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Systematic Review and Meta-Analysis: Risk of Post-ERCP Cholangitis with Air or CO_2 versus Contrast Cholangiography in Perihilar Malignant Biliary Obstruction

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Abstract

Background Endoscopic retrograde cholangiopancreatography (ERCP) may be associated with a risk of postprocedural cholangitis in case of failed drainage of the injected contrast. The present meta-analysis was conducted to assess whether air cholangiography reduces the risk of post-ERCP cholangitis compared with contrast injection.

Methods A comprehensive search of MEDLINE, EMBASE, and Science Direct from inception to September 2022 was done for studies comparing air or CO_2 and contrast agent for cholangiography during ERCP, with the last search on September 31, 2022. Dichotomous outcomes were analyzed using risk ratios (RRs) with 95% confidence intervals (CIs).

Results A total of seven studies were included in the final analysis. Among these, there were three randomized trials and four retrospective studies. The included studies had moderate to high risk of bias. There was no difference in the clinical success rate (RR: 1.02, 95% CI: 0.94–1.09; $I^2 = 0\%$), but a lower risk of all-cause adverse events (AEs) (RR: 0.21, 95% CI: 0.12–0.36; $I^2 = 0\%$) with air cholangiography, compared with contrast cholangiography. Concerning individual AEs, this difference was seen only for cholangitis (RR: 0.51, 95% CI: 0.37–0.69; $I^2 = 0\%$) but not for post-ERCP pancreatitis, perforation, and bleeding. Reintervention and 30-day mortality remained comparable between groups. The certainty of evidence remained low to very low.

Conclusion Air or CO_2 cholangiography reduces the risk of overall AE, especially post-ERCP cholangitis, compared with contrast cholangiography. Further trials are required to validate the findings of the study.

Keywords
- ERCP
- cholangitis
- air cholangiography
- Klatskin tumor
- meta-analysis

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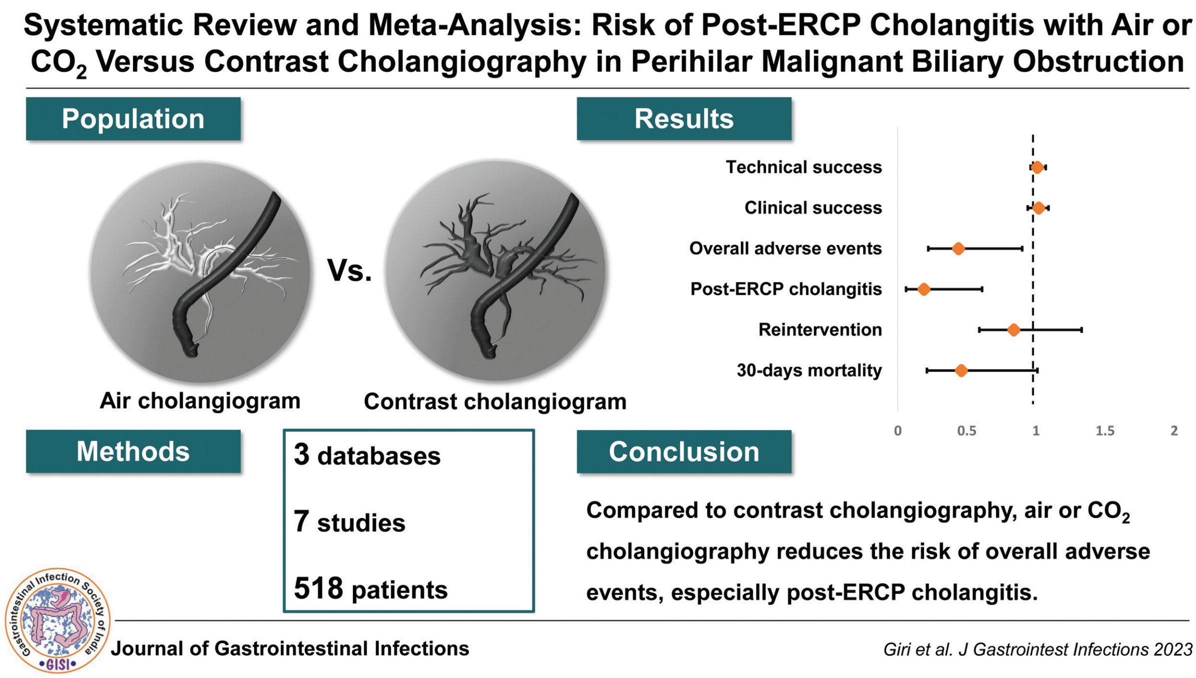

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is the procedure of choice for management of extrahepatic biliary obstruction. Proximal biliary obstruction is often secondary to perihilar cholangiocarcinoma, which portends a poor prognosis as compared with distal cholangiocarcinoma and is usually unresectable.[1] The incidence of post-ERCP cholangitis, especially in patients with Bismuth type IV hilar obstruction, is high despite the use of antibiotics.[2] Cholangitis is associated with significant morbidity and mortality and causes prolonged hospitalization, multiple interventions, and percutaneous biliary drainage.[3] It has also been observed that failure to drain the injected contrast completely during ERCP in such patients increases the risk of cholangitis.

In this regard, investigators have evaluated the utility of contrast-free methods, including air cholangiogram, in reducing the incidence of post-ERCP cholangitis compared with contrast injection.[4,5] In some studies, air cholangiography has been reported to be a safe and effective method for unilateral stenting in malignant hilar biliary obstruction.[6,7] In one study, no significant differences were reported between air and contrast cholangiography regarding technical and clinical success rates; however, a significantly lower incidence of cholangitis was observed with air cholangiography.[8] The feasibility and safety of CO_2 cholangiography have also been investigated.[9] Both CO_2 and air cholangiography have been shown to reduce the incidence of post-ERCP cholangitis compared with contrast injection.[9]

On the other hand, there have been reports of air embolism during ERCP during endoscopic insufflation due to intramural dissection of insufflated air into the portal venous system. It has been reported that the mortality from air embolism can reach up to 40%.[10,11] Therefore, as of now, the jury is still out on whether an air cholangiogram can be recommended instead of a contrast cholangiogram as a measure to reduce post-ERCP complications. The aim of the present systematic review and meta-analysis was to comprehensively summarize the current evidence comparing the incidence of adverse events (AEs) with contrast cholangiogram versus air cholangiogram in patients with malignant biliary obstruction.

Methods

Information Sources and Search Strategy

A comprehensive search of all suitable studies was conducted using the databases of MEDLINE, EMBASE, and Science Direct from inception to September 2022. The keywords used were: (Cholangiogram OR Cholangiography) AND (Air OR CO_2 OR 'Carbon dioxide') AND ERCP. The last search was conducted on September 31, 2022. To ensure that no potentially relevant items were overlooked, manual searching of reference lists of the included studies was also undertaken. The study methodology was designed and executed to adhere to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.[12]

Study Selection

The PICO criteria used for included comparative studies were: (1) Patients – malignant biliary obstruction; (2) Intervention – air or CO_2 cholangiogram; (3) Comparison – contrast cholangiogram; (4) Outcomes – all-cause AEs with individual AEs, technical and clinical success, reintervention, and 30-day mortality. Following the selection criteria above, the titles and abstracts of all studies were independently reviewed by two authors. A third reviewer resolved any disagreements. As long as the study outcomes are mentioned in the text, language was not restricted. The exclusion criteria used were: noncomparative studies, case series, and studies involving persons < 18 years of age.

Data Extraction

Two independent reviewers performed the data extraction, and a third reviewer resolved any disagreement. Data were collected under the following headings: study author and year, country of study, study design, number of patients, age and sex distribution, details of the lesion, type of intervention, and details of AEs.

Risk of Bias in Individual Studies

After data extraction, the same two reviewers performed a risk of bias (quality) assessment using validated tools. The Cochrane risk-of-bias tool was used for randomized controlled trials (RCTs),[13] and the Cochrane Collaboration's risk of bias in nonrandomized studies of interventions (ROBINS-I) tool for nonrandomized studies.[14]

Statistical Analysis

Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for all the dichotomous outcomes. Regardless of heterogeneity, the Mantel–Haenszel test for random effects was used. A Cochran's Q test and I^2 statistics were used to determine the heterogeneity between the studies. A p-value of Q test < 0.1 or I^2 value $> 50\%$ was considered to be significant. Visual inspection of funnel plots was used for publication bias assessment. The sensitivity analysis was performed using a leave-one-out meta-analysis, in which one study is excluded at each analysis to analyze each study's influence on the overall effect-size estimate and identify influential studies. RevMan software (version 5.4.1, Cochrane Collaboration) and STATA software (version 17, StataCorp., College Station, Texas, United States) were used for statistical analysis.

Results

Study Characteristics and Risk of Bias Assessment

A total of 1,097 records were identified with the above strategy, of which 859 records were screened after removal of duplicates. Finally, 7 studies were included in the meta-analysis.[7,8,15–19] ►**Fig. 1** shows the PRISMA flowchart for study selection, and inclusion process. ►**Table 1** summarizes

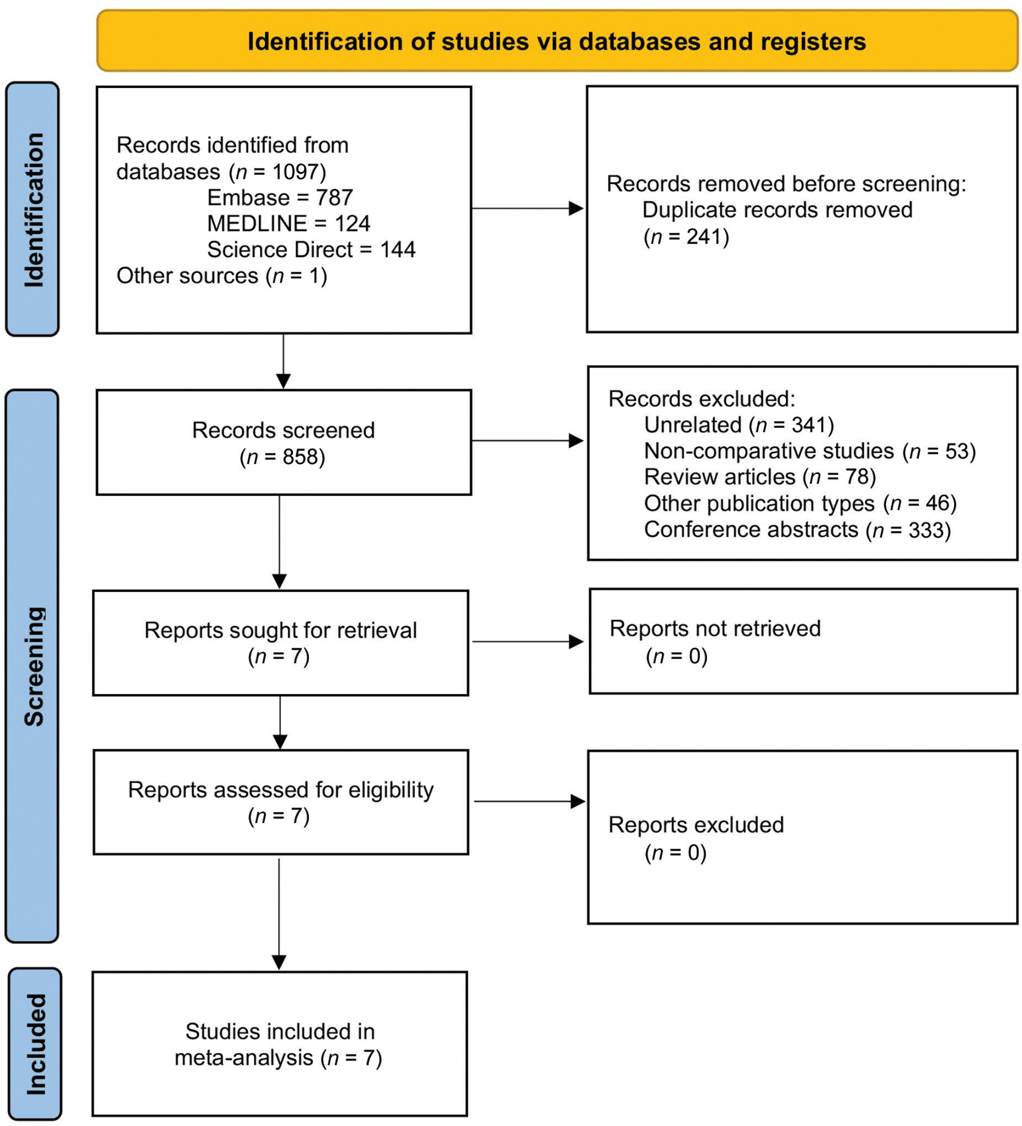

Fig. 1 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flowchart for study identification, selection, and inclusion process.

Table 1 Baseline characteristics of the included studies

Author, year	Country	Study design	Cholangiogram	No. of patients	Age	Male/Female	Diagnosis (CCA/GBC/O)	Bismuth III–IV	Stent	Follow-up duration
Pisello 2009[7,a]	Italy	Retrospective	Contrast	91	–	–	91/–/–	28 (30.8%)	Plastic	–
			Air (60–80 mL)	65	–	–	65/–/–	25 (38.5%)		
Zhang 2013[15,a]	China	RCT	Contrast	18	70.5 ± 8.5	12/6	10/3/5	9 (50%)	Uncovered metal stent	12 mo
			CO_2 (20–40 mL)	18	66.6 ± 10.5	10/8	12/3/3	12 (75%)		
Sud 2014[16,b]	India	RCT	Contrast	24	58.8 ± 10.6	13/11	6/17/1	4 (16.7%)	Uncovered metal stent	12 mo
			Air (10–15 mL)	25	55.4 ± 10.4	14/11	4/19/2	6 (24%)		
Lee 2016[8,b]	Korea	Retrospective	Contrast	24	68 (62–77)	15/9	12/11/1	19 (79.2%)	Uncovered metal stent	1 mo
			Air (10–15 mL)	23	69 (57–76)	13/10	12/7/4	18 (78.3%)		
Elshimi 2018[17,b]	Egypt	RCT	Contrast	40	55 ± 7	26/14	22/4/14	–	Plastic: 27, Metal: 13	1 mo
			Air (20–100 mL)	40	56 ± 8.5	28/12	20/4/16	–	Plastic: 29, Metal: 11	
Zhang 2020[18,b]	China	Retrospective	Contrast	22	57.7 ± 9.3	16/6	–	22 (100%)	Plastic	1 mo
			Air/CO_2 (10–15 mL)	18/30	58.5 ± 12.3	33/15	–	48 (100%)		
He 2022[19,b]	China	Retrospective	Contrast	45	61.6 ± 14.0	30/15	–	38 (84.4%)	Plastic stent ± ENBD tube	1 mo
			Air (10–15 mL)	35	64.5 ± 11.0	25/10	–	26 (74.3%)		

Abbreviations: ENBD, endoscopic nasobiliary drainage tube; RCT, randomized controlled trial; CCA, cholangiocarcinoma; GBC, Gall Bladder cancer; O, Others.
[a]Prophylactic antibiotics not given.
[b]Prophylactic antibiotics given.

the baseline characteristics of the studies included in the meta-analysis. Except for two studies,[7,17] the rest were from Asia.[8,15,16,18,19] Three studies were RCTs, while four were retrospective studies. One study used CO_2,[15] one used both air or CO_2,[18] and the rest five used air for cholangiography in the intervention group.[7,8,16,17,19] The most common etiology for perihilar malignancy was cholangiocarcinoma, followed by gallbladder cancer. Three studies used plastic stents,[7,18,19] one used both plastic and metal stents,[17] and three utilized metal stents only.[8,15,16] Two studies reported the use of nasobiliary drainage tube along with plastic stents.[18,19] ►**Fig. 2** shows the risk of bias assessment for included studies. Among the RCTs, two had moderate risk of bias,[15,16] while one had high risk of bias.[17] Among the nonrandomized studies, three had moderate risk of bias,[8,18,19] while one had high risk of bias.[7]

Technical and Clinical Success

Pooled data from three studies showed no difference in the technical success between the groups (RR 1.01, 95% CI: 0.96–1.07; $I^2 = 0\%$).[8,16,18] Five studies reported on the difference in the clinical success of ERCP between the two groups.[8,16–19] ►**Supplementary Table S1** (available in the online version) summarizes the definitions used in various studies. There was no difference in the clinical success rate between the two procedures with RR 1.02 (95% CI: 0.94–1.09; $I^2 = 0\%$). Similar results were obtained on subgroup analysis based on study design (►**Supplementary Fig. S1**, available in the online version).

All-Cause Adverse Events

All seven studies with 518 patients reported the incidence of AE with either of the procedures.[7,8,15–19] The use of air cholangiogram was associated with a significantly lower risk of all-cause AE with RR 0.21 (95% CI: 0.12–0.36; $I^2 = 0\%$). On subgroup analysis, the reduced risk with air cholangiogram was seen with both randomized (RR 0.44, 95% CI: 0.22–0.90; $I^2 = 0\%$) and nonrandomized studies (RR 0.53, 95% CI: 0.37–0.75; $I^2 = 0\%$) (►**Fig. 3**). However, on subgroup analysis based on stent type, air

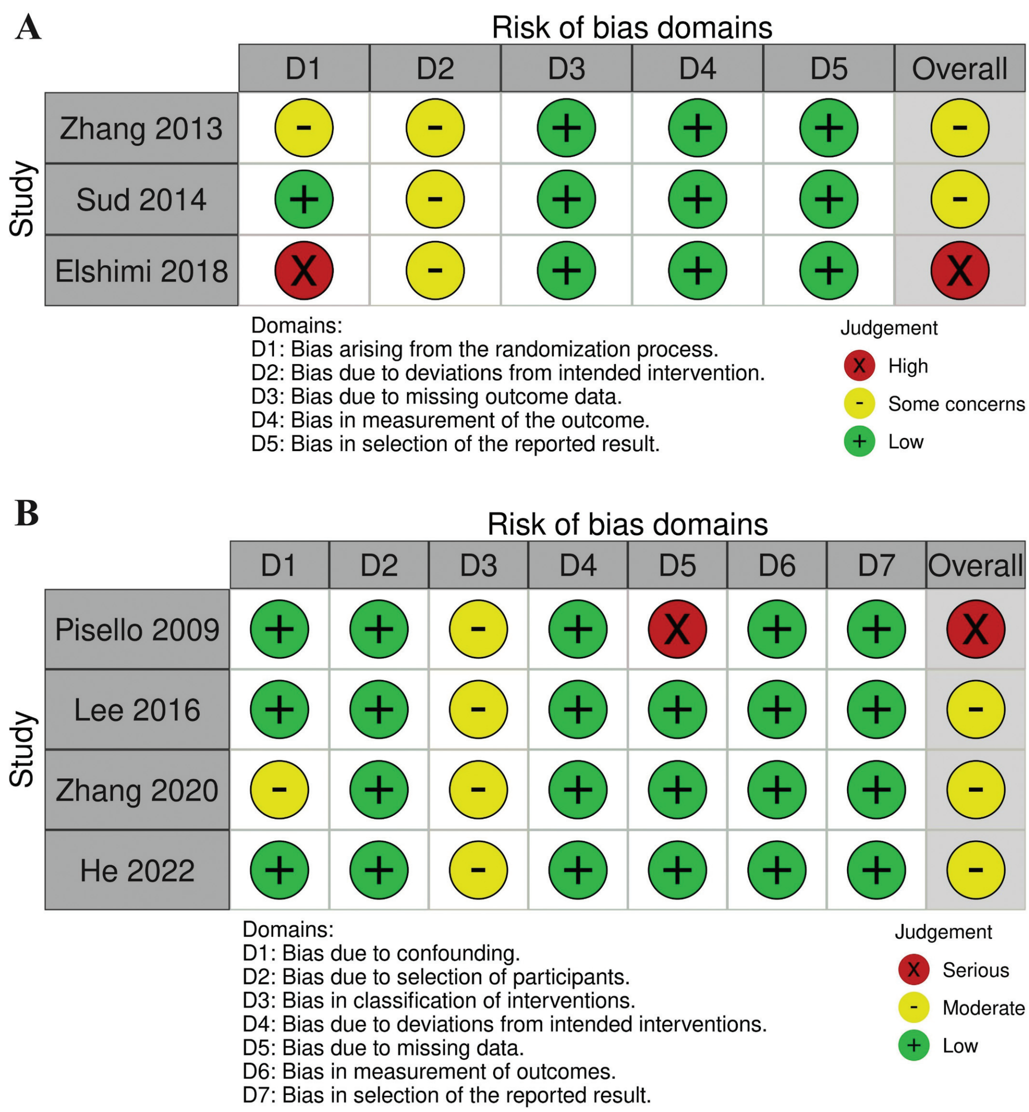

Fig. 2 Risk of bias assessment for (A) randomized trials and (B) nonrandomized studies.

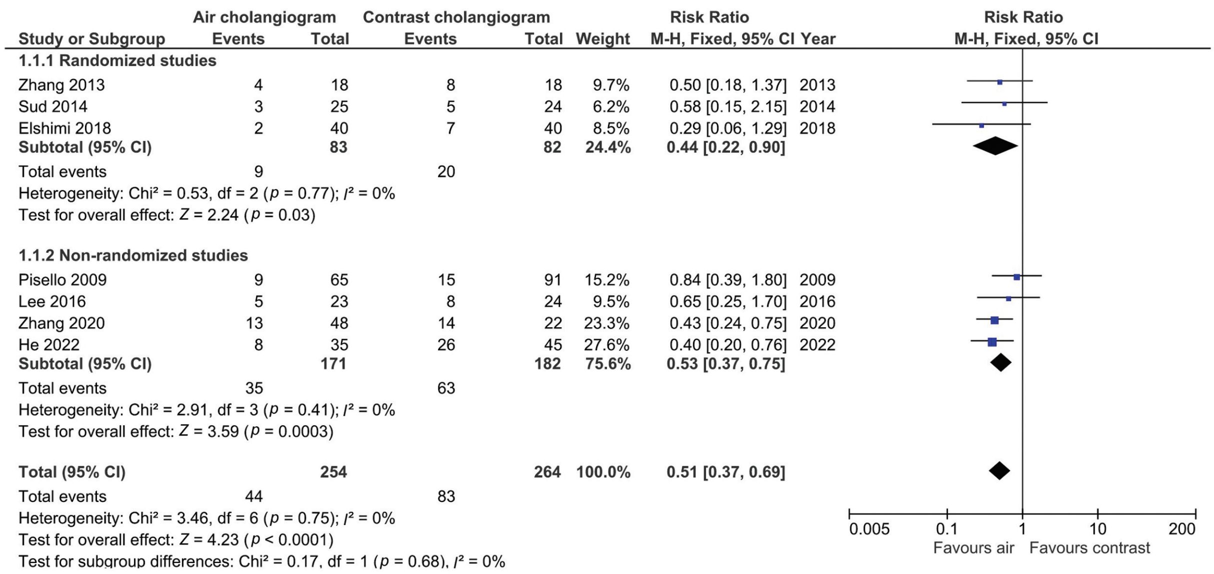

Fig. 3 Forest plot comparing the all-cause adverse event rate between air and contrast cholangiography with subgroup analysis based on study design.

cholangiogram had a lower risk of overall AE in the plastic stent subgroup (RR 0.51, 95% CI: 0.35–0.74; $I^2 = 23\%$), but not in the self-expanding metallic stent group (RR 0.58, 95% CI: 0.31–1.06; $I^2 = 0\%$).

Individual Adverse Events

Cholangitis

All seven studies compared the incidence of cholangitis between air and contrast cholangiogram.[7,8,15–19] The use of air cholangiogram was associated with a significantly lower risk of cholangitis with RR 0.51 (95% CI: 0.37–0.69; $I^2 = 0\%$) (►**Fig. 4**). The reduced risk was seen in subgroup analysis with both randomized (RR 0.19, 95% CI: 0.06–0.61; $I^2 = 0\%$) and nonrandomized studies (RR 0.22, 95% CI: 0.12–0.39; $I^2 = 0\%$). The risk of cholangitis was lower with air cholangiogram with (RR 0.25, 95% CI: 0.14–0.45; $I^2 = 0\%$) or without (RR 0.14, 95% CI: 0.04–0.44; $I^2 = 0\%$) the use of preprocedural antibiotics.

Pancreatitis

Six studies with 362 patients compared the incidence of pancreatitis between both groups.[8,15–19] There was no difference in the risk of pancreatitis between the groups with RR 0.90 (95% CI: 0.45–1.82; $I^2 = 0\%$) (►**Fig. 4**). Subgroup analysis also did not show any significant difference.

Perforation and Bleeding

Six studies compared the incidence of perforation and pancreatitis between both groups.[8,15–19] There was no difference between both groups with respect to bleeding (RR 1.20, 95% CI: 0.31–4.56; $I^2 = 0\%$) or perforation (RR 3.13, 95% CI: 0.13–73.01; $I^2 = 0\%$).

Reintervention

Five studies with 352 patients reported the risk of reintervention (percutaneous transhepatic biliary drainage or ERCP) due to stent block. The reintervention risk was comparable between air and contrast cholangiogram with RR 0.84 (95% CI: 0.59–1.20; $I^2 = 0\%$) (►**Supplementary Fig. S2**, available in the online version). A subgroup analysis, based on stent type did not show any difference in the reintervention rate between the groups.

Thirty Days Mortality

All seven studies compared the 30-day mortality rate between air and contrast cholangiogram.[7,8,15–19] The 30-day mortality risk was comparable between both the groups with RR 0.46 (95% CI: 0.21–1.01; $I^2 = 0\%$) with a similar effect on subgroup analysis (►**Supplementary Fig. S3**, available in the online version).

Publication Bias, Sensitivity Analysis, and Certainty of the Evidence

Publication bias was not conducted as there were less than 10 studies. On leave-one-out analysis, with the exclusion of the study by Lee et al, there was a reduced risk of 30-day mortality with air compared with contrast cholangiogram with RR 0.39 (95% CI: 0.16–0.94; $I^2 = 0\%$). The overall certainty of evidence remained low (for all-cause AE and cholangitis) to very low (rest other outcomes).

Discussion

Endoscopic biliary drainage in cases of malignant obstruction is technically more demanding. Post-ERCP cholangitis has been reported in 34 to 45% of these patients.[20] The primary cause of post-ERCP cholangitis, especially in patients with malignant biliary obstruction, is the incomplete or impossible to drain biliary segments which have been injected with contrast. Air, being far less dense than liquid contrast, may have less unintended spillage into undrained segments, hence a lower incidence of cholangitis. However, most endoscopists consider a cholangiogram

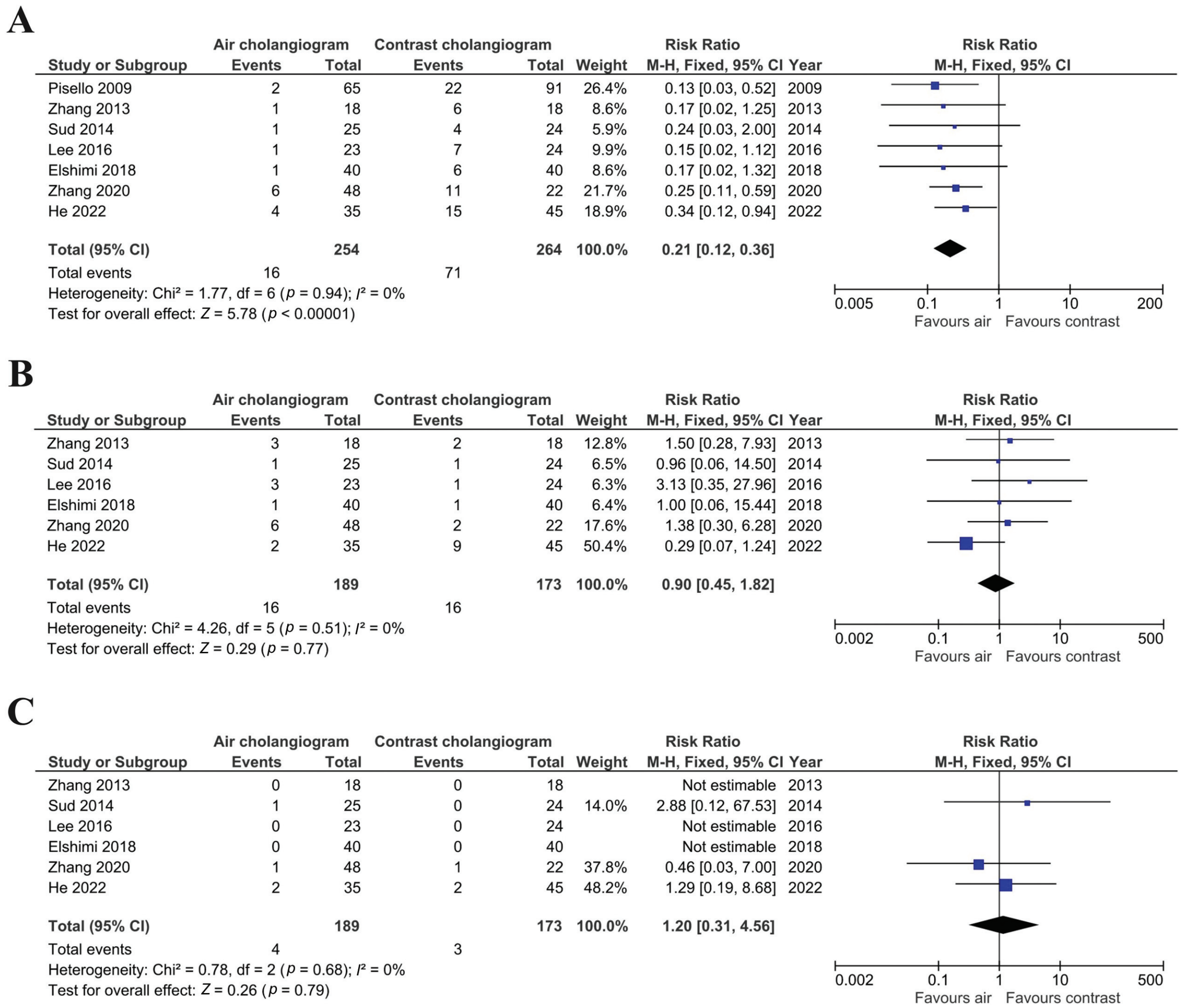

Fig. 4 Forest plot comparing air and contrast cholangiography with respect to the risk of (**A**) cholangitis, (**B**) pancreatitis, and (**C**) bleeding.

mandatory to avoid failure of ERCP (cystic duct cannulation, proximal end of the stent below the stricture).[4] The current meta-analysis was conducted to compare the outcome of air versus contrast cholangiogram. There was no significant difference in clinical success between the groups. But air cholangiogram was associated with a significantly lower risk of all-cause AE with RR 0.21 (95% CI: 0.12–0.36). This lower risk of overall AE was predominantly due to a lower incidence of cholangitis (RR 0.51, 95% CI: 0.37–0.69) rather than other AEs (pancreatitis, bleeding, and perforation), which were comparable between the groups.

The study by Pisello et al demonstrated that neither the number of stents nor the use of prophylactic antibiotics decreased the rates of post-ERCP cholangitis. The single most important factor was the number of undrained biliary segments. Their study of 188 cases of unresectable hilar cholangiocarcinoma demonstrated decreased postprocedure cholangitis rates in patients with air cholangiogram.[7] Two studies by Sud et al and Singh et al demonstrated zero incidences of cholangitis after air cholangiography in patients with Bismuth type II and III malignant hilar obstruction.[4,6] A subsequent prospective randomized controlled study by Sud et al including patients with malignant hilar biliary obstruction, of which 25 patients underwent air cholangiography, demonstrated a statistically significant decrease in the rates of post-ERCP cholangitis in these patients.[16] The 30-day mortality, need for reintervention, and mean survival were similar in both groups. Although a drawback alluded to for using air cholangiogram is the difficulty of interpretation, the authors considered a pre-procedure magnetic resonance cholangiopancreatography sufficient to dispel any doubts. Even in technically difficult procedures like bilateral stenting using the stent-in-stent technique for malignant hilar obstruction, where knowing the real-time anatomy is of paramount importance, air cholangiography is comparable to iodine contrast. Lee et al demonstrated in their study of 47 patients, of whom 23 underwent air-assisted cholangiography, that the rates of post-ERCP cholangitis were significantly lower (4.3% vs. 29.2%, $p = 0.048$).[8] The rates of technical and functional success was comparable between the two groups.

Issues with air cholangiogram may include difficult interpreting the type of block, especially if the image quality acquired by the C-arm is poor. However, no study has looked at possible under- or overestimation the level of block by air cholangiogram. The most feared AE with air cholangiography is the risk of air embolism via dissection into biliary radicles and through the portal venous system. Mortality rates with this complication can be as high as 40%.[10] Fortunately, this risk is extremely rare in ERCP. One fatality was recently reported during direct peroral cholangioscopy, possibly due to preexisting bilio-venous shunt.[21] CO_2 is absorbed much faster than air and has a theoretically lower risk of embolism. Zhang et al, in their study of 36 patients, of which 18 underwent CO_2 cholangiography, reported lower rates of cholangitis and all-cause AEs. There was no case of air embolism in their series.[15] This may also be related to the very low volumes of CO_2 used as compared with peroral cholangioscopy. Because of its faster absorption, a greater amount of CO_2 may be required compared with air. Whether this can lead to other AEs is not yet known. Hence, further large-scale prospective data are required to support its routine use.

One advantage associated with the use of conventional contrast cholangiography is the lower amount of radiation dose required. This was demonstrated by Elshimi et al in their prospective study of 80 patients with hilar cholangiocarcinoma. The X-ray dose was lower in the Urografin cholangiogram group. The procedure time was longer in patients with an air cholangiogram, but the results were not statistically significant.[17] There is a paucity of data that looks at these parameters.

In the present meta-analysis, rates of post-ERCP pancreatitis did not differ with the use of air cholangiography. Although this finding was consistent with all previous data, it is surprising, as one of the causes mentioned for post-ERCP pancreatitis is an inadvertent injection of contrast into the pancreatic duct. Since intraductal pressure is directly proportional to the density of the contrast injected and air being significantly less dense as compared with contrast media, the rates may be expected to be lower. Another reason may be the shift toward wire-guided cannulation which prevents inadvertent pancreatic cannulation and contrast or air injection, thereby reducing post-ERCP pancreatitis. When other parameters like perforation, bleeding, rates of reintervention, and 30-day mortality were compared, there was no difference between the two groups.

To the best of our knowledge, this is the first and only meta-analysis that assessed the feasibility and outcomes of using air cholangiography in patients with malignant biliary obstruction. In addition, to post-ERCP cholangitis, which is the most common parameter studied, we also looked at other post-ERCP AEs. Heterogeneity was low with respect to majority of the outcomes adds to the strength of the study. Despite this, there are also limitations to the present meta-analysis. First, all the included studies were not randomized trials. The period of follow-up reported in most studies was inadequate. Second, most procedures were performed by expert endoscopists. Whether similar results will translate into general practice with trainee involvement is open to question. Third, we could not reach a consensus on whether the use of CO_2 is better than air contrast cholangiography concerning outcomes.

In conclusion, the present meta-analysis demonstrates that endoscopic drainage with similar technical and clinical success rates can be achieved in patients with malignant biliary obstruction with fewer AEs. Accordingly, this technique deserves due consideration. However, further large-scale prospective studies are required to validate its utility in routine practice.

Authors' Contribution

Conceptualization: S.G., S.S.; Data curation: S.G., S.H., P.A.; Formal analysis: S.G., S.H., P.A., L.K.; Funding acquisition: N/A; Investigation: S.G., S.H., L.K.; Methodology: S.G., S.H., P.A., S.S.; Project administration: S.G., S.S.; Resources: S.G., S.H., S.S.; Software: S.G.; Supervision: S.S.; Validation: S.G., S.H., S.S.; Visualization: S.G.; Roles/Writing - original draft: S.G., S.H., P.A.; Writing - review & editing: S.G., S.H., P.A., L.K., S.S.

Conflict of Interest

None declared.

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