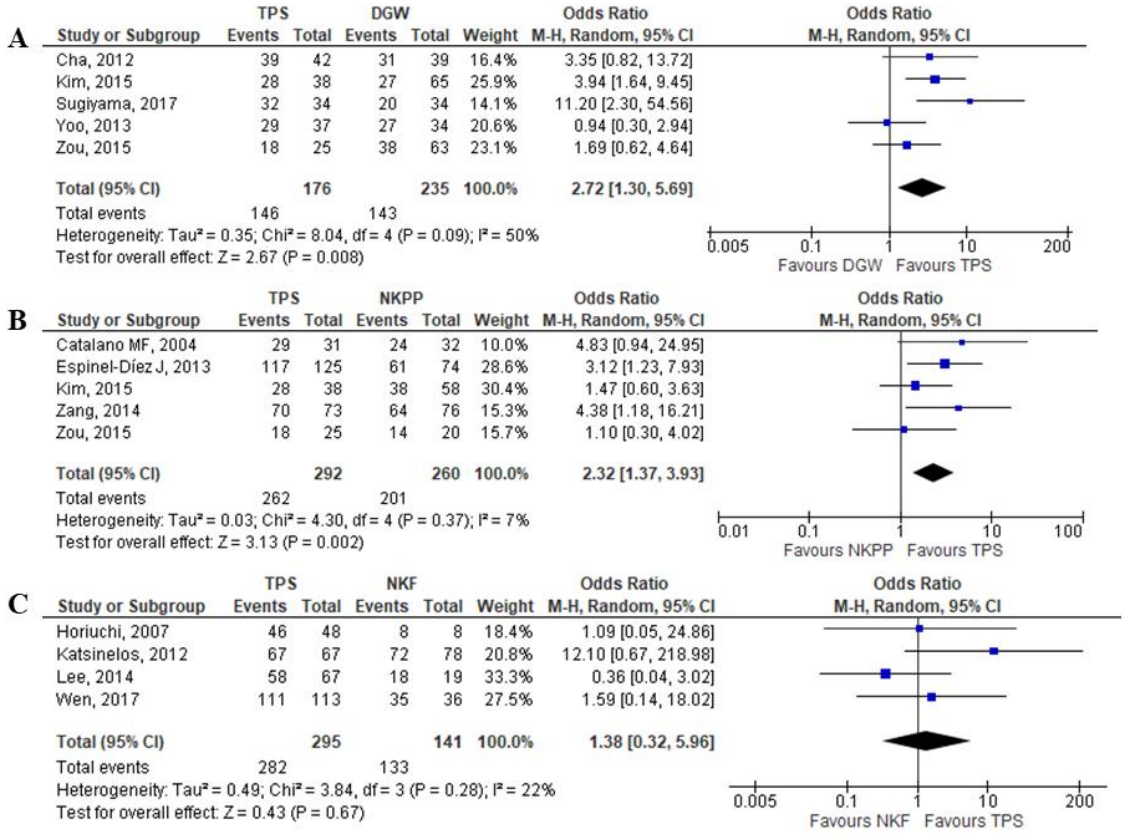


Figure 16: A) Forest plot of cannulation success rate of transpancreatic sphincterotomy (TPS) versus double-guidewire technique (DGW) in prospective studies; B) comparison of cannulation success rate of TPS versus needle-knife precut papillotomy (NKPP) in prospective studies; C) comparison of cannulation success rate of TPS versus needle-knife fistulotomy (NKF) in available comparative retrospective studies; (CI: confidence interval)

4.2.6. Post-ERCP pancreatitis

No significant difference was found between the TPS vs. DGW (OR 0.72; 95% CI 0.24-2.10; 151 and 134 patients, respectively; I^2 =55%) (Figure 17A) and TPS vs. NKPP (OR 1.63; 95% CI 0.48-5.47; 265 and 242 patients, respectively; I^2 =57%) (Figure 17B)

comparisons. However, the TPS technique showed a higher PEP rate compared to NKF method (OR 4.62; 95% CI 1.36-15.72; 295 and 141 patients, respectively; I^2 =16%) (Figure 17C).

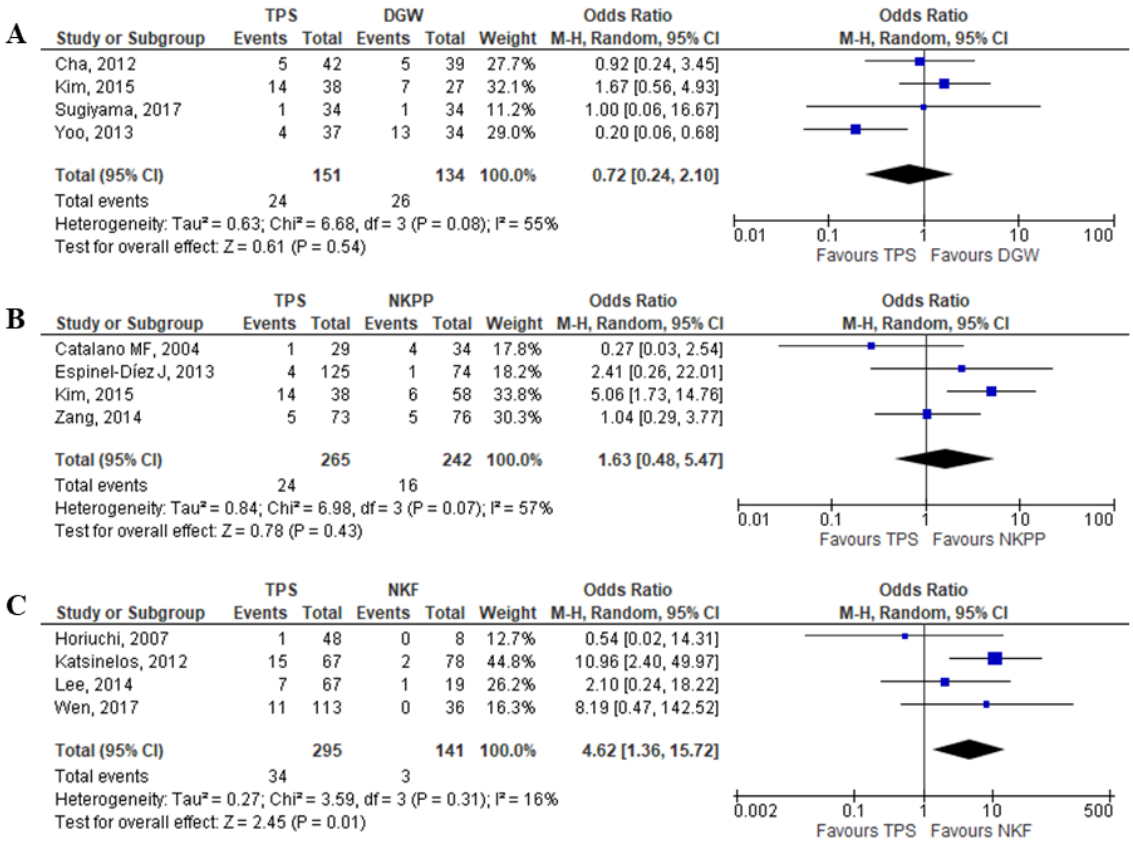


Figure 17: A) Forest plot of post-ERCP pancreatitis (PEP) rate of transpancreatic sphincterotomy (TPS) versus double-guidewire technique (DGW) in prospective studies; B) comparison of PEP rate of TPS versus needle-knife precut papillotomy (NKPP) in prospective studies; C) comparison of PEP rate of TPS versus needle-knife fistulotomy (NKF) in available comparative retrospective studies; (CI: confidence interval)

If we excluded abstracts from the NKF vs. TPS comparison, the significant difference disappeared (OR 3.49; 95% CI 0.20-62.21; 86 and 115 patients, respectively; I^2 =63%) and expectedly, a wide confidence interval could be seen. In the other subgroups, no differences were found when sequential studies or abstracts were omitted from the

analyses. Exclusive inclusion of RCTs did not result in a change in significance regarding TPS vs. DGW and TPS vs. NKPP comparisons.

The overall PEP rate of TPS was 8.1% (49/604) in prospective studies, 7.1% (183/2590) in all studies, and 7.4% (16/217) in RCTs (Table 10).

4.2.7. Prophylactic pancreatic stent and NSAID suppository use

Only one recently published study used PPS in all patients undergoing TPS (77), while all the others reported no or only some PPS implantation in the TPS cases (Table 7). NSAID suppositories were not used or not reported in any of the prospective studies included in the meta-analyses (Table 7).

4.2.8. Bleeding

The pooled analysis did not show any difference in bleeding rate when TPS were compared to DGW (risk difference /RD/ 0.01; 95% CI -0.03-0.05; 109 and 95 patients, respectively; I^2 =0%) (Figure 18A), NKF (RD 0.00; 95% CI -0.03-0.03; 295 and 141 patients, respectively; I^2 =0%) (Figure 18B) and NKPP (RD -0.00; 95% CI -0.03-0.04; 268 and 239 patients, respectively; I^2 =20%) (Figure 18C).

Subgroup analyses did not alter the findings of bleeding rates significantly.

The overall bleeding rate of TPS was 3.4% (19/562) in prospective studies, 2.0% (50/2548) in all studies, and 1.7% (3/175) in RCTs (Table 10).

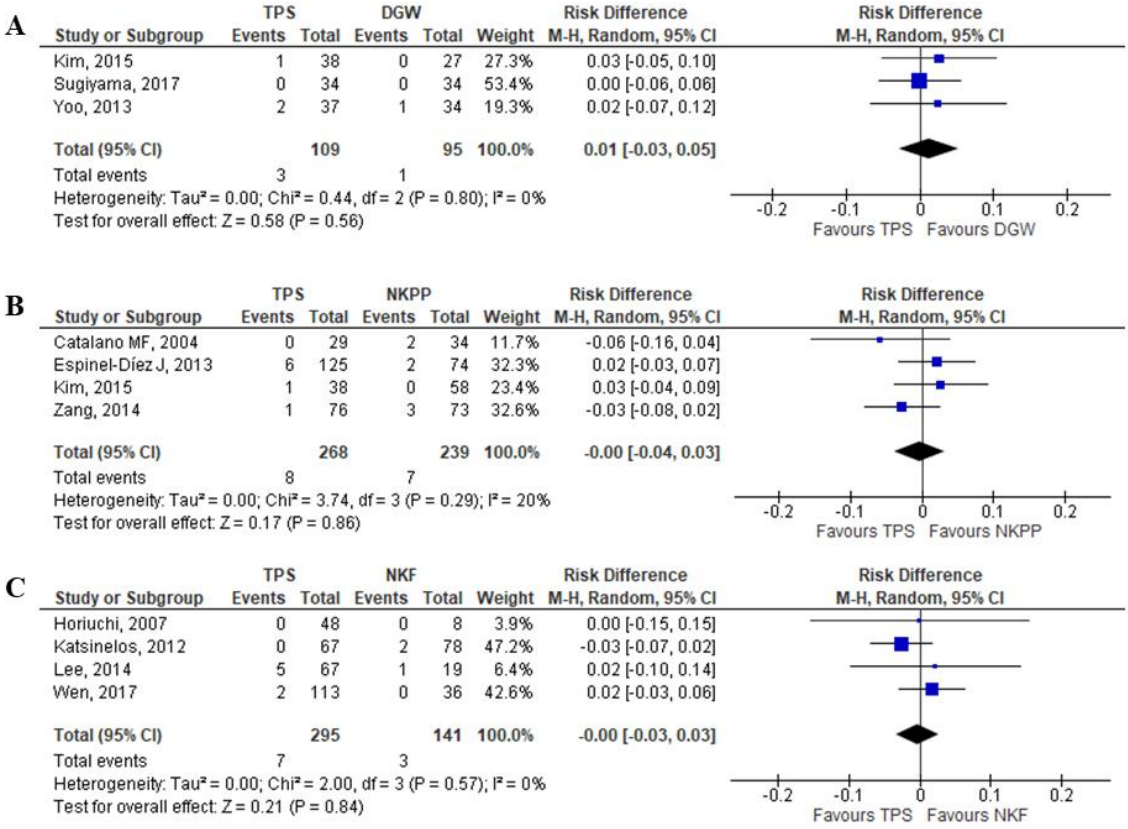


Figure 18: A) Forest plot of bleeding rate after transpancreatic sphincterotomy (TPS) versus double-guidewire technique (DGW) in prospective studies; B) comparison of bleeding rate after TPS versus needle-knife precut papillotomy (NKPP) in prospective studies; C) comparison of bleeding rate after TPS versus needle-knife fistulotomy (NKF) in available comparative retrospective studies; (CI: confidence interval)

4.2.9. Perforation

Perforation rates did not differ when comparing TPS vs. DGW (RD -0.01; 95% CI -0.04-0.03; 109 vs. 95; I^2 =0%) (Figure19A), TPS vs. NKPP (RD -0.00; 95% CI -0.02-0.01; 267 and 240 patients, respectively; I^2 =0%) (Figure 19B) and TPS vs. NKF (RD 0.00; 95% CI -0.02-0.03; 295 and 141 patients, respectively; I^2 =0%) (Figure 19C).

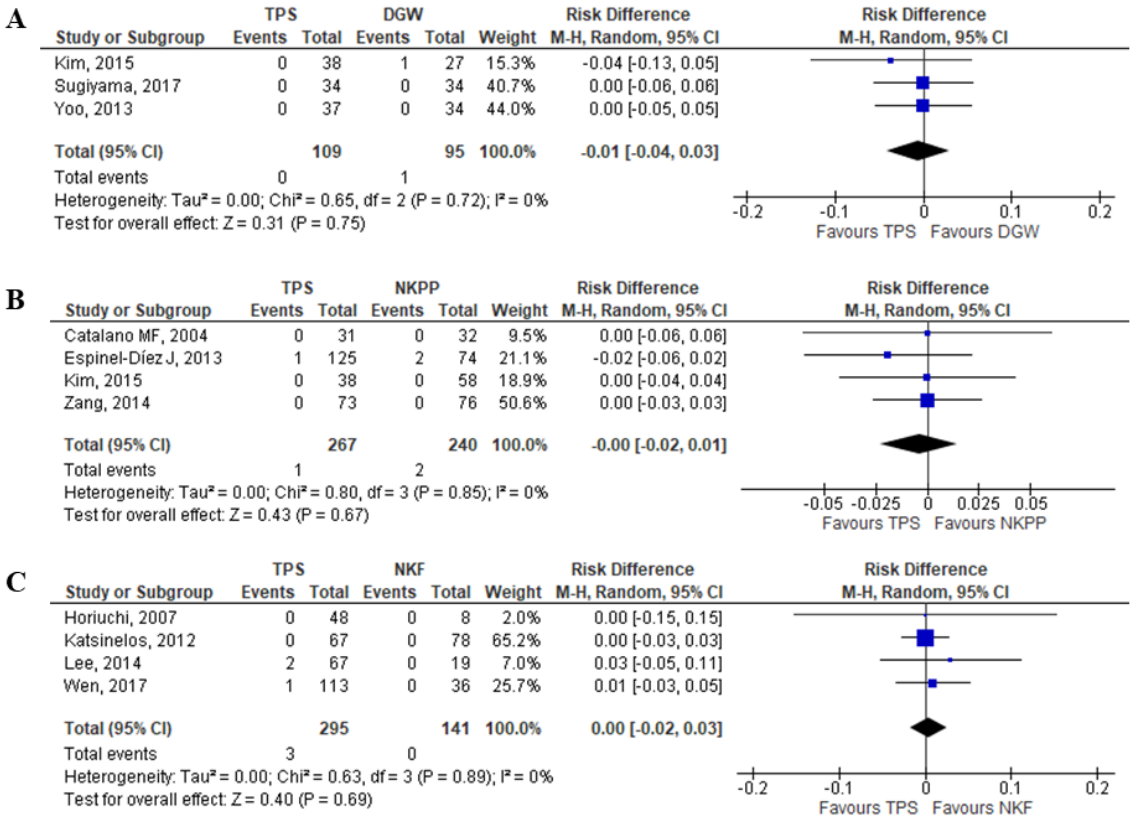


Figure 19: A) Forest plot of comparison of perforation rate after transpancreatic sphincterotomy (TPS) versus double-guidewire technique (DGW) in prospective studies; B) comparison of perforation rate after TPS versus needle-knife precut papillotomy (NKPP) in prospective studies; C) comparison of perforation rate after TPS versus needle-knife fistulotomy (NKF) in available comparative retrospective studies; (CI: confidence interval)

Subgroup analyses did not alter the findings in perforations rates significantly.

The overall perforation rate was 0.5% (3/562) in prospective studies, 0.4% (11/2548) in all studies, while 0% (0/175) in RCTs (Table 10).

4.2.10. Sensitivity and subgroup analyses

Application of other meta-analytical models (fixed effects vs. random effects analysis) and summary statistics (OR vs. RR vs. RD vs. Peto's OR) did not affect the outcomes significantly in the main analyses, thus, our conclusions remain unaltered (Table 13).

However, subgroup analyses excluding non-RCTs, sequential trials and studies only available in an abstract form significantly altered some results (i.e., success rate in TPS vs. DGW and PEP rate in TPS vs. NKF comparisons, respectively).

Clinicaloutcome	Statistical model	Random / fixed effectsmodel	
		Comparison	95% CI
Cannulationsuccess rate		**TPS vs. DGW**	
	OR	2.72 / 2.76	1.30-5.69/ 1.70-4-47
	RR	1.29 / 1.30	1.05-1.58 / 1.15-1.47
	RD	0.18 / 0.19	0.05-0.31/ 0.11- 0.27
	Peto's OR	2.66	1.69-4.19
		TPS vs. NKPP	
	OR	2.32 / 2.37	1.37-3.93 / 1.45-3.88
	RR	1.14 / 1.14	1.07-1.23 / 1.06-1.23
	RD	0.11 / 0.11	0.06-0.17 / 0.05-0.17
	Peto's OR	2.33	1.45-3.73
		TPS vs. NKF	
	OR	1.38 / 1.62	0.32-5.96 / 0.60-4.35
	RR	1.02 / 1.02	0.96-1.08/0.98-1.07
	RD	0.01 / 0.02	-0.05-0.08/-0.02-0.06
	Peto's OR	1.51	0.55-4.15
Post-ERCP pancreatitis		**TPS vs. DGW**	
	OR	0.72 / 0.71	0.24-2.10 / 0.38-1.33
	RR	0.77 / 0.76	0.33-1.81 / 0.46-1.26
	RD	-0.04 / -0.05	-0.17-0.09 / -0.13-0.04
	Peto's OR	0.70	0.37-1.33
		TPS vs. NKPP	
	OR	1.63 / 1.93	0.48-5.47 / 0.99-3.78
	RR	1.54 / 1.79	0.55-4.30 / 0.99-3.22
	RD	0.03 / 0.05	-0.06-0.13/ 0.00-0.09
	Peto's OR	1.97	1.00-3.86
		TPS vs. NKF	
	OR	4.62/5.70	1.36-15.72/ 1.98-16.42
	RR	4.13/5.06	1.35-12.65/1.92-13.33
	RD	0.10/0.13	0.03-0.17 / 0.07-0.18

	Peto's OR	4.60	2.19-9.63
Bleeding		**TPS vs. DGW**	
	OR	1.99 / 2.00	0.28-14.05 / 0.28-14.05
	RR	1.94 / 1.95	0.29-12.86 / 0.29-12.91
	RD	0.01 / 0.02	-0.03 -0.05 / -0.03-0.06
	Peto's OR	2.41	0.33-17.60
		TPS vs. NKPP	
	OR	0.96 / 0.94	0.28-3.28 / 0.35-2.53
	RR	0.97 / 0.94	0.29-3.16 / 0.35-2.49
	RD	-0.00 / -0.00	-0.04-0.03 / -0.03-0.03
	Peto's OR	0.90	0.32-2.55
		TPS vs. NKF	
	OR	0.93 / 0.85	0.20-4.36 / 0.22-3.29
	RR	0.94 / 0.86	0.21-4.19 / 0.22-3.39
	RD	-0.00 / 0.00	-0.03-0.03/ -0.04-0.03
	Peto's OR	0.94	0.22-4.00
Perforation		**TPS vs. DGW**	
	OR	0.23 / 0.23	0.01-5.85 / 0.10-5.85
	RR	0.24 / 0.24	0.01-5.66 / 0.01-5.66
	RD	-0.01 / -0.01	-0.04-0.03 / -0.05-0.03
	Peto's OR	0.09	0.00-4.81
		TPS vs. NKPP	
	OR	0.29 / 0.29	0.03-3.26 / 0.03-3.26
	RR	0.30 / 0.30	0.03-3.21 / 0.03-3.21
	RD	-0.00 / -0.01	-0.02-0.01 / -0.03-0.01
	Peto's OR	0.28	0.03-2.94
		TPS vs. NKF	
	OR	1.22 / 1.23	0.13-11.26 / 0.13-11.30
	RR	1.21 / 1.23	0.14-10.72 / 0.14-10.75
	RD	0.00 / 0.01	-0.02-0.03 / -0.02-0.04
	Peto's OR	3.69	0.25-55.41

Table 13: Detailed results of the sensitivity analyses: OR (odds ratio), RR (relative risk), RD (risk difference) (first value is the result of random, while the second is the fixed effect model calculation) and Peto's OR (only calculated with the fixed effects model) values calculated for every outcome with 95% confidence intervals (CI). (TPS /transpancreatic sphincterotomy/, DGW /double-guidewire method/, NKPP /needle-knife precut papillotomy/, NKF /needle-knife fistulotomy/)

4.2.11. Follow-up

Pancreatic duct stricture or chronic pancreatitis could potentially develop after pancreatic sphincterotomy, therefore a longer follow-up period to detect these adverse outcomes is

needed (110). Small caliber pancreatic stents could rarely cause pancreatic ductal changes in long-term (1 month or longer) (111,112). Only one prospective study, a case-series with 116 patients reported a median 5-month follow-up (range 2-35) with no late adverse events (87). Another paper similarly did not report late chronic pancreatitis or ductitis from PPS, no strictures were described during longer, however not specified follow-up (79) (Table 9). A few retrospective studies also published longer term results: Miao et al. reported no stricture after four months of follow-up period (104), while Barakat et al. found no late stricture formation after an unknown length of "long-term" follow-up (93).

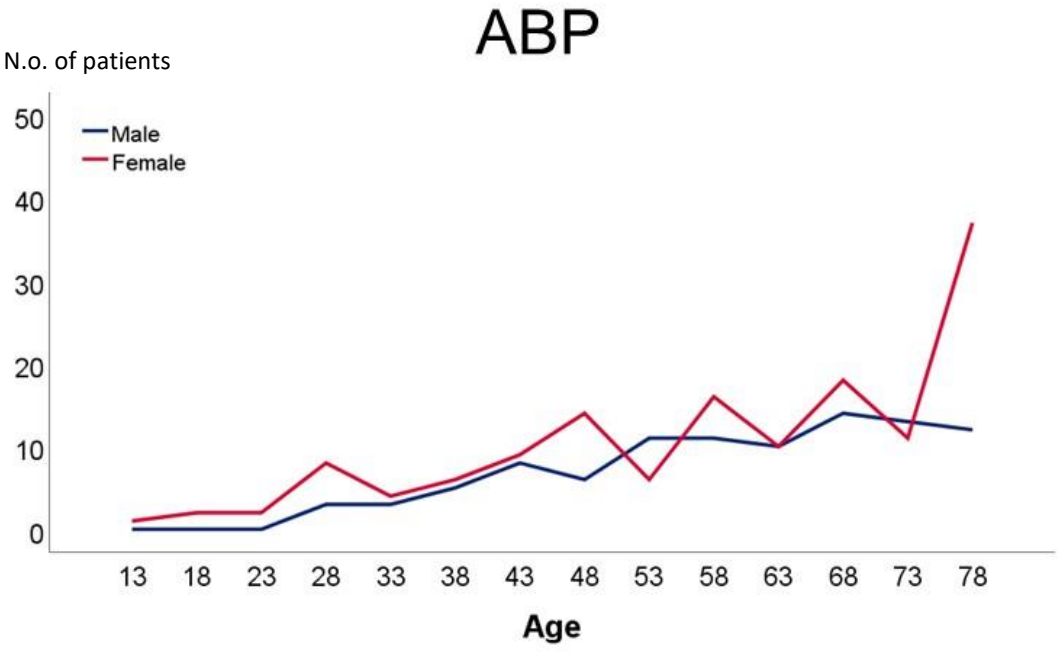
4.3.Results for AIM 3 (Difficulty of ERCP in ABP and AC)

4.3.1. General characteristics of the cohort

AC patients were significantly older than ABP patients, while more females were in the ABP group (63.1 vs. 69.6 years, p<0.001) (Table 14; Figure 20). A higher proportion of ASA I patients was in the younger ABP group, while more ASA III patients were in the older AC group. No significant difference was found in the anticoagulation and antiplatelet use between the two groups. Interestingly, more juxtapapillary diverticula were observed in AC patients (26.8% vs. 12.9%, p<0.001) (Table 14).

	ABP (n=240)	**AC (n=250)**	**p-value**
Mean age (SD)	63.13 (16.74)	69.56 (15.65)	**<0.001**
Sex ratio (female/all)	0.60	0.50	**0.026**
ASA I	80	52	**0.002**
ASA II	130	140	0.648
ASA III	23	54	**<0.001**
ASA IV	6	2	0.139
Previous anticoagulation or antiplatelet therapy	65/240	83/250	0.140
Juxtapapillary diverticulum	31/240	67/250	**<0.001**

Table 14: Comparison of the general characteristics of the cohort (ABP: acute biliary pancreatitis, AC: acute cholangitis, ASA: American Society of Anesthesiology, SD: standard deviation)



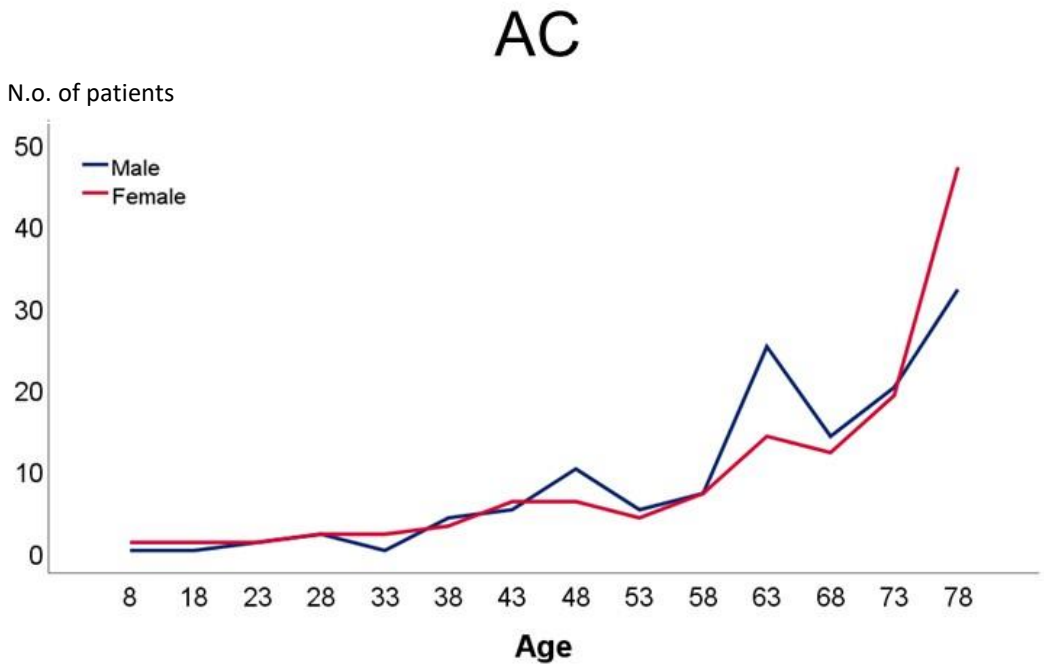


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Figure 20: Age distribution of the acute biliary pancreatitis (ABP) and acute cholangitis (AC) cases (red line: females, blue line: males)

4.3.2. Findings of ERCP

Normal cholangiogram was observed more frequently in ABP than in AC cases (20.0% vs. 12.3%, p=0.026). Dilated CBD without stone or sludge was found during ERCP in a higher proportion of ABP patients, compared to AC patients (22.6% vs. 12.8%, respectively, p=0.005). Biliary sludge without stones and small CBD stones (≤10 mm) were found equally frequently in ABP and AC group (14.3% vs. 9.1% (p=0.073) and 39.1% vs. 46.9% (p=0.088), respectively). Large CBD stones were present more commonly in AC patients (3.9% vs. 18.9%, p<0.001). Expectedly, purulent bile was more frequently found in AC cases than in ABP cases (6.5% vs. 22.2%, p<0.001) (Table 15).

	ABP (n=230)	**AC (n=243)**	**p-value**
Normal cholangiogram	46 (20.0%)	30 (12.3%)	**0.026**
Dilated CBD without stone or sludge	52 (22.6%)	31 (12.8%)	**0.005**
Biliary sludge only	33 (14.3%)	22 (9.1%)	0.073
Small (≤10 mm) stones	90 (39.1%)	114 (46.9%)	0.088
Large (>10 mm) stones	9 (3.9%)	46 (18.9%)	**<0.001**
Purulent bile	15 (6.5%)	54 (22.2%)	**<0.001**

Table 15: Findings of cholangiograms in the ABP and AC groups (ABP: acute biliary pancreatitis, AC: acute cholangitis, CBD: common bile duct)

4.3.3. Biliary cannulation success rates

Successful biliary access was achieved in ABP cases in 230/240 (95.8%) vs. 243/250 (97.2%) in AC cases (p=0.409) during the initial ERCP. Simple cannulation succeeded less frequently in the ABP group (54.6% vs. 75.6%; p<0.001), however, no difference was found in the success rate of advanced cannulation methods in the two groups (91.7% vs. 88.5%; p=0.503) (Figure 21).

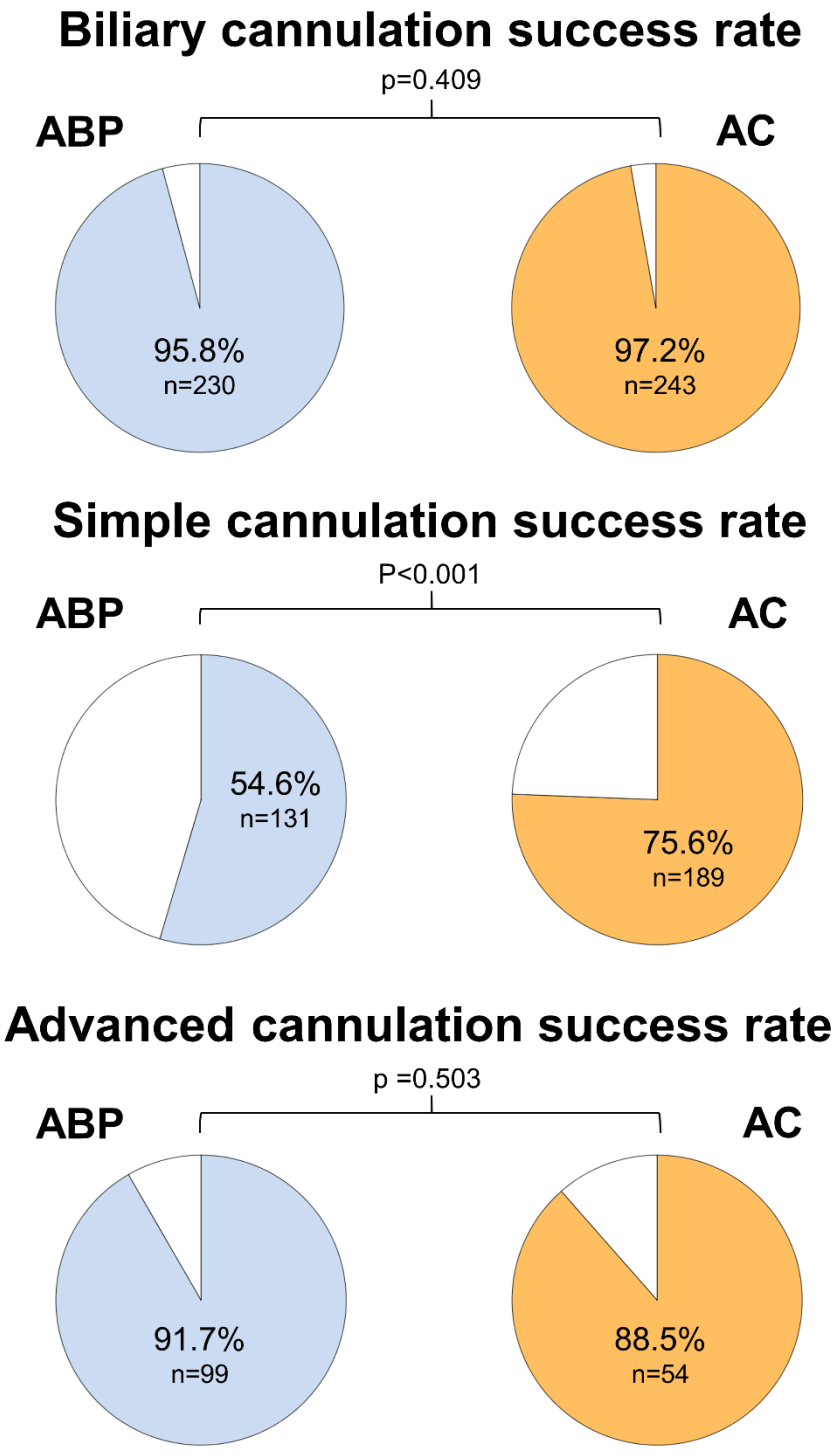

Figure 21: Analysis of successful biliary access rate in all, simple cannulation and advanced cannulation cases (ABP: acute biliary pancreatitis, AC: acute cholangitis)

4.3.4. Advanced cannulation methods and post-ERCP pancreatitis prophylaxis

Advanced cannulation methods were used in 108/240 (45.0%) cases of ABP, while only in 61/250 (24.4%) of AC cases ($p<0.001$). Multiple advanced methods were used in 13/61 in AC and 30/108 in ABP cases, respectively ($p=0.354$). More pancreatic duct manipulations were found in the ABP group (31.3% vs. 17.2%, $p<0.001$) and also more prophylactic pancreatic stents were inserted in these patients (19.6% vs. 4.8%; $p<0.001$). No difference was seen in the NSAID suppository use between the two groups (67.1% vs. 62.0%; $p=0.240$) (Table 16).

Carrying out a binary logistic regression for the main outcomes (advanced cannulation rate, pancreatic cannulation, pancreatic stent placement) did not change ORs significantly by the adjustment (Table 16).

	ABP (n=240)	AC (n=250)	OR (95%CI)	p-value	adjusted OR (95%CI)	p-value
Advanced biliary cannulation rate	108 (45.0%)	61 (24.4%)	2.54 (1.73, 3.72)	**<0.001**	2.388 (1.691 – 3.522)	**<0.001**
Pancreatic cannulation **1x** **multiple**	75 (31.3%) 43 (17.9%) 32 (13.3%)	43 (17.2%) 19 (7.6%) 24 (9.6%)	2.19 (1.43, 3.35) 2.54 (1.43, 4.50) 1.45 (0.83, 2.54)	**<0.001** **0.001** 0.194	1.921 (1.241 – 2.974)	**0.003**
Sequential advanced methods needed	30/108 (27.8%)	13/61 (21.3%)	1.42 (0.68, 2.99)	0.354	-	-
Primary PGW/PPS-assisted advanced method used	36/108 (33.3%)	14/61 (22.9%)	1.68 (0.82, 3.44)	0.156	-	-
Primary NK advanced method used	72/108 (66.7%)	47/61 (77.0%)	0.60 (0.29, 1.22)	0.156	-	-
PPS inserted	47 (19.6%)	12 (4.8%)	4.83 (2.49, 9.36)	**<0.001**	4.687 (2.415 – 9.098)	**<0.001**
NSAID suppository use	161 (67.1%)	155 (62.0%)	1.25 (0.86, 1.81)	0.240	-	-

Table 16: Analysis of advanced cannulation method use and post-ERCP pancreatitis prophylaxis in the ABP and AC groups (ABP: acute biliary pancreatitis, AC: acute cholangitis, PGW: pancreatic guidewire, PPS: prophylactic pancreatic stent, NK: needle knife, NSAID: non-steroidal anti-inflammatory drugs, OR: Odds ratio; 95%CI: 95% confidence interval)

4.3.5. Adverse event rates

Only a low number of clinically significant bleeding (0% vs. 0.8%), perforation (0.8% vs. 1.2%), cholecystitis (1.3% vs. 1.6%), immediate bleeding cases (9.6% vs. 7.2%) were detected, and no significant difference could be detected between the groups in this regard (Table 17).

	ABP (240)	AC (250)	p-value
Intraprocedural, immediate bleeding	23 (9.6%)	18 (7.2%)	0.341
Late, clinically significant bleeding	0 (0.0%)	2 (0.8%)	0.499
Conservatively managed perforation	2 (0.8%)	3 (1.2%)	1.000
Cholecystitis	3 (1.3%)	4 (1.6%)	1.000
Post-ERCP pancreatitis	N.A.	3 (1.2%)	N.A.

Table 17: Comparison of adverse event rates in the ABP and AC groups (ABP: acute biliary pancreatitis, AC: acute cholangitis, ERCP: endoscopic retrograde cholangiopancreatography, N.A.: not applicable)

4.3.6. Cannulation times

The mean biliary cannulation time was significantly longer in the ABP group (248 sec vs. 185 sec, p=0.043) (Figure 22), however, that difference could not be found when the simple (113 sec vs. 116 sec) or the advanced cannulation time (409 sec vs. 396 sec) were separately analyzed. The number of more than 5-minute cannulation was higher in the ABP patients (28.2% vs. 19.3%; p=0.037) (Figure 22), and with normal cholangiograms, the cannulation lasted longer in the ABP group (324 sec vs. 154 sec; p=0.040). This difference could also be seen in patients without JPD (261 sec vs. 158 sec, p=0.005) (Table 18).

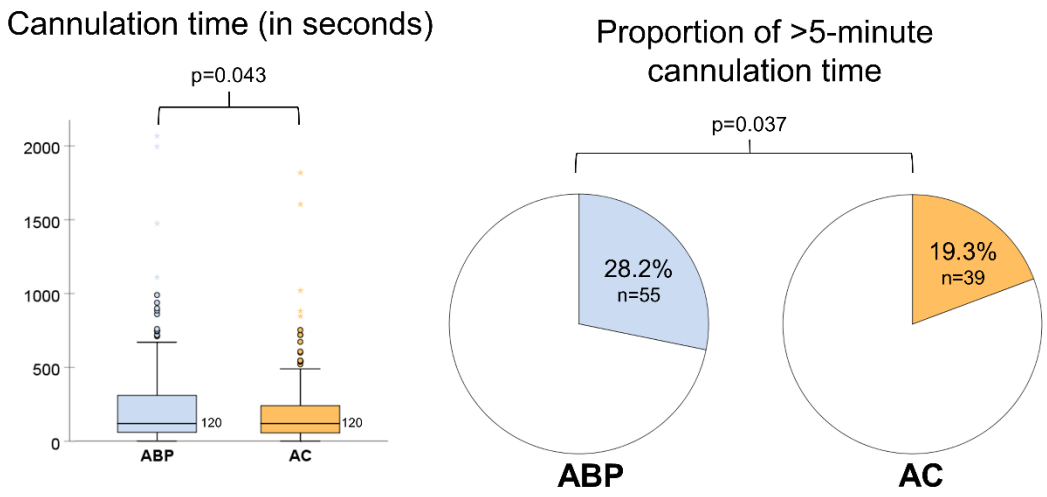

Figure 22: Comparison of cannulation time (median, in seconds) and proportion of more than 5-minute cannulation time in the ABP and AC group (ABP: acute biliary pancreatitis, AC: acute cholangitis)

	ABP (n=198) Mean (SD) or ratio	**AC (n=202) Mean (SD) or ratio**	**p-value**
Mean biliary cannulation time (s)	248 (310)	185 (241)	**0.043**
Mean simple cannulation time (s)	113 (207)	116 (142)	0.637
mean advanced cannulation time (s)	409 (337)	396 (340)	0.734
Ratio of >=5 min cannulation time	55/195	39/202	**0.037**
Normal cholangiogram cannulation time (s)	324 (386)	154 (106)	**0.040**
Abnormal cholangiogram cannulation time (s)	233 (292)	189 (255)	0.175
JPD mean CT (s)	147 (158)	257 (359)	0.234
No JPD (s)	261 (323)	158 (172)	**0.005**

Table 18: Comparison of cannulation times (CT) in the ABP and AC groups (ABP: acute biliary pancreatitis, AC: acute cholangitis, SD: standard deviation. JDP: juxtapapillary diverticulum)

4.3.7. Fluoroscopy time

Fluoroscopy time was longer in the AC group, when all cases (91 sec vs. 107 sec; p=0.009) (Figure 23), and the simple cannulation cases (91 sec vs. 107 sec; p=0.008) were compared. When stone extraction was done in AC patients, it took significantly longer, most probably due to the higher rate of larger (>1 cm) stones (89 sec vs. 107 sec; p=0.009). In other subgroups, no differences were found (Table 19).

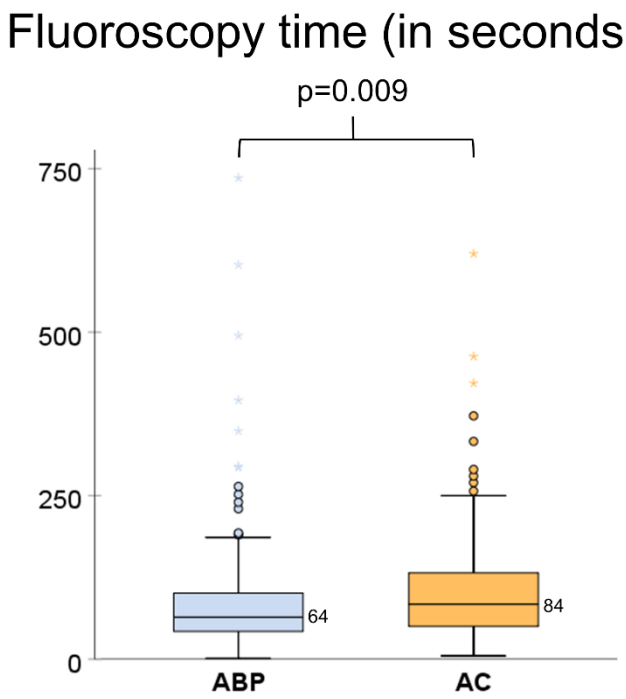

Figure 23: Comparison of fluoroscopy times in the ABP and AC groups (median, in seconds) (ABP: acute biliary pancreatitis, AC: acute cholangitis)

	ABP Sec (SD)	AC Sec (SD)	p-value
Mean fluoroscopy time	91 (95)	107 (87)	**0.009**
Fluoroscopy time in advanced methods used	91 (71)	108 (83)	0.237
Fluoroscopy time in simple methods used	91 (112)	107 (89)	**0.008**
Fluoroscopy time in stone extraction	89 (102)	104 (80)	**0.009**
Fluoroscopy time in stone extraction with Dormia basket	86 (79)	91 (67)	0.441
Fluoroscopy time in stone extraction with balloon	89 (115)	82 (67)	0.960
Fluoroscopy time in stone extraction with balloon+Dormia	114 (153)	122 (84)	0.122

Table 19: Comparison of fluoroscopy times in the ABP and AC groups (ABP: acute biliary pancreatitis, AC: acute cholangitis)

5. DISCUSSION

In this study, we report initial multicenter data from a newly initiated ERCP Registry in Hungary. The goal of the project is to monitor performance and quality indicators and to support prospective research initiatives as a platform. Seven, high-volume centers reported data, and further centers also expressed their interest to join to the Registry. Here we found that this Registry is suitable to monitor the most important performance measures and most quality indicator goal are met. However, there is room for improvement in PEP prophylaxis, indomethacin and also pancreatic stents should be used more consistently following guidelines by every centers. According to our data, with the use of advanced cannulation methods PEP and late bleeding rate was similar to simple cannulation in native papilla cases, while intraprocedural bleeding was more frequent with the use of advanced cannulation methods.

This study has a number of strengths, here we present a high case number, prospectively collected registry data from seven Hungarian tertiary centers. There is more quality check built-in that should limit incorrect data entry and underreporting.

Some limitations of the study should be mentioned. All participating hospitals and endoscopist were high-volume and case distribution varied among centers that hinder generalizability.

In the future, we plan to expand the registry to all centers that perform ERCP in Hungary. These plans to monitor quality indicators could direct efforts to ensure safer ERCP practices possibly in lesser number of hospitals with higher levels of expertise and case numbers. Prospective, observational studies and also randomized controlled trials could be developed on the basis of the registry. With the expanding infrastructure and backing by the community of endoscopist we are considering many directions of research in the field (e.g. ERCP training, post-ERCP pancreatitis prophylaxis, advanced cannulation methods).

The second project is a systematic review and meta-analysis which show that TPS could be equally successful or even slightly better in the setting of difficult biliary access compared to other advanced cannulation methods. Analyzing only the prospective studies, with regard to cannulation success rates TPS seem superior to DGW and NKPP while TPS and NKF are equally effective. DGW and NKPP carry a similar risk of PEP compared to TPS; however, PEP occurs more frequently with TPS than with NKF. No difference in bleeding and perforation rates were found when comparing TPS to the other advanced cannulation methods.

Whenever possible, we only analyzed prospective observational studies and RCTs to gain the best evidence. Heterogeneity between the studies was low or moderate in most analyses, making our conclusions more accurate. Sensitivity analyses and applying different statistical and meta-analytical methods did not reveal any significant changes in the main associations. However, subgroup analyses excluding sequential studies revealed that the significant difference disappeared in some analyses, thereby weakening our

conclusion in the success rate of TPS vs. DGW and PEP rate in TPS vs. NKF. However, this is most probably the result of the low case numbers leading to imprecision and wider confidence intervals.

A new Scandinavian RCT published in 2021 comparing TPS vs. DGW concluded that TPS achieved higher rate of successful biliary access than DGW while PEP rate was not significantly different between the two techniques (113). Prophylactic pancreatic stents were used only in 8.7% and 11.1% in the two groups and a considerably high PEP rate was registered with 13.5% and 16.2%. Including this new RCT in our previous meta-analysis of successful biliary cannulation and PEP rate, analyzing only RCTs a significantly better success (RR 1.22, 1.03-1.40, p=0.02) and not significantly lower PEP rate (RR 0.65, 0.37-1.15, p=0.14) was found in the TPS group.

There are several limitations of our analyses. First of all, the low number of prospective studies with only small cohorts of patients weakens the conclusions. Sequential studies were also included which could alter our results. However, in the comparison of DGW or NKPP vs. TPS, sequential designs could affect the TPS cannulation success and adverse event rate only to the worse. The lack of information on the use of preventive methods (PPS, NSAID suppositories) undermines the assessment of PEP rates. New studies are lacking in this field with the consistent use of PPS and NSAID suppositories. It should be noted, however, that the PEP rate was only 1.1% in the study of Sugiyama et al (77), where all patients received PPS after TPS, compared to the rate of 7.1% pooled from all studies where most patients did not have PPS. Besides that, the definitions of outcomes were not standardized in all cases. Nonetheless, most prospective studies used the consensus definitions (14). Publication bias cannot be ruled out due to the low number of studies per analysis.

In the cases of sequential studies, exceptionally low cannulation rates (as low as 72%) and high PEP rates (36.8%) could be seen (Table 8), that could be probably explained by the previous DGW attempts which should be avoided to minimize papillary trauma and

consequential edema. For that reason, we recommend using the TPS technique as first choice.

The overall cannulation success rate of TPS is close to 90% (67.9%-100%) in all studies and subgroups by study designs, which makes this pancreatic guidewire assisted method a successful alternative to DGW. The overall success of DGW is only 63% in the studies where TPS was also used. While in a meta-analysis of 7 RCTs with DGW successful cannulation was achieved in 82% of cases (114). The mean cannulation success rate of NKPP seems to be approximately 80% (647/812) in our previous meta-analysis of all NKPP studies and 77% (201/260) in prospective studies (53).

PEP rate of TPS is similar to other advanced cannulation methods (7.1%; 183/2590; 0-30%), NKF however could be better to avoid PEP. With the uniform use of PPS and NSAID suppositories in all TPS cases PEP rate might be even lower (14, 65) as the significant protective effect of PPS has been well proven. Importantly, its insertion should not be problematic since the guidewire is already in the pancreatic duct while performing TPS. In this regard, NKPP seems comparable to TPS with its 8.8% overall PEP rate measured in our previous meta-analysis (53). Bleeding rate of TPS is in the range of 2-4%, which is comparable to the widely accepted and frequently used needle knife precut techniques (4%; 30/745 if all NKPP studies included) (53). The rate of perforation was around 0.5% which is remarkably low for a precut technique, and no difference was found in this respect between TPS and the other advanced cannulation techniques.

The possible benefit of TPS over the free-hand precut techniques is that it is a wire assisted method, with better controlled cut. For that reason, it could be appealing to beginners and the PPS insertion could be also easily achieved with the guidewire inside the pancreatic duct. In the unfortunate cases when TPS fails, additional needle-knife incision could be helpful at times to reach deep biliary cannulations and should be used as salvage technique in the appropriate situations.

The third part, an analysis of the ERCP Registry data to address the issue of difficulty of ERCP in ABP. Our data support the ASGE grading of difficulty for pancreatitis in ERCP

(48). Several parameters suggest that ERCP is more challenging in ABP cases than in AC cases. We found that the rate of advanced cannulation method, and the rate of inadvertent pancreatic cannulation were higher, the cannulation time was longer in ABP patients than in AC cases. These observations point to the fact that we face difficult biliary cannulation in ABP more frequently compared to AC cases, where similar pathologic changes related to the biliary tree are expected. Importantly, the cannulation success rate and the rate of adverse events were not influenced by this. We also found a higher number of cases with normal cholangiogram in the ABP group (20.0%) compared to AC (12.3%). In these cases, spontaneous passage of stones or sludge by the time of ERCP is one possible explanation for the initial worsening of cholestatic parameters. Additionally, this also might be due to the difficulty of diagnosing AC when acute pancreatitis is also present, but also can be explained by the suboptimal availability of preprocedural endoscopic ultrasound evaluation in the participating Hungarian centers. ERCPs could have been avoided in these cases, cost and avoidable invasiveness should be highlighted, as a potential benefit (115).

Our study has several strengths, first of all, it is a quite large, prospectively collected, nationwide dataset from several centers in Hungary. Consecutively collected ABP and AC cases were available in almost equal numbers with good data quality, detailed data set, and in an appropriate sample size. Secondly, our registry system has a built-in quality assurance program that could limit false data entry and underreporting. Multivariable statistics also confirmed the robustness of our findings.

There are some limitations to our study. Post hoc questions raised in a prospective registry database might result in confounding effects. All cases come from high-volume centers and endoscopists, and case distribution is varied among centers that hinder generalizability. The inherent biases of observational studies and retrospective designs e.g., selection bias should be noted in our study as well. There were some differences between the two groups, firstly, AC patients were older, and had more comorbidities (more ASA III patients). Secondly, more juxtapapillary diverticula were found in the AC group. For this reason, binary logistic regression model was used to adjust for these

differences. Thirdly, the differentiation of AC cases in the ABP group could not have been done due to the lack of reliable guidelines or tools to confirm the presence of cholangitis in ABP (73). We were curious about the additional worsening effect of ABP on AC and non-AC cases, but we could not reliably separately analyze AC+ABP and ABP cases without AC. These factors could somewhat limit our analysis.

Based on our data, ABP cases should be handled by more experienced endoscopists who are familiar with a wide range of cannulation techniques, pancreatic guidewire assisted (double guidewire and TPS), as well as needle knife precut techniques (53,77). To lower the worsening effect of inducing more pancreatic edema, the insertion of a prophylactic pancreas stent might potentially improve disease course (116).

6. CONCLUSIONS

An easy-to-use ERCP Registry system has been developed with great prospect in quality assurance, monitoring of training and licensing. We provide the results of the first multicenter data analysis of the Hungarian ERCP Registry which showed a generally good practice of ERCP in the participating high-volume centers. Some improvement in the field of PEP prophylaxis (e.g., NSAID suppository and pancreatic stent use) could be expected in the future by disseminating the results of this analysis.

Based on the results of the systematic review and meta-analysis, the late adverse events of TPS, e.g., pancreatic duct stricture and chronic pancreatitis (110), could not be assessed properly because only one study reported a longer-term (more than 30-day) follow-up with no late adverse events (87). We think that follow-up studies should be extended up to one year or longer to detect late adverse events, e.g., pancreatic stricture formation or the development of chronic pancreatitis. These findings show the short-term safety and efficacy of TPS and also highlight the necessity of long-term follow-up studies after precut papillotomies.

The grade 3 difficulty classification by ASGE seems to be justified for the ABP cases, and these patients should not be left to the less experienced endoscopists. Additionally, determining the appropriate indication of ERCP is vital in ABP patients. Hence, we would

like to emphasize the need for the broader application of less invasive diagnostic tools (e.g., EUS) in this patient population to decrease the number of unnecessary ERCPs.

7. NEW RESULTS

1. We carried out the first multicenter data analysis of the Hungarian ERCP Registry, which provides data on quality indicators, cannulation techniques, success and adverse events. A generally good practice was registered in the participating centers. A pilot study with single center data has been published to get attention to this project in Hungary (37). According to our multicenter results, the use of PEP prophylaxis methods (NSAID suppositories and pancreatic stents) was underutilized, and the rate of perforations were higher than the expected target levels. With the dissemination of the results, we aim to achieve a better adoption of the current guidelines.
2. We carried out the first systematic review and meta-analysis of the TPS and other advanced cannulation methods (52).We did ancillary analyses to our previous meta-analysis published in Endoscopy (53). This article is cited in the ESGE guideline on ERCP-related adverse events (15). We provide evidence on the potential effectiveness and safety of TPS which is an underutilized method among the advanced cannulation techniques. TPS cannulation success rate was higher than DGW and NKPP while NKF was equally effective in this regard. PEP occurs more frequently with TPS compared to NKF, but DGW and NKPP carries a similar risk of PEP compared to TPS. No difference in bleeding and perforation rates were found when comparing TPS to the other advanced cannulation methods. Based on this recommendation TPS might be used more frequently in expert centers. However, to get the final conclusion further randomized controlled studies are needed.
3. We provide the first evidence that ERCP in ABP cases are objectively more difficult than in similar cases with only AC. This is based on the results that the rate of advanced cannulation method use and the rate of inadvertent pancreatic

cannulation were higher, the cannulation time was longer in ABP patients than in AC cases. The consensus-based grade 3 classification of ERCPs in ABP cases is justified based on our data.

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10. SCIENTOMETRICS

Publications and metrics rely on the MTMT2 and Google Scholar, the data were extracted on 28th January 2021.

Scientific papers:

- Total: 32
- English-language: 28

Impact factor (since 2016):

- First author: 16.324
- Cumulative: 97.121

Citations (since 2016):

- Cumulative: 356 (MTMT: 259)
- Hirsh index: 13 (MTMT: 11)

11.LIST OF PUBLICATIONS

Papers upon which this thesis relies (n=5, cumulative impact factor: 13.573, cumulative citation: 22):

1. **Pécsi D**, Hegyi P, Szentesi A, Gódi S, Pakodi F, Vincze Á. [The role of endoscopy registries in quality health care. The first data from the Hungarian Endoscopic Retrograde Cholangiopancreatography (ERCP) Registry]. Orv Hetil. 2018;159(37):1506–15. DOI: 10.1556/650.2018.31145 (**Q3, IF: 0.564, cited: 2**).
2. **Pécsi D**, Tóth M, Vincze Á. Endoszkópos regiszterek a minőség szolgálatában. MAGYAR BELORVOSI ARCHIVUM 2019; 72 (2): 95–100. (**cited: 0**)
3. **Pécsi D**, Farkas N, Hegyi P, Varjú P, Szakács Z, Fábián A,Varga G, Rakonczay Z, Bálint ER, Erőss B,Czimmer J, Szepes Z, Vincze Á. Transpancreatic sphincterotomy is effective and safe in expert hands on the short term. Dig Dis Sci. 2019;64: 2429–2444.DOI: 10.1007/s10620-019-05640-4 (**Q1, IF: 2.751, cited: 5**)
4. **Pécsi D**, Farkas N,Hegyi P, Balaskó M, Czimmer J, Garami A, Illés A, Mosztbacher D, Pár G, Párniczky A, Sarlós P, Szabó I, Szemes K, Szűcs Á,

Vincze Á. Transpancreatic sphincterotomy has a higher cannulation success rate than needle-knife precut papillotomy-a meta-analysis. Endoscopy 2017; 49(9): 874-887. DOI: 10.1055/s-0043-111717 (**Q1, IF:6.629, cited: 15**)

5. **Pécsi D**, Gódi S, Hegyi P, Hanák L, Szentesi A, Altorjay I,Bakucz T, Czakó L, Kovács G, Orbán-Szilágyi Á, Pakodi F, Patai Á, Szepes Z, Gyökeres T, Fejes R, Dubravcsik Z, Vincze Á, Hungarian Endoscopy Study Group. ERCP is more challenging in cases of acute biliary pancreatitis than in acute cholangitis – Analysis of the Hungarian ERCP registry data. Pancreatology. In Press.DOI: 10.1016/j.pan.2020.11.025 (**Q1, IF$_{2019}$: 3.629, cited: 0**)

Papers loosely related to the topic of the thesis (n=3):

1. **Pécsi D**, Vincze Á. Az endoszkópos retrográd kolangiopankreatográfiát követő pancreatitis megelőzésének lehetőségei. MAGYAR BELORVOSI ARCHIVUM. 2019; 72 (5): 246–251. (**cited: 0**)
2. Halász A, **Pécsi D**, Farkas N, Izbéki F, Gajdán L, Fejes R, Hamvas J, Takács T, Szepes Z, Czakó L, Vincze Á, Gódi S, Szentesi A, Párniczky A, Illés D, Kui B, Varjú P, Márta K, Varga M, Novák J, Szepes A, Bod B, Ihász M, Hegyi P, Hritz I, Erőss B, Hungarian Pancreatic Study Group. Outcomes and timing of endoscopic retrograde cholangiopancreatography for acute biliary pancreatitis.Dig Liv Dis. 2019; 51(9): 1281-1286. DOI: 10.1016/j.dld.2019.03.018 (Q2, IF: 3.570, cited: 9)
3. **Pécsi D**, Vincze Á. Are Suprapapillary Biliary Stents Superior to Transpapillary Biliary Stents?. Dig Dis Sci, 2020 (65):925–927 (Q1, IF: 2.751, cited: 0)

Other papers (n=24):

1. **Pécsi D**, Paulovicsné KM, Czimmer J, Gódi S, Hunyady B, Illés A, Sarlós P, G. Kiss G, Vincze Á: [Experiences with Livopan sedation during colonoscopy]. Cent Eur J GastroentHepatol. 2018 (4) 4: 220-223.

2. Szakó L, Mátrai P,HegyiP,**Pécsi D**,Gyöngyi Z,CsuporD,Bajor J,Erőss B,Mikó A,Szakács Z, Vincze Á. Endoscopic and surgical drainage for pancreatic fluid collections are better than percutaneous drainage: Meta-Analysis, Pancreatology. 2020 (20)1: 132-141. (Q1, IF: 3.629, cited: 1)
3. Csekő K, **Pécsi D**, Kajtár B, Hegedűs I, Bollenbach A, Tsikas D, Szabó IL, Szabó S, Helyes Z. Upregulation of the TRPA1 Ion Channel in the Gastric Mucosa after Iodoacetamide-Induced Gastritis in Rats: A Potential New Therapeutic Target, Int J Mol Sci. 2020 (21)16, 5591. (Q1, IF: 4.556, cited: 0)
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5. Zsiborás C, Mátics R, Hegyi P, BalaskóM, Pétervári E, Szabó I, Sarlós P, Mikó A, Tenk J, Rostás I, **Pécsi D**, Garami A, Rumbus Z, Huszár O, Solymár M. Capsaicin and capsiate could be appropriate agents for treatment of obesity: A meta-analysis of human studies, Crit Rev Food Sci Nutr. 2018 (58)9: 1419-1427. (Q1, IF: 6.704, cited: 35)
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17. Mikó A, Erőss B, Sarlós P, Hegyi JP, Márta K, **Pécsi D**, Vincze Á, Bódis B, Nemes O, Faluhelyi N, Farkas O, Papp R, Kelemen D, Szentesi A, Hegyi E, Papp M, Czakó L, Izbéki F, Gajdán L, Novák J, Sahin-Tóth M, Lerch MM, Neoptolemos J, Petersen OH, Hegyi P. Observational longitudinal multicentre investigation of acute pancreatitis (GOULASH PLUS): follow-up of the GOULASH study, protocol. BMJ Open. 2019. 9,8,e025500. (Q1, IF:2.496, cited: 2)
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19. Mosztbacher D, Hanák L, Farkas N, Szentesi A, Mikó A, Bajor J, Sarlós P, Czimmer J, Vincze Á, Hegyi PJ, **Pécsi D**, Varjú P, Szakács Z, Darvasi E, Párniczky A, Hegyi P. Hypertriglyceridemia-induced acute pancreatitis: A prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases. Pancreatology. 2020.(20): 608-616. (Q1, IF:3.629, cited: 13)

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23. Vörhendi N, Soós A, Anne Engh M, Tinusz B, Szakács Z, **Pécsi D**, Mikó A, Sarlós P, Hegyi P, Erőss B. Accuracy of the Helicobacter pylori diagnostic tests in patients with peptic ulcer bleeding: a systematic review and network meta-analysis. Ther Adv Gastroent. 2020. 13,1756284820965324. (Q1, IF: 3.52, cited:0)
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Az endoszkópos regiszterek szerepe a minőségi betegellátásban

Az új magyar Endoszkópos Retrográd Cholangiopancreatographia (ERCP) Regiszter első eredményei

Pécsi Dániel dr.[1] ▪ Hegyi Péter dr.[1, 3] ▪ Szentesi Andrea dr.[3]
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Bevezetés: Az emésztőszervi endoszkópiában a minőségi mutatók folyamatos követése mára alapvető követelménnyé vált. A jelenleg használatos szabad szöveges formátumú leletekből a követendő adatok jelentős része nem nyerhető ki, ezért strukturált, internetalapú adatgyűjtő rendszert fejlesztettünk ki a pancreatobiliaris endoszkópos beavatkozások mutatóinak rögzítésére.
Célkitűzés: Egy ERCP-vizsgálatokat tartalmazó prospektív adatgyűjtő rendszer, úgynevezett ERCP Regiszter kialakítása és használhatóságának tesztelése.
Módszer: 2017 januárjától kezdve a Pécsi Tudományegyetem Klinikai Központjának I. Belgyógyászati Klinikáján az összes elvégzett ERCP-vizsgálat adatait rögzítettük a regiszterben. Az első évben történt 595 vizsgálat adatainak feldolgozásával a rendszer tesztelése lezárult.
Eredmények: 447 betegen 595 vizsgálat történt, a kanülációk sikerességi aránya 93,8% volt. Ép papilla esetén a beavatkozások 32,1%-ában az epeúti kanülálást nehéznek minősítettük, ezekben az esetekben 81,0%-ban volt sikeres a kanülláció az első vizsgálat során. ERCP után 13 alkalommal alakult ki hasnyálmirigy-gyulladás (2,2%), 2 alkalommal (0,3%) jelentkezett klinikailag szignifikáns vérzés, míg vizsgálat alatti átmeneti hypoxiát 27 esetben (4,5%) észleltünk. A betegek 75,5%-át sikerült 30 nappal a beavatkozás után telefonon felkeresni késői szövődmények észlelése céljából. Az Amerikai Gastrointestinalis Endoszkópos Társaság (ASGE) által lefektetett minőségi mutatók mindegyikét tudtuk követni a regiszter segítségével. A legtöbb mutatónak a centrumunk már most is megfelel.
Következtetések: Az endoszkópos beavatkozások minőségi mutatóinak folyamatos monitorozását a jelenlegi kórházi informatikai rendszerek nem támogatják, de regiszterünk használatával ez lehetővé válik. A betegellátás minőségének követésére és klinikai kutatások végzésére is alkalmas eszköz az ERCP Regiszter. Időközben több endoszkópos centrum csatlakozott már a kezdeményezéshez, és további vizsgálóhelyek számára is elérhető a regiszter weboldalunkon (https://tm-centre.org/hu/regiszterek/ercp-regiszter/).
Orv Hetil. 2018; 159(37): 1506–1515.

Kulcsszavak: endoszkópos retrográd cholangiopancreatographia, endoszkópia, regiszterek, egészségügyi minőségi mutatók

The role of endoscopy registries in quality health care

The first data from the Hungarian Endoscopic Retrograde Cholangiopancreatography (ERCP) Registry

Introduction: The continuous monitoring of quality indicators in gastrointestinal endoscopy has become an essential requirement nowadays. Most of these data cannot be extracted from the currently used free text reports, therefore a structured web-based data-collecting system was developed to record the indicators of pancreatobiliary endoscopy.
Aim: A structured data-collecting system, the ERCP Registry, was initiated to monitor endoscopic retrograde cholangiopancreatography (ERCP) examinations prospectively, and to verify its usability.
Method: From January 2017, all ERCPs performed at the First Department of Medicine, University of Pécs, have been registered in the database. In the first year, the detailed data of 595 examinations were entered into the registry. After processing these data, the testing period of the registry is now finished.

Results: On 447 patients, 595 ERCPs were performed. The success rate of cannulation is 93.8% if all cases are considered. Difficult biliary access was noted in 32.1% of patients with native papilla, and successful cannulation was achieved in 81.0% of these cases during the first procedure. Post-ERCP pancreatitis was observed in 13 cases (2.2%), clinically significant post-papillotomy bleeding was registered in 2 cases (0.3%), while 27 patients (4.5%) developed temporary hypoxia during the procedure. 30-day follow-up was successful in 75.5% of the cases to detect late complications. All of the quality indicators determined by the American Society of Gastrointestinal Endoscopy (ASGE) were possible to monitor with the help of the registry. Our center already complies with most of these criteria.
Conclusions: Continuous monitoring of the quality indicators of endoscopic interventions are not supported by the current hospital information system but it became possible with our registry. The ERCP Registry is a suitable tool to detect the quality of patient care and also useful for clinical research. Several endoscopy units have joined already this initiative and it is open for further centres through our web page (https://tm-centre.org/hu/regiszterek/ercp-regiszter/).

Keywords: endoscopic retrograde cholangiopancreatography, endoscopy, registries, health care quality indicators

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Rövidítések

ASA = (American Society of Anesthesiologists) Amerikai Aneszteziológiai Társaság; ASGE = (American Society of Gastrointestinal Endoscopy) Amerikai Gastrointestinalis Endoszkópos Társaság; DGW = (double guidewire technique) kettős vezetődrótos technika; ERCP = (endoscopic retrograde cholangiopancreatography) endoszkópos retrográd cholangiopancreatographia; ESGE = (European Society of Gastrointestinal Endoscopy) Európai Gastrointestinalis Endoszkópos Társaság; FNA = (fine-needle aspiration) finomtű-aspiráció; PEP = post-ERCP-pancreatitis; PGW = (pancreatic guidewire) pancreasvezetékbe helyezett vezetődrót; PPS = profilaktikus pancreasszstent; PTE = Pécsi Tudományegyetem; TPS = transpancreaticus sphincterotomia

Az egészségügyi ellátással kapcsolatos különböző regiszterek szerepe a XXI. századra megkérdőjelezhetetlenné vált, fontosságukat több szempont is alátámasztja [1]. Elsőként hangsúlyozandó a betegellátás minőségi mutatóinak követése. Ebből a célból fontos a nemzetközileg is elfogadott, standardizált, bizonyítékokon alapuló orvoslás elveit követő irányelvek betartásának folyamatos figyelése. A regiszterben gyűjtött adatok könnyen elemezhetők, a kívánt mutatók adatait így összehasonlíthatjuk nemzeti és nemzetközi értékekkel. A klinikai kimenetelek vizsgálatával, a javítandó tényezők azonosításával az adott betegségcsoportra nézve is jelentős hatást gyakorolhatunk a morbiditási és mortalitási mutatókra és a kórházi bennfekvés hosszára [2–4].

A betegellátásból származó költségekre is kihatással lehet a minőségi mutatók követése. Kimutatható, hogy a bizonyítékokon alapuló orvoslás irányelveinek betartásával a költségek csökkenhetnek a rövidebb kórházi bennfekvésnek és a hatékonyabb erőforrás-hasznosításnak köszönhetően. Az újabb és drágább módszerek elterjedésével a betegellátás kiadásai jelentősen növekednek, a források optimális felhasználása szükségessé teszi a különböző mutatók folyamatos rögzítését. Az egyes betegségek ellátásának részletes megfigyelésével és követésével, a legköltséghatékonyabb eljárások alkalmazására hívhatjuk fel mind az azokat felhasználók, mind a finanszírozók figyelmét [3, 5].

Mindezeken túl a klinikai regiszterek szerepe az orvosi kutatásokban is igen jelentős, mivel ezek az adatbázisok szolgáltatják az alapot az úgynevezett „real world evidence”-hez, melynek szerepe manapság egyre inkább felértékelődik. A regiszterek randomizált vizsgálatok alapját is szolgálhatják, megkönnyítve a prospektív adatgyűjtést, valamint értékes klinikai adatokat nyújthatnak genetikai, képalkotó és biomarkermódszerekkel kiegészítve [6, 7].

Az invazív endoszkópos módszerek terjedésével a beavatkozások megfelelő minőségének biztosítása érdekében, az úgynevezett „minőségi endoszkópia” követelményeinek ellenőrzése céljából a klinikai regiszterek használata elkerülhetetlenné vált. Jó példa erre a colorectalis szűrőprogramok elindítása, melyek során a kolonoszkópia minőségi mutatóinak folyamatos követése szükséges a megfelelő minőségi kontroll biztosítására. Az adatbázisban rögzített adatok alapján megfelelő képet kaphatunk a szűrőprogram hatékonyságáról, illetve annak gyenge pontjairól is, így a programba való beavatkozásra is lehetőség nyílik [8, 9].

A minőségi mutatók monitorozásának igénye talán az ERCP esetén a legjelentősebb, mivel ez a beavatkozás jár a legmagasabb szövődményrátával a rutin emésztőrendszeri endoszkópos eljárások között. Fontos a tanulási folyamat figyelemmel követése is annak meghatározására, hogy a kezdő endoszkópos mikor képes egyedül is megfelelően teljesíteni és komplex helyzeteket is megoldani [10, 11]. Felmérhető az ERCP-vizsgálatok indikációs

köre, a beavatkozás sikeressége, a vizsgálatok nehézségével korreláltatva, illetve a nehéz epeúti elérések különböző módozatai és ezek sikeressége, illetve szövődményei [12, 13]. A különböző centrumok és akár egyes endoszkóposok eredményei szintén összehasonlíthatóvá válnak, lehetőséget adva a változtatásokra is [14]. A vizsgálat szövődményeit megelőző módszerek, mint a nemszteroid gyulladáscsökkentő kúpok és a protektív pancreassztentek irányelveknek megfelelő alkalmazását és azok hatékonyságát is egyszerűen követhetjük. A betegek elégedettsége is fontos a későbbi orvos–beteg együttműködés szempontjából, amelynek felmérésére szintén több kezdeményezés történt [15, 16]. A betegek utánkövetése a vizsgálat után a késői szövődmények felismerését jelentősen növeli, ezért fontos része az endoszkópos regisztereknek [17]. Az *1. táblázatban* összefoglaltuk a külföldön már működő ERCP-s regisztereket: számos sikeres program nagy esetszámmal rendelkezik, és szinte a teljes országos lefedettséget sikerült elérniük (például Svédország, GallRiks-program) [12–15, 17–26].

Módszer

A fenti megfontolásokból a Pécsi Tudományegyetem Transzlációs Medicina Központjának kezdeményezésére klinikai regiszterek kialakítása kezdődött gasztroenterológiai témákban. Ennek a kezdeményezésnek a része az ERCP Regiszter is. Országos szakmai egyeztetés során a nemzetközileg ajánlott minőségi mutatók [27] figyelembevételével határoztuk meg a gyűjtendő vizsgálati paramétereket és hoztunk létre egy internetalapú adatgyűjtő rendszert. 2017 januárjától a Pécsi Tudományegyetem Klinikai Központja I. Belgyógyászati Klinikájának Gasztroenterológiai Tanszékén prospektív adatgyűjtés kezdődött, amelynek keretében a klinikán végzett összes ERCP-vizsgálat eredményei a regiszterbe feltöltésre kerülnek. A tudományos célú adatgyűjtést az Egészségügyi Tudományos Tanács Tudományos és Kutatásetikai Bizottsága jóváhagyta (engedélyszám: 35523-2/2016/EKU). Minden beteg tájékoztatása a kutatásetikai elveknek („good clinical practice") megfelelően történik. A *2. táblázatban* foglaljuk össze a gyűjtött adatok főbb pontjait.

A rögzítendő adatokhoz tartozik a betegek 30 napos telefonos és/vagy kórházi informatikai rendszerbeli utánkövetése is, amelynek során az esetleges késői szövődményeket mérjük fel.

Az adatgyűjtést a vizsgáló orvos által kitöltött űrlap segíti, majd az arról felvitt adatokat négylépcsős ellenőrzési rendszerben hitelesítjük. Elsőként a helyi adminisztrátor hagyja jóvá az adatlapot, ezt a vizsgálatot végző orvos ellenőrzése követi. Ezek után kerül sor a bevitt adatok központi adminisztratív és szakmai ellenőrzésére és jóváhagyására. Csak ezen ellenőrzési lépések után történik az adatok véglegesítése és elemzése.

A vizsgálatok indikációjának meghatározása az ASGE által elfogadott indikációkat követve történt [27]. A vizsgálatok objektív nehézségének megítélése az amerikai (ASGE-) ajánlásoknak megfelelően a módosított Schutz-osztályozás alapján történt (1. fokozat [grade]: a kívánt vezeték mély kanülálása; major papilla-mintavétel; epeúti sztent eltávolítása/cseréje; 2. fokozat: epeúti kőeltávolítás <10 mm; epecsorgás kezelése; extrahepaticus benignus és malignus szűkületek kezelése; profilaktikus panc-

1. táblázat | Külföldön működő ERCP-regiszterek: az eddig közölt ERCP-k számával, a program nevével és a gyűjtött adatokkal

Ország	Referencia	ERCP-szám	A program neve	Terápia	Indikáció	Szövődmények	Medikáció	ASA/komorbiditás	Sikeresség	30 napos utánkövetés
Egyesült Királyság	18	40 668	–	–	✓	✓	–	–	–	✓
Egyesült Királyság	13	4 561	–	✓	✓	–	–	✓	–	–
Egyesült Királyság	19	5 264	–	✓	✓	✓	✓	✓	–	–
Amerikai Egyesült Államok	20	16 855	–	✓	–	✓	–	–	–	–
Amerikai Egyesült Államok	21	11 497	GI Trac	✓	✓	✓	–	✓		–
Amerikai Egyesült Államok	22	411 409	–	✓	✓	–	–	–	–	–
Norvégia	15	2 808	–	✓	✓	✓	✓	✓	–	–
Hollandia	12	8 575	RAF-E	✓	✓	–	–	✓	✓	–
Svédország	17	37 860	GallRiks	✓	✓	✓	✓	✓	✓	✓
Ausztria	23	13 513	B. ERCP	✓	✓	✓	–	–	✓	–
Japán	24	1 176	JED	✓	✓	✓	✓	✓	–	✓
Európa	25	1 042	GASTER	✓	✓	–	–	–	–	–
Finnország	26	480	–	✓	✓	✓	–	–	–	–

ASA = Amerikai Aneszteziológiai Társaság; ERCP = endoszkópos retrográd cholangiopancreatographia

2. táblázat | Az ERCP Regiszterben gyűjtött adatok fő pontjai

A beavatkozás előtt rögzítendő adatok		
1.	Személyes adatok	Betegadatok: regiszterazonosító, születési év, nem, testsúly, testmagasság, alkoholfogyasztás, dohányzás A vizsgálóhely és a vizsgáló személyek adatai
2.	Indikáció és tervezett beavatkozás	A vizsgálat sürgőssége, az ERCP indikációja, endoszkópos sphincterotomia, epeúti sztent behelyezése és egyéb beavatkozások indikációi
3.	ASA-pontszám	Az Amerikai Aneszteziológiai Társaság szerinti kategória (I–V.)
4.	Aggregációgátló és/vagy antikoaguláns kezelés	Hatóanyag, dózis, az utolsó adag bevételének ideje
5.	Véralvadási zavar	INR- és TCT-értékek, hemofília; történt-e korrekció?
A beavatkozás paraméterei		
6.	Szedáció és gyógyszeres profilaxis	Hatóanyag, dózis, antidotum, a PEP gyógyszeres profilaxisa
7.	Vizsgálati idő	Endoszkóp be- és kivezetése, a szelektív kanülálásig eltelt idő, a fluoroszkópia ideje, sugárdózis
8.	Anatómia	Operált gyomor, deformáltság, szűkület, a Vater-papilla anatómiája
9.	Kanülálás	Az epevezeték, pancreasvezeték kanülálási módja, sikeressége
10.	A cholangiographia és a pancreatographia lelete	Kóros eltérés esetén a részletes paraméterek megadása
11.	Terápiás beavatkozások	A sphincterotomia, tágítás, kőeltávolítás, sztentbehelyezés adatai
A beavatkozás után rögzítendő adatok		
12.	További kezelési/kivizsgálási javaslat	Infúzió, *per os* táplálás, antibiotikus kezelés, kontroll-laborvizsgálatok, további képalkotó vizsgálatok stb.
13.	Szövődmények és ellátásuk	Azonnali és késői szövődmények, 30 napos követés adatai
14.	A vizsgálat nehézsége	Objektív (Schutz-ASGE beosztás) és szubjektív (1, nagyon könnyű – 10, nagyon nehéz) értékelés

ASGE = Amerikai Gastrointestinalis Endoszkópos Társaság; ERCP = endoszkópos retrográd cholangiopancreatographia; INR = (international normalized ratio) nemzetközi normalizált arány; PEP = post-ERCP-pancreatitis; TCT = thrombocyta

reassztent; 3. fokozat: epeúti kőeltávolítás >10 mm; minor papilla kanülálás/terápia; proximalisan migrált sztent eltávolítása; intraductalis képalkotás, biopszia, FNA; akut vagy rekurrens pancreatitis kezelése; pancreasszűkületek kezelése; pancreaskő-eltávolítás <5 mm; hilaris tumorok kezelése; benignus epeúti szűkületek kezelése hilusban vagy intrahepaticusan; Oddi-sphincter-dyskinesis; 4. fokozat: proximalisan migrált pancreassztent eltávolítása; intraductalis terápia; pancreaskő-eltávolítás, impaktált és/vagy >5 mm; intrahepaticus kövek; pseudocystadrenázs, necrosectomia; ampullectomia, Whipple- vagy Roux-en-Y bariátriai sebészet utáni ERCP) [28, 29].

Az ERCP-vizsgálathoz kapcsolódó szövődményeket a nemzetközileg elfogadott konszenzusdefiníciók alapján [30], a nehéz epeúti kanülálást az Európai Gastrointestinalis Endoszkópos Társaság (ESGE) 2016-ban kiadott irányelve alapján határoztuk meg [31] *(3. táblázat)*.

Nehezen elérhető epevezeték esetén az emelt szintű technikák korai, a kitartó kanülálási próbálkozásokat kiváltó alkalmazása megfelelően képzett endoszkópos kezében – a természetesen nem elhanyagolható szövődménykockázat ellenére – csökkentheti a post-ERCP-pancreatitis előfordulását a megfelelő profilaktikus módszerek alkalmazása mellett [32].

Az egyik ilyen emelt szintű kanülálási technika a kettős vezetődrótos módszer (DGW: double guidewire), melynek során a pancreasvezetékben lévő vezetődrót mellett egy másik vezetődróttal az epeutak irányába kanülálunk [33]. A másik, pancreasvezetékbe helyezett vezetődrótos technikánál papillotommal vagy kanüllel próbáljuk meg az epeutak elérését, ez a pancreaticus vezetődrót- (pancreatic guidewire, PGW) asszisztált technika. A pancreasvezetékbe helyezett sztent is segítheti a kanülálást, amely történhet vezetődróttal, papillotommal vagy akár tűkéssel [31].

E fenti, emelt szintű kanülálási módszerek mellett számos előmetszési technikát is ismerünk és használunk. Amennyiben a pancreasvezeték sem kanülálható, a leggyakrabban tűkéssel segítjük elő az epeúti elérést. Ezt a Vater-papilla orificiumából kiindulva vagy suprapapillarisan kezdve a metszést, úgynevezett fistulotomiával is megtehetjük [34, 35]. Előmetszéshez használhatunk még Erlangen-típusú rövid papillotomot is, ilyenkor 11 óra irányában ejtünk bemetszést a papillotom végének orificiumba illesztésével, azt stabilizálva [36, 37]. Míg az úgynevezett transpancreaticus (biliaris) sphincterotomia esetében (a pancreasvezetékben lévő vezetődrót stabilizálása mellett) papillotommal a pancreasvezetékből epeirányban metszünk (más néven transpancreaticus septotomiának is hívják), így segítve elő az epeutak elérését [38].

Jelenleg a Pécsi Tudományegyetem I. Belgyógyászati Klinikájáról származó adatok ellenőrzése történt meg. Több centrum is csatlakozott 2017 őszétől a kezdemé-

3. táblázat | Az ERCP szövődményeinek osztályozására használt definíciók és a nehéz epeúti kanülálás definíciója

	Enyhe	Középsúlyos	Súlyos
Post-ERCP-pancreatitis	a) Klinikai pancreatitis ÉS b) az amiláz legalább a 3-szorosa a felső határértéknek több, mint 24 órával a beavatkozás után, ÉS c) kórházi felvételt igényel, vagy a tervezett felvételt 2–3 nappal meghosszabbítja	4–10 nap kórházi ellátást igénylő pancreatitis	a) Több, mint 10 nap hospitalizációt igényel, VAGY b) haemorrhagiás pancreatitis, phlegmone, pseudocysta vagy fertőzés kialakulása, VAGY c) perkután drenázs vagy sebészi beavatkozás szükségessége
Vérzés	Klinikai (például nem csak endoszkópos) jelei vannak a vérzésnek; a hemoglobinesés <30 g/l, és nincs szükség transzfúzióra	Transzfúziós igény (<4 egység), nem szükséges angiographiás vagy sebészi beavatkozás	>5 egység transzfúziós igény vagy sebészi/angiographiás beavatkozás
Perforáció	Lehetséges vagy csak nagyon enyhe kontraszt vagy folyadékszivárgás, 3 napon belül gyógyul folyadékpótlás és szívás hatására	4–10 nap hospitalizációt igénylő definitív perforáció	>10 nap kórházi kezelést vagy sebészi/perkután beavatkozást igénylő perforáció
Cholangitis	>38 °C-os testhőmérséklet, és 24–48 óráig tart	Lázas vagy szeptikus betegség, amely több, mint 3 nap hospitalizációt igényel, vagy endoszkópos/perkután beavatkozást igényel	Szeptikus sokk vagy műtét szükségessége
Hypoxia	A vizsgálat közben 90% alatti oxigénszaturációt észleltünk		
Nehéz epeúti kanülláció	Több, mint 5 kontakt a papillával, VAGY több, mint 5 perc kanülációs kísérletek, VAGY több, mint egyszer nem szándékosan a pancreasvezetékbe vezetődrót jut, vagy kontrasztanyaggal ábrázolódik		

ERCP = endoszkópos retrográd cholangiopancreatographia

nyezéshez (Szegedi Tudományegyetem, Debreceni Egyetem, Magyar Honvédség Egészségügyi Központ, Markusovszky Egyetemi Oktatókórház), így a vizsgálati adatok folyamatosan gyűlnek a regiszterben. A regiszter további vizsgálóhelyek számára is elérhető a weboldalunkon (https://tm-centre.org/hu/regiszterek/ercp-regiszter/).

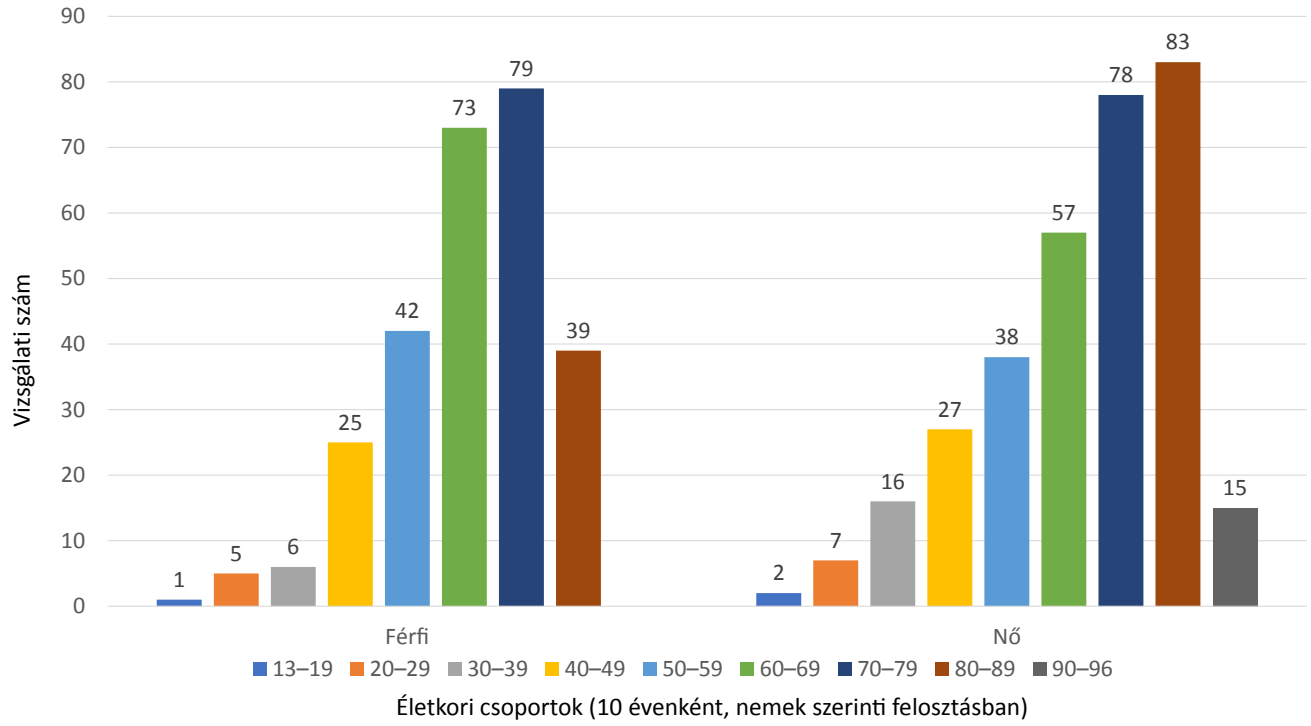
Eredmények

A PTE I. Belgyógyászati Klinikáján 2017-ben végzett ERCP-vizsgálatok közül 447 beteg 595 vizsgálatának adatait dolgoztuk fel (az összes vizsgálat 97,4%-a). Az 595 vizsgálatból 268 esetben (45%) férfi beteget vizsgáltunk, 15-től 87 évesig terjedően (átlagéletkor: 65,5 év), míg 327 beavatkozás (55%) történt nőbetegekben (13–96 éves kor, átlagéletkor: 67,9 év). Az életkori megoszlást vizsgálva fiatalabb életkorban nőknél történt több ERCP-vizsgálat; ez az arány az 50–70 éves korosztályban megfordul, majd 80 év felett újra visszatér a női dominancia *(1. ábra)*.

Összesen 111 páciensnek (24,8%) volt 2 vagy több ERCP-vizsgálata, 2 vizsgálata volt 86 betegnek, míg három ERCP-je 15, négy vizsgálata 8, öt vizsgálata két betegnek. Ezen betegek nagy részénél tervezett sztentcsere történt, jó- vagy rosszindulatú epeúti szűkületek miatt volt szükség ismételt beavatkozásra, de az első lépésben sikertelen beavatkozások ismétlése is emelte az ERCP-k számát.

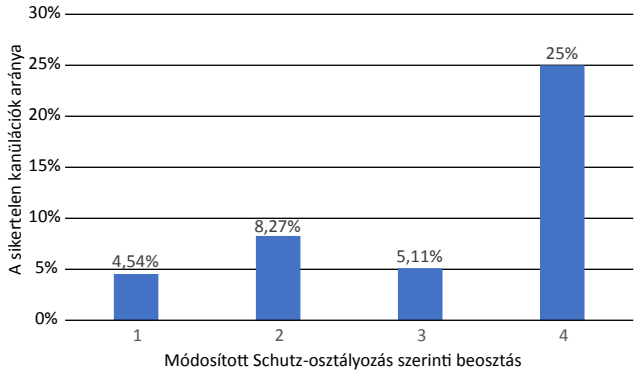
Az ERCP-k leggyakoribb indikációja az akut cholangitis volt, 244 (41,0%) vizsgálat történt emiatt. Az epevezeték betegségeiként jelölt tág indikációs csoport kerül a második helyre, 182 vizsgálatra (30,6%) került sor epeúti kő és a különböző etiológiájú epevezeték-eltérések miatt, akut cholangitis vagy obstrukciós icterus nélkül. Az elzáródásos sárgaság, cholangitis nélkül, 115 vizsgálatnál (19,3%) jelentette az indokot a beavatkozásra. A két legritkább indikáció az akut biliaris pancreatitis (32 ERCP – 5,4%), illetve a hasnyálmirigy egyéb betegségei (22 vizsgálat – 3,7%) voltak.

A vizsgálatok eloszlása a nehézségi szintek függvényében az alábbiak szerint alakult: 1-es nehézségű (legkönnyebb) volt 44 (7,53%), 2-es 387 (65,8%), 3-as 137 (23,3%), végül 4-es (legnehezebb) 20 (3,4%) vizsgálat. A sikertelen kanülálás megoszlását a vizsgálat objektív nehézsége szerint a *2. ábra* mutatja. Az 1–3-as nehézségi szintű vizsgálatoknál 10%-nál kevesebb volt a sikertelenség aránya, míg a 4-es nehézségű szintű vizsgálatok esetén ez az arány jelentősen nagyobb, 25%-os volt. 7 esetben nem állt elég információ rendelkezésünkre a Schutz-osztály szerinti besoroláshoz (nagy juxtapapillaris diverticulum vagy duodenumszűkület miatt kivihetetlen vizsgálatoknál).



1. ábra Az ERCP-vizsgálatokon átesett betegek életkori megoszlása (vízszintes tengely: életkor és nemi megoszlás; függőleges tengely: vizsgálati szám)

ERCP = endoszkópos retrográd cholangiopancreatographia



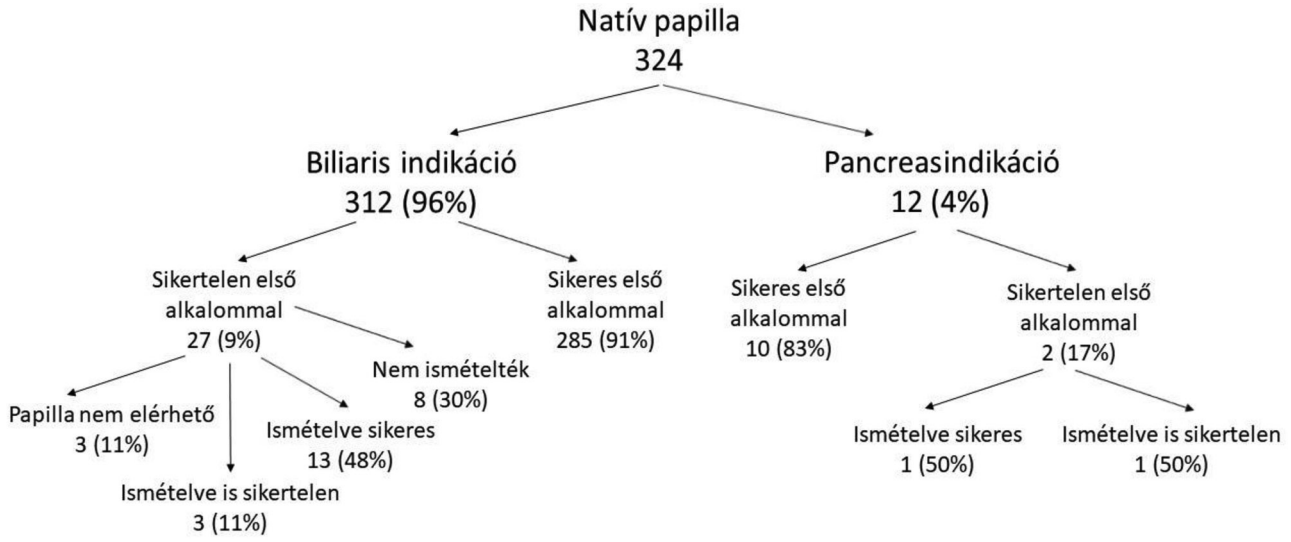
2. ábra A sikertelen ERCP-k aránya a vizsgálatok objektív nehézségének függvényében (módosított Schutz-osztályozás) (vízszintes tengely: módosított Schutz-fokozatok [1–4.]; függőleges tengely: a sikertelen vizsgálatok százalékos megoszlása)

ERCP = endoszkópos retrográd cholangiopancreatographia

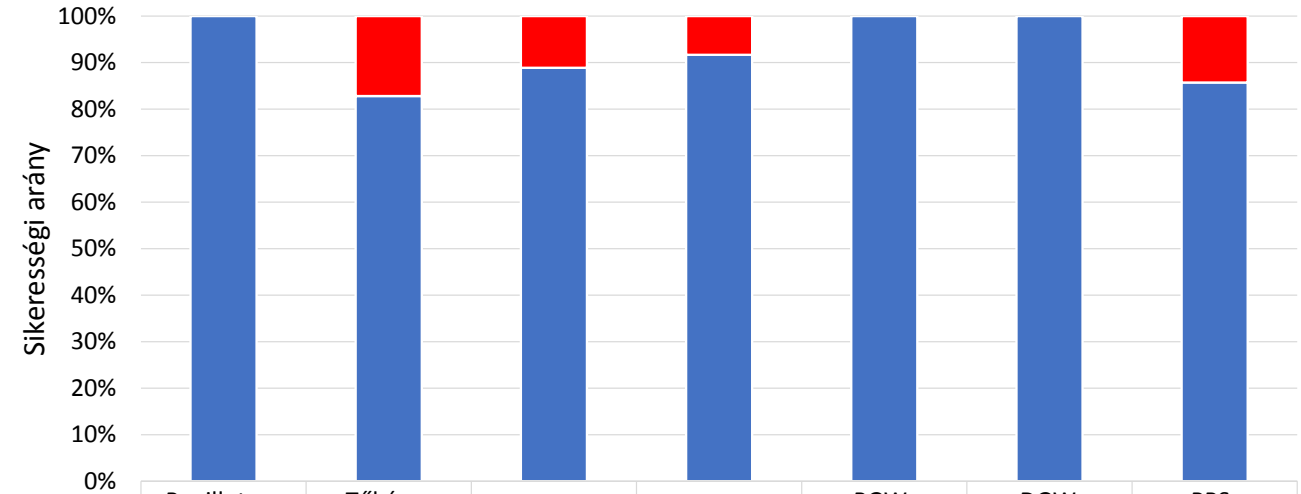
A sikertelen kanülálást követő ismételt ERCP-k kanülációs sikerességét az *3. ábrán* tüntettük fel. A natív papilla mellett végzett összes ERCP-t (n = 324) és az ismételt vizsgálatokat is figyelembe véve 95,4%-os volt a sikeres kanülálás aránya. Biliaris indikációban (az ismételt vizsgálatokat is figyelembe véve) az epeútelérés 298/312 esetben (95,5%), míg pancreasindikációban a pancreasvezeték-elérés 11/12 esetben (91,7%) volt sikeres. Ép papilla esetén nehéz epeúti kanülálást 312 esetből 100-ban (32,1%) véleményeztünk az ESGE által meghatározott kritériumok szerint [31]. Ezekben az esetekben 81 alkalommal (81,0%) volt eredményes az epeúti kanülálás emelt szintű, másodlagos kanülálási módszerek alkalmazása mellett az első vizsgálat során. Több alkalommal (összesen 21 esetben) korai (5 percen belüli) előmetszést (precut) vagy egyéb emelt szintű kanülációs technikákat alkalmaztunk az epeúti elérés elősegítése céljából. Az összes emelt szintű kanülálási módszer sikerességét mutatja be a *4. ábra*, ezek szövődményeit pedig a *4. táblázat* összegzi.

Azonnali szövődményeket az összes vizsgálat tekintetében 59 esetben (9,9%) észleltünk. Vérzés 38 esetben (6,4%) jelentkezett a beavatkozás alatt, amelyek közül 36 klinikailag nem szignifikáns intraprocedurális vérzés volt, 29 esetben volt szükség endoszkópos vérzéscsillapításra, 2 esetben késői, klinikailag manifeszt vérzés jelentkezett. Enyhe hypoxia 27 alkalommal (4,5%) lépett fel, melyet orrszondán adott oxigénnel rendezni lehetett.

Post-ERCP-s pancreatitis (PEP) 13 betegben alakult ki (2,2%), ennek súlyossága 7 esetben enyhe, 5 esetben mérsékelten súlyos, 1 esetben súlyos volt. Epevezeték-gyulladást 5 esetben (0,8%) észleltünk ERCP-t követően. Manifeszt, klinikailag szignifikáns vérzés 2 betegben (0,3%) jelentkezett. Vörösvértest-transzfúzióra egyik esetben sem volt szükség, míg az egyik beteg friss fagyasztott plazmát, véralvadási faktort (Octaplex) és K-vitamint (Konakion) kapott az endoszkópos vérzéscsillapítás mellett. Perforációt 8 esetben (1,3%) észleltünk: 4 esetben (0,7%) a vezetődrót okozott epevezeték-perfo-



3. ábra | A vizsgálatok ismétlésének szükségessége és az ismételt beavatkozások kimenetele



	Papillotom precut	Tűkéses precut	Fistulotomia	TPS	PGW-asszisztált	DGW-technika	PPS-asszisztált
Sikertelen	0	11	2	1	0	0	2
Sikeres	5	53	16	11	2	6	12

4. ábra | Az emelt szintű, másodlagos kanülálási módszerek sikerességének összefoglalása

DGW = kettős vezetődrót; PGW = pancreasvezetékbe helyezett vezetődrót; PPS = profilaktikus pancreassztent; TPS = transpancreaticus sphincterotomia

rációt, 1 alkalommal (0,2%) sztentbehelyezéshez, egyszer (0,2%) papillotom szűkületen történő átvezetéséhez és 2 alkalommal (0,3%) előmetszéshez volt köthető a perforáció. A perforáció kezelése összesen két alkalommal vezetett hosszabb hospitalizációhoz, súlyosnak minősítve a komplikációt. Az egyik esetben a retroperitonealis perforáció konzervatív kezelés mellett gyógyult 13 napos bennfekvés során, míg a másik esetben sebészi beavatkozásra is szükség volt epés peritonitis miatt, a hospitalizáció 22 napos volt.

A hosszú távú kimenetel és késői szövődmények dokumentálása céljából 30 nap után telefonos és/vagy kórházi informatikai rendszerbeli utánkövetés történt. Az 595 vizsgálat után 449 (75,5%) esetben sikerült az ERCP után 30 nappal információt szerezni. A vizsgált időszakban 28 beteg (6,2%) hunyt el 30 napon belül az ERCP-t követően, egy esetben (0,2%) volt a vizsgálattal kapcsolatba hozható a letális kimenetel. Ebben az esetben Klatskin-tumor miatt ismételt sztentcserék ellenére sem javuló epeútgyulladás okozta a beteg halálát, perkután drenázs sem volt kivitelezhető szabad hasi és subcapsularis folyadék miatt.

Regiszterünk alkalmas az egyes endoszkópos vizsgálók teljesítményeinek elemzésére, összehasonlítására is a mi-

4. táblázat Az emelt szintű kanülációs technikák szövődményei. Cholangitis és késői manifeszt, vörösvértest-transzfúziót igénylő vérzés egyik esetben sem fordult elő

	Esetszám	Az epeútelérés sikeressége	PEP	Endoszkópos haemostasist igénylő vérzés	Spontán szűnő vérzés	Késői manifeszt vérzés	Perforáció
Papillotomos precut	5	5 (100%)	0	1 (20,0%)	1 (20,0%)	0	0
Tűkéses precut	64	53 (82,8%)	3 (4,7%)	8 (12,5%)	4 (6,3%)	1 (1,6%)	2 (3,1%)
Fistulotomia	18	16 (88,9%)	2 (11,1%)	1 (5,56%)	2 (11,1%)	0	0
TPS	12	11 (91,7%)	1 (8,3%)	1 (8,3%)	2 (16,7%)	1 (8,3%)	0
PGW-asszisztált	2	2 (100%)	0	0	0	0	0
DGW-technika	6	6 (100%)	0	1 (16,7%)	0	0	0
PPS-asszisztált	14	12 (85,7%)	0	4 (28,6%)	0	0	0

DGW = kettős vezetődrót; PEP = post-ERCP-pancreatitis; PGW = pancreasvezetékbe helyezett vezetődrót; PPS = profilaktikus pancreasszstent; TPS = transpancreaticus sphincterotomia

5. táblázat A vizsgálókra lebontott ERCP-vizsgálatok száma és kimenetele. A sikeresség a kívánt vezeték elérésére vonatkozik

	Az elvégzett vizsgálatok száma	A sikeres vizsgálatok száma (%)	Post-ERCP-pancreatitis (%)	Jelentős vérzés (%)
1. vizsgáló	298	279 (93,6%)	6 (2,0%)	0 (0%)
2. vizsgáló	169	155 (91,7%)	5 (3,0%)	2 (1,2%)
3. vizsgáló	119	97 (81,5%)	2 (1,7%)	0 (0%)
4. vizsgáló	6	4 (66,7%)	0 (0%)	0 (0%)
5. vizsgáló	2	2 (100%)	0 (0%)	0 (0%)

ERCP = endoszkópos retrográd cholangiopancreatographia

nőségi mutatók elemzése mellett. A vizsgálókra lebontott vizsgálatok számát, a kanülációsikerességét és leggyakoribb szövődményeit az *5. táblázat* tartalmazza. A *6. táblázat* az ASGE által meghatározott minőségi mutatóknak [27] való megfelelésről és a javasolt célértékekről tájékoztat a vizsgálóhely vonatkozásában.

Megbeszélés

A fenti kezdeti, egy centrumot reprezentáló eredmények alátámasztják azt, hogy az ERCP Regiszter a legtöbb minőségi mutató követésére alkalmas; ezek a paraméterek külön-külön megadhatók a vizsgálóhely és az egyes vizsgálók vonatkozásában is. A vizsgált időszakban munkahelyünkön ezen indikátorok jelentős része a célértéknek megfelelő volt.

Számos külföldi példát is alapul véve, a magyar endoszkópos társadalom ennek a kezdeményezésnek a befogadásával és az ERCP Regiszter használatával ellen-

6. táblázat Az ASGE minőségi mutatói, a teljesítmény-célértékek és a mért értékek megadásával. 1C: közepesen erős ajánlás, változhat, ha erősebb bizonyíték elérhető; 1C+: erős ajánlás, a legtöbb gyakorlati beállításhoz a legtöbb szituációban alkalmazható; 2C: nagyon gyenge ajánlás, alternatív megoldások bizonyos körülmények között jobbak lehetnek; 3: gyenge ajánlás, valószínűleg változik, ha újabb adatok elérhetők lesznek. *: 6 esetben enyhe (1,0%), 2 esetben súlyos (0,3%) volt a perforációs szövődmény

Minőségi mutatók (ASGE 2014)	Az ajánlás foka	Teljesítménycél	Mért érték
Dokumentált megfelelő indikáció	1C+	>90%	100%
A tájékozott beleegyezés megtörtént/dokumentált	1C	>98%	99,0%
A páciens monitorozása szedálás esetén	3	>98%	98,3%
A gyógyszerek dózisainak és beadási módjának dokumentálása	3	>98%	99,5%
Az azonnali szövődmények dokumentálása	3	>98%	100%
Mély kanülálás elérése natív papilla és nem megváltozott anatómia esetén	1C	>90%	93,8%
1 cm-nél kisebb epeúti kövek extrakciója szűkület nélkül	1C	>90%	94,2%
Bifurkáció alatti sztentelés	1C	>90%	90,4%
Post-ERCP-pancreatitis-ráta	1C	N/A	2,2%
Perforációs ráta*	2C	≤0,2	1,3%
Postsphincterotomiás vérzési ráta	1C	≤1	0,3%
A beavatkozás után legalább 14 nappal a páciensek megkeresése szövődmények észlelése céljából	3	>90%	75,5%

ASGE = Amerikai Gastrointestinalis Endoszkópos Társaság; PEP = post-ERCP-pancreatitis

őrizni tudja, hogy az elvégzett vizsgálatok minden vonatkozásban megfelelnek-e a nemzetközileg elvárt indikátoroknak. Könnyen azonosíthatók a változtatást igénylő területek is, javítva ezzel a pancreatobiliaris endoszkópos beavatkozások minőségét. A regiszterben mért 4,5%-os, vizsgálat alatti hypoxiaarány például szedációs gyakorlatunk átgondolására hívja fel a figyelmet a magas hypoxiarizikóval rendelkezők (például ASA>II. kategóriájú, idős, légzőszervi és cardiovascularis betegségben szenvedők) esetében. Ezen betegeknél a rutinszerű oxigénterápia (orrszondán át) és a szedatívumok óvatos adagolása csökkentheti az oxigénhiányos állapot kialakulását [39].

Természetesen látható, hogy az idézett külföldi példáktól még messze vagyunk vizsgálati számban és a hálózat kiépítésében, hiszen rendszerünk tesztelési fázisa még csak most zárul [13, 14, 20, 23, 24]. Az ERCP Regiszter általánossá válása és minden ERCP-t végző centrum által a napi rutinba építése az endoszkópos képzésben és a készségek szinten tartásában is segítséget adhat. A megfelelő endoszkópos jártasság ellenőrzéséhez a minőségi indikátorok folyamatos monitorozása szükséges, amire ez a rendszer alkalmas. Az ERCP vizsgálati paramétereinek rögzítése segítheti a képzés során a kompetencia elérésének objektív vizsgálatát is. A jövőbeli vizsgálók képzése során fontos a fejlődésmenetük részletes és visszajelzésekkel összekötött követése, amelyben szintén nagy segítséget adhat az ERCP Regiszter. A regiszter a napi rutinmunkában jól használható, bár az adminisztratív munka idejét jelen formájában növeli. A rendszer azonban alkalmassá tehető lelet készítésére is, amivel a kettős adminisztráció a későbbiekben elkerülhető.

Következtetés

Megállapítható, hogy a jelenleg általánosan alkalmazott szabad szöveges endoszkópos leletezőrendszerek nem teszik lehetővé a vizsgálatokkal kapcsolatosan elvárt minőségindikátorok ellenőrzését, ezért tartottuk fontosnak a regiszter létrehozását. Az ERCP Regiszter használatától az ellátás minőségének javulását várjuk, aminek végső soron betegeink lesznek a haszonélvezői.

Anyagi támogatás: A projekt az Emberi Erőforrások Minisztériuma ÚNKP-17-3-I kódszámú Új Nemzeti Kiválóság Programjának és a Gazdaságfejlesztési és Innovációs Operatív Programnak (GINOP-2.3.2 – 15 – 2016 – 00048) a támogatásával készült.

Szerzői munkamegosztás: P. D.: A közlemény alapjául szolgáló adatok ellenőrzése, elemzése és a cikk megírása. V. Á.: A közlemény témájának megfogalmazása, az adatok ellenőrzése, elemzése, a közleménnyel kapcsolatos szakmai javaslatok megfogalmazása, a kézirat megírása. H. P.: Az adatok rendelkezésre bocsátása, a közleménnyel kapcsolatos javaslatok tétele. Sz. A.: A regiszteradatok minőségi ellenőrzése, a kézirat véleményezése. G. Sz., P. F., V. Á.: ERCP-vizsgálatok végzése, adatok rögzítése a forrásdokumentumokban, a kézirat megírása. A cikk végleges változatát valamennyi szerző elolvasta és jóváhagyta.

Érdekeltségek: A szerzőknek nincsenek érdekeltségeik.

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„Homines dum docent, discunt." (Seneca)
(Tanítás közben az ember maga is tanul.)

ENDOSZKÓPOS REGISZTEREK A MINŐSÉG SZOLGÁLATÁBAN

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ÖSSZEFOGLALÁS: ***A modern orvostudomány számára a betegadatok rendszerezett gyűjtése és strukturált adatbázisok, klinikai regiszterek létrehozása nélkülözhetetlenné vált. Ezekkel az adatbázisokkal könnyen ellenőrizhetők, követhetőek azok a paraméterek, amelyek a betegellátás minőségét és hatékonyságát jellemzik. A klinikai regiszterek használata a betegellátás folyamatát és a kimenetelt bizonyíthatóan javítják. Az emésztőszervi endoszkópos eljárásoknál is kiemelkedően fontos a beavatkozásokhoz kapcsolódó adatok rendszerezett gyűjtése. Ezek révén válik lehetővé a minőségi paraméterek és teljesítményjelzők monitorozása, ami kulcsfontosságú a biztonságos betegellátás fenntartása szempontjából. Nagyon sok nemzetközi példa mutatja a különböző endoszkópos eljárások regisztereinek hasznát és használhatóságát. A Magyar ERCP Regiszter létrehozását is a fenti célok vezérelték, és a kezdeti tapasztalatok alapján alkalmas a teljesítménymutatók követésére. Használatától az ellátás minőségének javulását várjuk, aminek végső soron betegeink lesznek a haszonélvezői. Ezen felül a strukturált adatgyűjtés révén prospektív obszervációs klinikai vizsgálatok végezhetők, amelyek eredményei az intervenciós vizsgálatok megtervezését is segíthetik.***

Kulcsszavak: ***endoszkópos retrográd kolangiopankreatográfia, endoszkópia, regiszterek, egészségügyi minőségi mutatók***

Pécsi D, Tóth M, Vincze Á: ENDOSCOPIC REGISTRIES IN THE QUALITY OF CARE

SUMMARY: ***Organized collection of patient related data and structured databases, clinical registries became integral part of modern medicine. Parameters indicating the quality and efficacy of health care are easily monitored with these databases. Application of the clinical registries demonstrable improves the healthcare processes and outcomes. Structured collection of procedure related data in gastrointestinal endoscopy has also emerging importance. It allows to monitor the quality and performance indicators, which have key importance to maintain safe patient care. Large number of international examples are proving the benefit and usability of different endoscopic registries. The Hungarian ERCP Registry was also created with these aims, and it is suitable to monitor the performance indicators. Improvement of the quality of health care is expected from its application, which finally provides benefit to our patients. Furthermore, prospective observational clinical studies can be based on the structured data collection, and the results can support the planning of interventional studies.***

Keywords: ***endoscopic retrograde cholangiopancreatography, endoscopy, registries, health care quality indicators***

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A modern orvostudomány számára a betegadatok rendszerezett gyűjtése és strukturált adatbázisok, klinikai regiszterek létrehozása nélkülözhetetlenné vált. Ezekkel az adatbázisokkal könnyen ellenőrizhetők, követhetők azok a paraméterek, amelyek a betegellátás minőségét, hatékonyságát jellemzik. Ellenőrizhetővé válik az ellátóhely és -személyzet adherenciája az érvényben lévő klinikai irányelvekhez, továbbá az adott beavatkozások, eljárások kapcsán kialakuló szövődmények, esetleges megelőző intézkedések eredményessége is felmérhetővé válik. Mindezek segítségével azonosíthatók azok a pontok, amelyek változtatásával az ellátás minősége tovább javítható. Több betegségcsoportnál, így a kardiológia[28], az onkológia[17] és a neurológia[27] területén, e regiszterek mára már kiterjedten működnek, és hatalmas mennyiségű adatot szolgáltatnak az ellátók és a tudomány számára is. A klinikai regiszterek használata a betegellátás folyamatát és a kimenetelt bizonyíthatóan javítják.[15] Természetesen ez az igény felmerült a gasztroenterológián belül is, ahol már szintén több regiszter létesült. Az első magyarországi kezdeményezések között vannak a Magyar Hasnyálmirigy Munkacsoport által létrehozott hasnyálmirigy-betegségek regiszterei, amelyek mára több ezer beteg adatát foglalják magukban, és külföldi centrumok bevonásával nemzetközi összefogást is generál-

tak.[22] A minőségi betegellátás irányába tett lépés még az első magyar irányelv megírása ebben a betegségcsoportban, illetve ezen útmutató betartásának követése a regiszterek felhasználásával.[16]

Az emésztőszervi endoszkópos eljárásoknál is kiemelkedően fontos a beavatkozásokhoz kapcsolódó adatok rendszerezett gyűjtése, mert ezek révén válik lehetővé a minőségi paraméterek és teljesítményindikátorok monitorozása, ami kulcsfontosságú a biztonságos betegellátás fenntartása szempontjából. Az utóbbi években több endoszkópos társaság is meghatározta a legfontosabb mutatókat a felső tápcsatornai endoszkópia,[2, 3, 21] a kolonoszkópia[18, 24, 25] és az endoszkópos retrográd kolangiopankreatográfia (ERCP),[1] valamint az endoszkópos ultrahang[29] vonatkozásában. Az endoszkópos eljárások sikerességét befolyásoló tényezőket, a beavatkozásokhoz kapcsolódó szövődmények kockázati tényezőit és az ezek megelőzésére alkalmazott módszerek hatékonyságát is monitorozhatjuk.[6] Egyre több terápiás, minimálisan invazív modalitás is szerepel az endoszkóposok palettáján, e beavatkozások eredményességét és szövődményeit is megfigyelhetjük regiszterek segítségével. Ezen a területen számos újdonság megjelenését láttuk az elmúlt években, azonban a klinikai hatékonyság és költséghatékonyság mérésére alkalmas randomizált vizsgálatok szervezése igen bonyolult, sokszor nem is lehetséges. Ilyen regisztereket hoztak létre például az endoszkópos teljes rétegvastagságú reszekció,[26] vagy egy új hemosztatikus por[13] hatékonyságának vizsgálatára. Az endoszkópos regiszterek jól szervezett hálózatok kiépítésével a kutatási együttműködéseket is segíthetik.[12]

A regiszterek segítségével tükröt tarthatunk magunk számára, és vizsgálói, intézményi, országos és multinacionális szinten is összehasonlíthatóvá válik munkánk minősége. A beavatkozásokhoz kapcsolódó számos paraméter követésével azonosíthatóvá válnak azok a pontok, ahol a minőségi mutatók nem érik el a megkívánt szintet, és az ok azonosításával és javításával az ellátás színvonala tovább emelhető, ami végső soron betegeink javát szolgálja.

Nem utolsósorban az endoszkópos regiszterek tudományos célokra is használhatók. Prospektív, megfigyeléses klinikai vizsgálatok alapját képezhetik ezek az adatbázisok, nagy betegszámot biztosítva, amellyel például a vizsgálók tapasztalatát, a vizsgálat nehézségi szintjét lehet összefüggésbe hozni különböző kimeneteli mutatókkal. Új, kezdő vizsgálók esetén a tanulási folyamat követése kiemelkedően fontos, amit a regiszterek szintén támogathatnak. A megfelelő kompetenciaszint elérésének kérdése a mai napig nagy kihívást jelent az endoszkóposok számára.[9] Fentieken kívül a beavatkozással járó, multicentrikus klinikai vizsgálatok alapját is képezhetik ezek a rendszerek.

Az endoszkópos leletező rendszerekkel szembeni alapvető elvárás, hogy strukturált formában történjen az adatbevitel a szabad szöveges leletezéssel szemben, ami lehetővé teszi az adatkapcsolatot más rendszerekkel.[5] Egy ilyen rendszer biztosíthatná az automatikus adatátvitelt a minőség-ellenőrzési és kutatási célokra létrehozott adatbázisokba, regiszterekbe, megkönnyítve a folyamatos ellenőrzést és biztosíthatná a könnyű adatkeresést. Sajnos magyar viszonylatban ilyen leletezőrendszer még nem áll rendelkezésünkre, emiatt a nemzetközileg elfogadott kulcsfontosságú mutatók követése egyelőre csak regiszterek elindításával válik lehetővé.

Kolonoszkópos regiszterek

A colorectalis rák szűrés kibontakozásával a kolonoszkópiák száma jelentősen nőtt, és számos vizsgálat bizonyította, hogy a szűrés hatékonysága nagyban függ a vizsgálat minőségétől és a vizsgáló teljesítményétől. A kolonoszkópos minőségi indikátorok[18, 25] közül számos mutató jelentős hatással van a beteg további sorsára. Vizsgálófüggő paraméterek például a coecumelérési ráta, valamint a polip- és/vagy adenomadetekciós ráta (ADR), amelyek folyamatos mérésével az endoszkópos vizsgálók teljesítménye kiválóan jellemezhető. Az intervallumrákok aránya felére, míg a halálos kimenetelű colorectalis rákok (CRC) száma több mint 60%-kal csökkenhető megfelelően magas ADR mellett. Igazolt, hogy minden 1%-os ADR-növekedés a CRC incidenciáját 3%-kal képes csökkenteni.[7] Ez a példa jól szemlélteti a kulcsfontosságú paraméterek követésének szükségességét, mert csak így biztosítható a megfelelő minőségű betegellátás. Amennyiben a vizsgáló vagy a vizsgálóhely mutatói az elvárt szintektől elmaradnak, a munkatársak továbbképzésének biztosításával, vagy amennyiben a betegfüggő paraméterek nem megfelelőek, a betegtájékoztatás javításával a minőség könnyen javítható.

Az Egyesült Államokban számos kezdeményezés történt az endoszkópos beavatkozásokkal kapcsolatos adatok regisztrálására, szisztematikus gyűjtésére. A kolonoszkópia (és felső tápcsatornai endoszkópia) esetében kiemelendő a „Gastrointestinal Quality Improvement Consortium" (GIQuIC), amely 2015-ben már több mint 2 millió vizsgálat adatát tartalmazta és egy év alatt képes volt megduplázni a bevitt adatok számát (https://giquic.gi.org/). Sok endoszkópos leletezőrendszer automatikus adatátvitelt biztosít a GIQuIC regiszterbe, ahonnét valós idejű adateléréssel bármelyik minőségi mutató lekérdezhető. Ezek az adatok a minőség folyamatos javításához, akkreditációhoz, a finanszírozókkal történő elszámoláshoz, kutatáshoz és sok más célra is felhasználhatók. A másik ilyen nagy adatgyűjtő rendszer a Clinical Outcomes Research Initiative (CORI, https://repository.niddk.nih.gov/studies/cori/) nemzeti endoszkópos adatbázisa (National Endoscopic Database, NED). Ezt az endoszkópos adatbázist klinikai kutatás céljából hozták létre a gastrointestinalis endoszkópos beavatkozások kimenetelének vizsgálatára. Az endoszkópos leletező rendszerekből 1996-tól kerültek az adatok a NED adatbázisba, de csak a 2000 és

2014 közötti 15 év adatait tekintették megbízhatónak. A 15 év alatt évente 100 000-et meghaladó, a legintenzívebb 5 évben évi 250 000 vizsgálat adatait rögzítették. Ezen adatok elemzésével az endoszkópos gyakorlat, az endoszkópos eltérések gyakorisága és súlyossága, az endoszkópos és gyógyszeres kezelés feltérképezése történt. Az adatbázis hozzájárult kutatási hipotézisek megalkotásához, új tudományos eredmények születéséhez, és az egészségipar számára adatokat szolgáltatva kollaborációk kialakulásához.

Norvégia is jó példa az endoszkópos regiszterek fejlesztésére. A Gastronet projekttel az országban történő endoszkópiák jelentős részét rögzítik, 2015-ben a kolonoszkópiák 71%-át regisztrálták és a vizsgálatok 68%-áról betegvisszajelzést is kaptak, amely igen fontos a vizsgálathoz kapcsolódó szövődmények felderítése szempontjából. A súlyos szövődmények ötször gyakoribbak voltak egynapos utánkövetés során, mint ahogy azt a vizsgálatot követően a beteg elbocsátásáig észlelték.[14] Regiszterük adataiból az is kimutatható volt, hogy az endoszkóposok gyakorlattól függetlenül a főbb minőségi paramétereket jelentősen alábecsülik, míg a vizsgálattal járó fájdalmat inkább túlbecsülik. Következtetésként levonható, hogy az önértékelés-alapú kolonoszkópos minőségi mutatók nem pontosak, nem helyettesíthetik a indikátorok szisztematikus regisztrációját.[20]

Németországban a kolonoszkópos colorectalis szűrés bevezetésével egy időben egy regisztert is létrehoztak, ahova minden szűrő kolonoszkópia adatait feltöltik. A vizsgálatok térítése a feltöltéstől függ, így gyakorlatilag az összes vizsgálat bekerül a regiszterbe. Az első 10 éves periódusban 4,4 millió vizsgálat történt, aminek elemzése azt mutatta, hogy a nem előrehaladott adenomák észlelése jelentősen növekedett.[4] Ezt a növekedést a folyamatos képzés és a tapasztalatok növekedése, a kolonoszkópok technikai javulása, továbbá a javuló bélelőkészítés magyarázza, de a szűrőprogram alatti folyamatos minőségbiztosítás és a kolonoszkópos minőségi paraméterek javuló tudatossága is eredményezi.

ERCP-regiszterek

Az ERCP a legnagyobb szövődményarányú rutin endoszkópos beavatkozás, így a minőség biztosítása, megfelelés az elvárt szinteknek ebben az esetben még inkább kiemelendő. ERCP-regiszterekben az USA szintén az élen jár, az ún. ERCP Quality Network Project 3 év alatt több mint 18 ezer vizsgálatot regisztrált, az adatokból azt a következtetést tudták levonni, hogy az évente 100-nál kevesebb vizsgálatot végzők jelentősen alulteljesítenek a minőségi mutatók tekintetében az ennél több ERCP-t végzőkhöz képest.[8] A svéd Gallriks-regiszter az egyik legsikeresebb projekt az adatbázisok között, számos közlemény születettaz epeúti betegségekkel kapcsolatos hatalmas mennyiségű adatokból. Csupán két év alatt több mint 11 ezer ERCP-vizsgálat és a 30-napos utánkövetés adatait tudták rögzíteni. Megállapították, hogy az ERCP-k kimenetele, minősége és a szövődmények aránya a nemzetközi standardoknak megfelelt.[11] Hollandiában egyéves időszak alatt önkéntes részvételi alapon több mint 8000 ERCP-t regisztrálva, 61 kórház részvételével közöltek adatokat. A vizsgált időszakban az országban végzett összes ERCP-vizsgálat mintegy fele került be a regiszterbe. A holland adatok is jól mutatják a vizsgálók tapasztalata, éves vizsgálatszáma, illetve a sikeres beavatkozások közötti összefüggést. Kimutatták, hogy az évente 50 vagy több ERCP-vizsgálatot végzők esetén a vizsgálat sikertelenségének kockázata kisebb volt, mint az 50-nél kevesebb vizsgálatot végzőknél.[10] Emellett az osztrák ERCP-regiszter érdemel említést, amelyben 5 éven át mintegy 13 500 vizsgálat adatait rögzítették. Ez a vizsgálati szám az adott időszakban Ausztriában elvégzett összes vizsgálat körülbelül 16%-át képviseli, míg a résztvevő centrumokban végzett vizsgálatok 83%-a regisztrálásra került. Szövődményt 10,1%-ban, ezen belül poszt-ERCP-s pancreatitist 4,2%-ban, vérzést 3,6%-ban, továbbá beavatkozással kapcsolatos mortalitást 0,1%-ban írtak le.[19]

A Magyar ERCP Regiszter kifejlesztése

Az eddig említett külföldi példákat alapul véve 2016-ban a PTE Transzlációs Medicina Központ kezdeményezésére sok más gasztroenterológiai témájú regiszter mellett endoszkópos regiszterek fejlesztése is elindult. A strukturált kérdőív kidolgozására a hazai nagy volumenű centrumokban ERCP-t végző szakemberek meghívást kaptak és egy megbeszélésen konszenzusra jutottak a gyűjtendő vizsgálati paraméterek vonatkozásában, az Amerikai Gastrointestinalis Endoszkópos Társaság (ASGE) ajánlásának figyelembevételével.[1] A vizsgálatok rögzítésének etikai engedélyét a Tudományos és Kutatásetikai Bizottság jóváhagyta (ETT-TUKEB engedély száma: 35523-2/2016/EKU). 2017 januárjától a Pécsi Tudományegyetemen, a Klinikai Központ I. sz. Belgyógyászati Klinika Gasztroenterológiai Tanszékén prospektív adatgyűjtés kezdődött, amelynek keretében a klinikán történő valamennyi ERCP-vizsgálat részletei egy internetalapú rendszerbe feltöltésre kerülnek. A kutatásetikai elveknek megfelelően minden beteg tájékoztatása megtörtént és ők beleegyeztek a nyilvántartásba vételbe, illetve az utánkövetésbe. A regiszter első 400 vizsgálati adatainak elemzése alapján a legtöbb minőségi mutató elvárt szintjeit centrumunk teljesíti *(1. táblázat)*.[22] 2017 őszétől több centrum is csatlakozott a kezdeményezéshez (Szegedi Tudományegyetem, Debreceni Egyetem, Magyar Honvédség Egészségügyi Központ, Markusovszky Egyetemi Oktatókórház) *(2. táblázat)*. A vizsgálati adatok folyamatosan gyűlnek, 2018. március elejéig a centrumok több mint 1100 vizsgálat adatait töltötték fel. A Magyar ERCP Regiszter további vizsgálóhelyek számára is elérhető weboldalunkon (https://tm-centre.

1. táblázat. A Magyar ERCP Regiszter fejlesztésének folyamatábrája

2016. február	2016. június	2016. december	2017. január	2017. szeptember	2017. október
• Projekt indítása, első megbeszélés (Hungarian Endoscopy Study group) • Egyeztetés magyar centrumokkal • A gyűjtendő paraméterek, struktúra meghatározása	• Etikai engedély (Egészségügyi Tudományos tanács Tudományos Kutatásetikai Bizottság: **35523-2/2016/EKU** – 2016. június 30.) • Web-alapú adatlapok (eCRF) fejlesztése	• Web-alapú adatlapok (eCRF) véglegesítése • Adatminőségi ellenőrzés: elfogadás és véglegesítés 4 lépcsőben	• Prospektív adatgyűjtés kezdete • Egy centrum: PTE I. Belklinika Gasztroenterológiai Tanszék	• Több magyar centrum csatlakozása: ◦ SZTE I. Belklinika ◦ DE Gasztroenterológiai Tanszék ◦ Markusovszky Egyetemi Oktató Kórház, Szombathely ◦ Magyar Honvédség Egészségügyi Központ, Budapest	• 530 beavatkozás adata • Az első 400 ERCP-adat (Pécs) validálása és analízise ◦ UEGW 2017: poszter ◦ ESGE Days 2018: előadás

2. táblázat. A Magyar ERCP Regiszter ASGE szerinti minőségi mutatói, a teljesítmény-célértékek és a mért értékek megadásával

Minőségi indikátorok (ASGE 2014)	Javaslat szintje	Célérték	Mért érték
Dokumentált megfelelő indikáció	1C+	>90%	100%
Tájékoztatott beleegyezés megszerzése, dokumentálása	1C	>98%	96,5%
Betegmonitorozás szedáció során	3	>98%	97,2%
Gyógyszerek adagolásának dokumentálása	3	>98%	99,5%
Azonnali szövődmények dokumentálása	3	>98%	100%
A kívánt vezeték kanülálása ép papilla és normál anatómia mellett	1C	>90%	93,8%
1 cm-nél kisebb epeúti kövek eltávolítása (ha nincs szűkület)	1C	>90%	94,6%
Bifurkáció alatti epeúti szűkület sztentelése	1C	>90%	98,2%
Poszt-ERCP pancreatitis gyakorisága	1C	N/A	1,5%
Perforációk fajtája és gyakorisága	2C	≤0,2	1,25%*
Klinikailag jelentős vérzés papillotomia után	1C	≤1	0,9%
Betegkövetés gyakorisága 14 nappal vagy később a szövődmények észlelésére	3	>90%	76,3%

1C: közepesen erős ajánlás, változhat, ha erősebb bizonyíték elérhető, 1C+: erős ajánlás, a legtöbb gyakorlati beállításhoz a legtöbb szituációban alkalmazható, 2C: nagyon gyenge ajánlás; alternatív megoldások bizonyos körülmények között jobbak lehetnek és 3: gyenge ajánlás; valószínűleg változik, ha újabb adatok elérhetők lesznek.
*Epevezeték-perforáció (4x vezetődróttal – nem volt következmény, 1x sztent – antibiotikus kezelés)

org/hu/regiszterek/ercp-regiszter/), és bíztatunk minden minőségi endoszkópiában elkötelezett munkatársat a csatlakozásra.

Következtetés

Az endoszkópos beavatkozásoknál mára alapvető követelménnyé vált a kimenetelt befolyásoló mutatók folyamatos regisztrálása és követése, amelyek révén az adott beavatkozás színvonaláról mind az ellátó, mind pedig a finanszírozó visszajelzést kaphat. A jelenleg általánosan alkalmazott szabad szöveges endoszkópos leletező rendszerek nem teszik lehetővé a vizsgálatokkal kapcsolatosan elvárt minőség indikátorok ellenőrzését, ezért fontosnak tartjuk különböző endoszkópos regiszterek létrehozását. A colorectalis szűrés erre az évre tervezett elindítása során a kolonoszkópia minőségi mutatóinak ellenőrzése is szükségessé válik, de ez csak egy adatbázis létrehozásával lehetséges. Az ERCP Regiszter létrehozását is a fenti gondolatok indították el, és reményeink szerint egyre több centrum csatlakozik hozzá. Használatától az ellátás minőségének javulását várjuk, aminek végső soron betegeink lesznek a haszonélvezői. Ezen felül a strukturált adatgyűjtés révén prospektív obszervációs klinikai vizsgálatok végezhetők, amelyek eredményei intervenciós vizsgálatok megtervezését is segíthetik.

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Thieme

Transpancreatic sphincterotomy has a higher cannulation success rate than needle-knife precut papillotomy – a meta-analysis

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Fig. e2 – e5, Table e1,
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ABSTRACT

Background and aim While many studies have discussed the different cannulation techniques used in patients with difficult biliary access, no previous meta-analyses have compared transpancreatic sphincterotomy (TPS) to other advanced techniques. Therefore, we aimed to identify all studies comparing the efficacy and adverse event rates of TPS with needle-knife precut papillotomy (NKPP), the most commonly used technique, and to perform a meta-analysis.

Methods The Embase, PubMed, and Cochrane databases were searched for trials comparing the outcomes of TPS with NKPP up till December 2016. A meta-analysis focusing on outcome (cannulation success, post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), post-procedural bleeding, and total adverse events) was performed. The population, intervention, comparison, outcome (PICO) format was used to compare these cannulation approaches. Five prospective and eight retrospective studies were included in our meta-analysis.

Results NKPP has a significantly lower success rate (odds ratio [OR] 0.50, $P=0.046$; relative risk [RR] 0.92, $P=0.03$) and a higher rate of bleeding complications (OR 2.24, $P=0.02$; RR 2.18, $P=0.02$) than TPS. However, no significant differences were found in PEP (OR 0.79, $P=0.24$; RR 0.80, $P=0.19$), perforation (risk difference [RD] 0.01, $P=0.23$), or total complication rates (OR 1.22, $P=0.44$; RR 1.17, $P=0.47$).

Conclusion While TPS has a higher success rate in difficult biliary access and causes less bleeding than NKPP, there are no differences in PEP, perforation, or total complication rates between the two approaches. We conclude that TPS, in the hands of expert endoscopists, is a safe procedure, which should be used more widely in patients with difficult biliary access.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a therapeutic modality used frequently for the management of most pancreatobiliary disorders. Selective cannulation of the common bile duct (CBD) is required for most indications, and is followed by sphincterotomy and further therapeutic interventions. Successful biliary cannulation is easily achieved in most patients with a few cannulation attempts in the first few minutes of the procedure; however, the initial attempts are not successful in 10 % – 20 % of patients with a native major papilla, depending on the definition of difficult biliary access.

In such patients with difficult biliary cannulation, advanced cannulation techniques are used to facilitate biliary access. Dif-

ficult cannulation, prolonged cannulation attempts, and advanced techniques are known to increase the risk of adverse effects (post-ERCP pancreatitis (PEP), bleeding, perforation, and cholangitis, among others). The new guideline issued by the European Society of Gastrointestinal Endoscopy (ESGE) provides practical advice on achieving successful cannulation while minimizing the associated risk [1]. The success rate for cannulation may exceed 95 % when using these advanced techniques, while the adverse event rate should remain below 5 %, according to the recommended new standards of ERCP [2].

Difficult biliary access is defined in the ESGE guideline as more than five contacts with the papilla while attempting to cannulate, more than 5 minutes spent attempting to cannulate after visualization of the papilla, or more than one unintended pancreatic duct cannulation or opacification [1]. Another new international consensus defines difficult biliary access similarly, but extends the time limit for the standard cannulation technique to 10 minutes [3].

The algorithm recommended in such patients, when the guidewire cannot be inserted into the pancreatic duct, is needle-knife precut papillotomy (NKPP) or fistulotomy (NKF) first. In the case of unintentional pancreatic guidewire (PGW) insertion PGW-assisted cannulation is recommended. The guidewire is kept in the pancreatic duct, and cannulation of the bile duct is attempted by injecting contrast material (single-guidewire technique) or with a second guidewire (double-guidewire [DGW] cannulation). If biliary access is still not possible, transpancreatic biliary sphincterotomy (TPS) can be performed over the pancreatic wire with a standard sphincterotome to expose the biliary orifice.

TPS is a relatively new and underutilized technique, first described by Goff et al. [4], with limited outcome data. One advantage of this method is that the depth of incision is better controlled by the slow pullback of a traction-type sphincterotome in making the incision toward the 11-o'clock position to the direction of the CBD than with the free-hand needle-knife technique. Another advantage is that the sphincterotome does not need to be changed to a needle-knife. In certain types of papillary tracts (small, flat, intradiverticular papilla, or the presence of a small oral protrusion), TPS can be performed more safely than NKPP or NKF. However, for a protruding or swollen papilla, NKPP or NKF may be a more appropriate approach [5].

The alternatives to TPS, needle-knife precut techniques (NKF or NKPP), are the more frequently used. Early precut papillotomy is recommended within 5 – 10 minutes after the start of the procedure to decrease the PEP rate and, according to a recent review and meta-analysis [6], NKF seems to be better than NKPP. While the use of these advanced cannulation techniques can increase the success rate for CBD cannulation, they also have the potential to significantly increase the adverse event rate.

TPS and other precut techniques have not been compared in any previous meta-analysis. Our aim was, therefore, to identify all studies that compared the efficacy and adverse event rate of TPS and NKPP, and to perform a meta-analysis focusing on the published outcomes for the use of these methods.

Methods

Literature review

A meta-analysis was performed using the population, intervention, comparison, outcome (PICO) format. The selected studies had looked at: (P) patients with various indications for ERCP who had difficult biliary access; (I and C) who were managed with TPS or NKPP; with the outcomes (O) being successful biliary cannulation, PEP, post-procedural bleeding, and total adverse event rate.

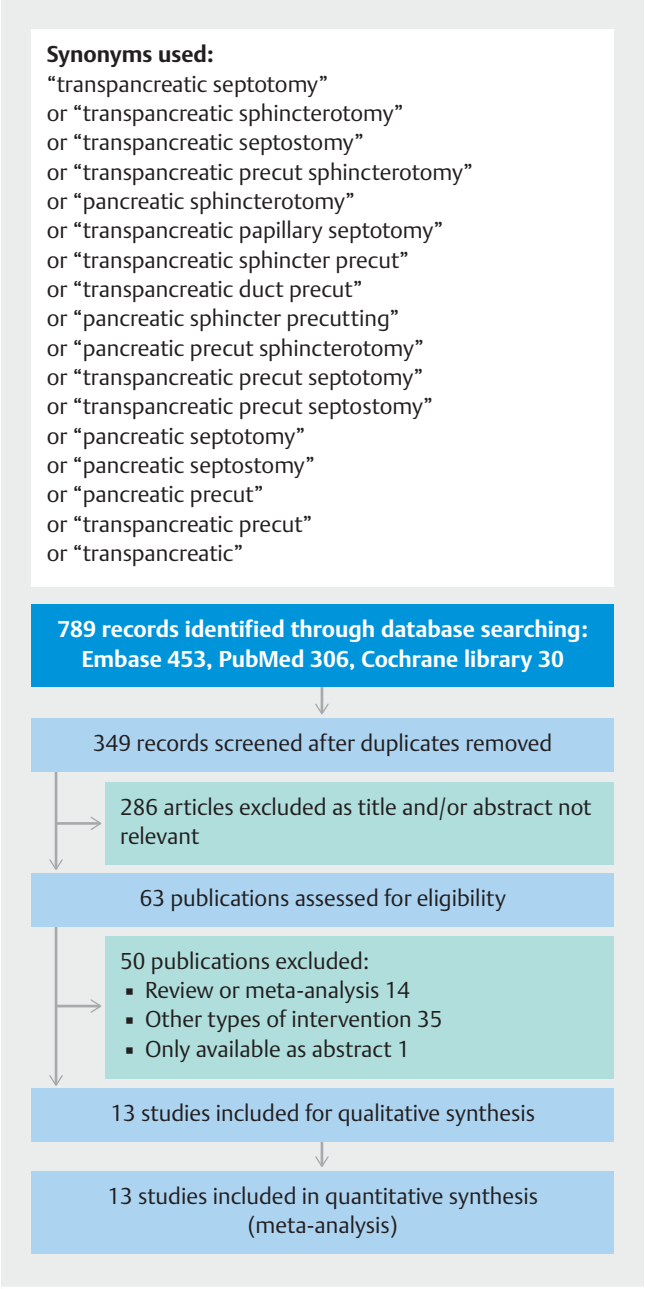
The electronic databases of Embase, PubMed, and the Cochrane Library were systematically searched for relevant studies. The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (▶ **Table e1**; available online) [7]. All articles comparing TPS and NKPP were searched irrespective of the study design, including randomized prospective, non-randomized prospective, and retrospective studies. There were no restrictions applied regarding the year of publication, language, age, sex, or otherwise. Embase, PubMed, and the Cochrane Library were searched for synonyms of TPS, which are interchangeably used in the literature [8]. The search included the terms "transpancreatic septotomy" OR "transpancreatic sphincterotomy" OR "transpancreatic septostomy" OR "transpancreatic precut sphincterotomy" OR "pancreatic sphincterotomy" OR "transpancreatic papillary septotomy" OR "transpancreatic sphincter precut" OR "transpancreatic duct precut" OR "pancreatic sphincter precutting" OR "pancreatic precut sphincterotomy" OR "transpancreatic precut septotomy" OR "transpancreatic precut septostomy" OR "pancreatic septotomy" OR "pancreatic septostomy" OR "pancreatic precut" OR "transpancreatic precut" OR "transpancreatic".

The latest date searched was 9 December 2016, which yielded 453, 306, and 30 articles in the Embase, PubMed, and Cochrane databases, respectively. An independent eligibility assessment was performed by each author, and disagreements were resolved by consensus. Duplicates, repeated publications, publications available only in abstract form, and review papers were excluded. The articles selected were published in English and compared the success and adverse event rates for the different treatment groups retrospectively or prospectively (▶ **Fig. 1**). Finally, 13 relevant full-text articles, both prospective and retrospective studies, were included in the quantitative synthesis of this meta-analysis.

The investigators extracted the data from each publication independently (number of subjects, method of cannulation, success rate, and different adverse event rates), and two investigators (D.P. and Á.V.) then validated these data. Disagreements were discussed and resolved by consensus. This meta-analysis has not been registered or published previously.

Quality assessment of the studies included

Randomized trials were assessed with the method described by Jadad et al. [9], while non-randomized studies were evaluated according to the Methodological Index for Non-Randomized Studies (MINORS) [10]. Two investigators (D.P. and Á.V.) asses-



▶ **Fig. 1** Flow diagram of the literature search.

sed the quality of each study included. Disagreements regarding the scoring were resolved by consensus.

Statistical methods

Pooled odds ratios (ORs), relative risks (RRs), and their 95 % confidence intervals (CIs) were calculated to compare the rates of success, PEP, bleeding, and total complications for the different cannulation techniques. The risk difference (RD) was calculated to compare the perforation rates to avoid overestimation because OR or RR calculations would exclude those studies where zero perforations were reported. In the case of a homogeneous subset of studies, we used the fixed-effect model described by Mantel and Haenszel [11]. The random-effect model of DerSimonian and Laird [12] was used when we pooled retrospective and prospective studies.

Heterogeneity was tested with two methods, namely the Cochrane's Q and the I^2 statistics. The Q test was computed by summing the squared deviations of each study's estimate from the overall meta-analysis estimate; P values were obtained by comparing the statistical results with a χ^2 distribution with k-1 degrees of freedom (where k was the number of studies). A P value of less than 0.05 was considered suggestive of significant heterogeneity. The I^2 statistic represents the percentage of the total variability across studies that is due to heterogeneity. I^2 values of 25 %, 50 %, and 75 % corresponded to low, moderate, and high degrees of heterogeneity, respectively, based on Cochrane's handbook [13].

Publication bias was examined by visual inspection of funnel plots, in which the standard error (SE) was plotted against the net change of outcome (i. e. success rate, complication rates) for each study.

Meta-analytic calculations were performed with Comprehensive MetaAnalysis software Version 3 (Biostat, Inc., Englewood, New Jersey, USA).

Results

Description of the studies selected

Five prospective studies [14 – 18] and eight retrospective studies [19 – 26] were identified during our search. Only two studies among the prospective studies were randomized, but neither of these was blinded (▶ **Table 2**). All of the studies provided data on success rates. PEP rate, bleeding rate, and total adverse event rate were not specified in the TPS group in one study, where TPS was performed sequentially after failed DGW cannulation [18]. A second study had the same sequential design [16]. A separate analysis was performed where these two studies were excluded, and we performed another separate analysis with the prospective studies.

The Jadad scoring system (where 0 means very poor and 5 means rigorous reporting) [9] was used to assess the two randomized studies. One of these [14] received only one point, which was because of the poor reporting of the randomization procedure and the lack of double blinding (which is impossible to carry out in endoscopic interventional trials). The other randomized trial [17] received three points because the randomization procedure was appropriately reported (▶ **Table 2**).

The non-randomized studies were assessed using the MINORS score, in which the maximum score for comparative studies is 24 [10]. Eight of the eleven studies received a medium score of 14 – 16, two trials received higher scores [18, 26], while only one got an underwhelming 10 points [20] for several weaknesses (inclusion of non-consecutive patients, more than 5 % loss to follow-up, non-equivalent groups, etc.) (▶ **Table 2**).

Funnel plot asymmetry tests were used to detect publication bias. No asymmetry was detected in the assessments of cannulation success rate and PEP rate, while there was asymmetry in the plots of bleeding and total complication rates (▶ **Figs. e2 – e5**; available online).

▶ **Table 2** Characteristics of studies comparing NKPP and TPS that were included in the meta-analysis.

Study	Study design	Quality of study		Number of included patients in the different treatment groups	
		Jadad scale[1] (0–5)	MINORS[2] (0–24)	NKPP	TPS
Catalano MF, 2004 [14]	Prospective, randomized	1	–	32	31
Espinel-Díez J, 2013 [15]	Prospective, non-randomized	–	16	74	125
Zang J, 2014 [17]	Prospective, randomized	3	–	76	73
Kim CW, 2015 [16]	Prospective, non-randomized, sequential	–	16	58	38
Zou XP, 2015 [18]	Prospective, non-randomized, sequential	–	22	20	25
Horiuchi A, 2007 [21]	Retrospective	–	14	30	48
Kapetanos D, 2007 [23]	Retrospective	–	14	15	40
Halttunen J, 2009 [20]	Retrospective	–	10	157	262
Wang P, 2010 [26]	Retrospective	–	18	76	140
Chan CHY, 2012 [19]	Retrospective	–	16	66	53
Katsinelos P, 2012 [24]	Retrospective	–	14	129	67
Miao L, 2015 [25]	Retrospective	–	16	33	36
Huang C, 2016 [22]	Retrospective	–	14	46	34

MINORS, Methodological Index for Non-Randomized Studies.
[1] Jadad scale: 0 = very poor, 5 = rigorous. Jadad AR et al. [9].
[2] MINORS: 12 items are scored (0 = not reported; 1 = reported, but inadequate; 2 = reported and adequate). The global ideal score is 16 for non-comparative studies and 24 for comparative studies. Slim K et al. [10].

Six out of the thirteen studies reported that there was no difference in the sex and age distribution between the NKPP and TPS groups [17, 19, 21, 24–26] (▶ **Table 3**). The other studies reported the male/female ratio and the mean age only for all of the involved patients together. The mean ages of the patient groups varied between 49 and 79 years in the analyzed studies. The number of women was more than double the number of men in the study of Huang et al. [22]; one study did not report these data [20]; while all the other studies reported nearly equal sex distribution (▶ **Table 3**).

Six of the analyzed studies [17, 19, 21, 24–26] also compared the indications for ERCP in the NKPP and TPS groups; only one study [24] showed significant differences for some of the indications. The indications were not separately analyzed in the other studies, but in general there were no major differences between the studies (▶ **Table 3**).

The experience of the endoscopist performing the different advanced cannulation techniques was not reported in three studies [20, 21, 25]; among these, only one study was carried out in a center with lower case volume (approximately 200 ERCPs/year) [21]. Experienced endoscopists performed the procedure in the other studies, although one study reported trainee involvement at the initial cannulation attempt [19], and another stated that approximately one-quarter of the interventions were performed by endoscopists with lower caseloads (≤ 3 ERCPs/week) [26] (▶ **Table 3**).

NKPP was performed in those patients where the pancreatic duct was not accessible in four studies [16, 18, 20, 26]. TPS or NKPP was randomly selected in three studies [14, 17, 25], while it was left to the preference of the endoscopist in the other studies.

Cannulation success

Four studies found that TPS was significantly better for cannulation success [15, 17, 20, 24]; one study showed just a tendency toward a better cannulation rate for TPS [14]; while no differences were found in the other studies.

Our data analysis allowed us to conclude that NKPP is significantly inferior to TPS with regard to cannulation success in terms of both OR (OR 0.50, 95 %CI 0.25–0.99; $P = 0.046$; n = 812 vs. 972; $Q = 50.21$, degrees of freedom [df(Q)] 12; $P < 0.001$; $I^2 = 76.10\%$; ▶ **Fig. 6**) and RR (RR 0.92, 95 %CI 0.85–0.99; $P = 0.03$; ▶ **Table 4**). The difference was even more significant when the meta-analysis was carried out using data from the prospective studies only [14–18]. In this comparison, the OR was 0.43 (95 %CI 0.26–0.72; $P = 0.001$; n = 260 vs. 292; $Q = 4.29$, df(Q) 4; $P = 0.37$; $I^2 = 6.85\%$; ▶ **Fig. 7**). The inferiority was also seen with a similar level of significance when RR values were calculated in the comparison of NKPP and TPS (RR 0.87, 95 %CI 0.82–0.94; $P < 0.001$; ▶ **Table 4**).

A separate analysis was performed that excluded the studies with sequential design. In this case, the difference between the

▶ **Table 3** Comparisons of patient characteristics, indications for ERCP, and endoscopist/center experience in the studies included in the meta-analysis.

Study	Sex	Age	ERCP indication	Endoscopist's experience	Center
Catalano MF, 2004 [14]	Male/female ratio not separately reported for groups (38 men; 25 women)	Mean age 68 years (range 52 – 83), not reported separately for groups	Therapeutic indications not reported separately for groups (SOD and previous failed ERCPs evenly distributed between the groups)	Not reported	High volume center (> 1000 ERCPs/year)
Espinel-Díez J, 2013 [15]	Male/female ratio not separately reported for groups (122 men; 125 women)	Mean age 74 years (range 25 – 93), not reported separately for groups	Therapeutic indications: no additional data	One experienced endoscopist performed all procedures (> 200 ERCPs/year)	High volume of therapeutic ERCPs, numbers not specified
Zang J, 2014 [17]	Male/female ratio evenly distributed in groups (71 men; 78 women)	No difference in groups (mean ages 54 and 55 years)	Therapeutic indications: no difference between groups	One experienced endoscopist performed all procedures (> 350 ERCPs/year)	No data on ERCP volume, high volume center can be assumed from number of included patients
Kim CW, 2015 [16]	Male/female ratio evenly distributed in NKPP and sequential groups; not reported in TPS group (55 men; 67 women)	No difference between NKPP and sequential groups; not reported in TPS group (65 and 64 years)	Therapeutic indications: no difference between NKPP and sequential groups; not reported in TPS group	Two similarly experienced endoscopists performed all procedures (> 1000 ERCPs in the past)	> 150 ERCPs/year in the study period for patients with a naïve papilla
Zou XP, 2015 [18]	Male/female ratio evenly distributed in NKPP and sequential groups; not reported in TPS group (44 men; 39 women)	No difference between NKPP and sequential groups; not reported in TPS group (69 and 66 years)	Therapeutic indications: no difference between NKPP and sequential groups; not reported in TPS group	Four experienced endoscopists performed all procedures (> 200 ERCPs/year during previous 3 years)	High volume center (> 1000 ERCPs/year during the previous 2 years)
Horiuchi A, 2007 [21]	Male/female ratio evenly distributed in groups (54 men; 24 women)	No difference in groups (mean ages 75 and 76 years)	Therapeutic indications: no difference between groups	Two endoscopists, experience not reported	Approximately 200 ERCPs/year
Kapetanos D, 2007 [23]	Male/female ratio not separately reported for groups (160 men; 164 women in original cohort [27])	Not reported separately for groups (mean age 65 years [range 17 – 96] in original cohort [27])	Therapeutic indications: not reported separately for groups	Two similarly experienced endoscopists performed all procedures (> 800 ERCPs in the past)	Approximately 150 ERCPs/year
Halttunen J, 2009 [20]	No data on sex distribution	No difference in groups (mean ages 73 and 79 years)	Therapeutic indications: some differences between groups, but statistical evaluation not reported (e. g. more papilla stricture and sclerosing cholangitis in TPS group)	Not reported	High volume center (> 600 ERCPs/year)

▶ **Table 3** (Continuation)

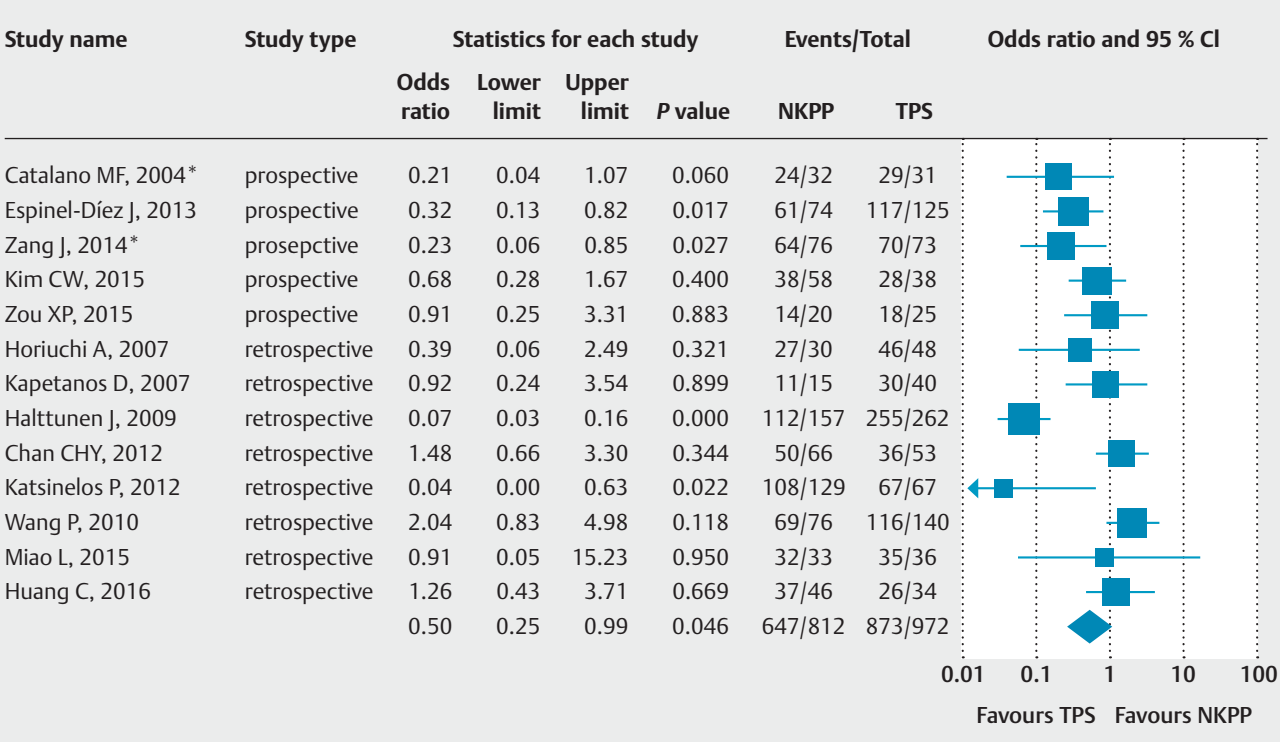
Study	Sex	Age	ERCP indication	Endoscopist's experience	Center
Wang P, 2010 [26]	Male/female ratio evenly distributed in groups (125 men; 91 women)	No difference in groups (mean ages 61 and 59 years)	Therapeutic indications: no difference between groups	All endoscopists had performed > 100 ERCPs/year in the preceding year, but 25 % of NKPPs and 28 % of TPSs were performed by endoscopists with low case volume (≤ 3 /week), no difference between groups	No data on ERCP volume (14 centers, 3178 ERCPs in 3 – 12 months)
Chan CHY, 2012 [19]	Male/female ratio evenly distributed in groups (55 men; 64 women)	No difference in groups (mean ages 71 and 68 years)	Therapeutic indications: no difference between groups	Three similarly experienced endoscopists performed all procedures (> 2000 ERCPs in the past), ERCP fellows were initially involved, but all interventions were performed by seniors	Two tertiary referral centers, but no exact data on ERCP volume
Katsinelos P, 2012 [24]	Male/female ratio evenly distributed in groups (93 men; 103 women)	No difference in groups (mean ages 72 and 73 years)	Therapeutic indications: statistically significant differences between groups (e. g. more CBD stones and less biliary leak in TPS group)	One experienced endoscopist performed all procedures (> 300 ERCPs/year)	> 300 ERCPs/year in the study period for patients with a naïve papilla
Miao L, 2015 [25]	Male/female ratio evenly distributed in groups (35 men; 32 women)	No difference in groups (mean ages 58 and 60 years)	Therapeutic indications: no difference between groups	Not reported	High volume center (> 1000 ERCPs/year)
Huang C, 2016 [22]	Male/female ratio not separately reported for groups (72 men; 158 women)	Mean age 49 years, not separately reported for groups	Therapeutic indications: not separately reported for groups	Three similarly experienced endoscopists performed all procedures (extensive ERCP experience)	> 400 ERCPs/year in the study period

ERCP, endoscopic retrograde cholangiopancreatography; SOD, sphincter of Oddi dysfunction; NKPP, needle-knife precut papillotomy; TPS, transpancreatic sphincterotomy; CBD, common bile duct.

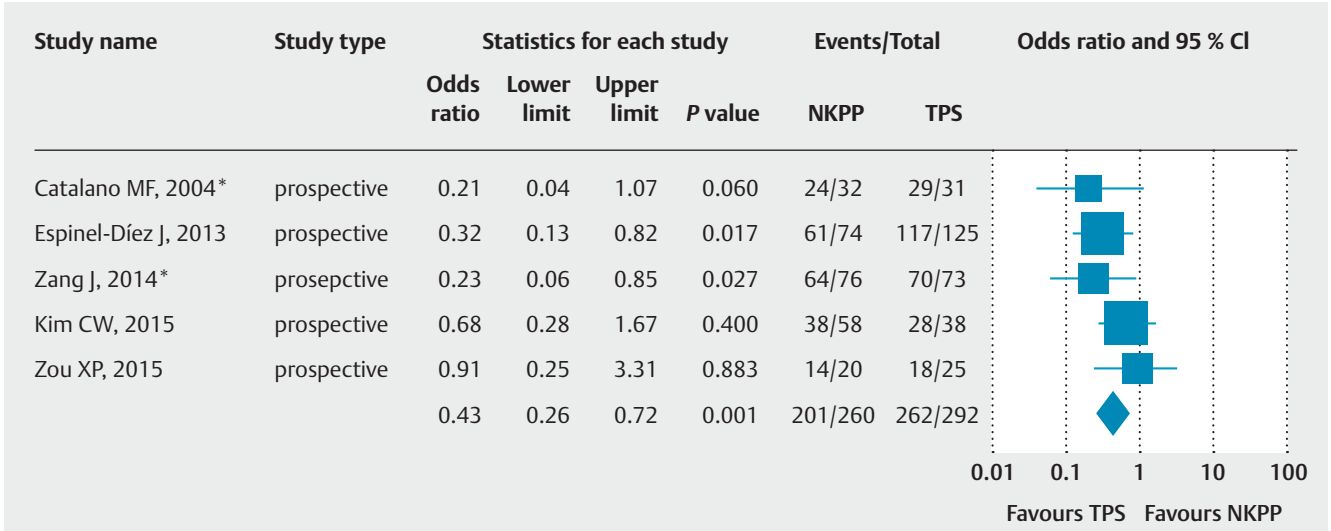
▶ **Table 4** Relative risk (RR) calculations for success rates in the needle-knife precut papillotomy (NKPP) and transpancreatic biliary sphincterotomy (TPS) groups.

Comparison	Included studies	RR[1]	95 %CI	*P* value
Success rate	**All**	**0.92**	**0.85 – 0.99**	**0.03**[2]
	Prospective	**0.87**	**0.82 – 0.94**	**< 0.001**
	Non-sequential	**0.92**	**0.85 – 1.00**	**0.047**
PEP rate	All	0.80	0.58 – 1.11	0.19
	Prospective	**0.51**	**0.27 – 0.97**	**0.04**
	Non-sequential	0.93	0.63 – 1.37	0.72
Bleeding rate	**All**	**2.18**	**1.15 – 4.13**	**0.02**
	Prospective	1.01	0.32 – 3.16	0.98
	Non-sequential	**2.40**	**1.25 – 4.60**	**0.008**
Total complication rate	All	1.17	0.72 – 1.78	0.47
	Prospective	0.61	0.36 – 1.02	0.06
	Non-sequential	1.33	0.96 – 1.83	0.08

CI, confidence interval; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis.
[1] RR < 1 indicates a lower rate in the NKPP group.
[2] Numbers in bold represent statistically significant differences.



▶ **Fig. 6** Forest plot of studies that evaluated success rate in needle-knife precut papillotomy (NKPP) and transpancreatic biliary sphincterotomy (TPS) groups (data pooled from all of the studies). CI, confidence interval.
* Prospective randomized trial.



▶ **Fig. 7** Forest plot of studies that evaluated success rate in needle-knife precut papillotomy (NKPP) and transpancreatic biliary sphincterotomy (TPS) groups (data pooled from the prospective studies). CI, confidence interval.
* Prospective randomized trial.

two methods did not reach the level of statistical significance, but a tendency toward inferiority of the NKPP technique could be seen (OR 0.45, 95 %CI 0.20 – 1.02; $P = 0.06$; n = 734 vs. 909; $Q = 49.18$, df(Q) 10; $P < 0.001$; $I^2 = 79.67\,\%$). The RR calculation from these studies revealed a significantly lower success rate in the NKPP group compared with the TPS group (RR 0.92, 95 %CI 0.85 – 1.00; $P = 0.047$) (▶ **Table 4**).

PEP rates

Only one study found NKPP significantly superior to TPS in terms of PEP rates [16], while the remaining articles found no difference between the two cannulation methods. An analysis of the pooled data did not reveal a statistical difference in PEP rates (OR 0.79, 95 %CI 0.53 – 1.17; $P = 0.24$; n = 794 vs. 939; $Q = 12.07$, df(Q) 11; $P = 0.36$; $I^2 = 8.85\,\%$) (▶ **Fig. 8**). The difference in PEP rates was close to the level of significance when only the prospective studies [14 – 17] were analyzed. There was a tendency toward lower PEP rates in the NKPP group (OR 0.49, 95 %CI 0.23 – 1.01; $P = 0.052$; n = 242 vs. 265; $Q = 6.947$, df(Q) 3; $P = 0.07$; $I^2 = 56.82\,\%$), while the RR calculation showed a significantly lower rate of PEP in this analysis (RR 0.51, 95 %CI 0.27 – 0.97; $P = 0.04$) (▶ **Table 4**).

No significant difference was found between the two techniques when the studies with non-sequential design were separately analyzed (OR 0.93, 95 %CI 0.63 – 1.37; $P = 0.72$; n = 736 vs. 901; $Q = 4.96$, df(Q) 10; $P = 0.89$; $I^2 = 0\,\%$).

Bleeding rates

The bleeding rates after TPS or NKPP did not differ significantly in any of the analyzed studies. Our meta-analysis showed that there is significantly more bleeding after NKPP compared with TPS (OR 2.24, 95 %CI 1.17 – 4.31; $P = 0.02$, n = 745 vs. 908; $Q = 5.21$, df(Q) 9; $P = 0.82$; $I^2 = 0\,\%$) (▶ **Fig. 9**). An analysis of the non-sequential studies showed the same results: NKPP was found to cause significantly more bleeding than TPS (OR 2.48, 95 %CI 1.27 – 4.84; $P = 0.008$; n = 687 vs. 870; $Q = 5.21$, df(Q) 9; $P = 0.82$; $I^2 = 0\,\%$).

An analysis of the data extracted from the prospective studies [14 – 17] revealed no difference in bleeding rates: OR 1.013, 95 %CI 0.32 – 3.16; $P = 0.98$, n = 239 vs. 268; $Q = 3.324$, df(Q) 3; $P = 0.34$; $I^2 = 9.75\,\%$.

The RR values for bleeding rate from all the studies, from prospective studies only, and from non-sequential studies showed the same differences (▶ **Table 4**).

Perforation rates

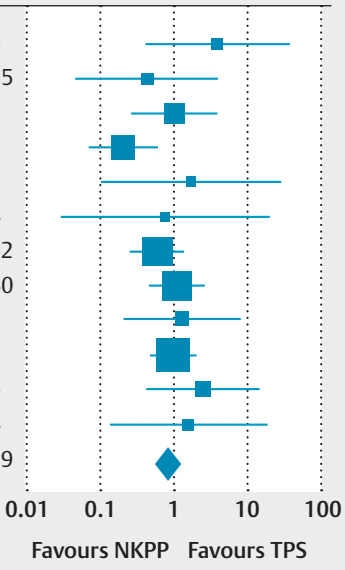
The perforation rates did not differ significantly in any of the analyzed studies. Altogether, seven perforations were reported after NKPP, while only one occurred after TPS. This difference was not statistically significant in our analysis (RD 0.01, 95 %CI 0.00 – 0.02; $P = 0.23$; n = 812 vs. 942; $Q = 2.06$, df(Q) 12; $P > 0.99$; $I^2 = 0\,\%$). The RD similarly did not show any differences between the groups in the separate analyses of prospective and non-sequential studies.

Total complication rates

Only one study [16] found that NKPP had significantly fewer total adverse events than TPS; the other studies did not find any differences. Our analysis found no difference between the two methods with regard to the total complication rates (OR 1.22, 95 %CI 0.74 – 2.00; $P = 0.44$; n = 794 vs. 939; $Q = 23.48$, df(Q) 11; $P = 0.02$; $I^2 = 53.15\,\%$).

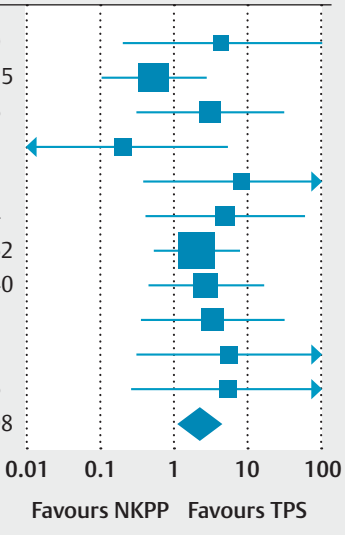
Excluding the studies with sequential design revealed a tendency for NKPP to cause more total complications than TPS (OR 1.33, 95 %CI 0.96 – 1.83; $P = 0.08$; n = 736 vs. 901; $Q = 7.88$, df(Q) 10; $P = 0.64$; $I^2 = 0\,\%$) (▶ **Fig. 10**). Calculations of RR, similarly to the OR values, did not show significant differences in the NKPP and TPS groups (▶ **Table 4**).

Study name	Study type	Statistics for each study				Events/Total		Odds ratio and 95 % CI
		Odds ratio	Lower limit	Upper limit	*P* value	NKPP	TPS	
Catalano MF, 2004*	prospective	3.37	0.39	35.46	0.251	4/34	1/29	
Espinel-Díez J, 2013	prospective	0.41	0.05	3.78	0.435	1/74	4/125	
Zang J, 2014*	prosepctive	0.96	0.27	3.46	0.947	5/76	5/73	
Kim CW, 2015	prospective	0.20	0.07	0.58	0.003	6/58	14/38	
Horiuchi A, 2007	retrospective	1.62	0.10	26.92	0.736	1/30	1/48	
Kapetanos D, 2007	retrospective	0.72	0.03	18.71	0.844	0/15	1/34	
Halttunen J, 2009	retrospective	0.56	0.24	1.28	0.168	8/157	23/262	
Wang P, 2010	retrospective	1.04	0.44	2.48	0.928	9/76	16/140	
Chan CHY, 2012	retrospective	1.21	0.20	7.55	0.835	3/66	2/53	
Katsinelos P, 2012	retrospective	0.92	0.45	1.87	0.814	27/129	15/67	
Miao L, 2015	retrospective	2.34	0.40	13.74	0.345	4/33	2/36	
Huang C, 2016	retrospective	1.50	0.13	17.25	0.745	2/46	1/34	
		0.79	0.53	1.17	0.235	70/794	85/939	



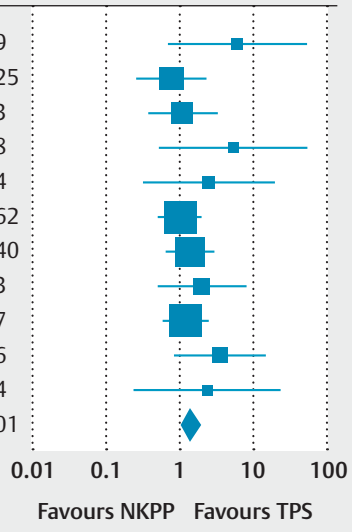
▶ **Fig. 8** Forest plot of studies that evaluated post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) rate in needle-knife precut papillotomy (NKPP) and transpancreatic biliary sphincterotomy (TPS) groups (data pooled from all of the studies). CI, confidence interval.
* Prospective randomized trial.

Study name	Study type	Statistics for each study				Events/Total		Odds ratio and 95 % CI
		Odds ratio	Lower limit	Upper limit	*P* value	NKPP	TPS	
Catalano MF, 2004*	prospective	4.54	0.21	98.45	0.335	2/34	0/29	
Espinel-Díez J, 2013	prospective	0.55	0.11	2.80	0.473	2/74	6/125	
Zang J, 2014*	prosepctive	3.21	0.33	31.63	0.317	3/73	1/76	
Kim CW, 2015	prospective	0.21	0.01	5.38	0.349	0/58	1/38	
Horiuchi A, 2007	retrospective	8.51	0.39	183.55	0.172	2/30	0/48	
Kapetanos D, 2007	retrospective	5.08	0.42	60.91	0.200	2/15	1/34	
Halttunen J, 2009	retrospective	2.12	0.56	8.02	0.268	5/157	4/262	
Wang P, 2010	retrospective	2.84	0.46	17.35	0.259	3/76	2/140	
Chan CHY, 2012	retrospective	3.35	0.36	30.95	0.286	4/66	1/53	
Katsinelos P, 2012	retrospective	5.96	0.32	109.50	0.229	5/129	0/67	
Miao L, 2015	retrospective	5.79	0.27	125.25	0.263	2/33	0/36	
		2.24	1.16	4.31	0.016	30/745	16/908	



▶ **Fig. 9** Forest plot of studies that evaluated the post-papillotomy bleeding rate in needle-knife precut papillotomy (NKPP) and transpancreatic biliary sphincterotomy (TPS) groups (data pooled from all of the studies). CI, confidence interval.
* Prospective randomized trial.

Study name	Study type	Statistics for each study				Events/Total		Odds ratio and 95 % CI
		Odds ratio	Lower limit	Upper limit	*P* value	NKPP	TPS	
Catalano MF, 2004*	prospective	6.00	0.68	53.12	0.107	6/34	1/29	
Espinel-Díez J, 2013	prospective	0.75	0.25	2.25	0.609	5/74	11/125	
Zang J, 2014*	prosepctive	1.11	0.38	3.23	0.849	8/76	7/73	
Horiuchi A, 2007	retrospective	5.22	0.52	52.72	0.161	3/30	1/48	
Kapetanos D, 2007	retrospective	2.46	0.31	19.38	0.392	2/15	2/34	
Halttunen J, 2009	retrospective	0.99	0.51	1.90	0.970	16/157	27/262	
Wang P, 2010	retrospective	1.35	0.64	2.86	0.427	14/76	20/140	
Chan CHY, 2012	retrospective	1.98	0.49	8.05	0.341	7/66	3/53	
Katsinelos P, 2012	retrospective	1.19	0.59	2.39	0.622	33/129	15/67	
Miao L, 2015	retrospective	3.52	0.85	14.64	0.083	8/33	3/36	
Huang C, 2016	retrospective	2.30	0.23	23.15	0.479	3/46	1/34	
		1.33	0.96	1.83	0.084	105/736	91/901	



▶ **Fig. 10** Forest plot of studies evaluating total complication rate in needle-knife precut papillotomy (NKPP) and transpancreatic biliary sphincterotomy (TPS) groups (data pooled from prospective and retrospective studies, excluding ones with sequential design). CI, confidence interval.

Discussion

Our meta-analysis indicates that TPS is more effective than NKPP with regard to the success of biliary tract cannulation. On the other hand, the PEP rate, the most frequent adverse event after ERCP, did not differ between the TPS and the NKPP groups when all the studies were analyzed together. The PEP rate was lower in the NKPP group in the separate analysis of prospective studies. The bleeding rate was lower after performing TPS in the analysis of all studies, while there was no difference between the bleeding rates of the two techniques if the prospective studies only were analyzed separately. Perforation rates did not differ statistically in the analysis of the two techniques, although only one perforation was observed after TPS in the analyzed studies, while seven perforations occurred after the NKPP technique.

It should be pointed out that TPS is not for novice endoscopists because multiple guidewire insertions or contrast injection into the pancreatic duct, thermal injury during papillotomy, and many other factors can cause PEP. Experienced endoscopists performed the procedures in almost all analyzed studies, which was an important factor in the high rate of cannulation success and low rate of complications. Adherence to the current guidelines regarding the prevention of PEP is also very important after TPS; therefore, insertion of a short 5-Fr pancreatic stent and administration of a non-steroidal suppository are strongly advised in this situation.

No difference in the total complication rates for the two groups was found; however, a significant asymmetry of the funnel plot analysis was detected in this case, which indicates publication bias that could have altered the results. Unfortunately, the less frequent adverse events, like cholangitis, sepsis, and procedure-related death, among others, were not analyzable because most of the studies did not report them. Mean cannulation times, procedure times, and radiation doses during the different cannulation techniques would also be interesting to compare, but these important data were only included in a minority of the studies. An analysis of these parameters, therefore, could not be performed.

We excluded one study that was published only in abstract form from the analysis. The study of Kawaguchi et al. is a retrospective data analysis with small sample size (22 patients with TPS vs. 10 patients with NKPP) [28]. They found no difference between the two techniques regarding cannulation success rate ($P = 0.73$), but NKPP had a significantly higher PEP rate ($P = 0.02$), while the bleeding and total complication rates were not reported.

There are several limitations to this meta-analysis. Firstly, there was significant heterogeneity among the studies with regard to cannulation success and total complication rate. The heterogeneity disappeared when the prospective studies were analyzed separately for cannulation success and when the two studies with sequential design were excluded in the analysis of total complication rate.

Several factors could have caused the heterogeneity among these studies. Difficult biliary access was defined with great variability in the analyzed studies, while other outcome measures were much more uniform. Although the definition of difficult cannulation has not yet been standardized, only the study of Huang et al. [22] fulfilled the criteria that were suggested in

the recent ESGE guideline [1]. The majority of the studies used a more permissive definition, while two studies [20, 24] did not define it (▶ **Table 5**). This theoretically might increase the rate of complications without influencing the success rate. Less heterogeneity was observed in the adverse events. Only the oldest study [14] did not specify how PEP was diagnosed, with all the other studies using the consensus criteria. Bleeding definition was in accordance with the consensus criteria in 10 out of 13 studies; two studies did not specify the definition [20, 22]; and another used different criteria [25] (▶ **Table 5**).

Unfortunately, very few randomized studies that analyze the efficacy and adverse event rates of advanced biliary cannulation methods are available in the literature. Differences in the study design might also have caused heterogeneity. We identified two studies, where TPS was only performed after DGW-assisted biliary access failed [16, 18]. These sequential attempts at biliary access might increase the rate of successful cannulation, but might also cause more adverse events as more papillary injury is induced this way.

In our analysis, the success rate was not influenced by the inclusion of these sequential studies, because only data from those patients who underwent a TPS attempt were included, while patients in the sequential DGW – TPS group with successful DGW-assisted cannulation were left out. The inclusion or exclusion of sequential studies from the meta-analysis did not influence the two most frequent adverse events: PEP rates were the same, while the bleeding rate was less in the TPS group than in the NKPP group, irrespective of the study design.

Secondly, the majority of the included studies contained retrospective outcome data. We also investigated the prospective studies separately, but the small number of prospective studies may limit the value of this separate analysis. The advantage of TPS in terms of successful cannulation was stronger when the prospective data were analyzed separately and the degree of heterogeneity was much lower. However, with regard to PEP rates, the degree of heterogeneity was higher when the prospective studies were analyzed separately and the RR of PEP favored the NKPP group, while the OR calculation did not show a statistical difference. The bleeding rate was lower in the TPS group than in the NKPP group in the analysis of all studies, but there was no difference in the analysis of the prospective studies, while a low degree of heterogeneity was observed in both analyses. Publication bias may have influenced this outcome because, in the analysis of all studies, a significant asymmetry was detected. However, funnel plot asymmetry and publication bias could not be assessed in the analysis of the prospective studies because of the low number of studies.

Thirdly, some of the analyzed studies did not specify the definition of bleeding after the intervention [20, 22] or used a different definition [25] compared with the consensus criteria (▶ **Table 5**) [29]. Furthermore, one of the selected studies [14] did not specify whether the consensus criteria were used to define PEP (▶ **Table 5**) [29]. Despite this heterogeneity, it is not likely that omitting this small number of studies from the final analysis would have altered our results.

The studies in our analysis were also heterogeneous with regard to the prophylaxis of PEP (▶ **Table 5**). It would also have been worth comparing PEP rates between subgroups where prophylactic measures were applied and those subgroups where no prophylaxis was given but, unfortunately, we could not extract sufficient data for such an analysis. Recent guidelines strongly recommend attempting prophylactic pancreatic stent (PPS) insertion in all patients who have had PGW-assisted methods used for biliary cannulation, along with routine rectal administration of diclofenac or indomethacin in all patients without a contraindication [1, 30]. Some of the studies were conducted before these guidelines were published, and PPS was not used uniformly in cases when the pancreatic duct was manipulated. Furthermore, no information was found on the administration of non-steroidal anti-inflammatory medication in these studies, which can also influence the rate of PEP. The outcome of the studies regarding this adverse event might have been different if these preventive measures had been uniformly applied (▶ **Table 5**).

If there is unintended PGW insertion or pancreas cannulation, the endoscopist can choose to continue directly with TPS or any of the precut techniques (NKPP or NKF), or to continue guidewire-assisted cannulation with a second guidewire (DGW). The latter possibility is seemingly less invasive than TPS or the precut techniques. Only two studies [16, 18] in this meta-analysis used DGW before TPS was attempted, and the rate of successful biliary access was similar to the NKPP group where the pancreatic duct was not accessed. A recent meta-analysis also showed that DGW does not improve biliary access but, on the other hand, almost doubles the risk of PEP where cannulation is difficult (RR 1.98, 95 %CI 1.14 – 3.42) [31].

According to our best knowledge, the three remaining options in this situation (TPS, NKPP, and NKF) have not yet been compared in any prospective studies. Based on this meta-analysis, TPS may be better than NKPP, but it is hard to tell whether NKF is superior or not. The cutting can be controlled more easily during TPS than in the freehand technique of NKF (or NKPP), because the position of the papillotome is stabilized by the PGW. This might prevent bleeding and perforation, while the risk of PEP can be reduced by PPS insertion.

It would be interesting to compare TPS and NKF as these two methods are recommended after failed PGW-assisted biliary cannulation in the ESGE guideline [1], but only a few articles that studied these two techniques alongside each other were identified during our search. Lee et al. [32] did not show any difference in success or adverse event rates between the two techniques in their study. The patients were not randomized and fistulotomy was attempted only in a small proportion of patients (n = 19) when the pancreatic duct was not accessible. Horiuchi et al. [21] selected the different cannulation methods based on the morphology of the major papilla. They applied the NKPP technique in patients with a large papillary tract with a 90 % success rate. The NKF technique was carried out when a swollen papilla was identified (only in eight patients); the biliary cannulation success rate was 100 %, without any complications. TPS, on the other hand, was used in patients with a small papillary tract and was successful in 48 patients (96 %), with one case of pancreatitis. In the study by Katsinelos et al. [24], NKPP, TPS, and NKF were all compared. NKF had a 92 % initial

▶ **Table 5** Definitions of difficult biliary access and of the possible complications that were used in the included studies.

Study	Difficult biliary access	PEP	Bleeding	PEP prophylaxis
Catalano MF, 2004 [14]	Cannulation was unsuccessful after more than 30 minutes and/or the pancreatic duct had been injected multiple times	Not defined	Consensus criteria	PPS in some of the patients, drugs were not used
Espinel-Díez J, 2013 [15]	More than five failed attempts to selectively cannulate the bile duct	Consensus criteria	Consensus criteria	Neither PPS nor drugs were used
Zang J, 2014 [17]	Standard cannulation was unsuccessful within 10 minutes and/or pancreatic duct insertion was attempted five times	Consensus criteria	Consensus criteria	Neither PPS nor drugs were used
Kim CW, 2015 [16]	10 unsuccessful attempts to selectively cannulate the bile duct	Consensus criteria	Consensus criteria	PPS after TPS in the latter half of the study, drugs were not used
Zou XP, 2015 [18]	Cannulation could not be accomplished by more than two experts cannulation time > 30 minutes and more than five accidental pancreatic duct passages	Consensus criteria	Consensus criteria	PPS in some of the patients (suspected SOD, multiple contrast injection), drugs were not used
Horiuchi A, 2007 [21]	> 15 minutes and/or the pancreatic duct had been injected/opacified multiple times	Consensus criteria	Consensus criteria	Neither PPS nor drugs were used
Kapetanos D, 2007 [23]	> 10 attempts to selectively cannulate the bile duct	Consensus criteria	Consensus criteria	No PPS, pentoxifylline in some patients (no effect of pentoxifylline on pancreatitis rates was shown in the original study [27])
Halttunen J, 2009 [20]	Not defined	Consensus criteria	Not defined	PPS in a small number of patients, drugs were not used
Wang P, 2010 [26]	Multiple unsuccessful attempts to selectively cannulate the bile duct	Consensus criteria	Consensus criteria	PPS in a small number of patients, drugs were not used
Chan CHY, 2012 [19]	At the discretion of the endoscopist	Consensus criteria	Consensus criteria	PPS in some of the patients, drugs were not used
Katsinelos P, 2012 [24]	Not defined	Consensus criteria	Consensus criteria	PPS and drugs in a small number of patients
Miao L, 2015 [25]	Failing to enter the bile duct but repeated (more than three times) insertion of the catheter into the pancreatic duct, a pancreatic guidewire or plastic stent was placed, and bile duct cannulation was attempted again	Consensus criteria	Vomiting or black stools after ERCP or hemoglobin < 95 % of normal level within 24 hours	All patients had PPS, drugs were not used
Huang C, 2016 [22]	More than five contacts with the papilla during the attempt to cannulate > 5 minutes attempting to cannulate or more than one unintentional pancreatic duct cannulation	Consensus criteria	Not defined	PPS after repeated cannulation or injection, indomethacin suppository in the later phase of the study

PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis; PPS, prophylactic pancreatic stent; ERCP, endoscopic retrograde cholangiopancreatography; SOD, sphincter of Oddi dysfunction; TPS, transpancreatic sphincterotomy; CBD, common bile duct.

cannulation success rate (in 78 patients), while TPS was successful in all cases (67 patients). In this study, the overall complication rate and the PEP rate were significantly lower in the NKF group than in the groups managed with the other techniques.

Differences in the timing of TPS or NKPP after failed biliary access can also cause considerable differences in the outcome. A recent meta-analysis showed that early precut can significantly decrease the PEP rate compared with persistent attempts, while not influencing the cannulation rate and overall complication rate [33]. Our meta-analysis showed that, despite

the time before the precut being variable in the included studies, the biliary cannulation rate with TPS was better and the PEP risk was similar.

Data about the long-term consequences of pancreatic sphincterotomy are scarce. As with biliary sphincterotomy, papillary stenosis can develop following a small incision, and proximal pancreatic duct stricture can also occur [34]. PPS is an important tool to prevent PEP, which is probably the most significant early complication of pancreatic sphincterotomy. Sometimes PPS itself can cause pancreatic duct and parenchymal injury, especially in patients with a normal caliber pancreatic duct [35]. However, the true prevalence of these changes, and therefore the long term clinical significance, is not yet known.

In summary, the present meta-analysis indicates that TPS increases the rate of biliary access compared with NKPP in patients with difficult CBD cannulation. This comes with a decreased frequency of bleeding, but the risk of total adverse events does not differ. These findings might reduce the prejudices against TPS and promote its more frequent application in patients with difficult biliary access, but low volume centers with less expertise in ERCP are not advised to use this technique.

Our suggested algorithm for patients with difficult biliary access would be precut papillotomy (preferably NKF) if a PGW cannot be inserted, or TPS after insertion of a PGW, followed by appropriate PEP prophylaxis. Further prospective multicenter studies are needed to compare the effectiveness and true adverse event rates for TPS and other advanced cannulation techniques when the current recommendations of early precut and prophylactic measures to prevent PEP are uniformly followed.

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Competing interests

None

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REVIEW

Transpancreatic Sphincterotomy Is Effective and Safe in Expert Hands on the Short Term

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Abstract

In cases of difficult biliary cannulation, transpancreatic sphincterotomy (TPS) can be an alternative approach of biliary access. However, its success and safety profile have not been studied in detail. A systematic review and meta-analysis were performed to study the overall cannulation success and adverse events of TPS. These outcomes were also compared to other advanced cannulation methods. A systematic literature search was conducted to find all relevant articles containing data on TPS. Successful biliary cannulation and complications rates [post-ERCP pancreatitis (PEP), bleeding, and perforation rates] were compared in the pooled analyses of prospective comparative studies. The overall outcomes were calculated involving all studies on TPS. TPS was superior compared to needle-knife precut papillotomy (NKPP) and the double-guidewire method (DGW) regarding cannulation success (odds ratio [OR] 2.32; 95% confidence interval [CI] 1.37–3.93; and OR 2.72; 95% CI 1.30–5.69, respectively). The rate of PEP did not differ between TPS and NKPP or DGW; however, TPS (only retrospective studies were available for comparison) proved to be worse than needle-knife fistulotomy in this regard (OR 4.62; 95% CI 1.36–15.72). Bleeding and perforation rates were similar among these advanced techniques. There were no data about long-term consequences of TPS. The biliary cannulation rate of TPS is higher than that of the other advanced cannulation techniques, while the safety profile is similar to those. However, no long-term follow-up studies are available on the later consequences of TPS; therefore, such studies are strongly needed for its full evaluation.

Keywords Cholangiopancreatography, endoscopic retrograde/adverse effects · Cholangiopancreatography, endoscopic retrograde/methods · Postoperative hemorrhage/etiology · Sphincterotomy, endoscopic/adverse effects · Sphincterotomy, endoscopic/methods

Introduction

Biliary access during endoscopic retrograde cholangiopancreatography (ERCP) is successful after a few attempts with basic cannulation methods in around 80% of the cases. The European Society of Gastrointestinal

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Endoscopy (ESGE) recommends guidewire-assisted cannulation over contrast material injection during the initial attempts because of the higher rate of success and a lower rate of post-ERCP pancreatitis (PEP) [1]. However, in challenging cases, the initial attempts to achieve selective biliary cannulation can fail even in the hands of experienced endoscopists. A consensus definition of difficult biliary cannulation is still lacking. The current ESGE guideline defines it as more than five contacts with the papilla while attempting to cannulate, more than 5 min spent attempting to cannulate the papilla after visualization, or more than one unintended pancreatic duct cannulation or opacification. The time limit of the standard cannulation technique is extended to 10 min, but other aspects are identical in another new international recommendation [2]. Early use of advanced cannulation techniques is advised in these situations to prevent further papillary trauma. Two scenarios are possible in case of failed biliary access: Needle-knife precut methods or pancreatic guidewire-assisted methods can be applied if the guidewire is inserted into the pancreatic duct [1].

Pancreatic guidewire-assisted methods can be classified as single-guidewire methods (cannulation attempts, contrast material injection, or precut after leaving the guidewire in the pancreatic duct), double-guidewire technique (DGW) [3], and transpancreatic (biliary) sphincterotomy (TPS) [4]. A recent meta-analysis of randomized controlled trials showed that the DGW technique has a higher PEP rate compared to other advanced methods despite its relative "noninvasiveness" [5]. Our previous meta-analysis showed that TPS is an effective technique which provides a higher rate of successful biliary access; furthermore, its application results in lower bleeding and PEP rates when compared to needle-knife precut papillotomy (NKPP) [6].

The needle-knife precut techniques are freehand precut starting either from the papillary orifice (NKPP) or at the papillary roof (needle-knife fistulotomy, NKF). These techniques can also be applied after pancreatic guidewire or prophylactic pancreatic stents (PPS) insertion. In fact, some studies are showing better outcomes (i.e., higher success and lower complication rates) with this method compared to the freehand precut [7]. NKPP with a small incision over a pancreatic stent improves the success rate and reduces the complication rate in difficult biliary cannulations [7] or when compared to standard cannulation [8]. Some studies suggest that NKF is superior to NKPP in terms of success and complications, providing a lower PEP rate by avoiding the trauma of the orifice [9].

In the present systematic review, the efficacy and safety of the rarely used TPS technique are scrutinized further by comparing them with other frequently used advanced cannulation methods. TPS was first described by Goff et al. [4], and he published results from 51 patients with remarkable success rate and safety profile of TPS later on [10]. Since then, several case series, retrospective and prospective comparative studies, and few randomized controlled trials (RCTs) have been published. On the other hand, concerns have been raised about the long-term safety of this technique [11]. The possibility of pancreatic stenosis, as seen in the cases of therapeutic pancreatic sphincterotomies, should not be ignored [11, 12]. Here, we summarize the available evidence of the success rate, immediate, and late adverse events related to TPS in comparison with other advanced cannulation methods by executing a systematic review.

Methods

Search Strategy

A systematic literature search was conducted to find all relevant articles containing data on TPS in accordance with the PRISMA guideline [13]. The search strategy included the following terms: "transpancreatic septotomy" or "transpancreatic sphincterotomy" or "transpancreatic septostomy" or "transpancreatic precut sphincterotomy" or "pancreatic sphincterotomy" or "transpancreatic papillary septotomy" or "transpancreatic sphincter precut" or "transpancreatic duct precut" or "pancreatic sphincter precutting" or "pancreatic precut sphincterotomy" or "transpancreatic precut septotomy" or "transpancreatic precut septostomy" or "pancreatic septotomy" or "pancreatic septostomy" or "pancreatic precut" or "transpancreatic precut" or "transpancreatic." EMBASE, PubMed, Scopus, Web of Science, ProQuest, and Cochrane Library databases were searched from their inception till February 8, 2018.

Inclusion Criteria

In order to compare TPS to DGW and NKPP, only prospective studies were included. However, only retrospective data were available in the comparison of TPS–NKF, and these were also included in our analysis. Appropriate conference abstracts were also analyzed to minimize publication bias, and additional subgroup analyses excluding them were carried out to show their effects on outcomes.

Comparative and also non-comparative prospective and retrospective studies were included in the calculation of overall success and complications rate of TPS. Randomized controlled trials (RCT) and prospective and retrospective observational studies were analyzed separately (Table 4).

Study Selection and Data Collection

Titles and abstracts of studies identified were screened by two authors (D.P. and Á.V.) independently, and then, the full-text articles were searched to identify eligible studies. Data extraction and risk of bias assessment were done independently by the authors. Peer-reviewed works and conference abstracts were included. Unpublished data were not requested from the authors. Any disagreement was resolved by discussion in plenum. Prophylactic measures to prevent PEP; furthermore, the length and results of follow-up were also collected and analyzed.

Risk of Bias Assessment

The Newcastle–Ottawa scale (NOS) was used for prospective and retrospective studies to assess risk of bias within the individual studies [14] (Table 5). Randomized controlled trials were assessed by the Cochrane Risk of Bias Tool [15] (Table 6).

Statistical Methods

Pooled odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to compare the biliary cannulation success and PEP rates among the different cannulation techniques. Risk difference (RD) was calculated to compare the bleeding and perforation rates in order to avoid overestimation since OR or RR calculations would exclude those studies where zero events were reported. The random-effect model of DerSimonian and Laird [16] was used in meta-analysis. Subgroup analyses excluding studies with sequential designs and that reported only in an abstract format were also carried out. Sensitivity analyses were carried out using four types of summary statistics (RR [risk ratio] vs. OR vs. RD vs. Peto's OR) and two types of meta-analytical models (fixed vs. random effects) to test the robustness of our findings [17]. Heterogeneity was tested with two methods, namely the Cochrane's Q and the I^2 statistics. The Q test was computed by summing the squared deviations of each study's estimate from the overall meta-analysis estimate; P values were obtained by comparing the statistical results with a χ^2 distribution with $k-1$ degrees of freedom (where k was the number of studies). A P value of less than 0.1 was considered suggestive of significant heterogeneity. The I^2 statistic represents the percentage of the total variability across studies that is due to heterogeneity, i.e., I^2 value between 0 and 40% indicates low, 30–60% moderate, 50–90% substantial, and 75–100% considerable heterogeneity, based on Cochrane Handbook for Systematic Reviews of Interventions [17]. Publication bias was planned to be examined by visual inspection of funnel plots and the Egger's method [18]. Meta-analytical calculations were done with Review Manager (RevMan) computer program (version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Study Selection

Altogether, 2787 records were identified during database search: 510 in EMBASE, 339 in PubMed, 968 in Scopus, 255 in Web of Science, 544 in ProQuest, and 171 in Cochrane Library, respectively. The latest search was run on February 8, 2018, and finally, 33 relevant studies were included in the qualitative synthesis, while data from 14 studies were extracted for the meta-analysis (Fig. 1).

Characteristics of Studies Included

Characteristics of the included studies with the applied PEP prophylaxis (Table 1), the definitions of difficult biliary access and the endoscopists/centers experience (Table 2), and the late adverse events are summarized in Table 3.

Three RCTs [19–21] and two prospective observational studies [22, 23] compared TPS and DGW. One of them was only available in abstract form [19]. Two of them used a sequential design [22, 23], applying TPS only after DGW, as a rescue technique.

Two RCTs [24, 25] and three prospective observational studies [22, 23, 26] provided data on the comparison of TPS vs. NKPP, two of them with sequential design [22, 23]. New prospective studies were not identified after our previous meta-analysis; however, we conducted further sensitivity and subgroup analyses in this comparison [6].

Comparison of TPS and NKF was not found in any prospective studies; four retrospective studies (two of them only in abstract form) were identified and analyzed to synthesize available comparative evidence [9, 27–29].

Two prospective case series of TPS without relevant comparisons to other advanced cannulation methods [30, 31] and, additionally, 23 retrospective observational studies with reported outcome data were included in the pooled analyses of overall outcomes of TPS [4, 9, 10, 27–29, 32–48] (Table 4).

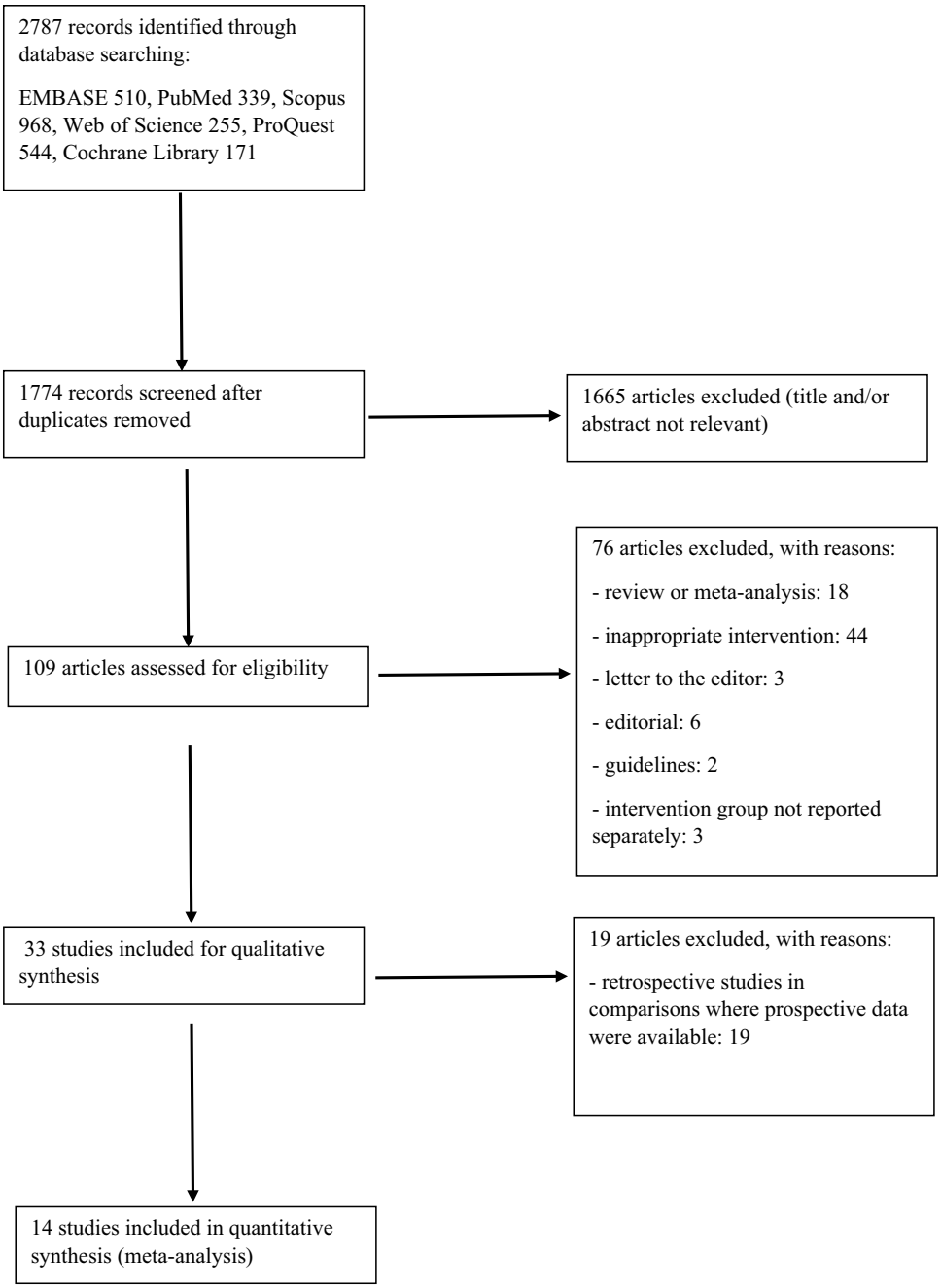

Fig. 1 Flow diagram of literature search

Methodological Quality and Risk of Bias Assessment

The risk of bias in the prospective (not RCTs) and the four retrospective studies included in the meta-analyses was analyzed with the NOS (Table 5). In most of the full-text studies, baseline characteristics of cohorts were reported with comparable, homogeneous groups. Technical details of interventions were thoroughly reported; all full-text studies defined precut methods appropriately. On the other hand, definitions of adverse outcomes somewhat varied; however, most studies used the consensus definitions [49]. The appropriate length of follow-up is questionable in the cases of late adverse events, and only one prospective study reported the length of follow-up as longer than 30 days [30]. The abstracts contained limited information about the above-mentioned details; therefore, they carry an unclear risk of bias.

Table 1 Characteristics of the studies included in the meta-analysis with the prophylactic measures to prevent post-ERCP pancreatitis (PEP)

Study	Study design	Comparison	Sequential design	Form of publication	PPS use	Pharmacologic prevention
Cha et al. [19]	RCT	DGW versus TPS	No	Abstract	NR	NR
Sugiyama et al. [20]	RCT	DGW versus TPS	No	Full text	In all cases	Nafamostat
Yoo et al. [21]	RCT	DGW versus TPS	No	Full text	No	No
Kim et al. [22]	Prospective	DGW versus TPS versus NKPP	Yes	Full text	2/27 (7%) in DGW group, 25/38 (66%) in TPS group, $P < 0.001$	No
Zou et al. [23]	Prospective	DGW versus TPS versus NKPP	Yes	Full text	14/63 (22%) in all patients compared, not reported separately in DGW/TPS groups	No
Catalano et al. [24]	RCT	NKPP versus TPS	No	Full text	PPS in some patients	No
Zang et al. [25]	RCT	NKPP versus TPS	No	Full text	No	No
Espinel-Diez [26]	Prospective	NKPP versus TPS	No	Full text	No	No
Horiuchi et al. [9]	Retrospective	NKF versus TPS	No	Full text	No	No
Katsinelos et al. [27]	Retrospective	NKPP versus NKF versus TPS	No	Full text	PPS in some patients	Diclofenac and somatostatin in some patients
Lee et al. [28]	Retrospective	NKF versus TPS	No	Abstract	No	Protease inhibitor
Wen et al. [29]	Retrospective	NKF versus TPS	No	Abstract	NR	NR
Kahaleh et al. [30]	Prospective	No	No	Full text	29/116 (25%) of all cases	NR
Weber et al. [31]	Prospective	No	No	Full text	No	NR

PPS prophylactic pancreatic stent, *RCT* randomized controlled trial, *DGW* double-guidewire cannulation, *TPS* transpancreatic biliary sphincterotomy, *NKPP* needle-knife precut papillotomy, *NKF* needle-knife fistulotomy, *NR* not reported

In case of RCTs, the Cochrane Risk of Bias Tool was used (Table 6). Only one study [21] reported the method of randomization and the method of ensuring allocation concealment. Blinding in studies of endoscopic interventions at participant and personnel level is difficult to execute and therefore could not be expected. However, blinded late outcome assessment (PEP, late bleeding, perforation) could be arranged more easily. Nevertheless, none of the studies reported blinding of any kind. Three out of five RCTs did not report the rate of cholangitis; therefore, this outcome could not be analyzed [19, 24, 25]. One RCT was only published in abstract form which makes the data quality questionable; consequently, this study carries a high risk of bias [19].

Publication bias could not be reliably assessed based on funnel plots or by the Egger's method because of the small number of included studies. According to the Cochrane Handbook, funnel plots and other statistical tests are not advised to assess small study effect and publication bias under ten studies per analysis [17, 18, 50].

Endoscopists' Experience and Centers' Case Volumes in the Prospective Studies

Most of the prospective studies reported endoscopists' experience in yearly case numbers, some in lifetime ERCP numbers, too. Based on the reported numbers, all endoscopists performed more than 200 ERCPs/year. In one study, the caseload of the endoscopists exceeded 500 ERCPs annually [30]. Trainee participation was not reported in any of the studies. Most of the centers reported high-volume ERCPs (even above 1000 procedures/year [23, 24]), only one study [9] reported lower numbers (< 300 ERCPs/year), while no information was found about center or endoscopist caseload in one study [29] (Table 2).

Biliary Cannulation Success Rate

TPS showed superiority in success rate compared to DGW (OR 2.72; 95% CI 1.30–5.69; 176 and 235 patients,

Table 2 Summary of the definitions of difficult biliary access, endoscopists' experience, and centers' case load in the studies included in the meta-analysis

Study	Definitions of difficult biliary access	Endoscopist's experience	Centers
Cha et al. [19]	Randomization when PGW inserted unintentionally	NR	Multicenter study, possibly high-volume university centers
Sugiyama et al. [20]	Unsuccessful biliary cannulation after 15 min or unintentional pancreatic duct cannulation more than three times	Seven endoscopists who had at least 3-year experience in the pancreaticobiliary team at the tertiary referral center, performed over 300 ERCPs per year, and was able to achieve selective deep cannulation in more than 90% of cases using standard techniques	2052 ERCP in 3 years (1 high-volume center)
Yoo et al. [21]	Unsuccessful biliary cannulation after 10 attempts or failure of biliary access after 10 min	One experienced endoscopist	1 center, between January 2005 and September 2010, a total of 1893 ERCPs
Kim et al. [22]	Unsuccessful biliary cannulation after 10 attempts	Two endoscopists with > 1000 ERCPs lifetime caseloads	> 150 ERCPs/year with native papilla during the study
Zou et al. [23]	Unsuccessful biliary cannulation by more than two experts; failure of biliary access after 30 min or unintentional pancreatic duct cannulation more than five times	Four endoscopists > 200 ERCPs/year in the last 3 years	> 1000 ERCPs/year in the last 2 years
Catalano et al. [24]	Unsuccessful biliary cannulation after 30 min and/or the pancreatic duct had been opacified multiple times	NR	> 1000 ERCPs/year in the center
Zang et al. [25]	Unsuccessful biliary cannulation after 10 min and/or unintentional pancreatic duct cannulation more than five times	One endoscopist with > 350 ERCPs/year caseload	Center caseload NR, likely high-volume center based on study inclusion numbers
Espinel-Diez et al. [26]	Unsuccessful biliary cannulation after five attempts	One endoscopist with > 200 ERCPs/year caseload	Numbers NR, high volume of therapeutic ERCPs, numbers not specified
Horiuchi et al. [9]	Unsuccessful biliary cannulation after 15 min and/or the pancreatic duct had been opacified multiple times	Two endoscopists, no caseload data reported	200 ERCPs/year approximately
Katsinelos et al. [27]	Unsuccessful biliary cannulation after 10 attempts	One experienced endoscopist performed all procedures (> 300 ERCPs/year)	> 300 ERCPs/year in the study period for patients with a naïve papilla
Lee et al. [28]	Repeated unintentional pancreatic duct cannulation within 5 min and/or unintentional pancreatic duct cannulation more than three times	One experienced endoscopist (> 150 therapeutic ERCPs/year)	One center
Wen et al. [29]	NR	One experienced endoscopist	One center
Kahaleh et al. [30]	Unintentional pancreatic duct opacification more than three times	All ERCPs were performed by two dedicated pancreaticobiliary endoscopists; both perform more than 500 ERCPs annually.	High-volume center
Weber et al. [31]	Not defined	NR	High-volume center

NR not reported, *PGW* pancreatic guidewire, *ERCP* endoscopic retrograde cholangiopancreatography

Table 3 Late adverse events in the prospective studies, where longer-term follow-ups were reported

Study	Study design	Length of follow-up	Type	Complications	PD stricture
Kim et al. [22]	Prospective, observational	NR	NR	No	No chronic pancreatitis or ductitis from PD stenting
Catalano et al. [24]	RCT	NR	Telephone contact and office visits	No	No
Kahaleh et al. [30]	Prospective, observational	Median follow-up was 5 months (2–35)	Clinic visit and/or telephone interview by a nurse	No	No

Studies without follow-up data are not shown

RCT randomized controlled trial, *PD* pancreatic duct, *NR* not reported

respectively; $I^2 = 50\%$) (Fig. 2a) and NKPP (OR 2.32; 95% CI 1.37–3.93; 292 and 260 patients, respectively; $I^2 = 7\%$) (Fig. 2b). The success rate of TPS and NKF did not differ (OR 1.38; 95% CI 0.32–5.96; 295 and 141 patients, respectively; $I^2 = 22\%$) (Fig. 2c).

In the TPS versus DGW comparison of cannulation success rates, no significant difference was detected between the two methods if only RCTs were included (OR 3.02; 95% CI 0.73–12.59; 113 and 107 patients, respectively; $I^2 = 69\%$), probably because of the greater confidence intervals of the results. On the other hand, subgroup analysis of full-text studies found the superiority of TPS over DGW with regard to cannulation success rate (Suppl. Figure 1).

The overall success rate of TPS in prospective studies was 89.7% (564/629). The success rate was the same if all studies were analyzed (89.6%, 2343/2615), as well as the separate analysis of RCTs resulted in similarly high value (91.7%, 199/217) (Table 4).

Post-ERCP Pancreatitis

No significant difference was found between the TPS versus DGW (OR 0.72; 95% CI 0.24–2.10; 151 and 134 patients, respectively; $I^2 = 55\%$) (Fig. 3a) and TPS versus NKPP (OR 1.63; 95% CI 0.48–5.47; 265 and 242 patients, respectively; $I^2 = 57\%$) (Fig. 3b) comparisons. However, the TPS technique showed a higher PEP rate compared to NKF method (OR 4.62; 95% CI 1.36–15.72; 295 and 141 patients, respectively; $I^2 = 16\%$) (Fig. 3c).

If we excluded abstracts from the NKF versus TPS comparison, the significant difference disappeared (OR 3.49; 95% CI 0.20–62.21; 86 and 115 patients, respectively; $I^2 = 63\%$) and expectedly, a wide confidence interval could be seen (Suppl. Figure 2). In the other subgroups, no differences were found when sequential studies or abstracts were omitted from the analyses. Inclusion of RCTs only did not result any change in significance regarding TPS versus DGW and TPS versus NKPP comparisons.

The overall PEP rate of TPS was 8.1% (49/604) in prospective studies, 7.1% (183/2590) in all studies, and 7.4% (16/217) in RCTs (Table 4).

Prophylactic Pancreatic Stent and Nonsteroid Anti-inflammatory Suppository Use

Only one recently published study used PPS in all patients undergoing TPS [20], while all the others reported no or only some PPS implantation in the TPS cases (Table 1). Pharmacologic prevention of PEP was applied in three studies [20, 27, 28]; however, the recommended nonsteroid anti-inflammatory drug (NSAID) suppositories were not used or not reported in any of the studies included in the meta-analyses (Table 1).

Bleeding

The pooled analysis did not show any difference in bleeding rate when TPS was compared to DGW (risk difference [RD] 0.01; 95% CI −0.03 to 0.05; 109 and 95 patients, respectively; $I^2 = 0\%$) (Fig. 4a), NKPP (RD −0.00; 95% CI −0.04 to 0.03; 268 and 239 patients, respectively; $I^2 = 20\%$) (Fig. 4b), and NKF (RD 0.00; 95% CI −0.03 to 0.03; 295 and 141 patients, respectively; $I^2 = 0\%$) (Fig. 4c).

Subgroup analyses did not alter the findings of bleeding rates significantly.

The overall bleeding rate of TPS was 3.4% (19/562) in prospective studies, 2.0% (50/2548) in all studies, and 1.7% (3/175) in RCTs (Table 4).

Perforation

Perforation rates did not differ when comparing TPS versus DGW (RD −0.01; 95% CI −0.04 to 0.03; 109 vs. 95; $I^2 = 0\%$) (Fig. 5a), TPS versus NKPP (RD −0.00; 95% CI −0.02 to 0.01; 267 and 240 patients, respectively; $I^2 = 0\%$)

Table 4 Summary of success rate and adverse events of transpancreatic sphincterotomy in published series

Studies	Design	Number of patients in TPS group	Successful biliary cannulation	%	PEP	%	Bleeding	%	Perforation	%
Catalano et al. [24]	RCT	31	29	93.5	1	3.2%	0	0.0%	0	0.0%
Cha et al. [19] (abstract)	RCT	42	39	92.9	5	11.9%	NA	NA	NA	NA
Sugiyama et al. [20]	RCT	34	32	94.1	1	2.9%	0	0.0%	0	0.0%
Yoo et al. [21]	RCT	37	29	78.4	4	10.8%	2	5.4%	0	0.0%
Zang et al. [25]	RCT	73	70	95.9	5	6.8%	1	1.4%	0	0.0%
Sum of RCTs		217	199	91.7	16	7.4%	3	1.7%[a]	0	0.0%[a]
Espinel-Diez et al. [26]	Prospective	125	117	93.6	4	3.2%	6	4.8%	1	0.8%
Kahaleh et al. [30]	Prospective	116	99	85.3	9	7.8%	3	2.6%	2	1.7%
Kim et al. [22]	Prospective, sequential	38	28	73.7	14	36.8%	1	2.6%	0	0.0%
Weber et al. [31]	Prospective	108	103	95.4	6	5.6%	6	5.6%	0	0.0%
Zou et al. [23]	Prospective, sequential	25	18	72.0	NA	NA	NA	NA	NA	NA
Sum of prospective studies		629	564	89.7	49	8.1%[a]	19	3.4%[a]	3	0.5%[a]
Akashi et al. [32]	Retrospective	172	163	94.8	10	5.8%	2	1.2%	0	0.0%
Barakat et al. [33] (abstract)	Retrospective	368	321	87.2	4	1.1%	1	0.3%	0	0.0%
Chan et al. [34]	Retrospective	53	36	67.9	2	3.8%	1	1.9%	0	0.0%
de-la-Morena-Madrigal et al. [35]	Retrospective	50	35	70.0	2	4.0%	1	2.0%	0	0.0%
de-la-Morena-Madrigal et al. [36]	Retrospective	78	75	96.2	5	6.4%	4	5.1%	4	5.1%
Esmaily et al. [37] (abstract)	Retrospective	105	81	77.1	6	5.7%	1	1.0%	1	1.0%
Goff [4]	Retrospective	32	29	90.6	4	12.5%	0	0.0%	0	0.0%
Goff [10]	Retrospective	51	50	98.0	0	0.0%	0	0.0%	1	2.0%
Halttunen et al. [38]	Retrospective	262	255	97.3	23	8.8%	4	1.5%	0	0.0%
Horiuchi et al. [9]	Retrospective	48	46	95.8	1	2.1%	0	0.0%	0	0.0%
Huang et al. [39]	Retrospective	60	51	85.0	2	3.3%	0	0.0%	0	0.0%
Javia et al. [40] (abstract)	Retrospective	20	15	75.0	1	5.0%	0	0.0%	0	0.0%
Kapetanos et al. [41]	Retrospective	34	29	85.3	1	2.9%	1	2.9%	0	0.0%
Katsinelos et al. [27]	Retrospective	67	67	100.0	15	22.4%	0	0.0%	0	0.0%
Lee et al. [28]	Retrospective	67	58	86.6	7	10.4%	5	7.5%	0	0.0%
Liao et al. [42] (abstract)	Retrospective	108	99	91.7	4	3.7%	2	1.9%	0	0.0%
Lin [43]	Retrospective	20	18	90.0	3	15.0%	1	5.0%	0	0.0%
McGonigle et al. [44] (abstract)	Retrospective	31	25	80.6	2	6.5%	1	3.2%	1	3.2%
Miao et al. [45]	Retrospective	36	35	97.2	2	5.6%	0	0.0%	0	0.0%
Miyatani et al. [46]	Retrospective	20	17	85.0	6	30.0%	1	5.0%	0	0.0%
Wang et al. [47]	Retrospective	140	116	82.9	16	11.4%	2	1.4%	0	0.0%
Wen et al. [29] (abstract)	Retrospective	113	111	98.2	11	9.7%	2	1.8%	1	0.9%
Zhong et al. [48]	Retrospective	77	73	94.8	8	10.4%	2	2.6%	0	0.0%
Sum of all study		2615	2343	89.6	183	7.1%[a]	50	2.0%[a]	11	0.4%[a]

NA not applicable, *TPS* transpancreatic sphincterotomy

[a]Calculated from those studies where the rate of this adverse event was available

Table 5 Risk of bias assessment of prospective, non-randomized, and retrospective studies with the Newcastle–Ottawa scale

	Selection		Comparison		Exposure		
	S/1	S/2	C/1	C/2	E/1	E/2	E/3
Espinel Diez, 2013	+	+	?	?	−	−	+
Horiuchi, 2007	+	+	+	+	−	?	?
Kahaleh, 2004*	+	−	−	−	−	+	+
Katsinelos, 2012	+	+	+	+	−	+	+
Kim, 2015	+	+	+	+	−	?	+
Lee (abstract), 2015	?	?	?	?	−	+	+
Weber, 2008*	+	−	−	−	−	?	?
Wen (abstract), 2017	?	?	?	?	−	?	?
Zou, 2015	+	+	+	+	−	?	?

S/1: Representativeness of the exposed cohort (transpancreatic sphincterotomy group compared to advanced cannulation technique group); S/2: Selection of the non-exposed cohort (advanced cannulation technique group); C/1: Comparability of cohorts on the basis of similar indications of procedure; C/2: Comparability of cohorts on the basis of age; E/1: Assessment of outcome (were blinded assessment executed?); E/2: Was follow-up long enough? (longer than 14 days); E/3: Adequacy of follow-up of cohorts (is any attrition of patients present?) Two studies are not comparing TPS to another advanced cannulation technique and are marked with an asterisk

(Fig. 5b), and TPS versus NKF (RD 0.00; 95% CI − 0.02 to 0.03; 295 and 141 patients, respectively; $I^2 = 0\%$) (Fig. 5c).

Subgroup analyses did not alter the findings in perforations rates significantly.

The overall perforation rate was 0.5% (3/562) in prospective studies, 0.4% (11/2548) in all studies, while 0% (0/175) in RCTs (Table 4).

Sensitivity and Subgroup Analyses

Application of other meta-analytical models (fixed-effect vs. random-effect analysis) and summary statistics (OR vs. RR vs. RD vs. Peto's OR) did not affect the outcomes significantly in the main analyses; thus, our conclusions remain unaltered (Suppl. Table 1).

However, subgroup analyses excluding non-RCTs, sequential trials, and studies only available in an abstract form altered significantly some results (i.e., success rate in TPS vs. DGW and PEP rate in TPS vs. NKF comparisons, respectively) (Suppl. Table 2, Figs. 1 and 2).

Follow-Up

Pancreatic duct stricture or chronic pancreatitis could potentially develop after pancreatic sphincterotomy; therefore, a longer follow-up period is needed to detect these adverse outcomes [11]. Small caliber pancreatic stents could rarely cause pancreatic ductal changes in long term (1 month or longer) [51, 52]. Only one prospective study, a case series with 116 patients, reported a median 5-month follow-up

Table 6 Risk of bias assessment of RCTs with the Cochrane Collaboration risk of bias tool

RCTs	1	2	3	4	5	6	7
Cha (abstract), 2012	?	?	−	−	−	−	−
Catalano, 2004	?	?	−	−	−	−	+
Sugiyama, 2017	?	?	−	−	+	+	+
Yoo, 2013	+	+	−	−	+	+	+
Zang, 2014	?	?	−	−	−	−	+

1: Random sequence generation; 2: allocation concealment; 3: blinding of participants and personnel; 4: blinding of outcome assessment; 5: incomplete outcome data; 6: selective reporting; 7: other bias

(range 2–35) with no late adverse events [30]. Another paper similarly did not report late chronic pancreatitis or ductitis from PPS; no strictures were described during longer, however not specified, follow-up [22] (Table 3). A few retrospective studies also published longer-term results: Miao et al. [45] reported no stricture after 4 months of follow-up period, while Barakat et al. [33] found no late stricture formation after an unknown length of "long-term" follow-up.

Discussion

This systematic review and meta-analysis show that TPS could be equally successful or even slightly better in the setting of difficult biliary access compared to other advanced cannulation methods. Analyzing only the prospective studies with regard to cannulation success rates TPS seems superior to DGW and NKPP, while TPS and NKF are equally effective. DGW and NKPP carry a similar risk of PEP compared to TPS; however, PEP occurs more frequently with TPS than with NKF. No difference in bleeding and perforation rates was found when comparing TPS to the other advanced cannulation methods.

Prospective observational studies and RCTs were analyzed whenever it was possible to gain the best evidence. Between-study heterogeneity was low or moderate in most analyses, making our conclusions more accurate. Sensitivity analyses and application of different statistical and meta-analytical methods did not reveal any significant changes in the main associations. However, subgroup analyses excluding sequential studies revealed that the significant difference disappeared in some analyses, thereby weakening our conclusion in the findings of success rate of TPS versus DGW and PEP rate in TPS versus NKF. However, this is most probably the result of the low case numbers, leading to imprecision and wider confidence intervals.

Exceptionally low cannulation rates (as low as 72%) and high PEP rates (36.8%) were seen in the sequential studies (Table 4) that probably could be explained by the previous DGW attempts causing papillary trauma and consequential edema. Our experience also shows that TPS after papillary trauma induced by precut results low rate of biliary access, while it is highly successful if applied primarily [53]. Based on these considerations, we recommend the TPS technique in the early phase of difficult biliary access when pancreatic guidewire insertion reached unintentionally.

The overall cannulation success rate of TPS is close to 90% in all studies and also in subgroups by different study designs, which makes this pancreatic guidewire-assisted method a good alternative to DGW and other advanced cannulation methods. The overall biliary cannulation success

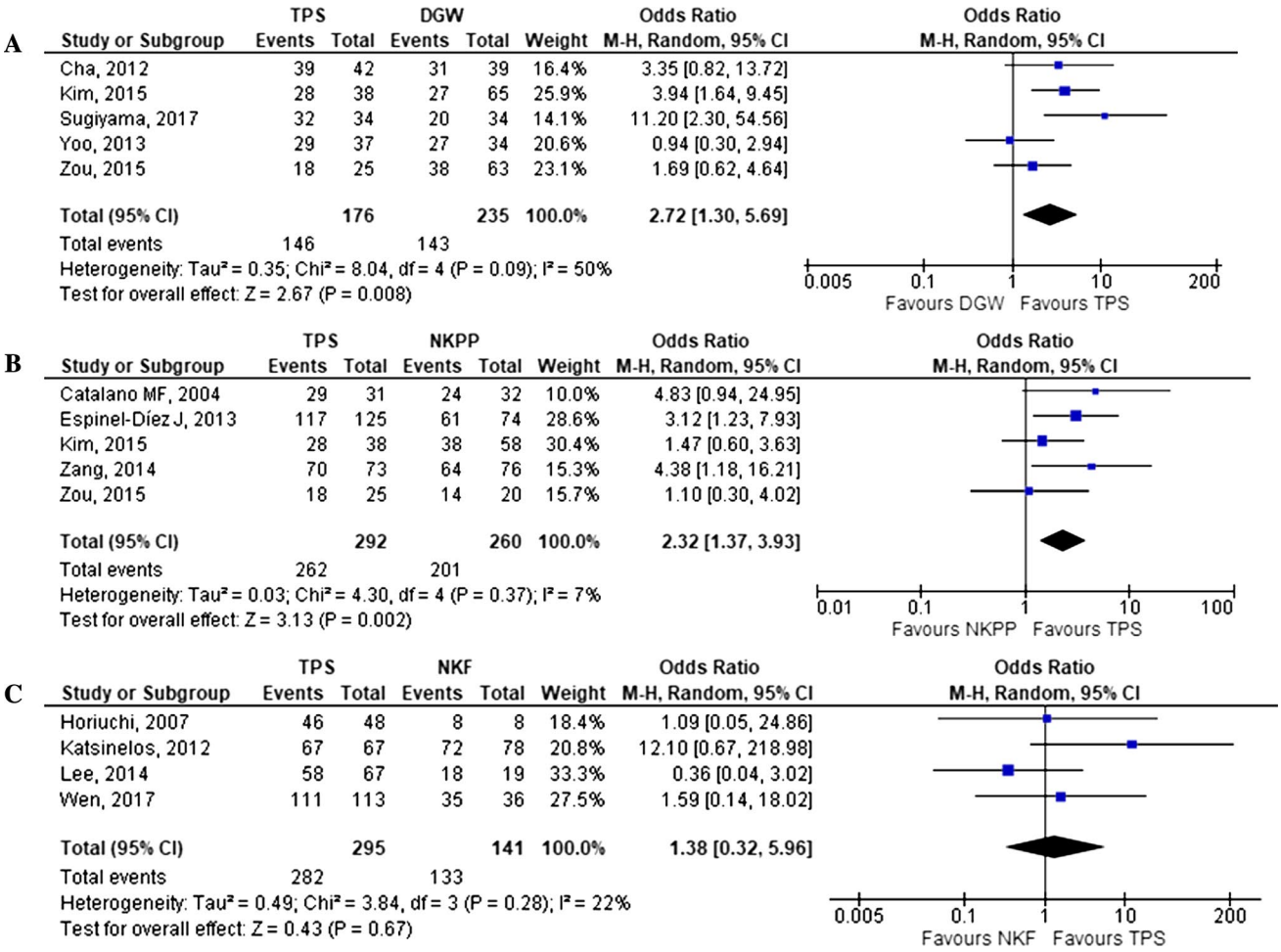

Fig. 2 **a** Forest plot of cannulation success rate of transpancreatic sphincterotomy (TPS) versus double-guidewire technique (DGW) in prospective studies; **b** comparison of cannulation success rate of TPS versus needle-knife precut papillotomy (NKPP) in prospective studies; **c** comparison of cannulation success rate of TPS versus needle-knife fistulotomy (NKF) in available comparative retrospective studies

rate of DGW was only 61% in the studies where it was compared to TPS (Fig. 2a). Furthermore, a meta-analysis of seven RCTs with DGW showed that successful biliary cannulation was achieved only in 82% of cases [5]. NKPP is also a frequently used method in cases of difficult biliary access. The average cannulation success rate of NKPP was approximately 80% (647/812) in all NKPP studies and 77% (201/260) in prospective studies according to our previous meta-analysis [6].

PEP rate of TPS is similar to other advanced cannulation methods (7.1%; 183/2590; 0–30%, Table 4). NKPP seems comparable to TPS with its 8.8% (70/794) overall PEP rate measured in our previous meta-analysis [6]. NKF, however, could be better to avoid PEP (Fig. 3c). With the uniform use of PPS and NSAID suppositories in all TPS cases, a PEP rate might be even lower [20, 48] as the significant protective effect of PPS has been well proven. Importantly, its insertion should not be problematic since the guidewire is already in the pancreatic duct while performing TPS.

Bleeding rate of TPS is in the range of 2–4%, which is comparable to the widely accepted and frequently used needle-knife precut techniques (4%; 30/745 of NKPP cases) [6]. The rate of perforation was around 0.5% which is remarkably low for a precut technique, and no difference was found in this respect between TPS and the other advanced cannulation techniques.

There are several limitations of our analyses. First of all, the low number of prospective studies with only small cohorts of patients weakens the conclusions. Sequential

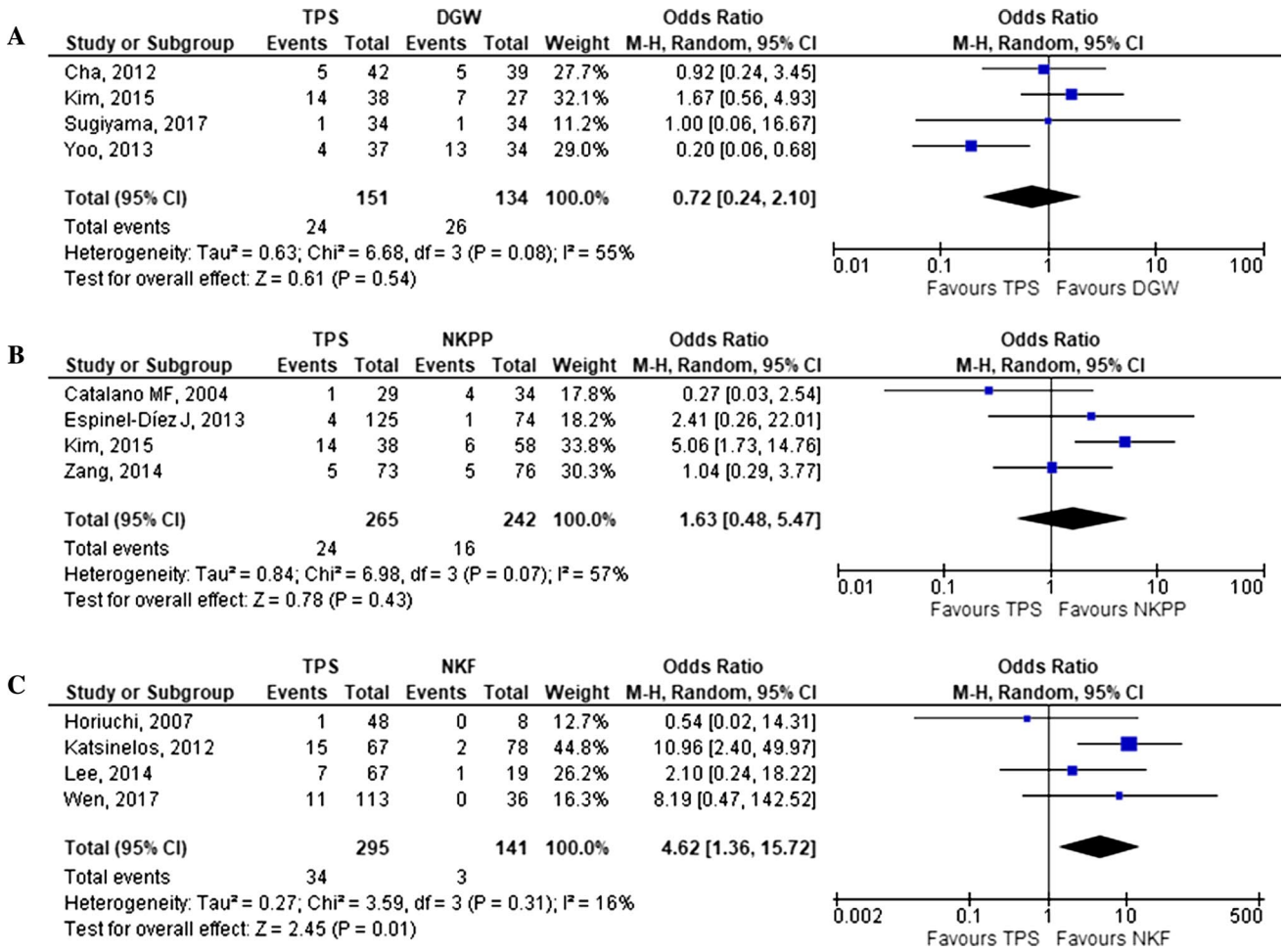

Fig. 3 **a** Forest plot of post-ERCP pancreatitis (PEP) rate of transpancreatic sphincterotomy (TPS) versus double-guidewire technique (DGW) in prospective studies; **b** comparison of PEP rate of TPS versus needle-knife precut papillotomy (NKPP) in prospective studies; **c** comparison of PEP rate of TPS versus needle-knife fistulotomy (NKF) in available comparative retrospective studies

studies were also included which could alter our results. However, in the comparison of DGW or NKPP vs. TPS, sequential designs could affect the TPS cannulation success and adverse event rate only to the worse due to the prolonged cannulation attempt and greater trauma of the papilla. The lack of information on the use of effective preventive methods (PPS, NSAID suppositories) undermines the assessment of PEP rates. New studies are lacking in this field with the consistent use of PPS and NSAID suppositories. It should be noted, however, that the PEP rate was only 1.1% in the study of Sugiyama et al. [20], where all patients received PPS after TPS, compared to the rate of 7.1% pooled from all studies where most patients did not have PPS. Besides that, the definitions of outcomes were not standardized in all cases. Nonetheless, most prospective studies used the consensus definitions [49]. Publication bias cannot be ruled out due to the low number of studies per analysis.

The possible benefit of TPS over the freehand precut techniques is that it is a wire-assisted method, with better control of the cut. For that reason, it could be appealing in those situations, where the papillary tract is smaller, or the position of the scope is unstable. Furthermore, the PPS insertion could also be easily achieved after the precut, since the guidewire is already inserted into the pancreatic duct. An additional benefit is that the sphincterotome does not need

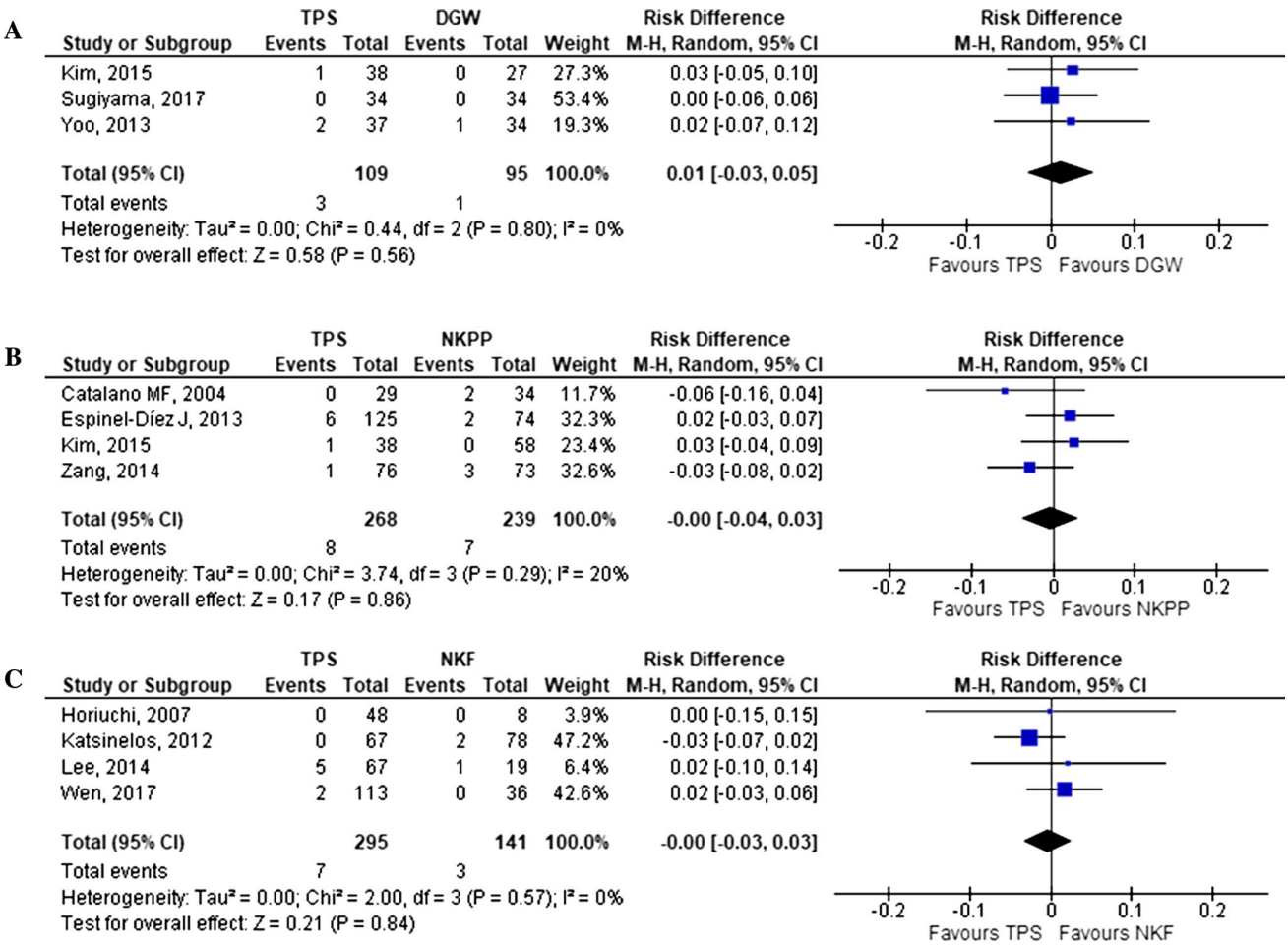

Fig. 4 **a** Forest plot of bleeding rate after transpancreatic sphincterotomy (TPS) versus double-guidewire technique (DGW) in prospective studies; **b** comparison of bleeding rate after TPS versus needle-knife precut papillotomy (NKPP) in prospective studies; **c** comparison of bleeding rate after TPS versus needle-knife fistulotomy (NKF) in available comparative retrospective studies

to be changed for the precut. In the unfortunate cases, when TPS fails, additional needle-knife incision could be helpful to reach deep biliary cannulations and might be used as salvage technique in appropriate situations.

The late adverse events of TPS, e.g., pancreatic duct stricture and chronic pancreatitis [11], could not be assessed properly because only one prospective study reported a longer-term (more than 30-day) follow-up with no late adverse events [30]. We think that follow-up studies should be extended up to 1 year or longer to detect late adverse events, e.g., pancreatic duct stricture formation or the development of chronic pancreatitis.

These findings show the short-term safety and efficacy of TPS and also highlight the necessity of long-term follow-up studies after precut papillotomy.

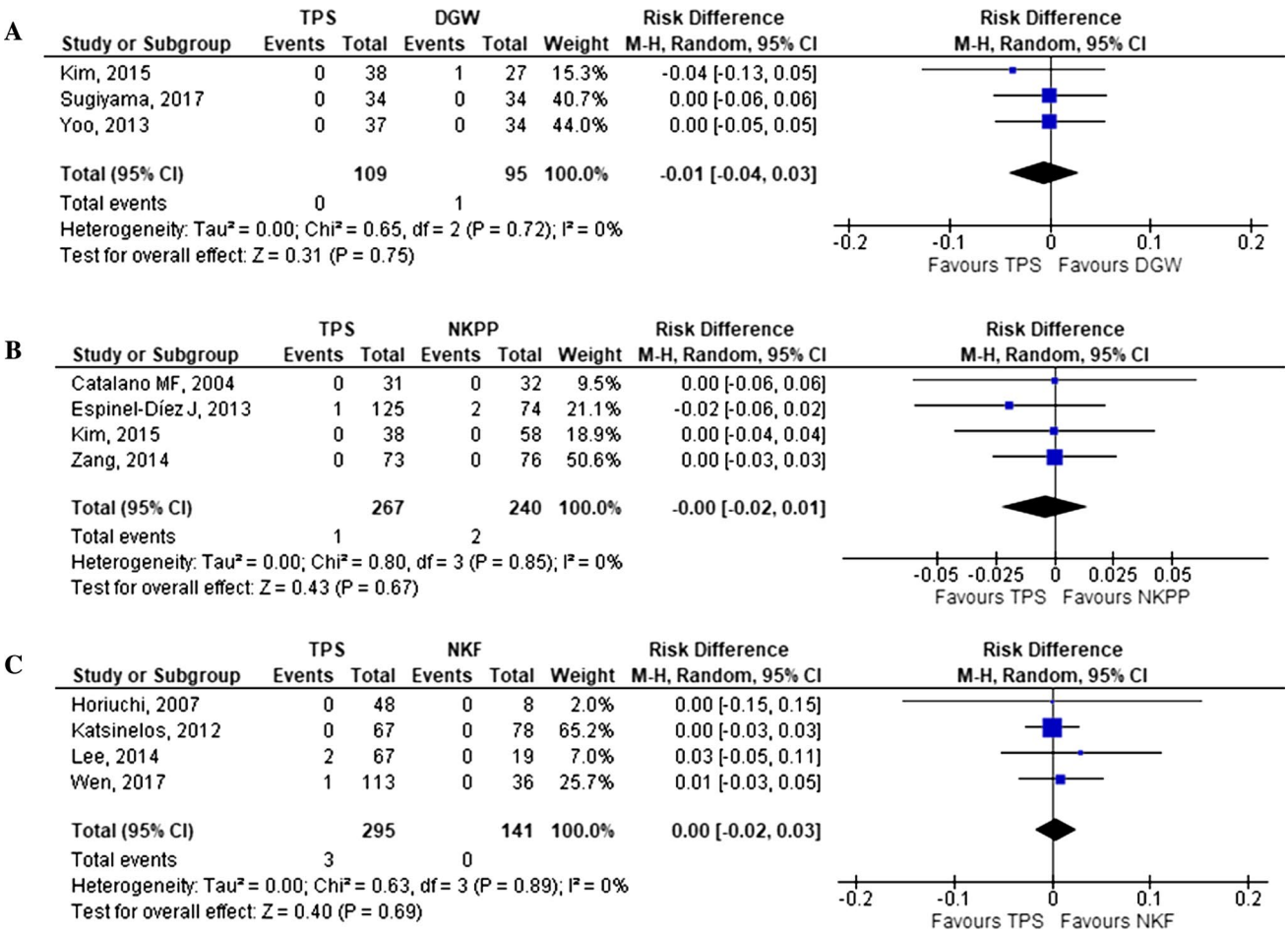

Fig. 5 **a** Forest plot of comparison of perforation rate after transpancreatic sphincterotomy (TPS) versus double-guidewire technique (DGW) in prospective studies; **b** comparison of perforation rate after TPS versus needle-knife precut papillotomy (NKPP) in prospective studies; **c** comparison of perforation rate after TPS versus needle-knife fistulotomy (NKF) in available comparative retrospective studies

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Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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ERCP is more challenging in cases of acute biliary pancreatitis than in acute cholangitis – Analysis of the Hungarian ERCP registry data

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ABSTRACT

Background: Endoscopic retrograde cholangiopancreatography (ERCP) is an important therapeutic modality in acute biliary pancreatitis (ABP) cases with cholangitis or ongoing common bile duct obstruction. Theoretically, inflammation of the surrounding tissues would result in a more difficult procedure. No previous studies examined this hypothesis.
Objectives: ABP and acute cholangitis (AC) without ABP cases were compared to assess difficulty of ERCP.
Methods: The rate of successful biliary access, advanced cannulation method, adverse events, cannulation and fluoroscopy time were compared in 240 ABP cases and 250 AC cases without ABP. Previous papillotomy, altered gastroduodenal anatomy, and cases with biliary stricture were excluded.
Results: Significantly more pancreatic guidewire manipulation (adjusted odds ratio (aOR) 1.921 [1.241–2.974]) and prophylactic pancreatic stent use (aOR 4.687 [2.415–9.098]) were seen in the ABP than in AC group. Average cannulation time in the ABP patients (248 vs. 185 s; $p = 0.043$) were longer than in AC cases. No difference was found between biliary cannulation and adverse events rates.
Conclusion: ERCP in ABP cases seem to be more challenging than in AC. Difficult biliary access is more frequent in the ABP cases which warrants the involvement of an experienced endoscopist.

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an invaluable minimal invasive therapeutic modality which changed the management of several pancreato-biliary disorders [1]. In acute cholangitis (AC), early achievement of biliary drainage is associated with better outcomes, especially in severe, septic cases as stated in the new 2018 Tokyo guideline for acute cholangitis [2]. In acute biliary pancreatitis (ABP), the role of ERCP is more ambiguous, when AC is also present early intervention is indicated, however, in cases with biliary obstruction only, the need for an early ERCP is questionable. The recent Dutch randomized controlled APEC trial, came to the conclusion that in patients with predicted severe acute biliary pancreatitis, early (<24 h) ERCP did not reduce rate of death and major complications [3].

Nevertheless, ERCP plays a significant role in the management of AC and ABP [4]. It is a common experience that in cases of ABP, duodenal and pancreatic edema might result in more difficult cannulation. There are some attempts to objectively grade the difficulty of ERCP, e.g., in the consensus-based ASGE grading system cases of acute pancreatitis get a higher, 3 points. However, no supporting data was found to this classification claim besides the

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consensus [5]. A retrospective study validated the grading system based on their center's data and found that procedural success and complications correlate well with the ASGE grades [6]. The previously widely used Schutz [7] and the newer HO.U.S.E. classification does not contain ABP as a factor for more complicated procedures [8].

For that reason, we intended to analyze data from the Hungarian ERCP Registry to quantify the difficulty of ABP cases compared to AC cases without pancreatitis.

Methods

General cohort from the Hungarian ERCP registry

Prospectively collected data from the Hungarian ERCP Registry were analyzed in this cohort study comparing ABP and AC cases. The Hungarian Endoscopy Study Group initiated the project of the Hungarian ERCP Registry in 2016 [9] and the number of participating centers growing gradually since then. Cases from 7 tertiary referral centers and 15 endoscopists were uploaded into the Registry (Suppl. Table 1). Quality indicators laid down by European and American Societies of Gastroenterology (ESGE and ASGE) were mostly met by our centers showing general good practice of ERCP [10,11], only NSAID suppository usage was significantly lower, while bleeding and perforation were somewhat higher than expected (Suppl. Table 2). All participating endoscopists uploaded all ERCP cases which were done by them consecutively, no trainee participation was recorded. Recruitment period lasted from September 2016 till April 2019. A 30-day telephone follow-up was carried out to detect late adverse events. Data quality was assured by a 4-step checking system built in the Registry (1: local check from administrator, 2: endoscopist, 3: central check by chief administrator, 4: registry coordinator (ÁV)) (more information is available at https://tm-centre.org/en/registries/ercp-registry/) [9] (Suppl. Table 3). The use of different cannulation methods could be found in Suppl. Table 4.

The Hungarian ERCP Registry has been ethically approved by the Scientific and Research Ethics Committee of the Medical Research Council (TUKEB-35523/2016/EKU).

Inclusion and exclusion criteria

Subjects with previous papillotomy, altered gastroduodenal anatomy (surgery, gastro-duodenal obstruction), and biliary strictures were excluded to reach a more homogenous patient population with biliary stones or sludge as main etiology. Based on these exclusion criteria from the total of 2734 cases, finally, 240 ABP and 250 AC cases without ABP were available for analysis (Suppl. Figure 1). Diagnosis of AC was established by the Tokyo guidelines, while the diagnosis of ABP was based on imaging and laboratory parameters, and other etiologies of pancreatitis were excluded.

Definitions

Indications of ERCP were defined in the Registry protocol according to international guidelines [2,4,11]. The definition of acute pancreatitis was based on the IAP/APA guidelines [4]. Presence of sludge or stone in the common bile duct and/or increase of bilirubin and/or increase of transaminase levels and/or inflammatory parameters during repeated testing in 12–24 h intervals were the indications of ERCP in both groups. Guidewire-assisted simple cannulation technique was first attempted at initial cannulation, in case of failure advanced cannulation methods (needle-knife precut, PGW-assisted techniques) were tried. PPS insertion was carried out only in cases of difficult biliary access, after unintentional PGW insertion. Cannulation algorithm laid down by ESGE was followed in all centers [12]. Adverse events such as bleeding, perforation, post-ERCP pancreatitis were defined as in the consensus paper from Cotton et al. [13].

Analyzed dataset

Besides the baseline, demographic data (gender, age, American Society of Anesthesiology (ASA) status), the presence of juxtapapillary diverticulum (JPD), anticoagulation/antiplatelet medication use, the rate of successful biliary access, the use of advanced cannulation methods, post-ERCP pancreatitis (PEP) prophylaxis measures (non-steroid suppositories, prophylactic pancreatic stent placement), adverse event rates (bleeding, perforation, PEP), cannulation and fluoroscopy times were compared in the two groups. This cohort study conforms with the STROBE guidelines [14].

Statistical analysis

Continuous measures are summarized and presented as means and standard deviations (SD) or as median and interquartile ranges (IQR). Categorical data are presented as observed and as percentages. To determine differences between continuous parameters, depending on the distribution of the data, we used the independent Student's t-test or the Mann–Whitney *U* test for two groups. We used the Chi-square test or Fisher's exact test to analyze the relations between the factors under examination and odds ratios were also calculated. Binary logistic regression with stepwise forward elimination was used to observe independent prognostic factors from the followings: age, gender, study groups (ABP vs AC), JPD and ASA score for the main outcomes (advanced cannulation rate, pancreatic cannulation, pancreatic stent placement) where significant differences were detected, and enough data was available. All analyses were performed with SPSS 25 statistical software (IBM Corporation, Armonk, NY).

We performed a sample size calculation before the study was

Table 1
Comparison of the general characteristics of the cohort (ABP: acute biliary pancreatitis, AC: acute cholangitis, ASA: American Society of Anesthesiology, SD: standard deviation).

	ABP (n = 240)	AC (n = 250)	p-value
Mean age (SD)	63.13 (16.74)	69.56 (15.65)	**<0.001**
Sex ratio (female/all)	0.60	0.50	**0.026**
ASA I	80	52	**0.002**
ASA II	130	140	0.648
ASA III	23	54	**<0.001**
ASA IV	6	2	0.139
Previous anticoagulation or antiplatelet therapy	65/240	83/250	0.140
Juxtapapillary diverticulum	31/240	67/250	**<0.001**

Table 2
Analysis of advanced cannulation method use and post-ERCP pancreatitis prophylaxis in the ABP and AC groups (ABP: acute biliary pancreatitis, AC: acute cholangitis, PGW: pancreatic guidewire, PPS: prophylactic pancreatic stent, NK: needle knife, NSAID: non-steroidal anti-inflammatory drugs, OR: Odds ratio; 95%CI: 95% confidence interval).

	ABP (n = 240)	AC (n = 250)	OR (95%CI)	p-value	adjusted OR (95%CI)	p-value
Advanced biliary cannulation rate	108 (45.0%)	61 (24.4%)	2.54 (1.73, 3.72)	**<0.001**	2.388 (1.691–3.522)	**<0.001**
Pancreatic cannulation 1x multiple	75 (31.3%)	43 (17.2%)	2.19 (1.43, 3.35)	**<0.001**	1.921 (1.241–2.974)	**0.003**
	43 (17.9%)	19 (7.6%)	2.54 (1.43, 4.50)	**0.001**		
	32 (13.3%)	24 (9.6%)	1.45 (0.83, 2.54)	0.194		
Sequential advanced methods needed	30/108 (27.8%)	13/61 (21.3%)	1.42 (0.68, 2.99)	0.354	–	–
Primary PGW/PPS-assisted advanced method used	36/108 (33.3%)	14/61 (22.9%)	1.68 (0.82, 3.44)	0.156	–	–
Primary NK advanced method used	72/108 (66.7%)	47/61 (77.0%)	0.60 (0.29, 1.22)	0.156	–	–
PPS inserted	47 (19.6%)	12 (4.8%)	4.83 (2.49, 9.36)	**<0.001**	4.687 (2.415–9.098)	**<0.001**
NSAID suppository use	161 (67.1%)	155 (62.0%)	1.25 (0.86, 1.81)	0.240	–	–

Table 3
Comparison of adverse event rates in the ABP and AC groups (ABP: acute biliary pancreatitis, AC: acute cholangitis, N.A.: not applicable).

	ABP (240)	AC (250)	p-value
Intraprocedural, immediate bleeding	23 (9.6%)	18 (7.2%)	0.341
Late, clinically significant bleeding	0 (0.0%)	2 (0.8%)	0.499
Conservatively managed perforation	2 (0.8%)	3 (1.2%)	1.000
Cholecystitis	3 (1.3%)	4 (1.6%)	1.000
Post-ERCP pancreatitis	N.A.	3 (1.2%)	N.A.

initiated which was based on the assumption that in the control group (AC) 20% advanced cannulation rate could be expected and we estimated the effect of ABP could increase the rate of advanced cannulation by an odds ratio of 2 (33%). Calculating by a two-sided significance level of 95%, 80% power, and the assumption mentioned above, at least 187 ABP and 187 AC cases would be needed to detect a significant difference. OpenEpi online calculator was used to estimate the sample size (https://www.openepi.com/SampleSize/SSCohort.htm).

Sensitivity analyses were carried out excluding ABP cases with questionable indication of ERCP, i.e. cases where stone or sludge were not detected during the ERCP to reinforce the robustness of the results.

Results

General characteristics of the cohort

AC patients were significantly older than ABP patients (69.6 vs. 63.1 years, $p < 0.001$), while more women were in the ABP group (60% vs. 50%) (Table 1; Suppl. Figure 2). A higher proportion of ASA I patients was in the younger ABP group, while more ASA III patients were in the older AC group. No significant difference was found in the anticoagulation and antiplatelet usage between the two groups. Interestingly, more juxtapapillary diverticula were observed in AC patients (26.8% vs. 12.9%, $p < 0.001$) (Table 1).

Findings of ERCP

Normal cholangiogram was observed more frequently in ABP than in AC cases (20.0% vs. 12.3%, $p = 0.026$). Dilated common bile duct (CBD) without stone or sludge was found during ERCP in a higher proportion of ABP patients, compared to AC patients (22.6% vs. 12.8%, respectively, $p = 0.005$). The prevalence of biliary sludge without stones and small CBD stones (≤10 mm) were not significantly different in ABP and AC group (14.3% vs. 9.1% ($p = 0.073$) and 39.1% vs. 46.9% ($p = 0.088$), respectively). Large CBD stones were present more commonly in AC patients (3.9% vs. 18.9%, $p < 0.001$). Expectedly, purulent bile was more frequently found in AC cases than in ABP cases (6.5% vs. 22.2%, $p < 0.001$) (Suppl. Table 5). No

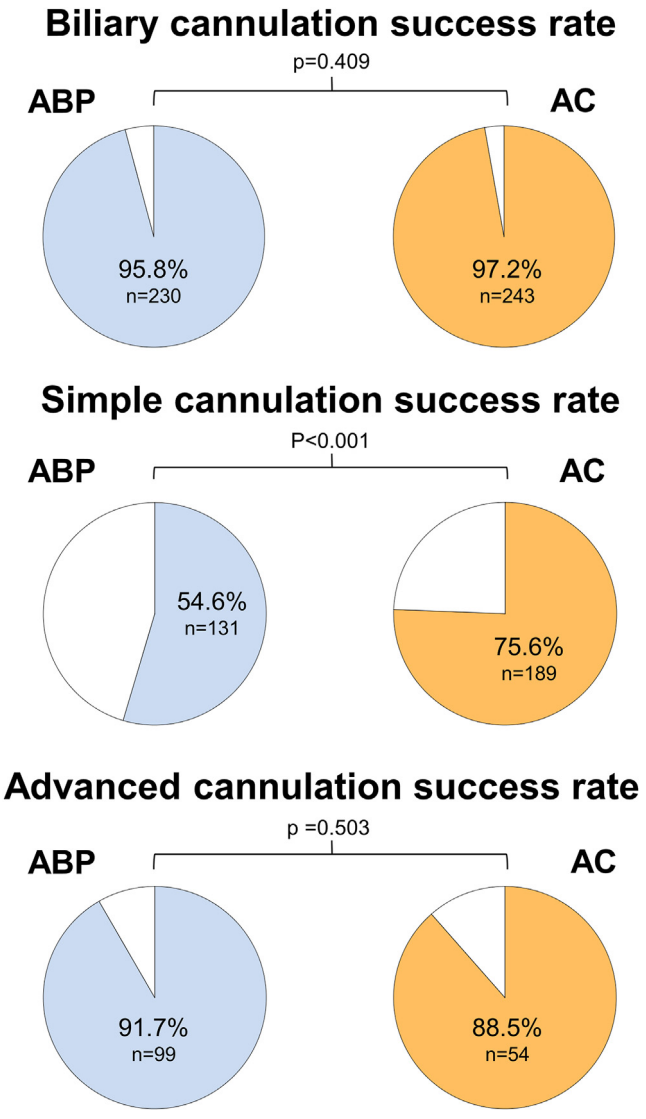

Fig. 1. Analysis of successful biliary access rate in all, simple cannulation and advanced cannulation cases (ABP: acute biliary pancreatitis, AC: acute cholangitis).

stone extraction was attempted, only a stent was inserted in 13/240 (5.4%) in ABP vs. 14/250 (5.6%) in AC cases, due to large stones or in patients with clopidogrel or oral anticoagulant therapy.

Biliary cannulation success rates

Successful biliary access was achieved in ABP cases in 230/240

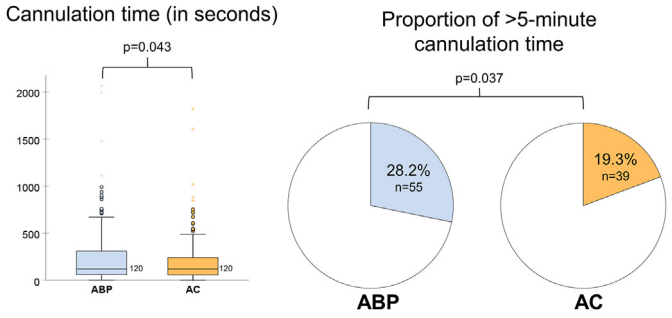

Fig. 2. Comparison of cannulation time (median, in seconds) and proportion of more than 5-min cannulation time in the ABP and AC group (ABP: acute biliary pancreatitis, AC: acute cholangitis).

(95.8%) vs. 243/250 (97.2%) in AC cases ($p = 0.409$) during the initial ERCP. Simple cannulation succeeded less frequently in the ABP group (54.6% vs. 75.6%; $p < 0.001$), however, no difference was found in the success rate of advanced cannulation methods in the two groups (91.7% vs. 88.5%; $p = 0.503$) (Fig. 1).

Advanced cannulation methods and post-ERCP pancreatitis prophylaxis

Advanced cannulation methods were used in 108/240 (45.0%) cases of ABP, while only in 61/250 (24.4%) of AC cases ($p < 0.001$). Multiple advanced methods were used in 13/61 in AC and 30/108 in ABP cases, respectively ($p = 0.354$). More pancreatic duct manipulations were found in the ABP group (31.3% vs. 17.2%, $p < 0.001$) and also more prophylactic pancreatic stents (PPS) were inserted in these patients (19.6% vs. 4.8%; $p < 0.001$). No difference was seen in the NSAID suppository use between the two groups (67.1% vs. 62%; $p = 0.240$) (Table 2).

Carrying out a binary logistic regression for the main outcomes (advanced cannulation rate, pancreatic cannulation, pancreatic stent placement) did not change ORs significantly by the adjustment (Table 2).

Excluding ABP cases with negative cholangiograms, the differences between the use of advanced cannulation methods (OR 2.47 [1.62–3.37], $p < 0.001$), pancreatic cannulation rate (OR 2.37 [1.52–3.70], $p < 0.001$), PPS insertion rate (OR 4.99 [2.53–9.83], $p < 0.001$) remained significantly different between the two groups.

Adverse event rates

Only a low number of clinically significant bleeding (0% vs. 0.8%), perforation (0.8% vs. 1.2%), cholecystitis (1.3% vs. 1.6%), immediate bleeding (9.6% vs. 7.2%) were detected, and no significant difference could be detected between the groups in this regard (Table 3).

Cannulation times

The average biliary cannulation time was significantly longer in the ABP group (248 vs. 185 s, $p = 0.043$) (Fig. 2), however, that difference could not be found when the simple (113 vs. 116 s) or the advanced cannulation time (409 vs. 396 s) were separately analyzed. The number of more than 5-min cannulation was higher in the ABP patients (28.2% vs. 19.3%; $p = 0.037$) (Fig. 2), and with normal cholangiograms, the cannulation lasted longer in the ABP group (324 vs. 154 s; $p = 0.040$). This difference could also be seen in patients without JPD (261 vs. 158 s, $p = 0.005$) (Suppl. Table 6).

Fluoroscopy time

Fluoroscopy time was longer in the AC group, when all cases (91 s vs. 107 s; $p = 0.009$) (Fig. 3), and the simple cannulation cases (91 s vs. 107 s; $p = 0.008$) were compared. When stone extraction was done in AC patients, it took significantly longer, most probably due to the higher rate of larger (>1 cm) stones (89 s vs. 107 s; $p = 0.009$). In other subgroups, no differences were found (Suppl. Table 7).

Discussion

Our data support the ASGE grading of difficulty for acute biliary pancreatitis in ERCP. Several parameters suggest that ERCP is more challenging in ABP cases than in AC cases. We found that the rate of advanced cannulation method use and the rate of inadvertent pancreatic cannulation were higher and cannulation time was longer in ABP patients than in AC cases. This observation points to the fact that we face difficult biliary cannulation in ABP more frequently compared to AC cases, where similar pathologic changes related to the biliary tree are expected. Importantly, the cannulation success rate and the rate of adverse events were not influenced by this. We also found a higher number of cases with normal cholangiogram in the ABP group (20.0%) compared to AC (12.3%). In these cases, spontaneous passage of stones or sludge by the time of ERCP is one possible explanation for the initial worsening of cholestatic parameters. Additionally, this also might be due to the difficulty of diagnosing acute cholangitis when acute pancreatitis is also present, but also can be explained by the suboptimal availability of preprocedural endoscopic ultrasound evaluation in the participating Hungarian centers. ERCPs could have been avoided in these cases, cost and avoidable invasiveness should be highlighted, as a potential benefit [15]. Fluoroscopy time does not correlate with the difficulty of biliary access in our study, more likely it depends on

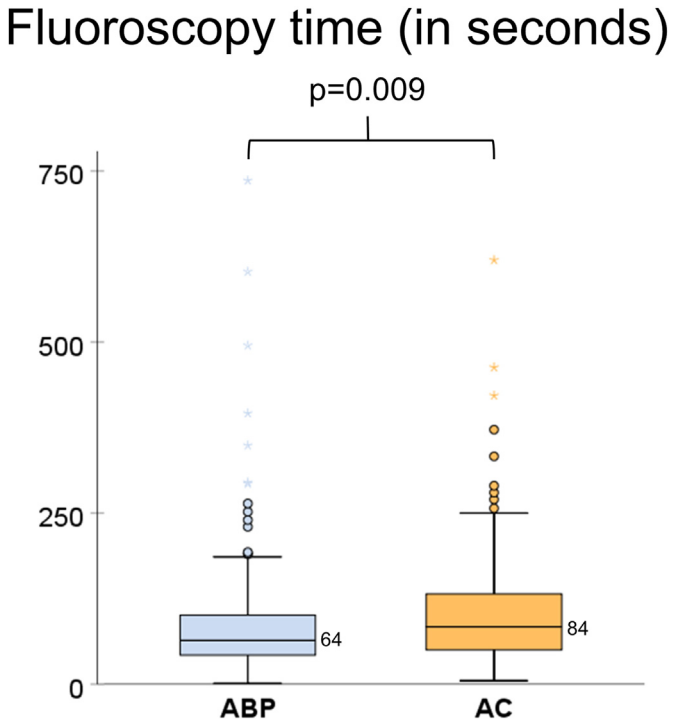

Fig. 3. Comparison of fluoroscopy times in the ABP and AC groups (median, in seconds) (ABP: acute biliary pancreatitis, AC: acute cholangitis).

the occurrence and size of bile duct stones, since large stones were more frequently found in the AC group.

Our study has several strengths, first of all, it is a quite large, prospectively collected, nationwide dataset from several centers in Hungary. Consecutively collected ABP and AC cases were available in almost equal numbers with good data quality, detailed data set, and in an appropriate sample size. Secondly, our registry system has a built-in quality assurance program that could limit false data entry and underreporting. Multivariable statistics also confirmed the robustness of our findings.

There are some limitations to our study. Post hoc questions raised in a prospective registry database might result in confounding effects. All cases come from high-volume centers and endoscopists, and case distribution is varied among centers that hinder generalizability (Suppl. Table 1). The inherent biases of observational studies and retrospective designs e.g., selection bias should be noted in our study as well. There were some differences between the two groups, firstly, AC patients were older, and had more comorbidities (more ASA III patients). Secondly, more juxtapapillary diverticula were found in the AC group. For this reason, binary logistic regression model was used to adjust for these differences. Thirdly, the differentiation of AC cases in the ABP group could not have been done due to the lack of reliable guidelines or tools to confirm the presence of cholangitis in ABP [16]. We were curious about the additional worsening effect of ABP on AC and non-AC cases, but we could not reliably separately analyze AC + ABP and ABP cases without AC. These factors could somewhat limit our analysis.

Based on our data, ABP cases should be handled by more experienced endoscopists who are familiar with a wide range of cannulation techniques, pancreatic guidewire assisted (double guidewire and transpancreatic sphincterotomy), as well as needle knife precut techniques [12,17,18]. To lower the worsening effect of inducing more pancreatic edema, the insertion of a prophylactic pancreas stent might potentially improve disease course [19].

Taken together, the grade 3 difficulty classification by ASGE seems to be justified for the ABP cases, and these patients should not be left to the less experienced endoscopists. Additionally, determining the appropriate indication of ERCP is vital in ABP patients. Hence, we would like to emphasize the need for the broader application of less invasive diagnostic tools (e.g., endoscopic ultrasound) in this patient population to decrease the number of unnecessary ERCPs.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgement

A different version of the abstract is published as a conference abstract at https://onlinelibrary.wiley.com/doi/full/10.1111/den.13598. This full article is not published nor is under publication elsewhere.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2020.11.025.

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