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Meta-Analysis

Performance of different approaches to difficult biliary cannulation in endoscopic retrograde cholangiopancreatography: A systematic review and network meta-analysis

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ABSTRACT

Background: It is unclear which is the best strategy for difficult biliary cannulation in endoscopic retrograde cholangiopancreatography (ERCP).
Aims: We compared the different techniques, through a network meta-analysis combining direct and indirect comparisons.
Methods: We identified 12 randomized controlled trials (1605 patients) comparing different techniques for difficult biliary cannulation (early and late needle knife techniques, pancreatic guidewire- and stent-assisted techniques, transpancreatic sphincterotomy, and endoscopic ultrasound rendez-vous [EUS-RV]) either with each other or with persistence with the standard cannulation techniques. The success rate of biliary cannulation and the incidence of post-ERCP pancreatitis (PEP) were the primary outcomes.
Results: Only transpancreatic sphincterotomy significantly outperformed pancreatic stent assisted cannulation (risk ratio [RR] 1.33, 1.00-1.55), whereas no difference was observed among the other techniques in terms of cannulation success. SUCRA ranking suggested EUS-RV and early needle knife techniques as the best performing approaches (SUCRA 0.78 and 0.68, respectively). In terms of PEP rate, only EUS-RV significantly outperformed pancreatic guidewire-assisted techniques (RR 0.21, 0.04-0.98).
Conclusions: Based on low quality of evidence, the several techniques for difficult biliary cannulation show similar results although a trend in favour of needle knife techniques and EUS-RV was observed. EUS-RV seems to decrease the risk of PEP.

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1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) represents the main therapeutic option for the management of several benign and malignant pancreaticobiliary conditions and it may be technically challenging even for experienced endoscopists. In fact, ERCP requires the successful cannulation of the common bile duct and/or (less commonly) the main pancreatic duct and cannulation is reported to be failed in up to 15 % of ERCPs overall and in less than 5 % at high-volume centers [1,2].

While new alternative endoscopic strategies for the management of malignant biliary obstruction with lower adverse events (AEs) have been recently proposed, such as endoscopic ultrasound (EUS) choledocoduodenostomy (CDS) [3,4] or gall bladder drainage (GBD) [5], ERCP procedural volumes in the United States have remained stable over time.

Although the definition of difficult biliary cannulation has traditionally been heterogeneous, the recent definition proposed by the European Society of Gastrointestinal Endoscopy (ESGE) suggests that biliary cannulation can be defined as "difficult" after 5 minutes or five attempts, or more than one unintended pancreatic duct cannulation [6].

The prolonged papillary manipulation with the risk of inadvertent cannulation with injection of pancreatic duct are well-known risk factors of PEP and a recent meta-analysis of 380 studies reported an overall post-ERCP pancreatitis (PEP) rate of 4.6 %, with a considerable increase up to 11.4 % in patients with difficult biliary cannulation [7].

Therefore, different cannulation methods have been proposed to achieve cannulation success with a favourable safety profile when facing a difficult biliary cannulation.

A recent network meta-analysis of 17 randomized-controlled trials (RCTs) suggested that transpancreatic sphincterotomy, followed by precut papillotomy represent the best option of difficult biliary cannulation increasing the success rate while marginalizing the risk of PEP [8]. However, this meta-analysis included RCTs with highly heterogeneous definitions of difficult biliary cannulations and most of the included studies had been published before the definition proposed by the ESGE and subsequent studies did not confirm these results [9]; moreover, since the publication of the previous meta-analysis, two large Indian RCTs tested EUS rendezvous (RV) [10,11], a technique characterized by the cannulation of the CBD under EUS guidance with the passage of the guidewire through a fine-needle aspiration (FNA) that showed promising results.

Therefore, given the scarce and conflicting results, we decided to perform a network meta-analysis including all the available RCTs comparing different techniques for difficult biliary cannulation.

In contrast to pairwise meta-analyses, network meta-analysis can provide also indirect evidence about the comparative effectiveness of multiple interventions and synthesize available data across a network of RCTs.

We also used Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [12] for network meta-analysis to appraise the quality of evidence.

2. Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was conducted following *a priori* established protocol [13].

2.1. Selection criteria

Studies included in this meta-analysis were RCTs published in English language meeting these inclusion criteria: (a) Patients: adults (age >18 years) undergoing ERCP for any biliary indication and presenting a difficult biliary cannulation; (b) Intervention: application of needle knife techniques (conventional precut sphincterotomy or fistulotomy), pancreatic guidewire or double guidewire assisted techniques, pancreatic stent-assisted technique, transpancreatic sphincterotomy, or EUS-RV; (c) Comparator: another of the above reported methods or persistence with standard cannulation techniques; and (d) Outcomes: rate of successful biliary cannulation, incidence of PEP, and procedural time. Non-comparative observational and retrospective studies, trials comparing different approaches within the same technique and trials assessing cannulation techniques in index ERCPs were excluded. In order to achieve a consistency in the definition of difficult biliary cannulation, we excluded also the RCTs with the definition of difficult biliary cannulation as failure to cannulate after at least 10 minutes or more than 5 attempts or more than 5 unintended pancreatic duct (PD) cannulations.

2.2. Search strategy

The search strategy was designed and conducted by an experienced medical librarian with the input from study's investigators, utilizing various databases with variant controlled vocabularies, expanded terminology, varying algorithms, and keyword capabilities, for RCTs published from inception through March 2025. Complementary manual search was performed on additional databases (Google Scholar, Cochrane library) and by checking the references of all the main review articles on this topic, in order to identify possible additional studies. The detailed literature search strategy is reported in the Online Supplement (eTable 1).

2.3. Data abstraction and quality assessment

Data on study-, patient- and treatment-related characteristics were abstracted onto a standardized form, by two authors independently (AF, GDA). The risk of bias of individual studies was assessed using the Cochrane Risk of Bias assessment tool [14].

2.4. Statistical analysis

The primary outcomes were the success rate of biliary cannulation and the incidence of PEP. A secondary outcome was the procedural time. The denominator was based on an intention-to-treat analysis as described in each included study.

The network meta-analysis was performed using a multivariate random-effects meta-regression with a frequentist approach based on a random-effects consistency model and the results were expressed as risk ratio (RR) or standardized mean difference (SMD) along with 95 % confidence intervals (CIs) [15]. A comparison of direct and indirect treatment estimates was performed to assess the consistency of network meta-analysis by using a node-splitting technique. We assessed statistical heterogeneity using I^2 statistic, with values over 50 % indicating substantial heterogeneity, and small study effects were assessed by examining funnel plot asymmetry [16].

A sensitivity analysis for the primary outcomes was performed restricting the inclusion to those RCTs strictly reporting the ESGE definition of difficult biliary cannulation [6].

Methods ranking was based on the surface under the cumulative ranking curve (SUCRA) score analysis, measured on a scale from 0 (worst) to 1 (best) [17].

Additionally, the incidence of specific adverse events (AEs), namely cholangitis, perforation, bleeding and overall AE were descriptively reported.

Network meta-analysis was conducted with R package *netmeta* (Foundation for Statistical Computing, Vienna, Austria).

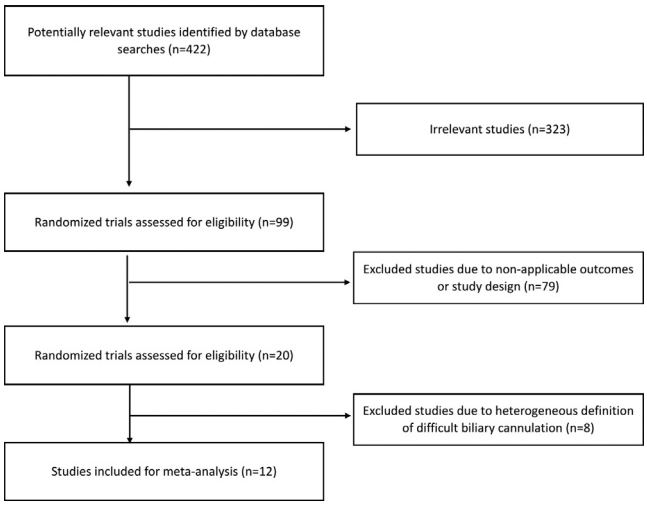

Fig. 1. Flow chart of the included trials.

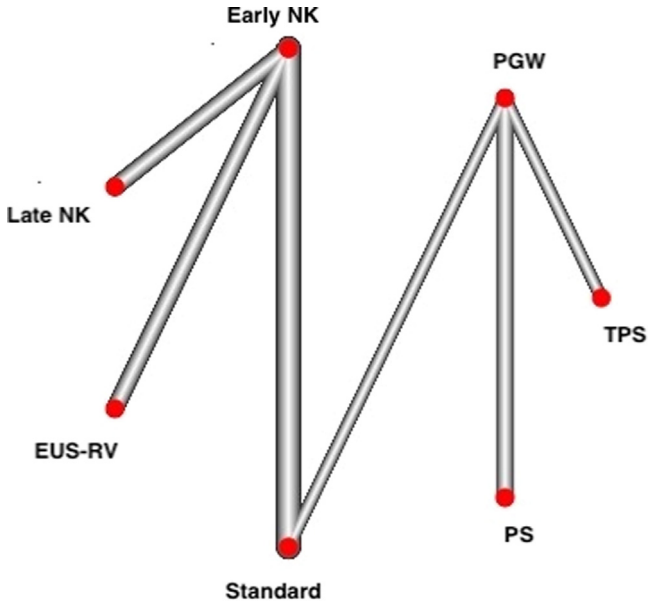

Fig. 2. Network of the included trials. Network of included studies with the available direct comparisons between endoscopic interventions for difficult biliary cannulation. The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively.
PGW: pancreatic guidewire-assisted technique; standard: persistence with standard techniques after randomization;TPS: transpancreatic sphincterotomy; early NK: needle knife techniques applied directly after randomization; Late NK: needle knife techniques applied 20 minutes after randomization; PS: pancreatic stent-assisted technique; EUS-RV: Endoscopic Ultrasound Rendez-Vous.

2.5. Quality of evidence

The quality of evidence derived from the pairwise and network meta-analysis was judged using the GRADE framework [12]. In this approach, the evidence from RCTs starts at high quality and can be rated down based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity) and/or publication bias, to levels of moderate, low and very low quality (eTable 2).

3. Results

From 422 studies initially identified using the search strategy, we ultimately included 12 RCTs in the network meta-analysis, comparing seven different strategies (early and late needle knife techniques, pancreatic guidewire-assisted technique, pancreatic stent-assisted technique, transpancreatic sphincterotomy, EUS-RV and persistence with standard cannulation techniques) for patients with difficult biliary cannulation [10,11,18–27]. The early needle knife techniques applied the papillotomy immediately after randomization. Fig. 1 depicts the study selection flowchart, and Fig. 2 shows the available direct comparisons and network of trials.

3.1. Characteristics of included studies

Table 1 summarizes the baseline characteristics of the RCTs included in the network meta-analysis. Overall, the included 12 trials enrolled 1605 patients. All 12 RCTs were two-arm controlled trials, of which four compared early needle knife techniques vs. persistence of standard cannulation techniques [20,22–24] two trials compared early vs. late needle knife techniques [18,27], two trials compared early needle knife techniques vs. EUS-RV [10,11], one trial compared pancreatic guidewire-assisted cannulation vs. persistence of standard cannulation techniques,[21] two trials compared pancreatic guidewire-assisted cannulation vs. pancreatic stent-assisted technique [19,25], one trial compared transpancreatic sphincterotomy vs. pancreatic guidewire-assisted technique [26].

Consistently with previously published meta-analyses and given the comparable efficacy of these approaches in terms of successful cannulation [8,28], the term "needle knife techniques" was used to describe both available variations of free-hand precut techniques (conventional precut sphincterotomy and fistulotomy).

Six studies complied strictly or at least partially to the ESGE definition of difficult biliary cannulation [10,11,21,22,26,27] whereas the other studies slightly deviated from this definition.

The baseline patient characteristics (sex and age) and the treatment-related features (e.g. indications for ERCP) were evenly distributed between the active and comparator groups and across different trials (Table 1). Of note, one RCT[10] included only benign indications and one RCT [11] only patients with malignant distal biliary obstruction.

Recruitment period ranged from 1995 to 2023 and the mean age between 48 and 70.4 years, while the most common indication for ERCP was choledocholitiasis.

As described in the eFigures 1A and B, all studies were at high risk of performance and detection bias.

3.2. Success rate of biliary cannulation

As reported in Table 2, the comparative results among different techniques were largely similar with overlapping CIs although differences. Only transpancreatic sphincterotomy significantly outperformed pancreatic stent assisted cannulation (RR 1.33, 1.00-1.55), whereas no difference was observed among the different techniques as compared to persistence of guidewire cannulation (Fig. 3A) or compared to each other (Table 2).

SUCRA ranking (Table 3) suggested EUS-RV and early needle knife techniques as the best performing approaches (SUCRA 0.78 and 0.68, respectively), with pancreatic stent-assisted technique ranking as the worst treatment (SUCRA 0.08).

These results were confirmed in the sensitivity analysis based on the strict ESGE definition of difficult biliary cannulation (eTables 3 and 4), where again early and late needle knife techniques and EUS-RV ranked as the best options for difficult biliary cannulation.

3.3. Incidence of post-ERCP pancreatitis

On network meta-analysis, only EUS-RV significantly outperformed pancreatic guidewire-assisted techniques (RR 0.21, 0.04-

Table 1
Characteristics of included randomized controlled trials comparing different methods for the management of difficult biliary cannulation.

Study (year)	Country	Design	Period	Interv-ention	Compar-ator	N	Definition of difficult biliary cannulation	Sex (m/f)	Age (years)	Indication for ERCP	Rate of difficult biliary cannulation in the cohort
Tang (2005) [20]	Canada	Single center	09/1995 - 11/1998	Early NK****	Standard	32/30	7 min fellow + 5 min senior	15/17 vs. 14/16	64.6 vs. 67.2	Dilated CBD 10 vs. 13, Choledocholithiasis 7 vs. 4, Cancer 11 vs. 10, History of pancreatitis 5 vs. 7, Abdominal pain 17 vs. 17, Jaundice 15 vs. 19, Fever 3 vs. 4, Abnormal LFT 20 vs. 20, Cholangitis 3 vs. 2	9.7 %
Cennamo (2009) [18]	Italy	Single center	05/2004 - 03/2006	Early NK*	Late NK*	36/32	5 min or 3 unintended PD passages	16/20 vs. 15/17	68 vs. 69	Choledocholithiasis: 24 vs. 23 Cancer: 12 vs. 9	17.3 %
Herreros de Tejada (2009) [21]	Spain	Multicenter	11/2004 - 10/2006	PGW	Standard	97/91	5 min	38/59 vs. 38/53	69.5 vs. 65.8	Choledocholithiasis 52 vs. 48, Malignant biliary/Pancreatic stricture 20 vs. 18, Acute cholangitis 5 vs. 4, Benign biliary stricture 3 vs. 2, Other 3 vs. 9, Cholestasis of unknown origin 10 vs. 7, Idiopathic pancreatitis/Suspected SOD 4 vs. 3	22.2 %
Cote (2012) [19]	USA	Multicenter	09/2008 - 01/2011	PGW	PS	42/45	6 min or 3 unintended PD passages	NR	58.1 vs. 57.4	NR	19.7 %
Swan (2013) [22]	Australia	Single center	07/2007 - 12/2009	Early NK*	Standard	39/34	5 min or 5 attempts or 2 unintended PD passages	11/28 vs. 12/22	59 vs. 57	Known CBD stone 10.3 % vs.17.6 %, Suspected CBD stone 51.3 % vs. 47.1 %, SOD 5.1 % vs. 8.8 %, Obstructive jaundice 7.7 % vs.5.9 %, Non-pancreatic malignancy 5.1 % vs 0 %, Bile leak 10.3 % vs. 2.9 %, PSC 0 % vs. 2.9 %, Dilated bile ducts - 5.1 % vs. 8.8 %, Cholangitis 2.6 % vs. 5.9 %, Benign biliary stricture 2.6 % vs. 0 %	15.7 %
Mariani (2015) [23]	Italy	Multicenter	01/2012 - 12/2013	Early NK***	Standard	185/190	5 min or 3 unintended PD passages	88/97 vs. 77/113	70.4 vs. 68.2	Bile duct stones 105 vs. 118, Malignant biliary stricture 76 vs. 63, Cholangitis 16 vs. 17, Suspected SOD 10 vs. 8, Benign biliary stricture (known or suspected) 11 vs. 7, Post-surgery biliary leakage 4 vs. 8, Other 3 vs. 8	9.5 %
Zagalsky (2016) [24]	Argentina	Multicenter	11/2011 - 12/2013	Early NK*	Standard	50/51	8 min or 3 unintended PD passages	16/34 vs. 15/36	52 vs. 49	CBD stones 78 % vs. 82.3 %, Malignant biliary obstruction 22 % vs. 17.7 %, Prior acute pancreatitis 6 % vs. 13.7 %, History of recurrent pancreatitis 2 % vs. 2 %, Other 14 % vs. 15.7	8.7 %
Eminler (2019) [25]	Turkey	Single center	01/2014 - 02/2016	PGW	PS	50/50	5 min or 5 unintended PD passages	24/26 vs. 16/34	56 vs. 52.9	Suspected CBD stone 41 vs. 35, Malignant biliary stricture 5 vs. 8, Benign biliary stricture 2 vs. 3, Bile leak 2 vs. 4	11 %
Kylanpaa (2021) [26]	Finland, Denmark, Norway, Sweden	Multicenter	09/2015 - 04/2019	TPS	PGW	104/99	5 min or 5 attempts or >1 unintended PD passages	58/46 vs. 40/59	66 vs. 68	CBD stones 47 vs. 40, Stricture 43 vs. 48, PSC 6 vs. 6, Post cholecystectomy leakage 8 vs. 9, Other 8 % vs. 12 %	17.1 %
Mandavd-hare (2021) [27]	India	Single center	04/2019-02/2020	Early NK*	Late NK*	20/20	5 min or 5 attempts or > 1 unintended PD passages	11/9 vs 6/14	48 vs 53	CBD stones 13 vs 13 Benign stricture 2 vs 1 Malignant stricture 3 vs 6 Others 2 vs 0	30.7 %
Choudhury (2024) [10]	India	Single center	07/2020-05/2021	EUS-RV	Early NK*	50/50	5 min or 5 attempts or > 1 unintended PD passages	13/37 vs 15/35	50.52 vs 52.96	CBD stones 43 vs 36 Benign stricture 5 vs 7 Biliary injury 2 vs 7	23.7 %
Dhir (2025) [11]	India	Single center	02/2013-04/2023	EUS-RV	Early NK*	104/104	5 min or 5 attempts	65/39 vs 67/37	65 vs 57	Malignant stricture 100 %	5.1 %

NR: not reported; PGW: pancreatic guidewire-assisted technique; standard: persistence with standard techniques after randomization; PD: pancreatic duct; TPS: transpancreatic sphincterotomy; early NK: needle knife techniques applied directly after randomization; Late NK: needle knife techniques applied 20 minutes after randomization; CBD: common bile duct; LFT: liver function tests; SOD: sphincter Oddi dysfunction; PS: pancreatic stent-assisted technique; PSC: primary sclerosing cholangitis; EUS-RV: Endoscopic Ultrasound Rendez-Vous
Needle knife techniques: *conventional needle knife from the papillary orifice to the roof of the papilla; **fistulotomy from the roof of the papilla toward the papillary orifice; ***both techniques used; ****the used technique is not specified

Table 2
GRADE Summary of Findings reporting the comparative efficacy of different methods for biliary difficult cannulation.
Risk ratios reaching the significance threshold are reported in bold.

	Success rate of biliary cannulation		Post-ERCP pancreatitis rate	
	Risk Ratio (95 % CI)	Quality of Evidence	Risk Ratio (95 % CI)	Quality of Evidence
All adjunctive treatments vs. Persistence with standard cannulation techniques				
Pancreatic guidewire-assisted technique	0.85 (0.59-1.22)	Low	1.74 (0.64-4.72)	Very low
Early needle knife techniques	1.08 (0.93-1.25)	Low	0.66 (0.36-1.23)	Low
Late needle knife techniques	1.05 (0.81-1.36)	Low	1.99 (0.08-50.60)	Very low
Pancreatic stent-assisted technique	0.68 (0.43-1.09)	Low	1.69 (0.42-25)	Very low
Transpancreatic sphincterotomy	1.03 (0.64-1.61)	Low	1.31 (0.39-5.26)	Very low
EUS Rendez-vous	1.62 (0.96-2.74)	Low	0.37 (0.11-1.18)	Low
vs. Pancreatic guidewire-assisted technique				
Early needle knife techniques	1.28 (0.86-1.88)	Low	1.12 (0.03-33.3)	Very low
Late needle knife techniques	1.23 (0.79-1.92)	Low	0.21 (0.05-23.1)	Very low
Pancreatic stent-assisted technique	0.81 (0.60-1.08)	Low	1.46 (0.31-11.1)	Very low
Transpancreatic sphincterotomy	1.21 (0.91-1.61)	Low	0.80 (0.36-1.88)	Low
EUS Rendez-vous	1.31 (0.85-2.04)	Low	0.21 (0.04-0.98)	Low
vs. Early needle knife techniques				
Late needle knife techniques	0.97 (0.78-1.20)	Low	1.67 (0.12-100)	Very low
Pancreatic stent-assisted technique	0.63 (0.38-1.04)	Low	1.80 (0.30-50)	Very low
Transpancreatic sphincterotomy	0.95 (0.58-1.53)	Low	1.54 (0.34-37)	Very low
EUS Rendez-vous	1.03 (0.86-1.23)	Low	0.55 (0.20-1.49)	Low
Vs Late needle knife techniques				
Pancreatic stent-assisted technique	0.65 (0.38 -1.12)	Low	1.39 (0.23-100)	Very low
Transpancreatic sphincterotomy	0.98 (0.57-1.40)	Low	0.63 (0.03-25)	Very low
EUS Rendez-vous	1.06 (0.76-1.29)	Low	0.18 (0.006-5.26)	Very low
Vs Pancreatic stent-assisted technique				
Transpancreatic sphincterotomy	1.33 (1.00-1.55)	Low	0.28 (0.07-2.18)	Low
EUS Rendez-vous	1.62 (0.96-2.74)	Low	0.11 (0.01-1.18)	Low
Vs Transpancreatic sphincterotomy				
EUS Rendez-vous	1.09 (0.65-1.82)	Low	0.25 (0.04-1.44)	Low

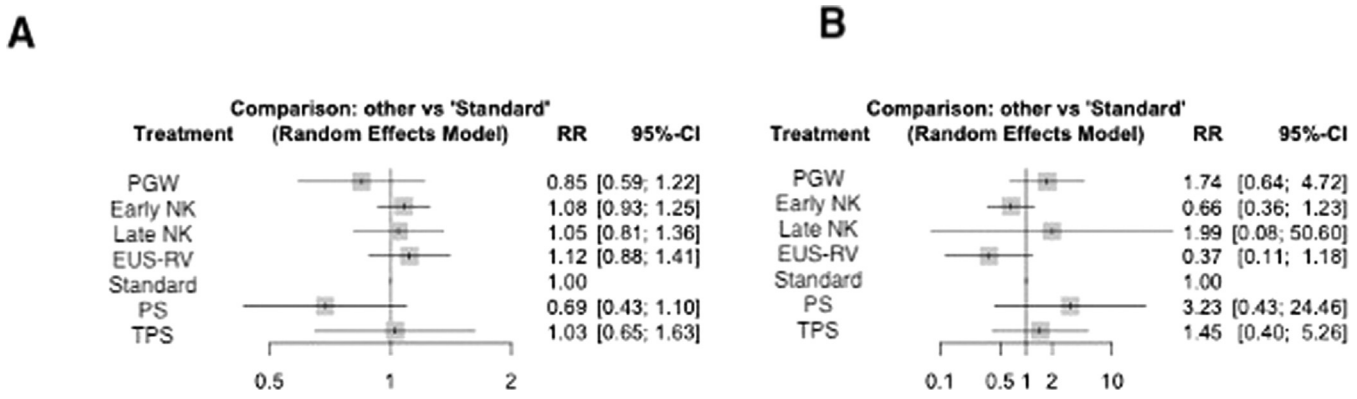

Fig. 3. Forest plots reporting estimates derived from network meta-analysis assessing (a) success rate of biliary cannulation, and (b) post-ERCP rate.
Persistence with standard cannulation techniques has been used as reference.
PGW: pancreatic guidewire-assisted technique; standard: persistence with standard techniques after randomization;TPS: transpancreatic sphincterotomy; early NK: needle knife techniques applied directly after randomization; Late NK: needle knife techniques applied 20 minutes after randomization; PS: pancreatic stent-assisted technique; EUS-RV: Endoscopic Ultrasound Rendez-Vous.

0.98), whereas no difference was observed in any of the other comparisons (Table 2). Of note, none of the tested techniques were significantly safer than the persistence with the standard cannulation (Fig. 3B).

As a consequence, EUS-RV was the best treatment in terms of safety (SUCRA 0.92), followed by early needle knife techniques (SUCRA 0.74) and persistence with standard cannulation (SUCRA 0.57). On the other hand, pancreatic guidewire assisted techniques and use of pancreatic stent resulted as the worst performers (SUCRA 0.29 and 0.20, respectively) (Table 3).

Again, these results were confirmed in the sensitivity analysis restricted to the ESGE definition of difficult biliary cannulation (eTables 3 and 4).

3.4. Procedural time and other adverse events

As reported in the eTables 5-6 and eFigure 2, no difference was observed among the several techniques in terms of procedural time and the SUCRA ranking suggested the persistence of standard cannulation, early needle knife techniques and EUS-RV as the best performing approaches in this setting. eTable 7 descriptively reports the specific incidence of bleeding, cholangitis, perforation and overall AEs in the included studies.

Overall, AEs were equally distributed among the tested treatments with bleeding as the most common complication. Pooled rates of bleeding were 2.7 % (1.3 %-4.1 %) after early needle knife techniques, 1.3 % (0 %-3.5 %) after transpancreatic sphincterotomy,

Table 3
SUCRA ranking overall for success rate and post-ERCP pancreatitis rate.

Success rate of biliary cannulation	SUCRA	Post-ERCP pancreatitis rate	SUCRA
EUS Rendez-vous	0.78	EUS Rendez-vous	0.92
Early needle knife techniques	0.68	Early needle knife techniques	0.74
Late needle knife techniques	0.61	Persistence with standard cannulation techniques	0.57
Transpancreatic sphincterotomy	0.57	Transpancreatic sphincterotomy	0.40
Persistence with standard cannulation techniques	0.54	Late needle knife techniques	0.35
Pancreatic guidewire-assisted technique	0.21	Pancreatic guidewire-assisted technique	0.29
Pancreatic stent-assisted technique	0.08	Pancreatic stent-assisted technique	0.20

1.1 % (0 %-2.3 %) with pancreatic guidewire-assisted technique, 1.3 % (0.5 %-2.1 %) with EUS-RV, and 2.4 % (1.1 %-3.7 %) with persistence with standard cannulation techniques.

3.5. Small study effects, network coherence and quality of evidence

There was no evidence of small study effects based on funnel plot asymmetry (data not shown), although the number of studies included in each comparison was small. There were no significant differences between direct and indirect estimates in closed loops that allowed assessment of network coherence (p-value for difference between groups where both direct and indirect estimates ranging from 0.23 to 0.76 for success rate of biliary and from 0.19 to 0.88 for PEP rate).

The quality of evidence was mainly judged as low due to the risk of performance/detection bias in the literature and imprecision (broad 95 % CIs crossing the unity).

There was no indirectness, inconsistency, or publication bias for any of the comparisons.

4. Discussion

In spite of the latest advancements in pancreatobiliary endoscopy, ERCP remains a complex procedure with a non-negligible rate of AEs such as PEP or bleeding and with a failure rate ranging from 5 % to 15 % [1,2]. Difficult biliary cannulation still represents a major challenge even to experienced endoscopists and several different cannulation methods have been studied with conflicting results.

A previous network meta-analysis suggested transpancreatic sphincterotomy as the best-performing strategy [8]; however, the heterogeneous definition of difficult biliary cannulation considered particularly in the RCTs testing transpancreatic sphincterotomy and the limited number of RCTs weakened these findings; moreover, the recent publication of two RCTs comparing EUS-RV to precut papillotomy [10,11], warranted a reappraisal of the available evidence in the field to draw more robust conclusions able to inform the guidelines.

Through a network meta-analysis, and using GRADE criteria to appraise the quality of evidence, we made several key observations. First, while no statistical difference was observed among the techniques in terms of successful cannulation, except for a slight superiority of transpancreatic sphincterotomy over pancreatic stent assisted cannulation, the SUCRA ranking suggested EUS-RV and early needle knife techniques as the best performing approaches (SUCRA 0.78 and 0.68, respectively). Of note, these results were confirmed in the sensitivity analysis based on the strict ESGE definition of difficult biliary cannulation [6]. Therefore, the stricter and more homogeneous inclusion criteria and the availability of new evidence on EUS-RV led to different conclusions as compared to the previous network meta-analysis [8], specifically without clear evidence in support of a potential superiority of the transpancreatic sphincterotomy as already suggested in other retrospective studies [9].

Second, EUS-RV significantly outperformed pancreatic guidewire-assisted techniques (RR 0.21, 0.04-0.98) in terms of PEP rate and it resulted as the best treatment in this regard (SUCRA 0.92), followed by early needle knife techniques (SUCRA 0.74) and persistence with standard cannulation (SUCRA 0.57).

EUS-RV is a relatively newer technique where the bile duct is punctured under EUS-guidance, and the guidewire is negotiated across the papilla to facilitate completion of ERCP. Therefore, the direct vision under EUS-guidance of the puncture of the bile duct while being away from the papilla are supposed to reduce the risk of PEP and increase the success rate, as suggested in preliminary retrospective reports [29,30]. On the other hand, EUS-RV is a complex technique requiring high endoscopic skills, potentially longer exposure times for x-rays, and may not be available in all the centers. While the trial by Choudhury et al. [10] did not show statistically significant difference in terms of PEP rate between EUS-RV and precut sphincterotomy, probably due to the limited sample size, in the subgroup at higher risk for PEP, i.e. those patients with at least 1 inadvertent PD cannulation, PEP rate with EUS-RV was 0 % vs 5.6 % in the precut group, thus showing a clear beneficial trend in this subset of patients [10]; similarly, PEP rate was higher in the precut group as compared to EUS-RV (8.7 % vs. 1.9 %, respectively) in the RCT by Dhir et al. [11]. Of note, both the RCTs [10,11] were designed to detect differences in biliary cannulation success (primary aim), not PEP reduction and they could be underpowered for this specific outcome. Therefore, although further evidence is needed, EUS-RV seems to represent a safer option in the case of difficult biliary cannulation but it still limited to centers with advanced expertise in this field.

The similar success rates among the different techniques support their use in the clinical practice depending on specific situations. For example, early needle knife techniques might be more difficult when the papilla is within a diverticulum, or it is flat or partially infiltrated by the tumor whereas EUS-RV could be more challenging in presence of a hugely dilated CBD, with the risk of repeated looping of the guidewire within the CBD. On the other hand, transpancreatic sphincterotomy may offer a better control of the incision's depth facilitated by the progressive pullback of the sphincterotome targeting the common bile duct towards the 11-o'clock position in the case of an easily accessible papilla, especially when compared to the other techniques requiring PD cannulation, namely the use of pancreatic stent and the double guidewire technique [31,32].

The choice of the cannulation technique is frequently influenced by the papillary morphology [33] which may have an impact on the final safety and efficacy outcomes as suggested in recent studies [34]. Unfortunately, the included RCTs did not report the morphological characteristic of the papilla and consequently did not perform subgroup analyses based on this feature.

It should be considered that measures for PEP prevention varied among included studies or were, at times, absent. Furthermore, the risk of PEP is higher in female patients or in the case of benign indications to ERCP and this aspect was heterogeneously reported across the included RCTs. The lack of specific subgroup data in the included RCTs prevented a valid assessment of this important point and further evidence is needed to adequately assess the synergistic impact of advanced cannulation techniques with specific methods to prevent PEP.

Above all, the aforementioned techniques used for difficult biliary cannulation require high expertise and should be used mainly in high volume centers and only by endoscopists who achieve the standards of quality as proposed by international societies [35].

There are certain limitations, related to both the network analysis, as well as individual studies, which merit further discussion. First, the paucity of direct head-to-head trials for certain comparisons, resulted in low to very low quality evidence for comparative efficacy of the different methods. It should be noted that multiple indirect comparisons in absence of head-to-head trials can lead to weak conclusions that can sometimes be erroneous, specifically concerning the interpretation of the SUCRA ranking. Moreover, the EUS-RV technique was supported by only two single-center RCTs and further evidence is needed to strongly recommend this approach. Second, network meta-analyses may be subject to misinterpretation due to conceptual heterogeneity, related to considerable differences in participants, interventions, co-interventions/background treatment and outcome assessment, which may limit comparability of trials. We tried to minimize this conceptual heterogeneity by including studies with difficult biliary cannulation defined according to the currently accepted ESGE "5-5-2" rule [6], with some slight deviations in some RCTs. Moreover, we applied a sensitivity analysis restricted only to those studies with a stricter compliance to the aforementioned validated definition of difficult cannulation. Unfortunately, a specific subgroup analysis based on the indication to ERCP or the methods to prevent PEP could not be feasible due to the lack of data.

Regarding limitations of individual studies, we acknowledge that most studies had a small sample size and a short length of follow-up, which prevented assessment of long-term safety of the investigated methods.

However, in spite of these limitations, this manuscript represents an updated network meta-analysis to assess methods applied in the management of difficult biliary cannulation, defined homogeneously as per current guidelines. While robust GRADE methodology demonstrated mainly a low level of evidence, we observed that the several techniques for difficult biliary cannulation show similar results although a trend in favour of needle knife techniques and EUS-RV was observed, particularly over those techniques which require direct manipulation of the PD. EUS-RV seems to decrease the risk of PEP, which in turn is higher with pancreatic guidewire and pancreatic stent assisted techniques. However, EUS-RV is an advanced technique requiring high endoscopy skills and it still not widely available. Given the low quality of evidence, further RCTs are needed to strengthen these results.

Author contributions

- Study concept and design: AF, GDA
- Acquisition of data: AF, GDA, MM, CC, MED
- Analysis and interpretation of data: AF, MM, LF, IB, JDM, MS
- Drafting of the manuscript: AF, SFC, LF, GDA
- Revision of the manuscript for important intellectual content: MS, ES, ADA, JS, JD, AA
- Approval of the final manuscript: all the authors
- Guarantor of the article: AF

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Declaration of competing interest

Authors declare no conflict of interests for this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.11.010.

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