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Performance and safety of percutaneous cholangioscopy: a systematic review and meta-analysis

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Abstract

Background Percutaneous cholangioscopy (PerC) offers an alternative for patients with an inaccessible biliary tree. This systematic review and meta-analysis aimed to evaluate the performance of this technique.

Methods A search in Medline, Cochrane and ClinicalTrials.gov databases was performed for studies assessing PerC up to October 2022. The primary outcome was diagnostic success, defined as successful stone identification or stricture workup. Secondary outcomes included therapeutic success (stone extraction, stenting) and complication rate. A subgroup analysis compared previous-generation and modern cholangioscopes. We performed meta-analyses using a random-effects model and the results were reported as percentages with 95% confidence interval (CI).

Results Fourteen studies (682 patients) were eligible for analysis. The rate of diagnostic success was 98.7% (95%CI 97.6-99.8%; I^2=31.19%) and therapeutic success was 88.6% (95%CI 82.8-94.3%; I^2=74.92%). Adverse events were recorded in 17.1% (95%CI 10.7-23.5%; I^2=77.56%), of which 15.9% (95%CI 9.8-21.9%; I^2=75.98%) were minor and 0.6% (95%CI 0.1-1.2%; I^2=0%) major. The Spyglass system showed null heterogeneity for all outcomes; compared with older-generation endoscopes it offered comparable diagnostic success, but yielded significantly superior therapeutic success (96.1%, 95%CI 90-100%; I^2=0% vs. 86.4%, 95%CI 79.2-93.6%; I^2=81.41%; P=0.02].

Conclusion PerC, especially using currently available cholangioscopes, is associated with high diagnostic and therapeutic success.

Keywords Cholangioscopy, percutaneous cholangioscopy, surgically altered anatomy

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Introduction

Access to the proximal biliary tree, for example above the liver hilum, may be precluded by pathology or previous surgery, even if biliary access can be achieved via endoscopic retrograde cholangiopancreatography (ERCP). ERCP, especially since the introduction of single operator cholangioscopy (SOC) into clinical practice, allows directly guided diagnostic and therapeutic manipulations in the biliary tree, increasing the successful cannulation of intrahepatic ducts [1-4]. Nevertheless, access to the intrahepatic ducts, especially when affected by strictures or stones, can be difficult. The concomitant manipulation of the duodenoscope, the cholangioscope and the through-the-scope devices makes these ERCP procedures challenging, and they are graded at the highest level within the Schutz classification [5].

Although the standard endoscopic approach of intubation of the alimentary tract to reach the biliary tree is effective in the great majority of situations, the development of percutaneous cholangioscopy (PerC) facilitates new perspectives in biliary endoscopy. An anterograde approach, introduced in the 1980s [6], can overcome the anatomical obstacles discussed above. Although the potential benefits of PerC were evident

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from the beginning, technical and equipment challenges have delayed the wide adoption of the technique, even in specialist centers. Since 2007, the availability of digital SOC (Spyglass-Legacy -DS, -DS2; Boston Scientific Inc., USA), and more recently a dedicated SOC for percutaneous use (Spyglass Discover; Boston Scientific Inc., USA), accompanied by dedicated diagnostic and therapeutic devices, has reinvigorated the field of PerC. Nevertheless, no distinct and cumulative data exist to assess the efficacy and the potential risks of this procedure. The aim of this systematic review and meta-analysis is to present the accumulated evidence about PerC, to evaluate its ability to provide clinical answers and therapeutic results, and to assess the rate of adverse events.

Materials and methods

Our research was based on a detailed study protocol, which was registered in the international prospective platform for systematic reviews (PROSPERO Registration Number: CRD42022385604). The concept and structure of our presented data were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary Table 1) [7].

Inclusion and exclusion criteria

The primary question of this review was based on the PICO framework and included the assessment of PerC in terms of diagnostic and therapeutic success, and adverse events [8]. Case series or cohorts evaluating this modality were included in the final analysis when the following prerequisites were met: (A) Patients: adult patients (>18 years old), with indication for biliary intervention/assessment, not amenable to ERCP or after failed attempts at ERCP, using (B) Interventions: percutaneous cholangioscopy, following initial biliary access under radiological guidance; (C) Comparators: no comparisons were feasible, given the design of existing studies in the literature; and (D) Outcomes: diagnostic success, as indicated by previous cross-sectional imaging (computed tomography or magnetic resonance cholangiopancreatography); for stones, the direct visualization of the stones and for strictures the successful workup of the stenosis based on optical features, pathology results after biopsy, and follow up; therapeutic success where indicated, with stone clearance or stent placement; the rate of adverse events. Case reports and studies with incomplete data were excluded from our analysis.

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Search strategy

An initial search was performed using PubMed/MEDLINE, Cochrane and ClinicalTrials.gov Databases, through 25th October 2022. The search algorithm included the following Boolean search terms: *"cholangioscopy" OR "percutaneous cholangioscopy" OR "anterograde cholangioscopy" OR "percutaneous choledochoscopy"*. Additional relevant articles were hand-searched in the reference lists of the retrieved publications as well as by using the "similar article" function within PubMed. Unpublished works, abstracts, and oral or poster presentations were excluded. In case of missing data, the first and/or the corresponding authors were contacted. Two investigators (AP, PG) independently selected articles of interest based on the aforementioned inclusion and exclusion criteria. In cases of multiple publications from the same study, only the most recent and complete article was included.

Data abstraction and quality assessment

Data on study-, participant- and intervention-related parameters were retrieved into a standardized form by 2 investigators (AP, KB) independently; discrepancies were resolved by consensus, referring to the original article, after consultation with a third reviewer (PG). The quality of the included studies was assessed by 2 authors independently (DR, GT) using the National Heart, Lung, and Blood Institute tool for case series that allows evaluation of cohort studies without a comparator [9].

Outcomes

The primary outcome of our meta-analysis was the diagnostic success, as defined above. The secondary outcomes included: 1) therapeutic success; and 2) rate of adverse events (including percutaneous access and cholangioscopy), interpreted as minor (post-procedural pain, infection, minor bleeding) or major (perforation, significant bleeding requiring blood products and/or additional interventions, pancreatitis, or unplanned hospital admission related to the procedure).

Statistical analysis

Pooled proportions and 95% confidence intervals (CIs) were calculated using the Der Simonian and Laird random-effects model, which incorporated both between-study and within-study variation [10]. Heterogeneity between study-specific estimates was assessed using the inconsistency index (I^2), and cutoff points of <30%, 30-59%, 60-75% and >75%

were considered to suggest low, moderate, substantial and considerable heterogeneities, respectively [11]. A subgroup analysis was conducted to assess the potential differences between previous-generation cholangioscopes and the more recently developed digital SOC (Spyglass- DS, -DS2; Boston Scientific Inc, USA), and their impact on heterogeneity. All results were compared between the subgroups to investigate statistically significant differences. Publication bias was estimated by assessing the funnel plot for primary outcome [12]. For all analyses, a P-value of <0.05 was considered statistically significant. The analyses were performed using R packages [13].

Quality of evidence

The quality of the provided evidence was rated based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) criteria [14].

Results

Characteristics of included studies

The initial literature search yielded 469 studies. After application of the exclusion criteria, 14 studies (682 patients) were eligible for inclusion [15-28]. Fig. 1 shows the PRISMA flowchart and Table 1 summarizes the main characteristics of the included studies. Only 1 study was prospective, comparing 2 different old-generation cholangioscopes [25], 1 retrospective compared PerC with double balloon enteroscopy [18], 5 were retrospective cohorts [15,16,20,21,23] and 7 case series [17,19,22,24,27-29]. It is noteworthy that the vast majority of patients (607/682, 89.0%) came from Asian countries.

The male-to-female ratio was 1.2:1 and the age ranged between 18 and 94 years. Ninety-three of the 569 that provided the data (16.3%) had surgically altered anatomy, and 4 cases (0.7%) had duodenal stricture, thereby not allowing conventional ERCP. In 21 cases (3.6%), at least 1 attempt to perform ERCP was made, albeit unsuccessfully. Interestingly, 469 cases (82.4%) primarily underwent PerC because of intrahepatic lithiasis. Regarding biliary pathologies, 68.3% (466 cases) had biliary stones, with 398 (85.4%) of the cases related to stones above the liver hilum. Stricture workup was the indication in 385 patients (56.5%), and some patients had more than 1 indication.

Quality assessment

Thirteen studies were graded to have good quality and 1 fair. The most common shortcoming was the absence of a detailed description of the statistics used, reflecting the fact that many studies were case series [16,17,19,21-23,26,28]. One study was graded as fair regarding quality [17], because of the absence of details regarding the included cases. Nevertheless, the presented results of all studies were adequate for our analysis (Supplementary Table 2).

Primary outcome – diagnostic success

The cumulative diagnostic success rate of PerC was 98.7% (95%CI 97.6-99.8%; 666/682; I^2=31.19%), with low heterogeneity (Fig. 2).

Secondary outcomes

Therapeutic interventions were indicated in 503 (73.8%) cases, and were successful in 88.6% of them (95%CI 82.8-94.3%; 420/503; I^2=74.92%) (Supplementary Fig. 1).

Adverse events

Adverse events were described in 17.1% of cases (95%CI 10.7-23.5%; 114/682; I^2=77.56%) (Fig. 3). Most of these (15.9%) were minor (95%CI 9.8-21.9%; 108/682; I^2=75.98%), whereas major complications accounted for 0.6% (95%CI 0.1-1.2%; 6/682; I^2=0%) (Supplementary Fig. 2). The most common adverse event was infection (75/682, 11%), including cholangitis, hepatic abscess and sepsis. Importantly, 2 deaths due to septic cholangitis were recorded, in a study with 45 infectious complications [23]. Considering cases with severe bleeding, 2 patients bled from the created fistula tract, requiring embolization. A bile leak was recorded in 5 cases. In 1 case, severe pain caused the procedure to be discontinued and repeated under general anesthesia.

Subgroup analysis

Subgroup analysis for the primary outcome resulted in similar diagnostic success between previous-generation cholangioscopes and the Spyglass (98.7%, 95%CI 97.4-100% and 95.7% (95%CI 90.5-100%, respectively), with null heterogeneity for both subgroups and a non-significant difference (P=0.72) (Supplementary Fig. 3A). On the other hand, the comparison regarding therapeutic success revealed a statistically significant difference (P=0.02) with old-generation cholangioscopes having a success rate of 86.4% (95%CI 79.2-93.6%; I^2=81.41%), which was inferior to the Spyglass 96.1% (95%CI 90-100%; I^2=0%) (Supplementary Fig. 3B). Although the overall percentage of adverse events in the Spyglass subgroup (8.2%, 95%CI 1.3-15.1%; I^2=0%) was lower than in the old-generation group (19.9%, 95%CI 11.8-27.9%; I^2=84.8%), the difference did not reach significance (P=0.18) (Supplementary Fig. 3C).

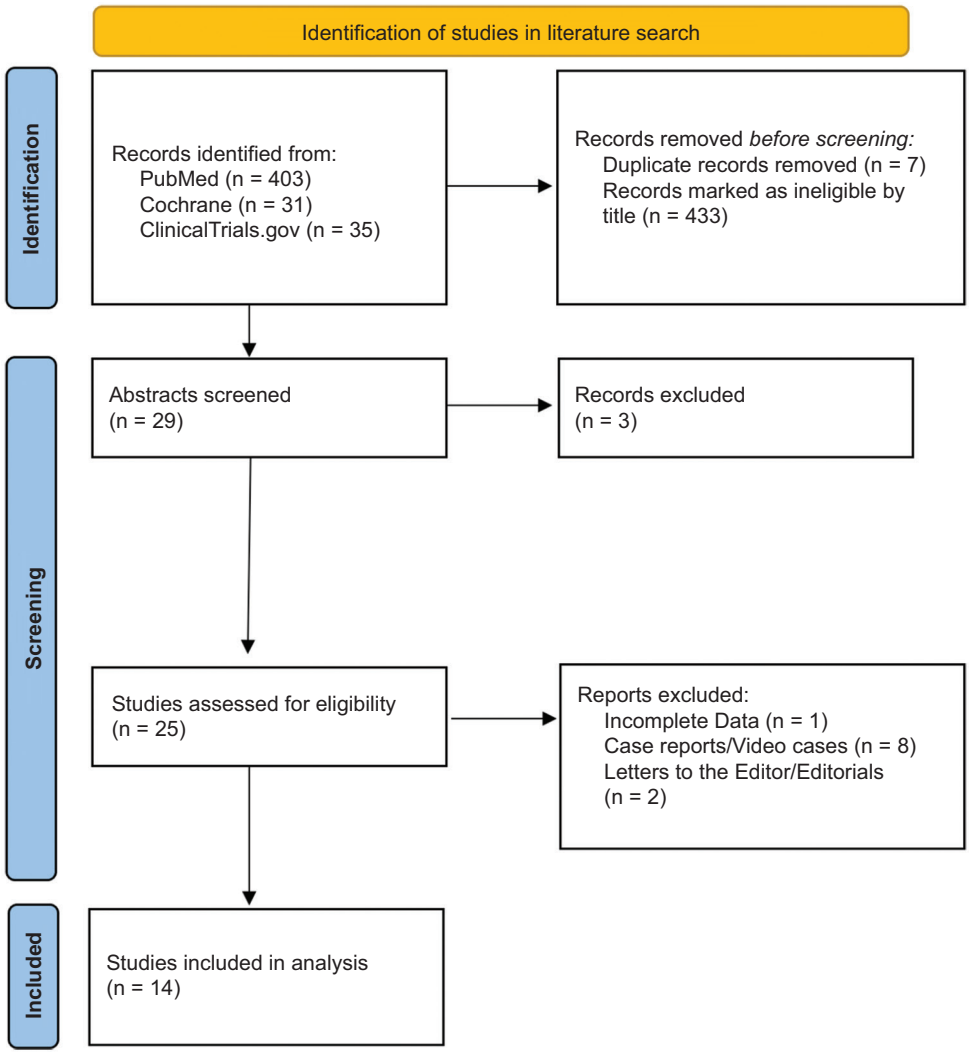

Figure 1 Study flowchart

Quality of evidence

Given that all of the included studies were observational, the quality of evidence was rated as low. No reasons for further downgrading were recognized. Therefore, based on the meta-analysis, the low quality of evidence supported the comparisons among the presented modalities.

Publication bias

The funnel plot considering the primary outcome is presented in Supplementary Fig. 4, and the apparent symmetry indicates the absence of publication bias.

Discussion

This review and meta-analysis is the first to assess the performance of PerC. Interestingly, PerC provided high rates of diagnostic success by recognizing biliary stones or assessing strictures in 98.7% (95%CI 97.6-99.8%) of the cases. This high rate was evident in both previous-generation and currently used cholangioscopes, thus providing a promising approach in patients with difficult biliary access. Moreover, this technique yielded high therapeutic success rates, with the most widely used recently-developed digital cholangioscopes providing significantly (P=0.017) superior therapeutic success, with no heterogeneity, compared with the previous-generation cholangioscopes.

Although PerC was introduced more than 3 decades ago, only 1 study exists comparing this technique with alternative endoscopic approaches. Tsutsumi *et al* [18] compared double-balloon enteroscopy (DBE)-assisted ERCP with PerC (using the CHF-240; Olympus Medical Systems, Tokyo, Japan) in patients with biliary stones in the setting of previous hepaticojejunostomy. PerC achieved access in all 8 cases, whereas the site of anastomosis could not be reached in 3/32 patients who underwent DBE. Although complete stone clearance was achieved in 100% of patients who underwent PerC, compared to 93% with DBE, this

Table 1 Main characteristics of included studies

Study data						Demographics		Reason for PerC			
Study [ref.]	Year of publication	Design	Country	Recruitment period	Number of patients	Mean age ± SD (or range)	Sex (female, %)	Surgically altered anatomy (%)	Unsuccessful ERCP (%)	Duodenal obstruction (%)	First choice (%)
Wang *et al* [25]	2016	Prospective comparative study	China	2007-2014	118	55.5 (21-94)	62 (52.5%)				118 (100%)
Tripathi *et al* [26]	2020	Case series	USA	n/a	5	63.4 (52-78)	1 (20%)	5 (100%)			
Van Steenbergen *et al* [28]	1996	Case series	Belgium	1993-1996	14	74 ± 9	n/a	4 (28.6%)	1 (7.1%)		9 (64.3%)
Yeh *et al* [23]	1995	Retrospective cohort	Taiwan	1980-1992	165	47.9 (21-80)	93 (56.4%)				165 (100%)
Tao *et al* [27]	2021	Case series	China	2014-2018	14	44 ± 15.1	4 (28.6%)	14 (100%)	9 (64.3%)		
Chon *et al* [22]	2021	Case series	Korea	2019-2020	13	71.4 [53-83]	6 (46.2%)	13 (100%)			
Hatzidakis *et al* [21]	2000	Retrospective cohort	Greece	1998-2000	21	61 (44-80)	10 (40.0%)		n/a		
Lee *et al* [20]	2001	Retrospective cohort	Korea	1993-1997	92	52.3 (24-82)	57 (62.0%)		n/a		
Nam *et al* [24]	2016	Case series	Korea	1992-2016	15	52 (14–64)	4 (26.7%)	15 (100%)	9 (60%)		
Gerges *et al* [16]	2021	Retrospective cohort	Germany, France, Italy, Argentina	2015-2020	28	63 (± 19)	11 (39.3%)	23 (82.1%)	1 (3.6%)	4 (14.3%)	
Jung *et al* [15]	2007	Retrospective cohort	South Korea	2000-2005	177	59.38 (23-81)	48 (27.2%)				177 (100%)
Tsutsumi *et al* [18]	2017	Retrospective comparative study	Japan	2001-2008	11	65 (30-81)	7 (63.7%)	11 (100%)			
Bhandari *et al* [19]	2016	Case series	India	2012-2015	5	29.6 (18-40)	1 (20%)	5 (100%)			
Du *et al* [17]	2015	Case series	Canada	n/a	4	60.8 (28-75)	2 (50%)	3 (75%)	1 (25%)		

(Contd...)

Table 1 *(Continued)*

Study data						Indication for PerC				Type of cholangioscope	Sheath diameter (Fr)
Study [ref.]	Year of publication	Design	Country	Recruitment period	Number of patients	CBD stones (%)	Intrahepatic stones (%)	Biliary stricture (%)	Other (%)		
Wang *et al* [25]	2016	Prospective comparative study	China	2007-2014	118		118 (100%)	81 (68.6%)		Old-generation	16-18
Tripathi *et al* [26]	2020	Case series	USA	n/a	5	4 (80%)		3 (60%)		SpyglassDS	12
Van Steenbergen *et al* [28]	1996	Case series	Belgium	1993-1996	14	11 (78.6%)		3 (21.4%)		Old-generation	18
Yeh *et al* [23]	1995	Retrospective cohort	Taiwan	1980-1992	165		165 (100%)			Old-generation	16
Tao *et al* [27]	2021	Case series	China	2014-2018	14	12 (85.7%)		14 (100%)		Old-generation	14-16
Chon *et al* [22]	2021	Case series	Korea	2019-2020	13	8 (61.5%)		5 (38.5%)		SpyglassDS	12
Hatzidakis *et al* [21]	2000	Retrospective cohort	Greece	1998-2000	21	9 (42.9%)	1 (4.8%)	10 (47.6%)	1 (4.8%)	Old-generation	12
Lee *et al* [20]	2001	Retrospective cohort	Korea	1993-1997	92		92 (100%)	76 (82.6%)		Old-generation	16-18
Nam *et al* [24]	2016	Case series	Korea	1992-2016	15	1 (6.7%)	10 (66.7%)	3 (20.0%)	1 (6.7%)	Old-generation	16-18
Gerges *et al* [16]	2021	Retrospective cohort	Germany, France, Italy, Argentina	2015-2020	28	12 (42.9%)	7 (25%)	9 (32.1%)		SpyglassDS	12
Jung *et al* [15]	2007	Retrospective cohort	South Korea	2000-2005	177			177 (100%)		Old-generation	16-18
Tsutsumi *et al* [18]	2017	Retrospective comparative study	Japan	2001-2008	11	11 (100%)				Old-generation	10-18
Bhandari *et al* [19]	2016	Case series	India	2012-2015	5		5 (100%)			SpyglassDS	14
Du *et al* [17]	2015	Case series	Canada	n/a	4			4 (100%)		SpyglassDS	18

PerC, percutaneous cholangioscopy; SD, standard deviation; ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct

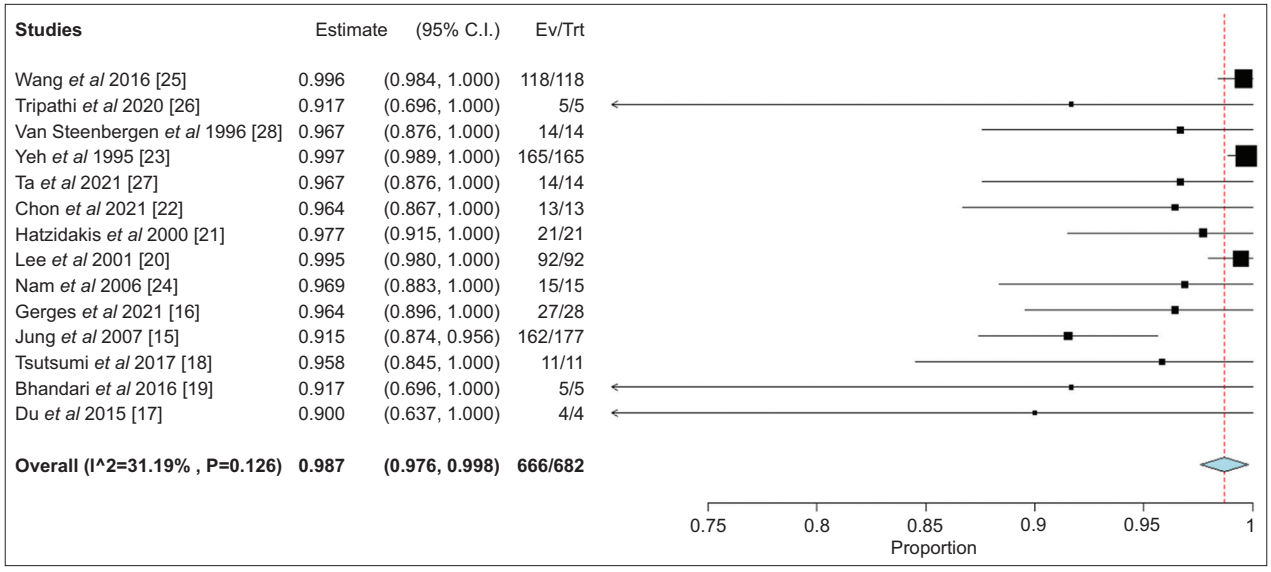

Figure 2 Forest plot reporting pooled results of the meta-analysis concerning diagnostic success rate

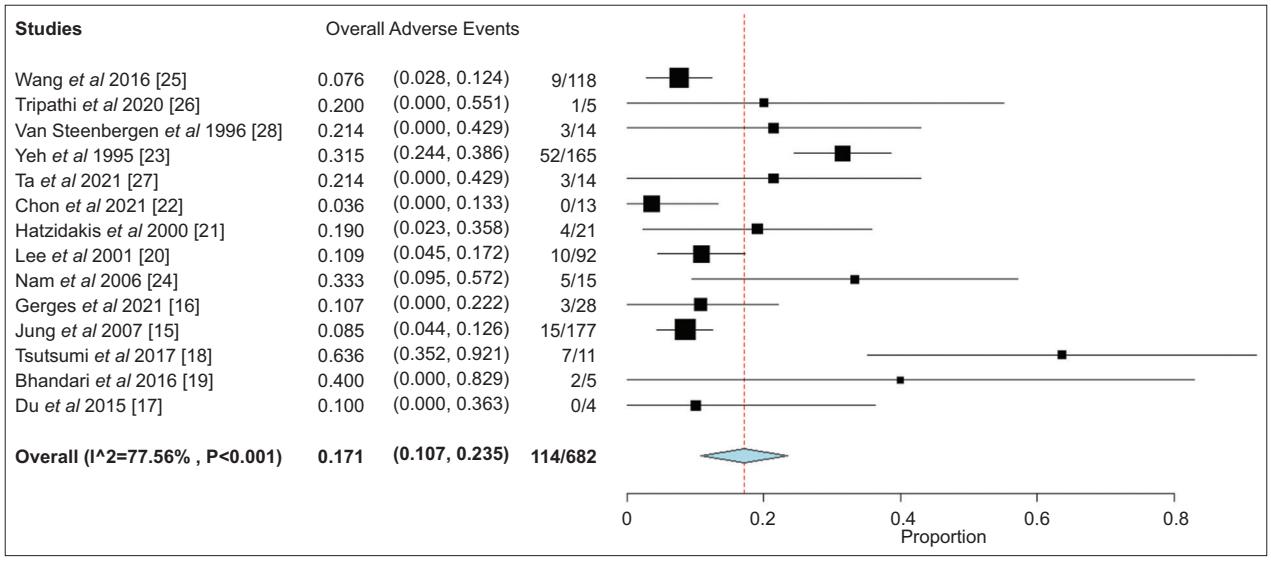

Figure 3 Forest plot reporting pooled results of the meta-analysis concerning adverse events rate

difference was not significant. On the other hand, all the PerC cases warranted more than 1 session, differing significantly from the DBE group, where the therapeutic result could be achieved mainly in 1 session. The success of DBE-assisted ERCP in this study is significantly higher than other studies, as intention to treat [30]. In addition, the performance of advanced therapeutic techniques (e.g., SOC for stone fragmentation) may be particularly challenging via DBE. Finally, adverse events were recorded in 45% of PerC cases compared to 10% of DBE, with 4/5 of complications in the PerC group being infections. Given the limitations of the aforementioned study, a comparison of the current PerC approach with alternative techniques would be of particular worth. In the absence of such studies, an indirect comparison of our subgroup analysis results with emerging data on alternatives, at least for the final therapeutic outcome, indicates a rate of 96.1% (95%CI 90-100%) for PerC, which is comparable to EDGE (97.9%, 95%CI 96.3-99.4%) and laparoscopy assisted-ERCP (98.5%, 95%CI 97.8-99.2%), and seems superior to EA-ERCP (69.1%, 95%CI 65.3-72.9%), although this comparison is arbitrary, needing large-scale studies at least to be confirmed [30].

A point of particular interest in this study is the rate of adverse events. Although PerC combines 2 techniques, percutaneous transhepatic tract formation and then cholangioscopy, the reported complications seem to be more commonly related to cholangioscopy. Given the well-recognized increased risks of percutaneous tract formation [31], it is likely that in the published retrospective series, patients who suffered significant complications (e.g., bleeding) did not proceed to cholangioscopy, and so cases in which a percutaneous transhepatic biliary tract could not be established are unlikely to have been included in

studies of PerC. Postprocedural infections represented 65.8% of all complications, and most of them (93.3%) were recorded in older studies using the previous-generation, reusable cholangioscopes. The explanation for this is uncertain, but may relate to a less rigorous focus on perioperative antibiotics and maintaining optimal biliary drainage peri/post-PerC in the past (including perhaps a lower threshold for percutaneous transhepatic biliary drain insertion post procedure). It might reflect the evolution and optimization of hygiene in endoscopy and the introduction of single-use disposable devices in the environment of the biliary tree [32,33]. Infection associated with reusable endoscopes has been widely reported and may be reduced/avoided with single-use endoscopes [34,35], although problems related to antibiotic prophylaxis and inadequate biliary drainage are much more likely culprits. Moreover, current guidelines recommending the use of antibiotic prophylaxis in all patients undergoing cholangioscopy and PerC did not cover the entire timeframe of included studies [36,37]. The creation of the percutaneous transhepatic tract represents a potentially traumatic part of the procedure and both severe bleeds presented in the included studies were associated with this [38,39]. Larger sheath insertion may tamponade bleeding [28] and lead to cessation in some cases, whereas embolization may be necessary in others. Outside the field of PerC, percutaneous transhepatic cholangiography is reported to be associated with significant bleeding (including pseudoaneurysm formation) in 2.5% of cases [40]. Notably absent from reported complications in these studies was procedure-related pancreatitis. Although the risk of pancreatitis following hepaticojejunostomy would be expected to be zero with PerC, other PerC involving intact biliary anatomy and any manipulation of instruments (e.g., wire, cholangioscope) or other material (e.g., stones) across the ampulla would be expected to carry a risk of procedure-related pancreatitis, as previously reported [41].

The introduction of the digital Spyglass SOC (Boston Scientific Inc., USA) in 2007, initially for ERCP, but adaptable for PerC, motivated endoscopists to reintegrate PerC into the management of complex biliary disease. A bespoke, shorter (65 cm) cholangioscope for percutaneous use (Spyglass Discover, Boston Scientific Inc., USA) was introduced in 2020. These narrower-caliber (10 Fr) cholangioscopes have an advantage in requiring only a 11-12-Fr tract channel/sheath compared to the 16-18-Fr sheaths used for old-generation endoscopes (Table 2). The 4-directional control, 120° tip deflection, digital quality imaging and availability of through-the-scope equipment may provide further diagnostic and therapeutic benefits. However, Spyglass cholangioscopy yielded significantly better therapeutic success rates, considering treatment targets and null heterogeneity for all outcomes, thus implying a stable performance among the studies. Another point of comparison could be the sessions required to achieve the planned effect for the studied subgroups. Although the existing studies do not provide enough data for comparison, Chon *et al* [22] concluded that for Spyglass a mean of 2 sessions of PerC were necessary, compared to a mean of 5.12 sessions with an old-generation cholangioscope [23]. The explanation for this is uncertain, but might relate to the use of narrower-caliber 10-Fr cholangioscopes, allowing greater scope maneuverability and facilitating access to smaller bore ducts [42-44].

PerC is a demanding and complex procedure, with a couple of prerequisites that have to be fulfilled. As a hybrid method, it generally requires the availability of both an interventional radiologist and an experienced biliary endoscopist (unless one individual is experienced in both). Another consideration is the presence of accessible (and usually dilated) intrahepatic ducts and a safe window for initial percutaneous puncture and cholangioscope insertion [45,46], and the decision to proceed with PerC should be based on a multidisciplinary team consensus. The most common practice has been for tract creation and PerC to take place in different sessions, although a single-session approach (with percutaneous transhepatic tract formation and cholangioscopy in the same procedure) does not seem to impact on safety and performance, as indicated by Tao *et al* in one of the included studies [27].

Despite its originality, this study had some limitations. The most significant is the design of the included studies, especially considering case series and sample size. Moreover, all studies but one were retrospective, thus increasing the risk of unknown variables affecting the results. This is reflected in our GRADE assessment, where the summary of evidence is classified as having low quality. Secondly, the technical success, the site of percutaneous access (right vs. left), the size of the punctured intrahepatic duct and the location of the targeted pathology could have an impact on the outcomes, but details of the pathology (e.g., stone size/number) were incomplete and did not allow further subgroup analyses. The inclusion of studies over a wide time period (1995-2021) may have had an effect on some results, due to potential differences in periprocedural approach and standard-of-care measures, such as use of antibiotics, endoscopy facilities and sanitization processes, and case record/reporting tools. For example, the fact that the percentage of PerC as a first-choice procedure represented the vast majority of cases

Table 2 Types of cholangioscopes available for percutaneous use

Cholangioscope	Manufacturer	Fibre-optic/ digital	Deflection	Length (cm)	Diameter (mm)	Working channel (mm)	Irrigation/ suction system	Single vs. multiple use
SpyGlass Discover	Boston Scientific	Digital	4-ways	65	3.5	1.2	Dual	Single use
SpyGlass DS	Boston Scientific	Digital	4-ways	230	3.5	1.2	Dual	Single use
CHF-CB30L\S	Olympus	Fibre-optic	2-ways	101	2.8	1.2	Single	Multiple use
CHF-V	Olympus	Fibre-optic	2-ways	380	4.8	2	Single	Multiple use
FCP-9P	Pentax Medical	Fibre-optic	2-ways	218	3.1	1.15	Single	Multiple use

(even in the presence of apparent intact foregut/biliary anatomy), and was much higher than patients with altered anatomy, was probably the result of inclusion of older studies, when current techniques, such as peroral SOC (and even ERCP in the early 1980s), were not widely available. Another factor that could have influenced our results is the experience of endoscopists in SOC (whether peroral or percutaneous). Until 2007, virtually the only experience endoscopists had with performing cholangioscopy was as part of (probably very infrequent) percutaneous procedures, using endoscopes not specifically designed for the purpose. Since the introduction of peroral SOC, endoscopists likely to be performing PerC have developed significant experience in diagnostic and therapeutic cholangioscopy, which is readily transferable to PerC, using very similar equipment. However, the absence of good comparative studies does not allow direct and reliable comparisons between PerC approaches and non-percutaneous approaches to biliary intervention. Nevertheless, given the fact that all of those procedures are elective and have limited availability among centers, it is difficult to design and conduct prospective, comparative studies, especially considering the particular subgroup of patients with altered anatomy.

The re-introduction of PerC into endoscopic practice provides an important tool in the management of complex biliary disease, with high rates of diagnostic and therapeutic success, albeit with a considerable rate of adverse events. Emerging improvements in cholangioscopes and assisting devices will facilitate a more effective and safer treatment approach for the diagnosis and management of biliary disease in patients with challenging anatomy.

Summary Box

What is already known:

- Biliary interventions in patients with surgically altered anatomy is challenging
- Advanced endoscopic techniques may allow improved access to the area of the ampulla, although they require high expertise and are associated with considerable side-effects
- Percutaneous access combined with cholangioscopy provides an alternative; however, no cumulative data on efficacy exist

What the new findings are:

- Percutaneous cholangioscopy (PerC) provides high rates of diagnostic and therapeutic success for biliary diseases
- The new-generation digital cholangioscopes are superior to the old-generation in terms of therapeutic efficacy
- When the percutaneous tract is established, PerC is associated with low rates of adverse events

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Supplementary material

Supplementary Table 1 PRISMA 2020 checklist of the presented objects in this review

Section and Topic	Item #	Checklist item	Reported (Yes/No)
		TITLE	
Title	1	Identify the report as a systematic review.	YES/p1
		BACKGROUND	
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	YES/p2
		METHODS	
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	YES/p2
Information sources	4	Specify the information sources (e.g., databases, registers) used to identify studies and the date when each was last searched.	YES/p2
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	YES/p2
Synthesis of results	6	Specify the methods used to present and synthesise results.	YES/p2
		RESULTS	
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	YES/p2
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	YES/p2
		DISCUSSION	
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g., study risk of bias, inconsistency and imprecision).	YES/p3
Interpretation	10	Provide a general interpretation of the results and important implications.	YES/p3

Study checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	Page 1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pages 2-3
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pages 5-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 6
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 8

(Contd...)

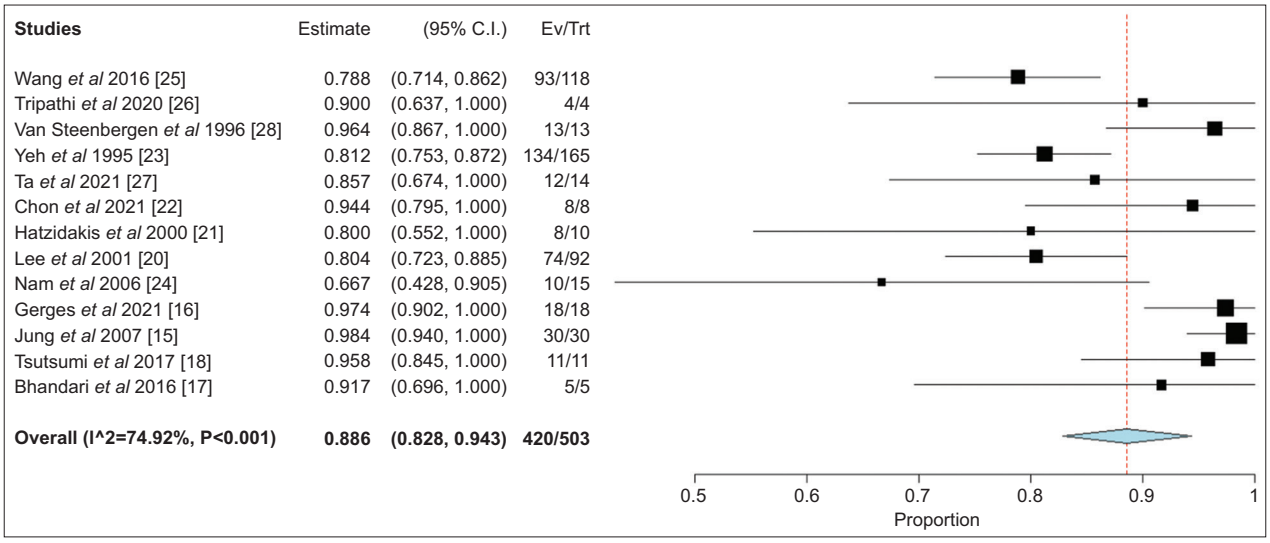
Supplementary Table 1 *(Continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7-8
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	Page 9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	Page 9
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 10, Fig. 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 10, Fig. 1
Study characteristics	17	Cite each included study and present its characteristics.	Page 10, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Pages 11 and Supplementary Table 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	Pages 10-11

(Contd...)

Supplementary Table 1 *(Continued)*

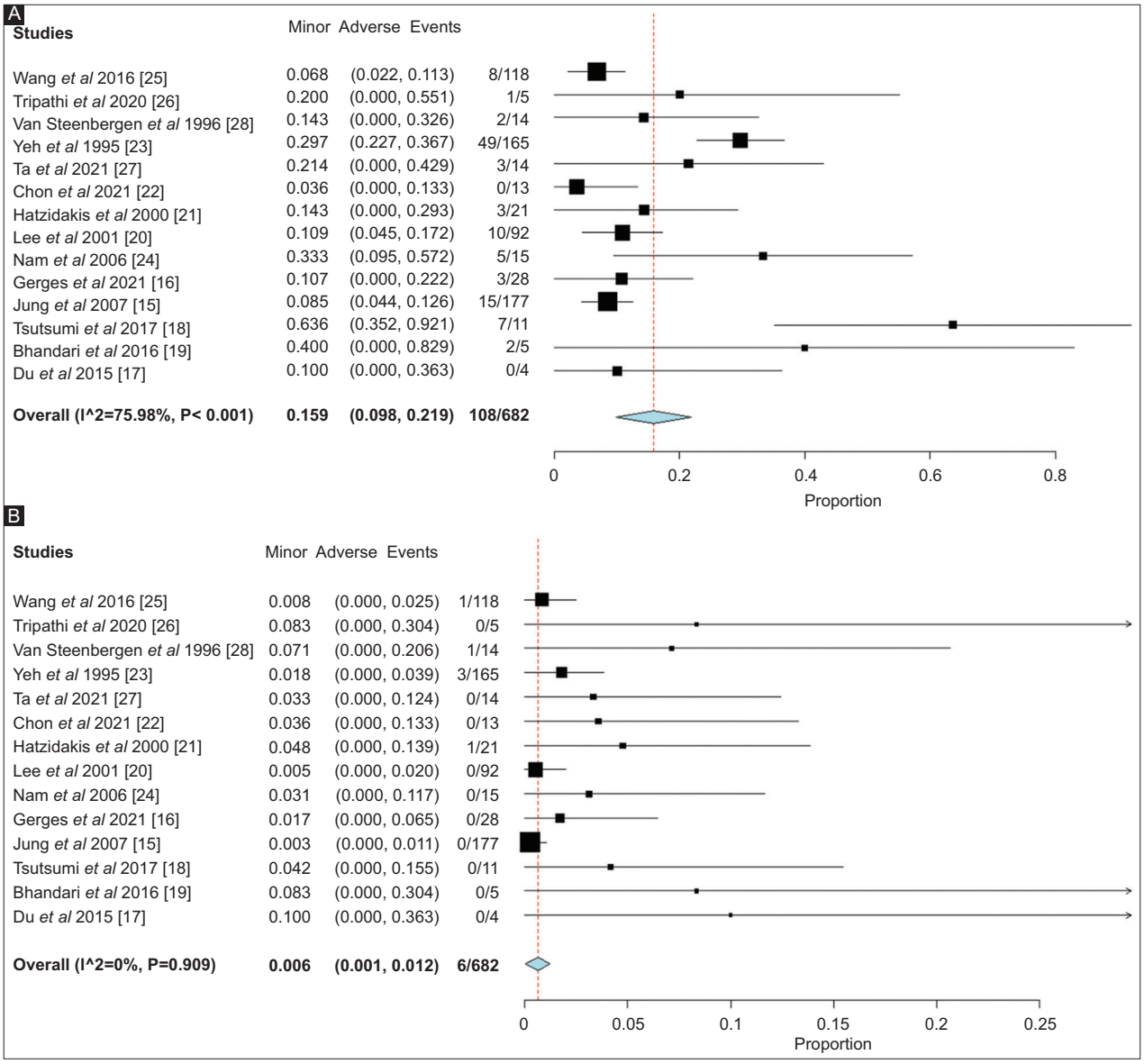
Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 11, Supplementary Table 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 11, Fig. 2,3 and Supplementary Fig. 1,2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 12, Supplementary Fig. 3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 12 Supplementary Fig. 4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 13-17
	23b	Discuss any limitations of the evidence included in the review.	Page 16
	23c	Discuss any limitations of the review processes used.	Page 16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 13-17



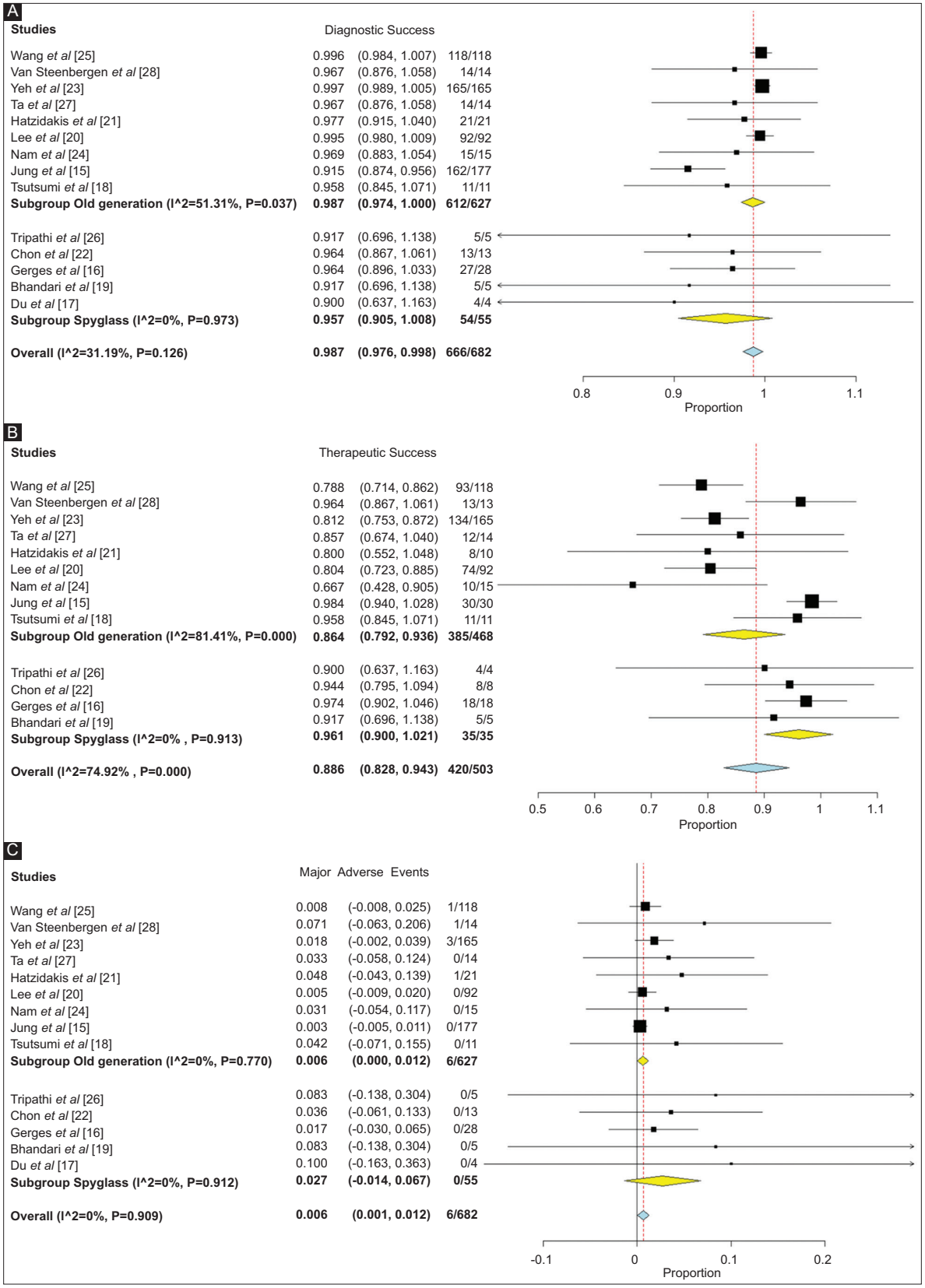
Supplementary Figure 1 Forest plot reporting pooled results of the meta-analysis concerning therapeutic success rate

Supplementary Table 2 The results of quality assessment based on the National Heart, Lung, and Blood Institute tool for case series

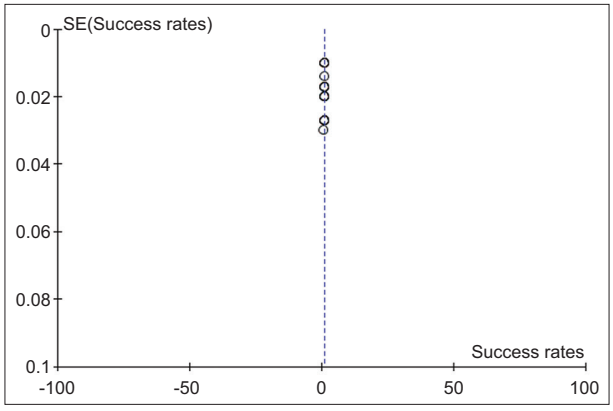
Studies	Quality assessment									
Author, year [ref.]	Was the study question or objective clearly stated?	Was the study population clearly and fully described, including a case definition?	Were the cases consecutive?	Were the subjects comparable?	Was the intervention clearly described?	Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the length of follow up adequate?	Were the statistical methods well-described?	Were the results well-described?	Quality rating (Good, Fair, Poor)
Wang *et al* [25]	YES	YES	YES	YES	YES	YES	YES	YES	YES	GOOD
Tripathi *et al* [26]	YES	YES	YES	YES	YES	YES	YES	N/A	YES	GOOD
Van Steenbergen *et al* [28]	YES	YES	YES	YES	YES	YES	YES	N/A	YES	GOOD
Yeh *et al* [23]	YES	YES	YES	YES	YES	YES	YES	NO	YES	GOOD
Tao *et al* [27]	YES	YES	YES	YES	YES	YES	YES	YES	YES	GOOD
Chon *et al* [22]	YES	YES	YES	YES	YES	YES	YES	N/A	YES	GOOD
Hatzidakis *et al* [21]	YES	YES	YES	YES	YES	YES	YES	NO	YES	GOOD
Lee *et al* [20]	YES	YES	YES	YES	YES	YES	YES	YES	YES	GOOD
Nam *et al* [24]	YES	YES	YES	YES	YES	YES	YES	YES	YES	GOOD
Gerges *et al* [16]	YES	YES	YES	YES	YES	YES	YES	N/A	YES	GOOD
Jung *et al* [15]	YES	YES	YES	YES	YES	YES	YES	YES	YES	GOOD
Tsutsumi *et al* [18]	YES	YES	YES	YES	YES	YES	YES	YES	YES	GOOD
Bhandari *et al* [19]	YES	YES	YES	YES	YES	YES	YES	N/A	YES	GOOD
Du *et al* [17]	YES	NO	N/A	YES	YES	YES	YES	N/A	YES	FAIR



Supplementary Figure 2 Forest plots reporting pooled results of the meta-analysis concerning (A) minor adverse events rate and (B) major adverse events rate



Supplementary Figure 3 Forest plots of the subgroup analysis (old-generation cholangioscopes vs. Spyglass) reporting pooled results: (A) diagnostic success rate, (B) therapeutic success rate, and (C) adverse events rate



Supplementary Figure 4 Funnel plot reporting publication bias of the analysis concerning the primary outcome of diagnostic success rate