SYSTEMATIC REVIEW AND META-ANALYSIS

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Effectiveness of Plastic Stent for the Treatment of Incomplete Clearance of Common Bile Duct Stone: A Systematic Review and Meta-analysis

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ABSTRACT

Background & Aims: Common bile duct stones (CBDs) can typically be treated by endoscopic retrograde cholangiopancreatography (ERCP) in 85–90% of cases. However, in the remaining 10–15% of patients, bile duct stones cannot be extracted. In such cases, the placement of a temporary biliary plastic stent is recommended.
Methods: We conducted a systematic review and meta-analysis (PROSPERO registration number: CRD42023459712; October 2023). An electronic search was carried out using the following databases: PubMed/MEDLINE, Scopus, and CENTRAL (last search: October 20, 2023). All published studies (both randomized clinical trials and non-randomized interventional studies) involving patients who had undergone ERCP for CBDs with incomplete biliary clearance were included. The risk of bias was assessed using the RoB 2.0 and ROBINS-I tools. The confidence in network meta-analysis tool was employed to estimate each study's contribution matrix within the network estimate.
Results: Twenty papers (comprising 902 patients) were selected for qualitative and quantitative synthesis and were included in the standard meta-analysis, while only five studies (254 patients) were used for the network meta-analysis. The pooled success rate of stenting intervention in difficult choledocholithiasis was 79% (95% CI:71-87%). In the network meta-analysis model, ursodeoxycholic acid and single or double stenting resulted in a higher probability of being the most effective treatments.
Conclusions: In cases of incomplete CBD clearance, the insertion of a temporary plastic stent achieves complete clearance in 79% of patients. Although not significantly superior in indirect comparison with stent alone, the adjunctive treatment with ursodeoxycholic acid appears to be the most likely to succeed.

Key words: endoscopic retrograde cholangiopancreatography – ERCP – common bile duct stones – ursodeoxycholic acid – UDCA – biliary stone – biliary stent.

Abbreviations: CBD: common bile duct; CBDs: CBD stones; DASE: dilation assisted stone extraction; EHL: electrohydraulic lithotripsy; ERCP: endoscopic retrograde cholangiopancreatography; EPLBD: endoscopic papillary large balloon dilatation; ESGE: European Society of Gastrointestinal Endoscopy; NMA: network meta-analysis; NRSI: non-randomized studies of intervention; OR: odds ratio; RCT: randomized clinical trial; REML: restricted maximum likelihood; SUCRA: surface under the cumulative ranking curve; UDCA: ursodeoxycholic acid.

INTRODUCTION

Gallstones are a prevalent issue in Western countries, with a prevalence of 6-9%. However, only 20-25% of gallstones become symptomatic over a person's lifetime, with an annual incidence of 2-3% per year [1-3].

The association with symptomatic gallstone-related disease is frequently due to their migration into the common bile duct (CBD). In cases of common bile duct stone (CBDs) migration, endoscopic retrograde cholangiopancreatography (ERCP) should be offered to both symptomatic and asymptomatic patients [4].

An ERCP with an adequate endoscopic sphincterotomy obtains a complete biliary clearance in about 85-90% of the patients [5]. However, in the remaining 10–15% of patients, bile duct stones cannot be extracted through ERCP because of several conditions: larger (≥ 15 mm) calculi, shortness (≤ 36 mm) and narrow angle (≤ 135°C) of distal CBD, impacted calculi and anatomical difficulties [6]. These are known as 'difficult' CBDs and cannot be removed using standard techniques.

Alternative interventional methods such as endoscopic papillary large balloon dilatation (EPLBD), mechanical lithotripsy, cholangioscopy with laser lithotripsy or electrohydraulic lithotripsy (EHL) can remove 90% of them [7]. In the case of irretrievable CBD stones, the guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) recommend the endoscopic placement of a temporary biliary plastic stent, to avoid stone impaction and prevent cholangitis and pancreatitis [4]. In addition, it probably decreases the stone size by causing friction between the stent and the CBDs, which can enhance the success rate of the subsequent ERCP [8]. Numerous non-randomized studies, both prospective and retrospective, have investigated the role of indwelling plastic stent in reducing the number and the size of CBDs with conflicting results [9-11].

The low cost and relative safety of this procedure represent two undeniable advantages. Moreover, the minimal time required for stent placement, compared to more advanced but costlier and time-consuming techniques, is another important consideration in the management of CBDs. Specifically, for high-risk patients (such as the elderly, those with numerous comorbidities, acute suppurative cholangitis, or in a state of shock), lengthy ERCP procedures may be unsafe and are not recommended [4].

Although few studies have investigated the effectiveness of plastic stents for the treatment of difficult common bile duct stones, the published data are highly heterogeneous, and the true efficacy of stent placement remains uncertain.

We conducted a systematic review and meta-analysis to elucidate the efficacy of plastic stents for the treatment of difficult CBDs.

METHODS

Protocol and Registration

This systematic review and meta-analysis were performed following a protocol designed a priori (PROSPERO n: CRD42023459712; October 2023) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [12].

No patient was involved in the conduction of the present study. No patient and public involvement has been planned or sought in the conduction of this systematic review.

Search and Selection Process

An electronic search for relevant publications (without language restriction or date of publication restriction) was performed by two investigators (S.F. and G.S.). Studies were identified using the following database: PubMed/MEDLINE, Scopus, and CENTRAL (data of last search 20/10/2023 – Supplementary file, Table I).

Each of the relevant publication (previous review articles and included studies) reference sections and Google Scholar was also screened for other applicable publications.

Clinical Trial.gov was investigated to find unpublished completed trials. Relevant abstracts from United European Gastroenterology week conference and Digestive Disease Week were also screened.

Eligibility Criteria and Data Items

All published studies, both randomized clinical trial (RCT) and non-randomized studies of intervention (NRSI) including patients who had undergone ERCP for CBDs with incomplete biliary clearance were included.

Observational studies (case reports, case series and single-arm retrospective studies) were considered in the synthesis, but only studies with experimental design were used in network meta-analysis (NMA) synthesis.

Inclusion criteria were: a) patients ≥ 18 year-old with CBD undergone ERCP; b) patients with irretrievable biliary stone and incomplete biliary drainage after endoscopic sphincterotomy and attempt of CBDs removal (ballon, basket, lithotripsy, and dilation assisted stone extraction (DASE) were allowed); c) plastic stent positioning after the first procedure; d) Second ERCP attempt for CBD clearance after at least 4 weeks.

Exclusion criteria were a) biliary malignant obstruction; b) other type of biliary benign or malignant stenosis: c) data concerning CBD clearance obtained after multiple ERCP.

All data was recorded independently by two literature reviewers (A.C. and S.F.) in separate databases and was compared at the end of the reviewing process to limit selection bias. The database was also reviewed by the senior author.

For each study\arm included, the following items were sought for retrieval: location and timespan of the study, study design, occurrence of prior lithotripsy or DASE, usage of UDCA, treatment type (single/double stenting), stenting type (standard straight/pigtail); number of included patients, number of clinical successful cases. A successful case was defined as complete clearance at the second ERCP.

Outcome of Interest and Synthesis Methods

The primary outcome was the success rate (computed as the rate of success cases over the total included patients) in achieving complete clearance of the CBD at the second ERCP.

As a secondary outcome, we aim to assess the most effective procedure among the studies, including a comparison between different arms (single stent, double stent, and UDCA treatment).

As suggested by Warren et al. [13], a series of random effects NMAs, increasing in complexity, were performed. The simplest model implemented, combining evidence from all retrieved studies, consisted in a point estimate of overall success rate for the intervention in each study/arm, unadjusted for potential covariates (Model A). Then, a classical subgroup analysis was employed, comparing usage of UDCA versus stenting alone (Model B). Finally, Model C consisted in comparison between all possible combinations of intervention type (single/double stenting) and UDCA, thus generating a network of 4 distinct treatment options.

A random-effects, restricted maximum likelihood (REML) model was used, considering the possibility of unidentified\ unclassified sources of variance among studies. For the model A and B, pooled success rate was used as summary measure. For the Model C, where comparison between different arms were involved, odds ratio (OR) was used to determine the most effective procedure. Treatment rankings and surface under the cumulative ranking curve (SUCRA) values were also computed and used for synthesis and recommendations.

For all analysis, as suggested by Weber et Al., continuity correction was used in case of 0% or 100% success rate, by adding an adding 0.5 to all cells of only those 2 × 2 tables containing at least one zero cell [14].

Stata® SE v.17.0 (College Station, TX: StataCorp LLC) software was used for analysis, and statistical significance level was set at $\alpha = 0.05$.

Risk of Bias Evaluation

Two authors (A.V. and F.I.) independently assessed the risk of bias in included studies. For included RCT, Risk of Bias was evaluated using RoB-2 tool [15]. For non-randomised retrospective studies, ROBINS-I tool was used instead [16]. Publication bias, which may affect the cumulative evidence estimates, was investigated using funnel plots and Egger's test [17]. Confidence in NMA (CINeMA) tool was used for estimating each study contribution matrix within the network estimate [18]. Inconsistency has been evaluated by calculating the I^2 statistic, which quantifies the proportion of variation in the point estimates due to differences between studies [19, 20]. Indirectness was addressed by defining population and treatment options, proceeding to progressive subgroup analysis, and excluding studies with missing information in the NMA.

Sensitivity and Subgroup Analyses

Subgroup analysis concerning the type of stent (standard straight vs pigtail) and the adjunctive treatment with UDCA vs stent alone was planned per protocol strategy.

For the primary outcome, a sensitivity analysis was planned by excluding all the included papers with a high risk of bias. Moreover, a trim and fill test was performed to detect and adjust for potential publication bias [21].

RESULTS

Of the 1685 articles identified via electronic search, 20 (including 902 patients) were selected for qualitative and quantitative synthesis. All the 20 studies were used for the standard meta-analysis, while only 5 (including 254 patients) were used for NMA [9, 10, 22-24]. Fig. 1 depicts the study selection process.

Three RCTs and 17 NRSI (two prospective and 15 retrospective) were included [8, 11, 23-37]. Among the included studies, nine allowed UDCA treatment, while 7 did not. The characteristics of the 20 selected studies, and the details of outcome measures are shown in Table I. The characteristics of excluded studies are summarized in Supplementary file, Table II in the appendix section.

Pooled success rate of stenting intervention in the incomplete clearance of CBDs is synthetized in Fig. 2 (Model A). Overall, success rate was 79% (95%CI: 71-87%). As expected, given the differences in treatment types, high heterogeneity was found (I^2=91.9%).

Subsequently, Model B was explored by comparing UDCA vs stenting alone (Fig. 3). Heterogeneity was only slightly lower among the UDCA group (I^2=76.28%). However, the pooled success rate was sensibly higher among UDCA studies, with a closer distribution (82%, 95%CI: 74-90%), compared with stenting alone (77%, 95%CI: 63-91%). Although the direction of the effect points towards UDCA supplementation, the difference between the two groups is not statistically significant (p = 0.58).

Model C also includes the stenting strategy (single vs double stenting and standard straight vs pigtail). The successful rate was 0.82 (95%CI: 0.72-0.92) and 0.88 (95%CI: 0.74-1.00) in the single and double stent group, respectively. Among the studies including patients treated with pigtail, the successful rate was 0.84 (95%CI: 0.76-0.91) while it was 0.88 (95%CI: 0.82-0.93) in the group treated with standard straight plastic stent (Fig. 4).

Most of the studies were focused either on single stenting vs UDCA supplementation, or on single vs. double stenting; no study compared Single + UDCA vs. Double + UDCA. The NMA model reported lack in connection among several nodes (Supplementary file, Fig. 1). Therefore, Model C was proposed for NMA, including 5 studies with at least two arms compared.

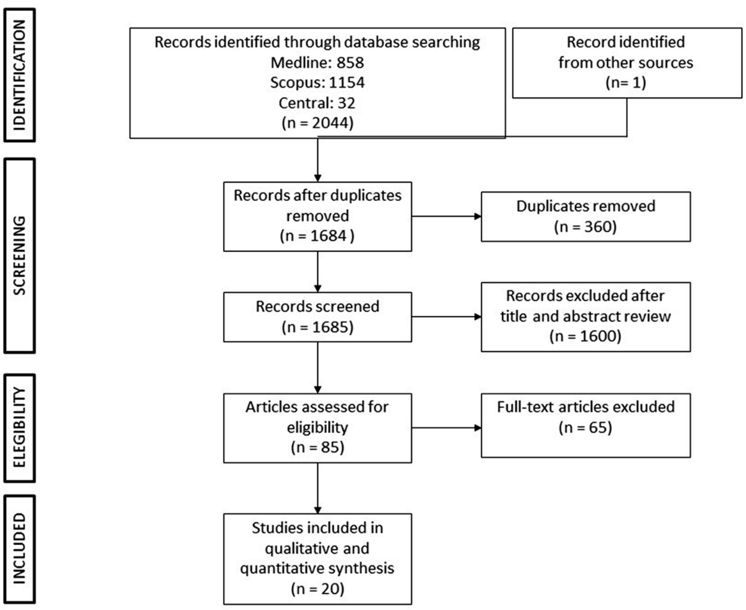

Fig. 1. Flowchart of study selection process.

Table I. Included studies

Study (Year)Country	Treatment	Type of stent	Included patients/ successful clearance (%)	CBDs Size	Definition of difficult CBDs
			RCTs		
Katsinelos (2008) A Greece [10]	UDCA plus single stent	Standard/ Bend	21/16 (76,20)	1.65 ± 0.76*	Not be removed by standard techniques and mechanical lithotripsy
Katsinelos (2008) B Greece [10]	Single stent	Standard/ Bend	20/15 (75)	1.64 ± 0.82*	
Lee (2011) A South Korea [9]	UDCA plus double stent	Pigtail	25/19 (76)	2.47 ± 0.38*	≥20 mm or > 3 and smallest ≥15 mm not removable by standard techniques, mechanical lithotripsy and DASE
Lee (2011) B South Korea [9]	Double stent	Pigtail	24/14 (58)	2.25 ± 0.76*	
Hormati (2020) A Iran [22]	Single stent	Standard/ Bend	32/27 (84.4)	3.22 ± 1.31*	≥15 mm and/or > 3 not removable by standard techniques
Hormati (2020) B Iran [22]	UDCA plus single stent	Standard/ Bend	32/30 (93.80)	4.09 ± 1.87*	
			NRSI		
Ismael AE (1994) – Retrospective Hong Kong [25]	Single stent	Standard/ Bend	15/15 (100)	n.a.	≥20 mm
Kubota Y (1994) – Retrospective Japan [26]	Both single and double	Pigtail	25/19 (76)	3.2 (2-5)**	Incomplete stone extraction (fragile patients)
Maxton DG (1995) – Retrospective U.S.A. [27]	UDCA plus both single	Pigtail	79/50 (63)	n.a.	Incompleate clearence with standard thecniques
Goh J (1997) A‡ - Retrospective Ireland [24]	Single stent	Not specified	22/3 (13,6)	n.a.	Incompleate clearence with standard thecniques
Goh J (1997) B‡ - Retrospective [24] Ireland	UDCA plus single stent	Not specified	16/14 (87.50)	n.a.	Incompleate clearence with standard thecniques
Chan (1998) – Retrospective Hong Knong/U.S.A. [11]	Single stent	Standard/ Bend	28/25 (89)	2.49 (1.1-4.6)**	Poor access (BII anatomy), not engaged by basket or packed stones in CBD; large stone > 2 cm
Jain (2000) – Prospective U.S.A. [28]	Single stent	Pigtail	17/15 (88.20)	1.7 (1-4)**	Not removed by sphincterotomy and balloon extraction (Mechanical lithotripsy was not available
Katsinelos (2003) – Retrospective Greece [29]	Single stent	Both standard and pigtail	25/11 (44%)	2.4 (1.4-4.2)**	Incompleate clearence with standard thecniques and mechanical lithotripsy
Han (2009) – Prospective South Korea [30]	UDCA plus single stent	Standard/ Bend	28/26 (92.80)	2.16 ± 0.62*	Incompleate clearence with standard thecniques and mechanical lithotripsy
Horiuchi (2010) – Retrospective Japan/U.S.A. [8]	Single stent	Pigtail	40/37 (93)	1.3 (0.5-2.5)**	Large ≥20 mm or multiple >3; fragile patients
Hong (2011) – Retrospective China [31]	Single stent	Standard/ Bend	52/49 (94.20)	1.66 ± 0.64*	Large ≥20 mm or multiple >3
Fan (2011) – Retrospective China/U.S.A. [32]	Both single and double	Standard/ Bend	45/32 (71.10)	2.26 (1.6-3.3)**	Large ≥15 mm; Incompleate clearence with standard thecniques and mechanical lithotripsy
Belvedere B (2012) – Retrospective Italy [33]	UDCA plus single stent	Standard/ Bend	48/41 (85.40)	n.a.	Incompleate clearence with standard thecniques and mechanical lithotripsy
Attaallah (2015) – Retrospective Turkey [34]	Single stent	Pigtail	43/37 (86)	1.5 (0.5-3.0)**	Incompleate clearence with standard thecniques and mechanical lithotripsy
Ye (2016) A – Retrospective China [23]	Single stent	Pigtail	32/34 (94.10)	1.74 ± 0.56*	Large ≥20 mm or multiple >3; Incompleate clearence with standard thecniques and mechanical lithotripsy

Table I (continued)

Ye (2016) B – Retrospective China [23]	Double stent	Pigtail	30/30 (100)	1.66 ± 0.47*	
Yüksel (2016) Turkey [35]	Both single and double	Both standard and pigtail	61/29 (47.50)	2 (0.8-4.2)**	Incompleate clearence with standard thecniques, mechanical lithotripsy and DASE
Jang (2020) Korea [36]	UDCA plus both single and double	Pigtail	85/55 (64.70)	2.20 ± 0.65*	large ≥20 mm) and/or multiple (≥3 and/or ≥15mm)
Meng (2023) China [37]	Single stent	Pigtail	57/51 (89.50)	1.95 ± 0.543*	single stone diameter ≥ 15 mm or ≥ 3 stones with diameters ≥ 10 mm

CBDs: common bile duct stones; RCT: randomized controlled trial; NRSI: non-randomized study of intervention; UDCA: ursodeoxycholic acid; DASE: dilation assisted stone extraction; ‡: Abstract; *: mean cm ± standard deviation; **: mean cm (range); ¶: data derived from the paper; BII: Bilroth II.

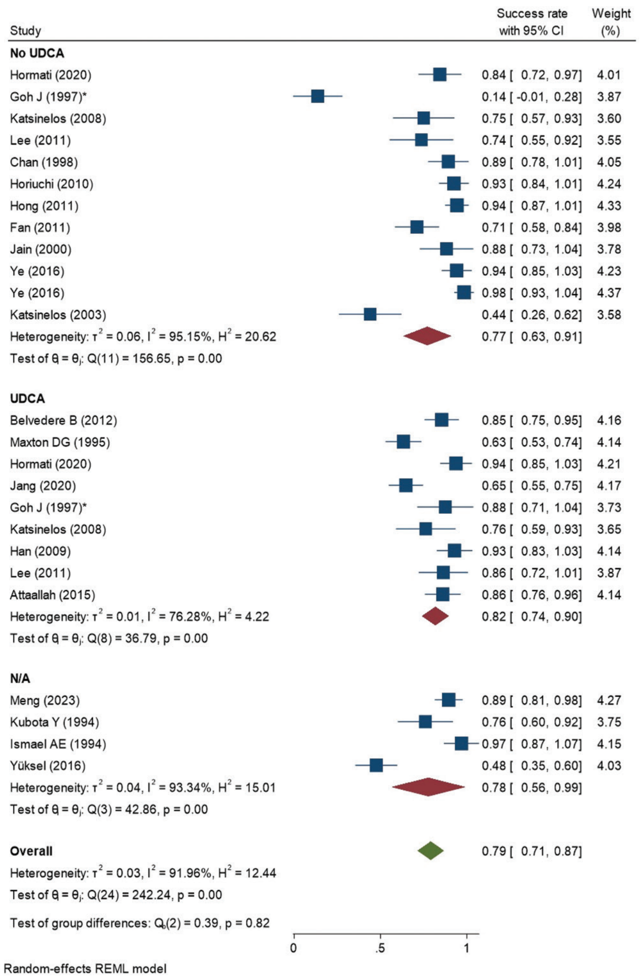

Fig. 2. Pooled success rate of stenting in the incomplete clearance of common bile duct stones.

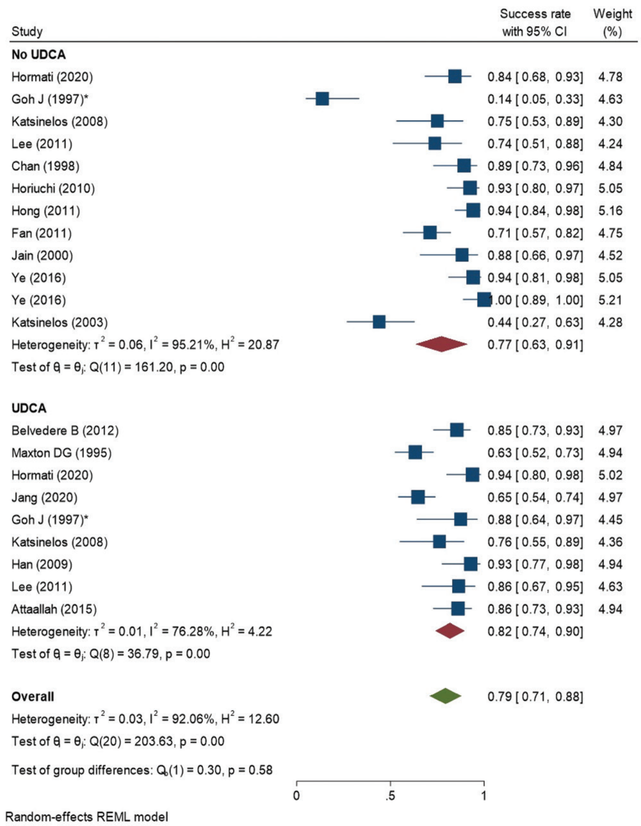

Fig. 3. Success rate of common bile duct (CBD) stones clearance in Ursodeoxycholic Acid (UDCA) user vs stent alone.

No source of inconsistency was found in the network model thus inconsistency was not investigated.

Arm comparison among the different treatment groups are reported in Table II. Treatment with stenting alone results the worst among all the evaluated strategies. On the other hand, UDCA and single or double stenting results in higher changes of being the best possible treatments, as suggested by each treatment SUCRA values (Supplementary file, Fig. 2).

Data concerning the risk of bias for each included study are reported in Supplementary file, Figs. 3 and 4 in the appendix section.

Among the included RCTs two presented some concerns in at least one domine, while the other one has been evaluated as low risk of bias in all the domines. On the other hand, 12 NRSI presented a moderate risk of bias at the ROBIN evaluation and 3 and 2 have been respectively judged as low and high risk of bias.

During the evaluation of the funnel plot, evidence of publication bias was detected. To mitigate the risk of bias arising from potentially missing studies, a trim-and-fill analysis was conducted. The results from the trim-and-fill analysis indicated a success rate of 72% (95%CI: 65-89%) following

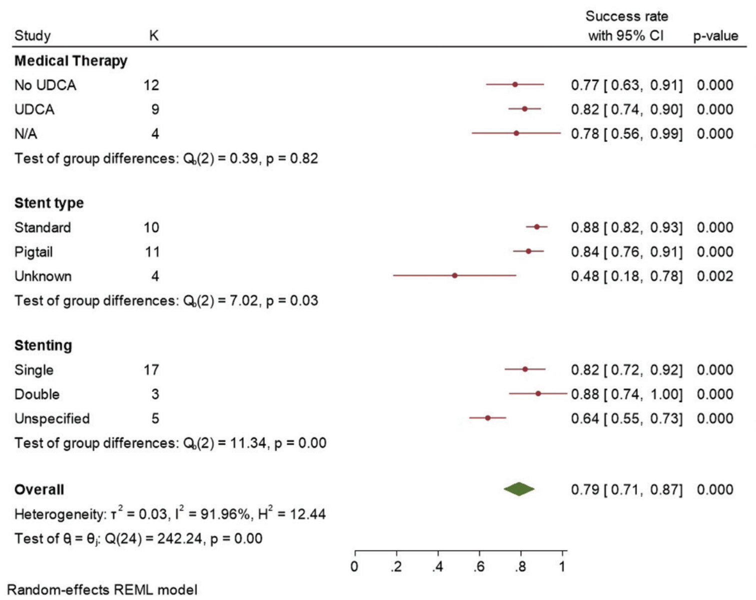

Fig. 4. Success rate of common bile duct (CBD) stones clearance among the evaluated subgroups.

the inclusion of 7 imputed studies (Supplementary file, Fig. 6). In the subgroup treated with stent alone, the pooled results after the inclusion of 3 hypothetical missing studies were 70% (95%CI: 57-83%) (Supplementary file, Fig. 7). No missing studies were found in the UDCA treated group (82%, 95%CI: 74-90%) (Supplementary file, Fig. 8).

To investigate the strength of the results, a sensitivity analysis excluding studies with a high risk of bias was performed for the primary outcome. After the exclusion of 2 NRSI, the pooled success rate was 0.78 % (95%CI: 0.70-0.86; I^2=92.33%) as shown in Supplementary file, Fig 5.

Table III show the main results of the meta-analysis regarding the certainty of the evidence and magnitude of the effect of the interventions examined.

DISCUSSION

In this meta-analysis, we evaluated the success rate of CBD stenting in achieving complete clearance of CBDs at the second ERCP in case of incomplete drainage at the first attempt. Regardless of the type of stent used and the concomitant treatment with UDCA, the overall success rate was 79% (95%CI: 71-87%; I^2=91.9%). The high heterogeneity observed in our primary outcome was primarily attributed to the UDCA treatment and the different types of stents employed.

In a subgroup analysis, the UDCA-treated group demonstrated a higher success rate of CBD clearance (82%, 95%CI: 74-90), whereas the pooled success rate was 77% (95%CI: 63-91) in the group that did not receive UDCA treatment.

The potential benefit of UDCA administration as an adjunctive treatment in cases of incomplete CBD clearance was further investigated through a subsequent NMA.

The NMA showed a higher probability of success in the UDCA group (irrespective of the stent strategy employed) compared to studies in which patients were treated with stenting alone (Table II).

The included studies exhibited considerable heterogeneity in their design details, particularly regarding the type of stent used and the adjunctive treatment with UDCA. Of note, the dosage of UDCA was similar among the studies that permitted this medical treatment (ranging from 600 to 900 mg), thereby not contributing significantly as a source of bias in this analysis.

The extensive temporal range of the included studies (from 1995 to 2023) could theoretically have influenced the heterogeneity observed in our primary outcome. However, the stringent inclusion criteria (incomplete clearance after endoscopic sphincterotomy and attempts with standard techniques such as basket or balloon) have, at least from a

Table II. Network Meta Analysis comparison among different treatment groups

	Treatment			
Comparator	A	B	C	D
A	.	4.692 (0.050, 436.731)	4.733 (0.545,41.071)	10.613 (0.031, 3667.340)
B	0.213 (0.002, 19.836)	.	1.009 (0.007, 153.039)	2.262 (0.057, 90.547)
C	0.211 (0.024, 1.833)	0.991 (0.007, 150.396)	.	2.242 (0.004, 1140.445)
D	0.094 (0.000, 32.557)	0.442 (0.11, 17.698)	0.446 (0.001, 226.827)	.

A: single stent; B: double stent, C: UDCA plus single stent; D: UDCA plus double stent

Table III. Summary of findings table

No of studies (Design)	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	N	Estimated success rate (%), (95% CI)	QoE	Comment
Success rate of stenting in Difficult Choledocholithiasis									
3 RCT 2 NRSI prospective 15 NRSI retrospective	Potential limitations are unlikely to lower confidence in the estimate of effect.	Substantial inconsistency	Indirectness in Interventions	No serious imprecision	Moderate Publication bias	896	79 (71-87)	Very low QoE ϴOOO	Stenting in CBDs results in high success rate thus is strongly recommended although the QoE is very low.
Success rate of stenting in Difficult Choledocholithiasis with or without UDCA treatment and different stent strategies									
3 RCT 2 NRSI – prospective 11 NRSI - retrospective	Potential limitations are unlikely to lower confidence in the estimate of effect.	Substantial inconsistency	Indirectness in Interventions	No serious imprecision	Undetected	601	NO UDCA: 77 (63-91) UDCA: 82 (74-90)	Low QoE ϴϴOO	UDCA in addition to stent positioning may result in an increase CBD clearance. Recommendation: Week for an intervention.
Single stenting vs UDCA supplementation on Single vs Double stenting									
3 RCT 2 NRSI - retrospective	Potential limitations are unlikely to lower confidence in the estimate of effect.	No serious inconsistency	No serious indirectness	Substantial imprecision	Undetected	248	SUCRA: UDCA + Double stenting: 0.7 UDCA + Single stenting: 0.6 Double stenting: 0.5 Single stenting: 0.2	Low QoE ϴϴOO	UDCA in addition to stent positioning may result in an increase CBD clearance. Recommendation: Week for an intervention.

N: number of included patients; CI: confidence Interval; NRSI: non-randomized study of intervention; RCT: randomized clinical trial; QoE: Quality of Evidence; UDCA: ursodeoxycholic acid.

clinical practice perspective, ensured the homogeneity of the evaluated treatment. Furthermore, the prevalence of NRSI and an underpowered NMA due to the scarcity of RCTs could have impacted the robustness of the secondary outcomes and cannot be overlooked.

Although clearance is achieved in the majority of patients undergoing ERCP, the presence of difficult CBDs often represents a challenging situation for biliary endoscopists [6].

Technological advancements have introduced numerous highly effective devices for the treatment of CBDs. Undoubtedly, endoscopic cholangioscopy is particularly appealing to therapeutic endoscopists, as the direct intraluminal view of the biliary duct system it provides enhances diagnostic and interventional possibilities. However, its high cost in terms of healthcare expenditure and time consumption necessitates its application in selected cases [38].

For these reasons, alternative therapeutic options must be often considered before in the therapeutic algorithm as suggested by the ESGE guidelines [4].

Although the insertion of plastic stents for difficult CBDs is a common therapeutic decision, robust data concerning its efficacy rate remain unknown. As reported in our meta-analysis, numerous heterogeneous studies have been conducted over the years, yielding a variety of results. Another highly relevant clinical issue evaluated in the meta-analysis was the administration of UDCA as an adjunctive therapy in this clinical setting. Robust data indicate that UDCA is not effective in preventing CBD recurrence in patients undergoing ERCP with complete clearance [39, 40]. Thus, this treatment is not suggested in the current European guidelines [4]. However, in cases of incomplete clearance, robust data were still lacking. The results presented in the meta-analysis, particularly in the NMA, indicated a high success rate in the group treated with both UDCA and stent compared to patients treated with stent alone. Undoubtedly, this meta-analysis presented a few limitations. First of all, the high heterogeneity among the included studies represents a non-negligible limit. Probably, the extensive temporal range among the studied included and the high prevalence of NRSI could significantly have contributed to this heterogeneity. Moreover, 12 of the NRSIs included presented a moderate risk of bias at the ROBIN evaluation. Finally, evidence of publication bias was detected in the funnel-plot evaluations. Despite notable limitations among the included studies, findings from all sensitivity analyses and the trim-and-fill test suggest the robustness of the reported results. In fact, after adjusting for potential missing data, the results consistently pointed in the same direction. No missing studies were found in the UDCA group, and a pooled success rate of 70% (95%CI: 57-83%) was assessed in the subgroup treated with stent alone after the inclusion of three hypothetical missing studies. Moreover, UDCA is a safe and cost-effective treatment, and its potential effectiveness in this clinical setting may be considered [41].

In case of incomplete endoscopic clearance of CBD stones, temporary plastic stent insertion achieves complete clearance in 79% of patients. Although the indirect comparison with stent alone was not statistically significant, adjunctive treatment with ursodeoxycholic acid appears to be the most likely to succeed.

Conflicts of interest: None to declare.

Authors' contribution: M.V. conceived of the work. M.V. and A.V. were responsible for the methodological assessment and statistical analysis. M.V and F.A drafted the manuscript. A.M., A.C. and S.F. extracted the data. S.F., G.S., and M.Mosca revised the literature. M.Magistroni and F.I. assessed the quality of evidence and data extraction. M.C, M.Magistroni and G.L. interpreted the data and criticaly revised the manuscript. All authors approved the final draft submitted. Each one of the authors was involved in the writing and revision of the manuscript.

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