Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE American Society for Gastrointestinal Endoscopy

ASGE guideline on the management of cholangitis

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This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy.

Cholangitis is a GI emergency requiring prompt recognition and treatment. The purpose of this document from the American Society for Gastrointestinal Endoscopy's (ASGE) Standards of Practice Committee is to provide an evidence-based approach for management of cholangitis. This document addresses the modality of drainage (endoscopic vs percutaneous), timing of intervention (<48 hours vs >48 hours), and extent of initial intervention (comprehensive therapy vs decompression alone). Grading of Recommendations, Assessment, Development, and Evaluation methodology was used to formulate recommendations on these topics. The ASGE suggests endoscopic rather than percutaneous drainage and biliary decompression within 48 hours. Additionally, the panel suggests that sphincterotomy and stone removal be combined with drainage rather than decompression alone, unless patients are too unstable to tolerate more extensive endoscopic treatment. (Gastrointest Endosc 2021;94:207-21.)

(footnotes appear on last page of article)

Patients with cholangitis may respond to medical therapy including antibiotics. However, decompression of the biliary tree is necessary in most cases. Mortality associated with surgical management of cholangitis ranges from 10% to 40% and has been correlated with disease severity.[1-3] Randomized comparative trials indicate that ERCP achieves biliary decompression with markedly less morbidity and mortality compared with surgery, regardless of clinical severity.[4] Percutaneous transhepatic biliary drainage (PTBD) represents an alternative option with a less defined role. Additionally, the timing of ERCP relative to the onset of cholangitis and whether duct clearance should be attempted during the initial ERCP remain controversial.

AIMS AND SCOPE

The aim of this document is to provide an evidence-based guideline for the treatment of cholangitis based on systematic review and synthesis of the literature using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. GRADE has been adopted by the American Society for Gastrointestinal Endoscopy (ASGE) as a system to rate the quality of evidence and strength of recommendations in a rigorous and transparent manner.[5] The document addresses the following clinical questions:

1. In patients with cholangitis, is endoscopic or percutaneous drainage the favored method of biliary decompression and does it vary by severity?
2. In patients with cholangitis, does early ERCP performed at (≤48 hours) after admission improve clinical outcome relative to patients undergoing ERCP at >48 hours?
3. In patients with cholangitis, what is the role of endoscopic therapy (sphincterotomy, lithotripsy, stone clearance) combined with decompression (stent or nasobiliary tube) versus decompression alone during the initial ERCP?

METHODS

Overview

A working group of the Standards of Practice (SOP) Committee of the ASGE drafted this document. The

TABLE 1. Summary of recommendations with strength of recommendation and quality of evidence derived by Grading of Recommendations, Assessment, Development, and Evaluation methodology

Statement	Strength of recommendation	Quality of evidence
1. For patients with cholangitis, we suggest ERCP over percutaneous transhepatic biliary drainage.	Conditional	Very low
2. For patients with cholangitis, we suggest the performance of ERCP in ≤48 h compared with 48 h.	Conditional	Very low
3. For patients with cholangitis, we suggest that biliary drainage should be combined with other maneuvers such as sphincterotomy and stone removal versus stent alone.	Conditional	Low

relevant questions and outcomes were developed by the SOP committee and approved by the ASGE Governing Board. GRADE methodology was used to derive questions 1 to 3, systematically review the best evidence, rate the quality of the evidence, and develop recommendations (Table 1). The full panel drafted all recommendations during a face-to-face meeting of the SOP committee on March 7, 2020.

Panel composition and conflict of interest management

The panel included 3 content experts with expertise in systematic review and meta-analysis (J.L.B., N.C.T., S.W.), a content expert independent of the SOP committee (B.J.E.), a GRADE methodologist (B.J.Q.), a hepatobiliary surgeon (E.P.C.), an interventional radiologist (A.R.), a patient representative (P.M.), and other members of the SOP Committee. All members were asked to disclose conflicts of interests based on the ASGE policy (https://www.asge.org/forms/conflict-of-interest-disclosure and https://www.asge.org/docs/default-source/about-asge/mission-andgovernance/asge-conflict-of-interest-and-disclosure-policy.pdf). Panel members who received funding for any technologies or companies associated with any of the population, intervention, comparator, and outcomes (PICOs) were asked to declare this before the discussion and did not vote on the final recommendation addressing that specific PICO question.

Formulation of clinical questions

The panel developed 3 clinical questions relevant to management of cholangitis that were amenable to a PICO approach (Table 2). For each PICO question, we identified the population (P), intervention (I), comparator (C), and outcome of interest (O). Patient critical outcomes included successful decompression and resolution of cholangitis and associated adverse events.

Literature search and study selection criteria

For each PICO question, existing systematic reviews were assessed, and, if unavailable, a de novo systematic review and meta-analysis was performed to address the topic. A health sciences librarian (H.S.) developed the search strategy and searched the following databases on July 15, 2019 for PICO 1 and on February 28, 2019 for PICO 3. This included PubMed (coverage 1946 to present), Embase and Embase Classic (coverage 1947 to present), Cochrane Library (coverage 1898 to present), and Web of Science (coverage 1900 to present). No filters were applied for date, study type, language, or any other limit. A combination of subject headings (when available) and key words were used for the concepts of cholangitis, endoscopic drainage, and percutaneous drainage. In an effort to capture unpublished studies, the librarian conducted searches in Google Scholar and ClinicalTrials.gov. Because of database constraints and lack of replicability, only the first 200 citations from Google Scholar were collected. Cross-referencing (snowballing) and forward searches of citations from articles fulfilling inclusion criteria and other pertinent articles were performed using Web of Science. The search for PICO 2 has been described by Iqbal et al.,[6] which contains the methods and evidence used to address the question. See Supplementary Tables 1 and 2 (available online at www.giejournal.org) for full search strategies and database details. Citations were imported into EndNote x9.2 (Clarivate Analytics, Philadelphia, Pa, USA), duplicates were removed using the Bramer method, and the remainder were uploaded into Covidence (Melbourne, Australia) for screening.[7]

Data extraction and statistical analysis

Two independent reviewers performed data extraction. Pooled effects were calculated using random effects models. The summary statistics included overall diagnostic odds ratios (OR) (PICOs 1-3), standardized mean differences (PICOs 1 and 3), and mean differences (PICO 2). Heterogeneity was quantified using the I^2 statistic and assessed by sensitivity analyses. Indirect comparisons were used to perform subgroup analyses for severity when direct comparative data were not available.

Certainty in evidence

The quality of the evidence and confidence in the estimated effects was determined using the GRADE approach addressing the following domains: bias of individual studies, imprecision, inconsistency, indirectness, and publication bias. Certainty was categorized into 1 of 4 levels: high, moderate, low, and very low (Table 3). The evidence profiles were generated using GRADEpro/GDT applications (https://gdt.guidelinedevelopment.org/app).

TABLE 2. List of population, intervention, comparator, outcomes questions addressed

Population	Intervention	Comparator	Outcomes	Rating
1. Cholangitis*	ERCP with decompression	Percutaneous cholangiography with drainage	1) Successful decompression	Critical
			2) Mortality	Critical
			3) Length of hospitalization	Important
			4) Adverse events (pancreatitis, bile leak, hemorrhage, perforation)	Critical
2. Cholangitis*	ERCP in ≤48 h	ERCP > 48 h	1) Mortality	Critical
			2) Length of hospitalization	Important
			3) Organ failure	Critical
			4) 30-Day organ failure	Critical
3. Cholangitis*	ERCP with sphincterotomy, stone removal, lithotripsy, and decompression	ERCP with decompression alone	1) Successful decompression	Critical
			2) Adverse events	Critical
			3) Repeat procedures (ERCP, percutaneous cholangiography, surgery)	Critical
			4) Length of hospitalization	Important

*Overall and stratified by disease severity.

Development of recommendations

The panel developed recommendations based on certainty in the evidence, overall balance of benefit and harm, patient values and preferences, cost-effectiveness, and resource utilization. The wording of the recommendation, in particular the direction and strength, was determined by consensus among the panel members. The GRADE approach was used, and the recommendations were categorized as strong or conditional. The word "recommend" is used for strong recommendation and "suggest" for conditional recommendations. Suggested interpretation of strong and conditional recommendations by patients, clinicians, and policymakers is provided in Table 4.

Patient values and preferences

Limited studies of patient preferences in regards to cholangitis management are available. The patient representative on the GRADE panel indicated that ERCP would likely be favored over PTBD given it was consistently associated with shorter hospitalization and did not result in the discomfort of an external catheter.[8-10] Patient preferences for ERCP <48 versus >48 hours and for combined therapy versus decompression alone also have not been formally studied. The advantage of shorter hospitalization associated with ERCP <48 hours and combined initial endoscopic therapy (vs decompression alone) were deemed to be desirable factors by the patient representative. Additionally, limited studies suggest that combined therapy may decrease the required number of endoscopic procedures versus decompression alone.[11]

Cost-effectiveness

Using the Nationwide Inpatient Sample (NIS) database of 248,942 patients with cholangitis, McNabb-Baltar et al[12] demonstrated that 54.7% of patients managed with PTBD accrued high hospital charges (>75th percentile) versus 32.7% treated via ERCP. Additionally, the length of hospitalization was consistently shorter for management by ERCP versus PTBD, which potentially translates into cost savings.[8-10]

Comparative studies of endoscopic decompression at ≤48 hours versus >48 hours did not report cost analysis.[6] Nevertheless, using data from 77,323 patients managed by ERCP for cholangitis using the NIS database, Parikh et al[13] demonstrated that hospitalization was significantly more costly for ERCP performed at >48 hours ($48,627 [95% confidence interval {CI}, 47,058-50,196]) than ERCP at 24 to 48 hours ($31,108 [95% CI, 29,987-32.230]), with the lowest cost for ERCP <24 hours ($25,836 [95% CI, 24,867-26,805]). Mulki et al[14] used the 2014 National Readmissions Database to show that cholangitis hospitalization costs less for ERCP ≤48 hours than for ERCP >48 hours ($16,939 vs $21,459, respectively). Similarly, using data from a tertiary care center, Khashab et al[15] reported that considerable hospitalization cost (>90th percentile) was more likely (odds ratio [OR], 11.3; 95% CI, 1.3-98) for ERCP >72 hours than ≤72 hours after admission. Interestingly, weekend ERCP did not significantly reduce hospitalization cost ($71,662 [95% CI, 70,499-72,605] vs

TABLE 3. GRADE categories of quality of evidence

GRADE quality of evidence	Meaning	Interpretation
High	We are confident that the true effect lies close to that of the estimate of the effect.	Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate	We are moderately confident in the estimate of the effect; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Further research is likely to have an impact on our confidence in the estimate of the effect and may change the estimate.
Low	Our confidence in the estimate of the effect is limited; the true effect may be substantially different from the estimate of the effect.	Further research is very likely to have an impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low	We have very little confidence in the estimate of the effect; the true effect is likely to be substantially different from the estimate of the effect.	Any estimate of the effect is very uncertain.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

TABLE 4. Interpretation of definitions of strength of recommendation using Grading of Recommendations, Assessment, Development, and Evaluation framework

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Compliance with to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders.

$71,469 [95% CI, 69,627-73,312] weekday ERCP) despite a delay of 1 to 2 days.[16] Formal cost-effectiveness analyses assessing the impact of timing of ERCP are lacking and need to be addressed in future studies.

Shorter length of stay was demonstrated for initial combination therapy (ERCP with biliary drainage combined with sphincterotomy and stone removal) versus decompression alone in a systematic review and meta-analysis, which likely translates to reduced cost savings, although financial considerations were not available in most source articles. Yamamiya et al[11] reported a median cost of $726 (interquartile range, 579-1028) for combined therapy versus $988 (interquartile range, 868-1033) for decompression alone.

RESULTS

The recommendations for the clinical questions addressed by GRADE methodology are summarized in Table 1 and Figure 1.

Question 1: **In patients with cholangitis, what is the role of ERCP compared with PTBD?**

Recommendation 1: **For patients with cholangitis, we suggest ERCP over PTBD.**

(*Conditional recommendation, Very low quality of evidence*).

Summary of the evidence

The important patient outcomes for this clinical question were mortality, successful decompression, length of hospitalization, and adverse events. The evidence profile is presented in Table 5. We performed a systematic review to compare endoscopic versus percutaneous drainage in the setting of cholangitis. A search from inception through July 15, 2019 identified 15,110 citations and were assessed by 2 independent reviewers (Supplementary Table 1). Eighty-nine citations met our inclusion criteria, which were treatment of cholangitis by ERCP or PTBD and not by surgical or other methods.

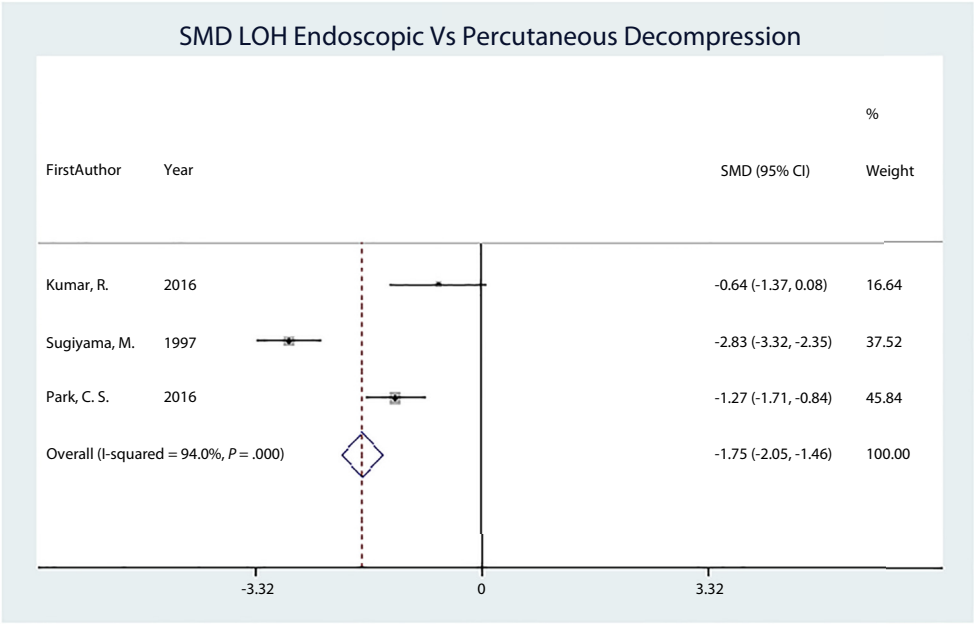

Figure 1. Comparative length of hospitalization (LOH) for endoscopic versus percutaneous drainage in cholangitis. *SMD*, Standardized mean difference; *CI*, confidence interval.

We identified 6 comparative observational trials. These studies reported on 745 patients with cholangitis managed by ERCP with internal stent or nasobiliary tube and 244 patients who underwent PTBD. Among the 244 patients undergoing PTBD, 12 had previously undergone an unsuccessful ERCP, and among those undergoing ERCP, 10 previously underwent failed PTBD. Based on the random effects model, there was no difference in mortality rates between ERCP and PTBD (OR, .3; 95% CI, .1-1.1; I^2 = 0) (Supplementary Fig. 1, available online at www.giejournal.org). Similarly, there was no difference in successful decompression for ERCP versus PTBD (OR, 1.8; 95% CI, .3-12), although significant heterogeneity was observed (I^2 = 83.1%) (Supplementary Fig. 2 and Supplementary Table 3, available online at www.giejournal.org). There was no difference in overall adverse events between the 2 treatment modalities (OR, .3; 95% CI, 0-2.1; 46.5%), although comparative data on overall adverse events were reported by only 2 studies (Supplementary Fig. 3, available online at www.giejournal.org). As for length of stay, ERCP was associated with shorter mean hospitalization (11.7 days [95% CI, 5.5-17.8], I^2 = 99%) than PTBD (23.1 days [95% CI, 8-38.4], I^2 = 98.8%); the standardized mean difference was 1.8 days (95% CI, 1.5- 2.1; I^2 = 94%) (Fig. 1).

Given the limited data, results could not be analyzed by cholangitis severity. To investigate the impact of this variable and to conduct a sensitivity analysis, we performed an indirect comparison of all 89 studies that provided results for percutaneous, endoscopic, or both modalities. This included 9100 patients managed by ERCP and 887 by PTBD. There was no difference in the proportion of patients successfully managed by ERCP (97% [95% CI, 96-98%]; I^2 = 83) and PTBD (94% [95% CI, 88-98]; I^2 = 85%) (Supplementary Table 4, available online at www.giejournal.org). These results did not differ among populations specified as severe or nonsevere cholangitis (Supplementary Table 5, available online at www.giejournal.org). In the analysis of noncomparative trials, PTBD was associated with a higher adverse event rate of 10% (95% CI, 7-14; I^2 = 17%) versus 5% (95% CI, 4-7; I^2 = 81%) for ERCP, which was largely driven by increased proportion of patients with bleeding in the PTBD group (Supplementary Tables 4 and 5). Mortality data stratified by cholangitis severity were limited. Although overall cholangitis mortality was comparable between the treatment modalities, it appeared to be higher among those with severe cholangitis managed by PTBD (14% [95% CI, 1-35]; I^2 = 0) compared with ERCP (4% [95% CI, 2-6]; I^2 = 0). The mean length of stay tended to be greater after PTBD (23.2 days [95% CI, 8-38.4]; I^2 = 75%) than after ERCP (10.4 days [95% CI, 9-11.8]; I^2 = 99%), but this did not reach statistical significance. Hospitalization length stratified by disease severity was not available for those managed by PTBD.

Certainty in the evidence

There were significant issues with bias, particularly related to the degree of selection and comparability of patients managed by endoscopic versus percutaneous approaches as determined using the Newcastle-Ottawa tool (Supplementary Table 6, available online at www.giejournal.org). We also rated down for inconsistency

TABLE 5. Evidence profile for population, intervention, comparator, and outcomes 1: ERCP vs PTBD in the management of cholangitis

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Drainage success						
6	Observational studies	Not serious	Serious*†	Not serious	Not serious	None
Overall all adverse events						
2	Observational studies	Not serious	Not serious	Not serious	Serious	None
30-day mortality						
3	Observational studies	Not serious	Not serious	Not serious	Serious*	None
Mean length of stay						
3	Observational studies	Not serious	Not serious	Not serious	Serious*	None

PTBD, Percutaneous transhepatic biliary drainage; *OR,* odds ratio; —, insufficient data available.
*Low number of events.
†High I^2.

given the high I^2 values (Table 5). There did not appear to be serious indirectness.

Considerations

The panel had significant discussions regarding the overall quality and certainty of research evidence, desirable and undesirable effects of the treatments, and the implications for resource utilization and patient experience. Although both methods achieved comparable clinical success, the desirable effects of ERCP included a significantly shorter length of stay. Unfavorable aspects of PTBD included a higher rate of adverse events and bleeding, although this was demonstrated only using indirect comparison. Postprocedure pancreatitis is the major disadvantage of ERCP, although there is insufficient evidence to conclude if it occurs more frequently after ERCP versus PTBD in the specific setting of cholangitis.

Overall, the panel judged that the quality of evidence was very low, particularly with regard to the subanalyses assessing severe cholangitis. Studies addressing patient quality of life and preferences were lacking, although the patient advocate on the panel (P.M.) expressed a strong preference for ERCP, citing substantial value in shorter hospitalization length, favorable adverse event profile, and the negative impact of external drains on quality of life. The consensus of the panel was that these desirable effects favored ERCP versus PTBD for cholangitis.

Discussion

Endoscopic and percutaneous drainage are the primary decompression strategies in cholangitis.[4,12] Although the 2 procedures have the same goal, they involve markedly different technical approaches and have different adverse event profiles. PTBD is associated with bleeding, bacteremia, and abscess formation, whereas the dominant adverse event of ERCP is pancreatitis.[17,18] We performed a systematic review and meta-analysis using direct and indirect evidence of the approaches and found that the technical success was comparable. We demonstrated a significantly reduced length of stay for endoscopic drainage. Additionally, indirect comparison revealed greater adverse events for PTBD, particularly periprocedure hemorrhage.

The panel favored ERCP over PTBD given the reduced length of stay, adverse events, and assessment of patient values. This correlates with data from the NIS of nearly a quarter million patients with cholangitis, which demonstrates that between 1998 and 2009 there was an increased use of ERCP (54.2%-57%) relative to PTBD (5.0% to 4.6%) and surgery (8.2% to 2.8%).[12] The mortality rate was lower among patients managed with ERCP compared with those undergoing PTBD (3.3% vs 8.9%).[12] Similarly, fewer patients treated with ERCP had a prolonged (>10 day) length of stay (26.8 vs 55.5%).[12] It should be noted that although the authors attempted to adjust for confounding variables including hospital volume, a greater proportion managed by PTBD compared with ERCP had malignancy (30.2% vs 11.2%).[12] More frequent malignancy and comorbidities may have skewed the results in favor of ERCP. Additionally, the retrospective nature of the included studies further limits the strength of our conclusions.

Additionally, a significant portion of patients managed by PTBD had a surgically altered anatomy, which would have made ERCP technically challenging.[19] Among those who have undergone procedures in the setting of a Roux-en-Y gastrojejunostomy, PTBD may be more quickly

TABLE 5. Continued

No. of patients		Effect		Certainty	Importance
ERCP	PTBD	Relative (95% confidence interval)	Absolute (95% confidence interval)		
Drainage success					
699/745 (93.8%)	208/244 (85.2%)	OR, 1.75 (.26-12.03)	58 more per 1000 (from 252 fewer to 133 more)	⊕◯◯◯ VERY LOW	CRITICAL
Overall all adverse events					
6/93 (6.5%)	13/73 (17.8%)	OR, .28 (.04-2.05)	121 fewer per 1000 (from 169 fewer to 129 more)	⊕◯◯◯ VERY LOW	CRITICAL
30-day mortality					
2/93 (2.2%)	4/73 (5.5%)	OR, .25 (.06-1.10)	41 fewer per 1000 (from 51 fewer to 5 more)	⊕◯◯◯ VERY LOW	CRITICAL
Mean length of stay					
386	96	—	Mean difference, 1.75 days lower (2.05 lower to 1.46 lower)	⊕◯◯◯ VERY LOW	CRITICAL

performed and require less sedation than ERCP combined with device-assisted (ie, double-balloon) enteroscopy. Furthermore, the role of new approaches for these challenging scenarios, such as EUS-guided biliary drainage, has not been comprehensively studied in the context of cholangitis.[20] Data on disease severity and factors that were influential in the decision-making process to proceed with PTBD have not been well defined. The panel acknowledged that a subset of critically ill patients may not be ideal candidates for ERCP, and hence PTBD may be an acceptable treatment approach given the ability to perform PTBD with minimal sedation or topical analgesia. Future studies are needed to assess the role of EUS-guided biliary drainage in patients with cholangitis in whom the traditional ERCP approach is not feasible or has failed. A detailed description of EUS-guided drainage approaches is beyond the scope of this document.

Question 2: **In patients with cholangitis, does ERCP performed at ≤48 hours after admission improve clinical outcomes relative to patients undergoing ERCP at >48 hours?**

Recommendation 2: **For patients with cholangitis, we suggest the performance of ERCP in ≤48 hours compared with >48 hours.**

(*Conditional recommendation, Very low quality of evidence*).

Summary of the evidence

For this clinical question, the outcomes of interest were inpatient mortality, 30-day mortality, organ failure, and length of hospitalization. Although no randomized trials have compared ERCP ≤48 hours versus >48 hours, the topic has recently been the subject of a systematic review and meta-analysis by Iqbal et al.[6] Evidence profiles are presented in Table 6. The authors systematically reviewed the literature from inception through April 2019 and identified 9 observational studies (7534 patients); 2 were prospective and 7 retrospective. Performance of ERCP ≤48 hours versus >48 hours led to a decrease in inpatient mortality (OR, .52; 95% CI, .28-.98; $I^2 = 0$) (Fig. 2). Three trials (6400 patients) addressed 30-day mortality and found no difference (OR, .39; 95% CI, .1-1.1; $I^2 = 79\%$) (Supplementary Fig. 4, available online at www.giejournal.org). Additionally, there was no significant difference in persistent organ failure with ERCP ≤48 hours (OR, .7; 95% CI, .3-1.6; $I^2 = 66\%$). Performance of ERCP at ≤48 hours decreased the mean length of stay by 5.6 days (95% CI, 1.5-9.5; $I^2 = 74\%$) among 494 patients (Fig. 3). There were insufficient data among the observational studies to stratify by disease severity.

Certainty in the evidence

There were significant issues with bias, particularly related to the comparability of patients, with only fair scores based on the Newcastle-Ottawa tool (Supplementary Table 7, available online at www.giejournal.org). We also rated down for inconsistency given the high I^2 values for length of stay. There did not appear to be serious indirectness.

Considerations

The panel highlighted desirable effects of ERCP ≤48 hours included lower inpatient mortality, 30-day readmission, and shorter length of stay. Data from national databases suggest a lower 30-day mortality when ERCP is performed ≤48 hours. There were no significant

TABLE 6. Evidence profile for population, intervention, comparator, and outcomes 2: timing of ERCP in the management of cholangitis: ≤48 h vs >48 h

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Same admission mortality						
5	Observational studies	Not serious	Not serious	Not serious	Serious*	None
30-day mortality-cohort studies						
3	Observational studies	Not serious	Serious†	Not serious	Serious*	None
30-day mortality: national database studies						
2	Observational studies	Serious‡	Not serious	Not serious	Not serious	None
Length of stay						
3	Observational studies	Not serious	Serious†	Not serious	Not serious	None

OR, Odds ratio; —, insufficient data available.
*Low number of events.
†High I^2.
‡National studies.

undesirable effects of ERCP at ≤48 hours. The patient representative preferred ERCP ≤48 hours given the likelihood of shorter length of hospital stay. Nevertheless, the quality of the evidence of the systematic review and meta-analysis was very low. Two large studies using the NIS indicate that there may be cost savings for earlier ERCP, although rigorous cost-effectiveness studies are lacking.

Discussion

The timing of ERCP in the context of cholangitis is controversial because of concern for inadequate resuscitation and increased periprocedural bacterial translocation if performed too early versus the accrual of cholangitis-associated morbidity if source control is delayed. Systematic review of the timing of ERCP indicates that ERCP within 48 hours reduces inpatient mortality by 2-fold and is associated with a significant reduction in the length of hospitalization.[6] The 48-hour interval was chosen because this is the cut-point in the preponderance of literature on the topic and addresses the workforce and financial concerns of weekend procedures.

Several studies have addressed the impact of ERCP timing on additional clinical outcomes (Supplementary Table 8, available online at www.giejournal.org). Khashab et al[15] demonstrated that a delay >72 hours was associated with an increased composite outcome of death, organ failure, or intensive care unit admission (OR, 5.5; P = .004). Navaneethan et al[21] found that ERCP >48 hours was associated with an increased likelihood of 30-day readmission (OR, 2.5; 95% CI, 1.0-6.1). Using data from the 2014 National Readmission Database, Mulki et al[14] identified 4570 patients with cholangitis and demonstrated that ERCP within 48 hours reduced mortality (OR, .5; 95% CI, .76-.83), 30-day mortality (OR, .5; 95% CI, .3-.7), and 30-day readmission (OR, .6; 95% CI, .5-.7) compared with those who underwent ERCP >48 hours. These findings remained significant both for those with mild to moderate and severe cholangitis. ERCP in <24 hours or 24 to 48 hours versus >48 hours appears to shorten the length of hospitalization but does not impact inpatient or 30-day mortality, organ failure, or other core clinical outcomes.[13,14,22-25] Nevertheless, among patients in septic shock who do not respond to fluid resuscitation, delay of ERCP is associated with adverse events and ERCP in <24 hours may be considered in this population.[26]

Question 3: **In patients with cholangitis, what is the role of endoscopic therapy (sphincterotomy, lithotripsy, stone clearance) combined with decompression (stent or nasobiliary tube) versus decompression alone during the initial ERCP?**

Recommendation 3: **For patients with cholangitis, we suggest that biliary drainage be combined with other maneuvers such as sphincterotomy and stone removal versus stent placement without attempted stone removal.**

(*Conditional recommendation, Low quality of evidence*).

Summary of the evidence

The initial endoscopic treatment of cholangitis is controversial. It has been advocated that initial management should be limited to decompression alone using a biliary stent, although the alternative is to perform therapeutic maneuvers to remove obstruction including sphincterotomy and stone extraction in addition to

TABLE 6. Continued

No. of patients		Effect			
ERCP <48 h	ERCP >48 h	Relative (95% confidence interval)	Absolute (95% confidence interval)	Certainty	Importance
Same admission mortality					
25/469 (5.3%)	23/293 (7.8%)	OR, .52 (.28-.98)	36 fewer per 1000 (from 55 fewer to 1 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
30-day mortality-cohort studies					
111/3976 (2.8%)	89/2424 (3.7%)	OR, .39 (.14-1.08)	22 fewer per 1000 (from 31 fewer to 3 more)	⊕◯◯◯ VERY LOW	CRITICAL
30-day mortality: national database studies					
46/3042 (1.5%)	51/1528 (3.3%)	OR, .44 (.30-.67)	18 fewer per 1000 (from 23 fewer to 11 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Length of stay					
337	157	—	Mean difference, 5.6 days lower (9.5 lower to 1.6 lower)	⊕◯◯◯ VERY LOW	CRITICAL

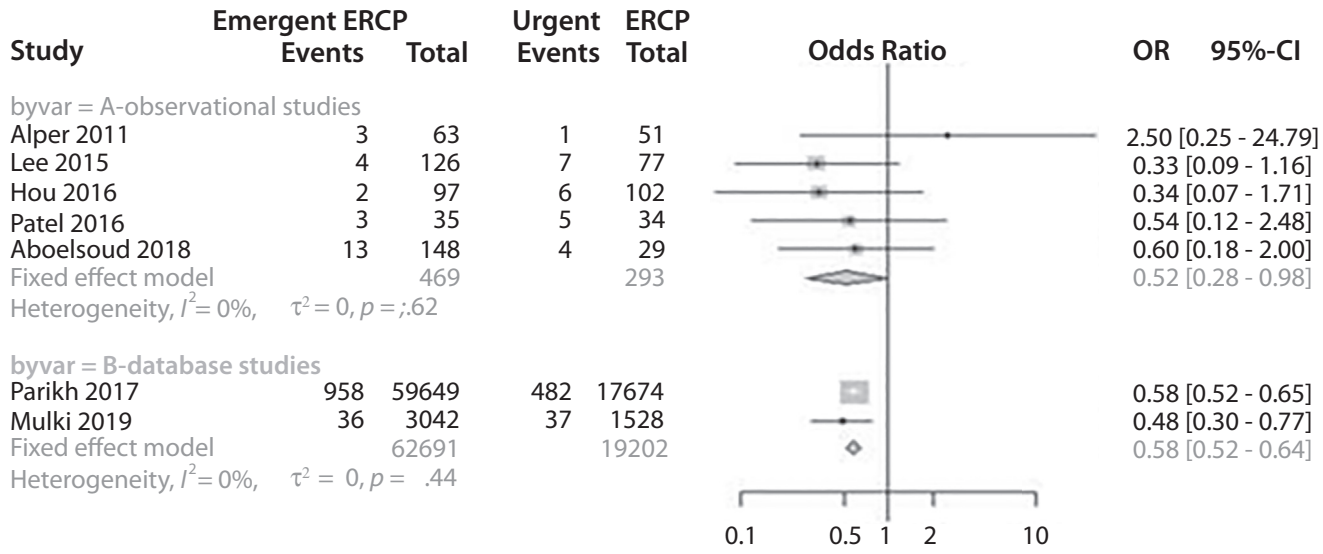

Figure 2. Inpatient mortality for cholangitis managed by ERCP <48 hours (emergent) versus >48 hours (urgent). *OR*, Odds ratio; *CI*, confidence interval.

decompression. The outcomes of interest for this clinical question include effective decompression, adverse events, length of hospitalization, and the need for reintervention. We performed a systematic review and meta-analysis to address the question of whether decompression alone or decompression combined with other endoscopic therapy is favored. Other endoscopic therapy included sphincterotomy alone with other procedures including stone removal. We conducted a literature search from inception to March 2019. The search (Supplementary Table 2) yielded 10,417 citations that were assessed by 2 reviewers and data extraction from 9 studies fulfilling inclusion and exclusion criterion, which was treatment of cholangitis by decompression alone or combined with other endoscopic therapies, followed by analysis of 219 full text articles.

The analytic set included 1 randomized trial and 8 comparative retrospective observational studies reporting on 903 patients, 418 who underwent endoscopic decompression (stent or nasobiliary tube) alone and 485 who underwent decompression combined with other forms of endoscopic therapy. The evidence profile for this PICO is presented in Table 7 and detailed clinical outcomes in Supplementary Table 9 (available online at www.

giejournal.org). Overall, there was no difference in successful decompression between the 2 groups (OR, 1.0; 95% CI, .4-2.3; I^2 = 0) (Supplementary Fig. 5, available online at www.giejournal.org).

Based on the random effects model there were more adverse events after endoscopic therapy combined with decompression compared with decompression alone (OR, 2.0; 95% CI, 1.0-3.9; I^2 = 7.8%) (Fig. 4). This was driven by significantly more bleeding for combination therapy (OR, 3.9; 95% CI, 1.5-10.1; I^2 = 0), with no difference in post-ERCP pancreatitis (OR, 1.0; 95% CI, .4-2.6; I^2 = 0) (Fig. 5, Supplementary Fig. 6, available online at www.giejournal.org). No perforations occurred in any study.

The mean length of stay was significantly shorter for those who underwent endoscopic therapy combined with decompression (9.8 days [95% CI, 7.8-11.7]; I^2 = 93.1%) relative to those who underwent decompression

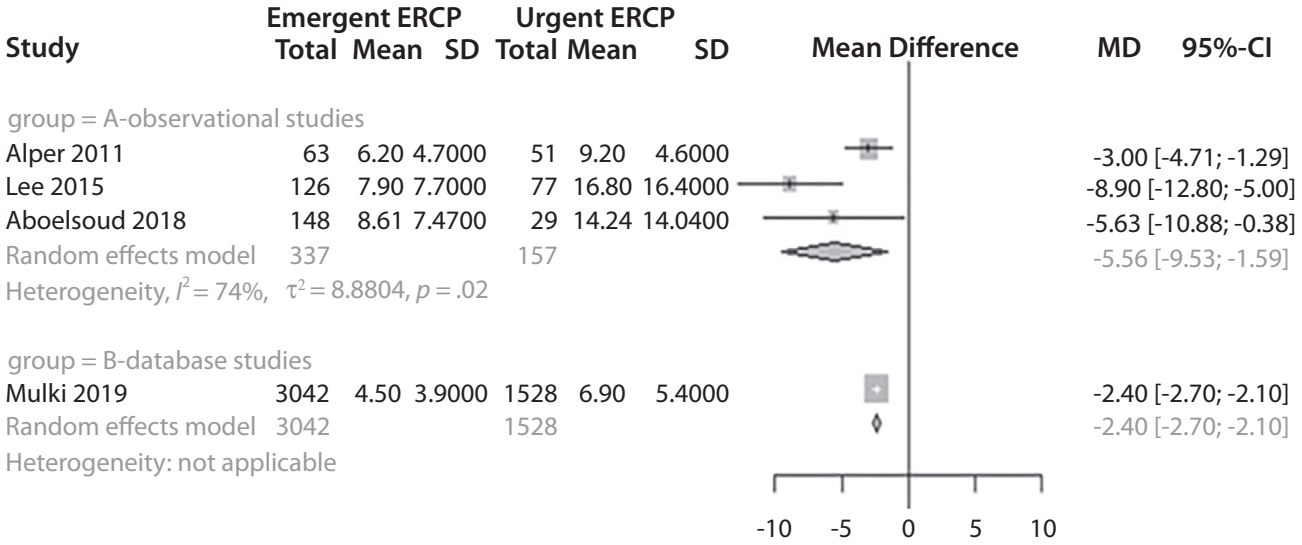

Figure 3. Length of stay by ERCP ≤48 hours (emergent) versus >48 hours (urgent). *SD*, standard deviation; *MD*, mean difference; *CI*, confidence interval.

TABLE 7. Evidence profile for population, intervention, comparator, and outcomes 3: combined endoscopic therapy versus endoscopic decompression in the management of cholangitis

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Drainage success						
3	Observational studies	Not serious	Not serious	Not serious	Serious*	None
Adverse events						
6	Observational studies	Not serious	Not serious	Not serious	Serious*	None
Bleeding						
7	Observational studies	Not serious	Not serious	Not serious	Not serious	None
Pancreatitis						
7	Observational studies	Not serious	Not serious	Not serious	Serious*	None
Length of stay						
6	Observational studies	Not serious	Serious†	Not serious	Not serious	None

OR, Odds ratio; —, insufficient data available.
*Low number of events.
†High I^2.

alone (14.1 days [95% CI, 10.4-17.9]; I^2 = 97.5%), with a standardized mean difference of .8 (95% CI, .4-1.2; I^2 = 80.6%) (Fig. 6). There was no difference in mortality, although this outcome was only reported in 1 study (OR, .5; 95% CI, 0-5.6).[28] Additionally, only 2 studies captured the total number of ERCPs in their cohort. Ueki et al[27] reported a mean of 2.8 ± 1.4 ERCPs for combination therapy versus 3.3 ± 0.9 for decompression alone, whereas Yamamiya et al[11] reported a median of 1 ERCP for combination therapy versus 2 for those initially managed with decompression alone.

We stratified the meta-analyses by cholangitis severity (severe vs nonsevere). Although data for these more specific populations were limited, bleeding risk was more pronounced for those with severe (OR, 8.4; 95% CI, 1-67; I^2 = 0) versus nonsevere cholangitis (OR, 3.9; 95% CI, 1.1-13.4; I^2 = 0) (Supplementary Table 10, available online at www.giejournal.org).

Certainty in the evidence

There were significant issues with bias. Several studies excluded those with coagulopathy, and other relegated those with risk factors for bleeding to the decompression alone arm, suggesting both selection and comparability bias (Supplementary Table 11, available online at www.giejournal.org). The latter was also compromised in several studies in which patients in the 2 arms had different baseline biochemical profiles (ie, higher bilirubin), and in others these features were not reported. We also rated down for inconsistency given the high I^2 values for several of the outcomes, including length of hospitalization. Indirectness was not an apparent problem.

Considerations

The panel discussed the balance or benefits and harms of the 2 strategies. The current evidence indicates that ERCP with combined therapy will reduce hospitalization relative to decompression alone. This was deemed to be a significant desirable effect given patient values and cost. The undesirable effect of combined therapy is bleeding. However, the panel believed that although the risk of hemorrhage during the index procedure was less in the decompression alone strategy, overall rates of adverse events of treatment would likely be similar after accounting for adverse events occurring during subsequent procedures to remove bile duct stones (Supplementary Table 12, available online at www.giejournal.org). Additionally, bleeding was managed conservatively in most cases (Supplementary Table 13, available online at www.giejournal.org). The panel therefore judged that the balance of effects favored intervention. However, given that hemodynamically unstable patients might not tolerate procedural bleeding or adverse events, it was believed that decompression alone should be considered in this group as well as for patients who are coagulopathic and/or are receiving antithrombotic agents and those who would need to have anticoagulation resumed immediately after sphincterotomy (eg, patients with mechanical heart valves).

TABLE 7. Continued

No. of patients		Effect			
Combined endoscopic therapy	Endoscopic decompression	Relative (95% confidence interval)	Absolute (95% confidence interval)	Certainty	Importance
286/323 (88.5%)	283/292 (96.9%)	OR, .95 (.39-2.34)	2 fewer per 1000 (from 45 fewer to 17 more)	⊕◯◯◯ VERY LOW	CRITICAL
34/485 (7.0%)	20/418 (4.8%)	OR, 2.02 (1.04-3.90)	44 more per 1000 (from 2 more to 116 more)	⊕◯◯◯ VERY LOW	CRITICAL
27/485 (5.6%)	4/418 (1.0%)	OR, 3.87 (1.48-10.12)	26 more per 1000 (from 5 more to 79 more)	⊕◯◯◯ LOW	CRITICAL
15/485 (3.1%)	9/418 (2.2%)	OR, 1.00 (.38-2.61)	0 fewer per 1000 (from 13 fewer to 33 more)	⊕◯◯◯ VERY LOW	CRITICAL
295	295	—	Standardized mean difference, .81 lower (1.21 lower to .4 lower)	⊕◯◯◯ VERY LOW	CRITICAL

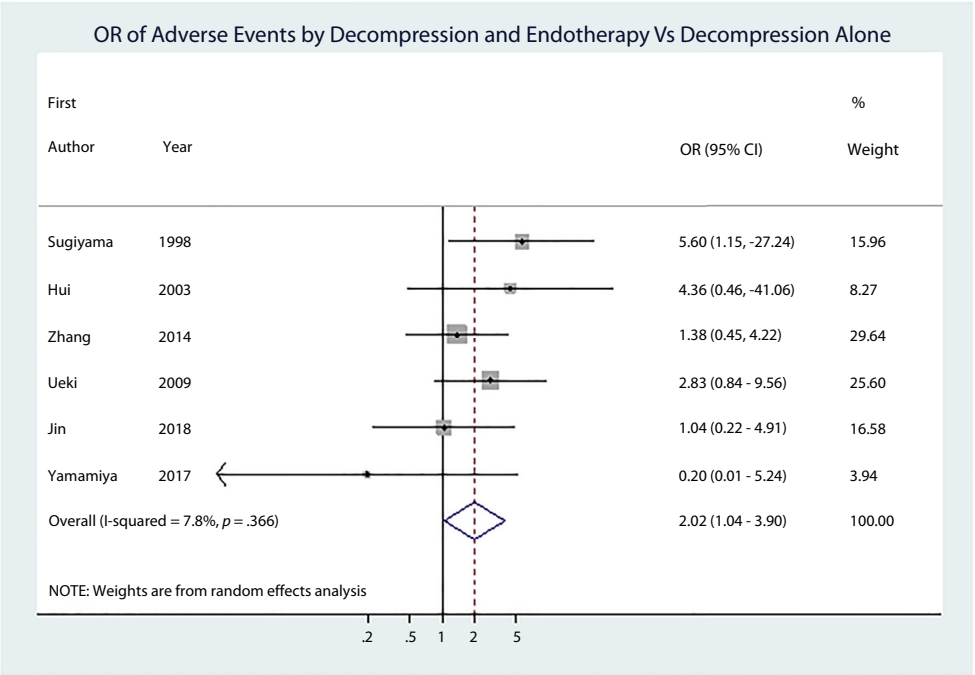

Figure 4. OR of adverse events for combined therapy versus decompression alone in cholangitis. *OR,* Odds ratio; *CI,* confidence interval.

DISCUSSION

After reports of increased bleeding associated with sphincterotomy for cholangitis therapy, the ideal endoscopic treatment approach to cholangitis has been controversial. Sugiyama and Atomi[10] reported bleeding in 4% of patients after sphincterotomy. In contrast, none of the patients managed with an initial decompression alone strategy developed bleeding during subsequent procedures. Four additional trials reported increased bleeding for combined therapy (sphincterotomy, stone removal, and drainage) relative to decompression alone but did not clarify whether only the first ERCP or all procedures needed to manage the bile duct problem were included.[27-30] This potentially biased against combination therapy where bleeding risk is encountered upfront versus decompression alone where it is delayed until subsequent procedures. Additionally, it was not possible to account for possible tendencies of endoscopists to use decompression alone in sicker patients.

Furthermore, it is unclear whether the rate of bleeding with sphincterotomy in the setting in cholangitis is definitely higher than sphincterotomy performed for other indications. Limited data suggest that bleeding primarily occurs in cholangitic patients with coagulopathy or ongoing anticoagulant use.[10] In several trials comparing combination therapy versus stent alone, patients with an elevated international normalized ratio and ongoing anticoagulant or antithrombotic use were either excluded or assigned to the decompression alone group.[11,31] Favorably, among the 31 bleeding episodes that occurred in 903 patients, 23 (74%) were managed conservatively, 7 (22%) responded to endoscopic therapy, and only 1 needed to be treated by embolization by interventional radiology. Of special consideration are patients with cholangitis who are physiologically compromised to the point that adverse events such as bleeding may not be tolerated. In this group a decompression alone strategy may be favored.

The emerging practice of using short fully covered metal stents in these cases may mitigate bleeding risk. The role of balloon sphincteroplasty versus sphincterotomy in cholangitis also requires further study.

Length of hospitalization was significantly decreased among those who underwent combined endoscopic therapy versus those who underwent decompression alone. It is unclear whether this was because patients remained hospitalized until complete duct clearance was achieved or until improvement of other clinical markers was accomplished. Several studies have indicated that sphincterotomy favors more rapid normalization of white blood cell count and total bilirubin.[29,32] Additionally, combined approaches may reduce the number of procedures and cost as described above in Patient values and preferences and Cost-effectiveness sections.

Controlled studies are needed to define the outcomes of specific endoscopic therapies for cholangitis, especially because of common bile duct stones. Adverse events and cost of initial procedure as well as subsequent treatment need to be accounted for. To optimally guide clinical management, studies should report and stratify outcomes by disease severity and rigorously address new endoscopic techniques and technologies in cholangitis.

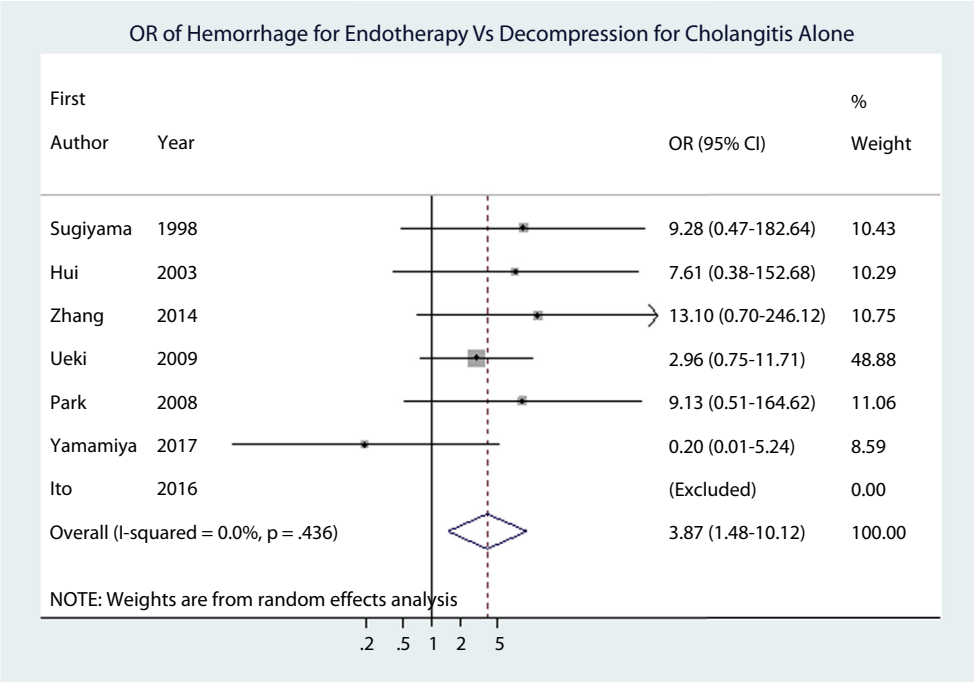

Figure 5. OR of hemorrhage for combined therapy versus decompression alone in cholangitis. *OR*, Odds ratio; *CI*, confidence interval.

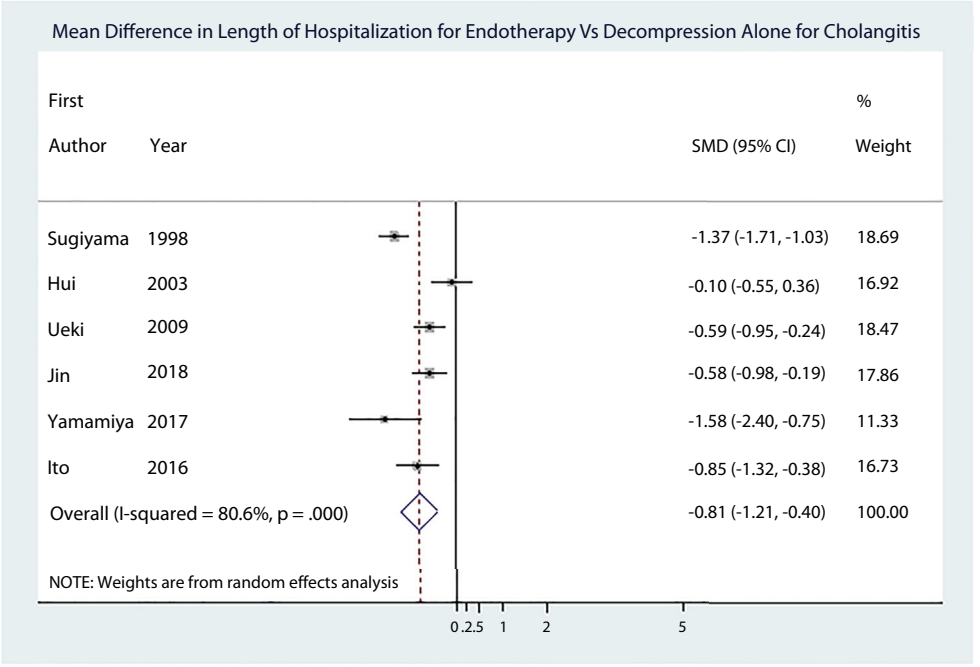

Figure 6. Length of stay for combined therapy versus decompression alone in cholangitis. *SMD*, Standardized mean difference.

SUMMARY AND CONCLUSIONS

GRADE methodology was used to derive clinical practice guidelines for management of cholangitis. These guidelines are evidenced-based approaches that will help management in patients with cholangitis; this included the role of ERCP versus PTBD for compression, ERCP ≤48 hours versus >48 hours after presentation, and whether patients with cholangitis should be managed with decompression alone versus more extensive endoscopic therapy. The goal of this document is to enable clinicians to use the best available literature to provide informed care for patients with cholangitis.

GUIDELINE UPDATE

ASGE guidelines are reviewed for updates approximately every 5 years, or in the event that new data may influence a recommendation. Updates follow the same ASGE guideline development process.

DISCLOSURE

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Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; NIS, Nationwide Inpatient Sample; OR, odds ratio; PICO, population, intervention, comparator, outcome; PTBD, percutaneous transhepatic biliary drainage; SOP, Standards of Practice.

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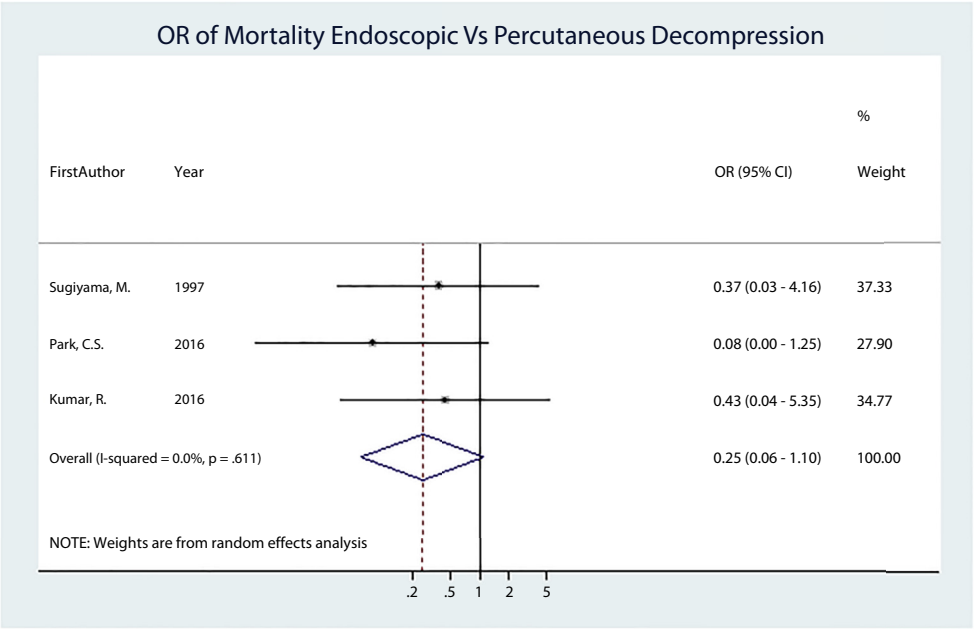
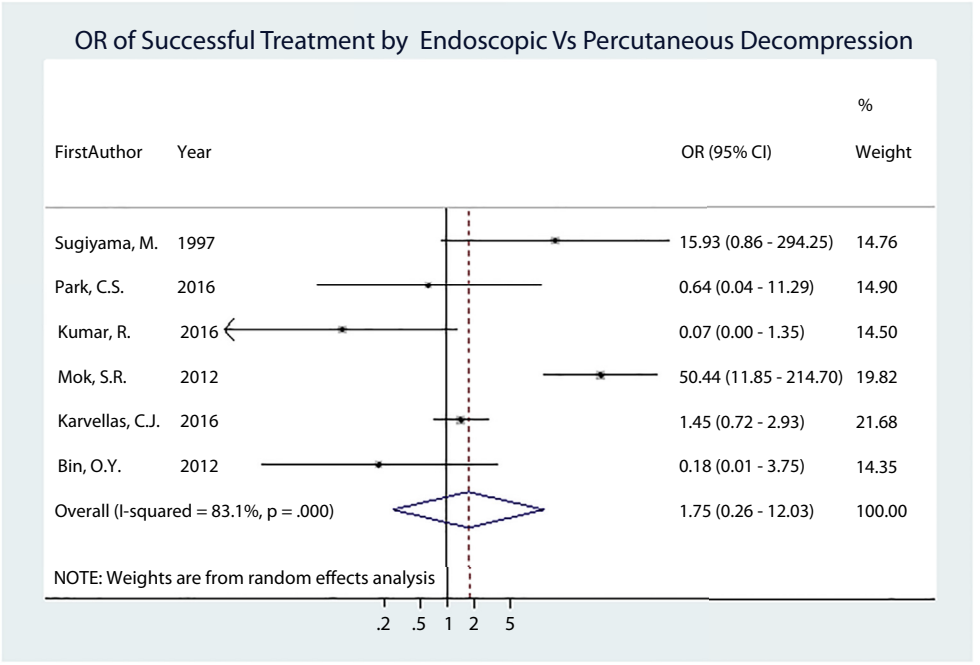
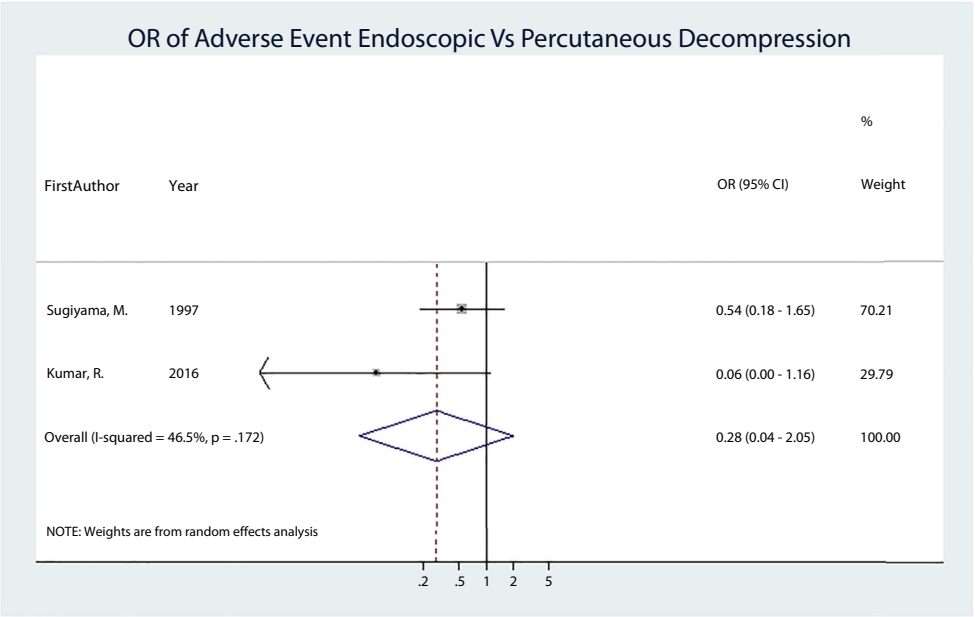


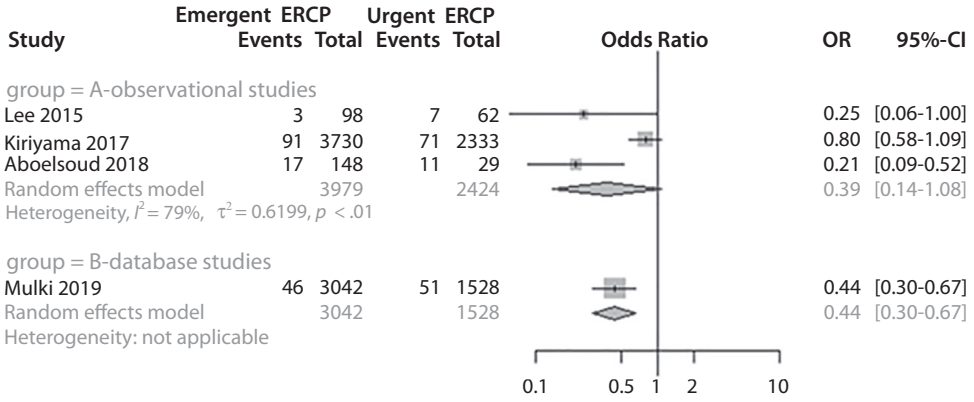
Supplementary Figure 1. Mortality for endoscopic versus percutaneous drainage for direct comparative studies of cholangitis management. *OR*, Odds ratio; *CI*, confidence interval.



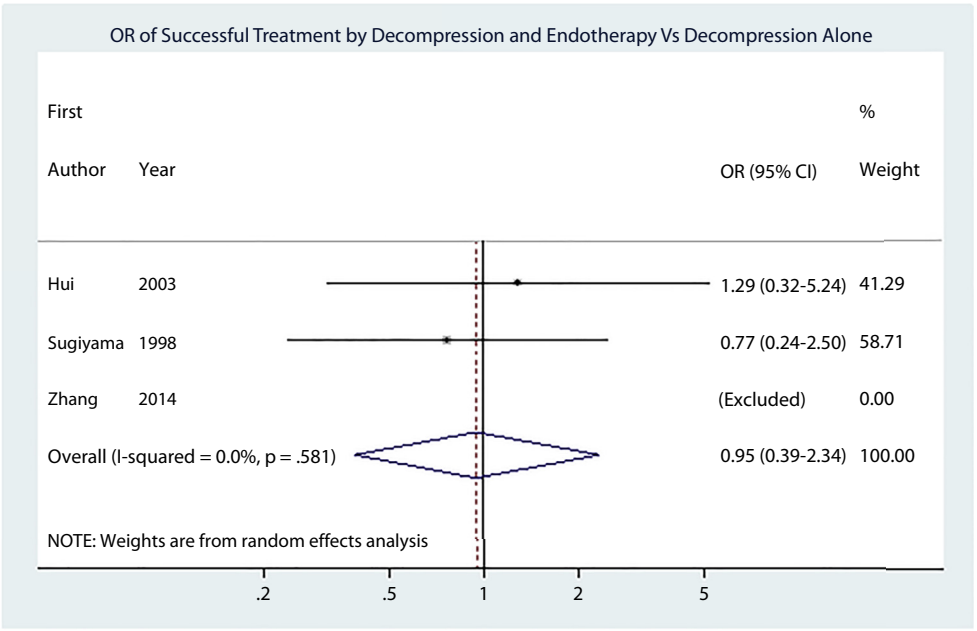
Supplementary Figure 2. Successful treatment by ERCP versus percutaneous transhepatic biliary drainage in cholangitis. *OR*, Odds ratio; *CI*, confidence interval.



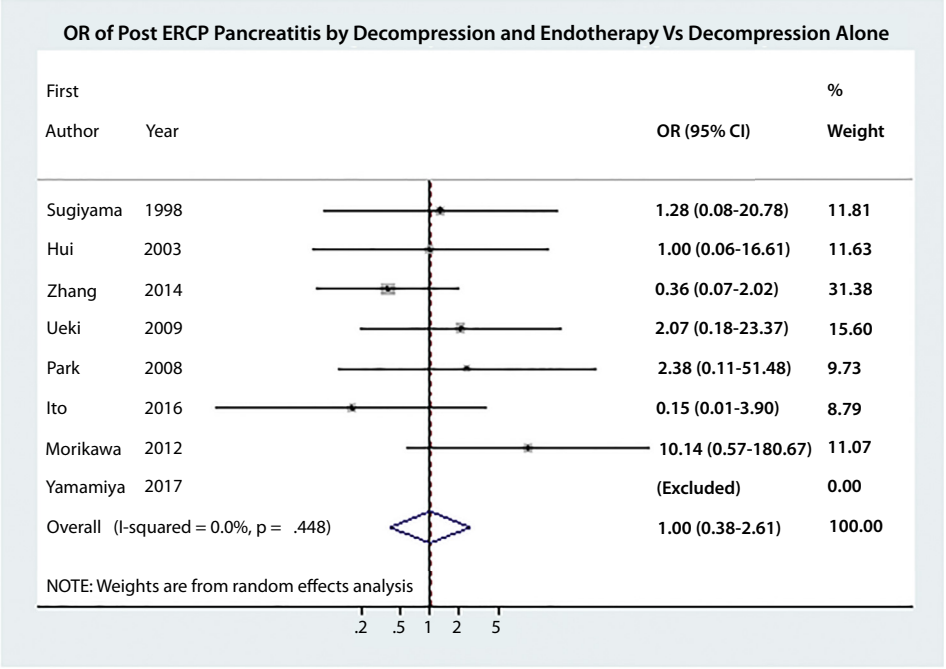
Supplementary Figure 3. OR of adverse events for ERCP versus percutaneous transhepatic biliary drainage in cholangitis. *OR*, Odds ratio; *CI*, confidence interval.



Supplementary Figure 4. Thirty-day mortality for cholangitis managed by ERCP ≤48 hours (emergent) versus 48 hours (urgent). *OR*, Odds ratio; *CI*, confidence interval.



Supplementary Figure 5. OR of successful treatment by decompression and endotherapy versus decompression alone. *OR*, Odds ratio; *CI*, confidence interval.



Supplementary Figure 6. OR of post-ERCP pancreatitis for combined therapy versus decompression alone in cholangitis. *OR*, Odds ratio; *CI*, confidence interval.

SUPPLEMENTARY TABLE 1. Search Strategy for population, intervention, comparator, and outcomes 1

Database	Search criteria
Database name: PubMed Database vendor: U.S. National Library of Medicine Database coverage: 1946 to present Date last searched: July 15, 2019	("Cholangitis"[Mesh] OR Cholangitis OR Cholangitides OR angiocholitis OR cholangeitis OR cholangiitis) AND ("Stents"[Mesh] OR "Drainage"[Mesh] OR "Plastics"[Mesh] OR "Prosthesis Implantation"[Mesh] OR "Prostheses and Implants"[Mesh] OR "Sphincterotomy, Endoscopic"[Mesh] OR "Sphincterotomy, Transduodenal"[Mesh] OR "Cholangiopancreatography, Endoscopic Retrograde"[Mesh] OR "Catheterization"[Mesh] OR "Catheters"[Mesh] OR "Decompression"[Mesh] OR drain* OR stent* OR Endoscopic Retrograde Cholangiopancreatograph* OR ERCP OR Sphincterotom* OR Papillotom* OR Sphincteroplast* OR nasobiliary catheter* OR Decompression OR percutaneous transhepatic cholangiograph*)
Database name: Embase & Embase Classic Database vendor: Elsevier Database coverage: 1947 to present Date last searched: July 15, 2019	('cholangitis'/exp OR Cholangitis OR Cholangitides OR angiocholitis OR cholangeitis OR cholangiitis) AND ('biliary tract drainage'/exp OR 'biliary drain'/exp OR 'stent'/exp OR 'sphincterotomy'/exp OR 'endoscopic sphincterotomy'/exp OR 'vater papillotomy'/exp OR 'endoscopic retrograde cholangiopancreatography'/exp OR 'catheterization'/exp OR 'catheters and tubes'/exp OR 'decompression'/exp OR 'percutaneous transhepatic cholangiography'/exp OR drain* OR stent* OR (Endoscopic AND Retrograde AND Cholangiopancreatograph*) OR ERCP OR Sphincterotom* OR papillotom* OR Sphincteroplast* OR (nasobiliary AND catheter*) OR Decompression OR (percutaneous AND transhepatic AND cholangiograph*))
Database name: Cochrane Library Database vendor: Wiley Database coverage: Cochrane Database of Systematic Reviews (1995–present) Cochrane Central Register of Controlled Trials (1898–present) Date last searched: July 15, 2019	ID Search No. 1 MeSH descriptor: [Cholangitis] explode all trees No. 2 Cholangitis No. 3 Cholangitides No. 4 angiocholitis No. 5 cholangeitis No. 6 cholangiitis No. 7 no. 1 or no. 2 or no. 3 or no. 4 or no. 5 or no. 6 No. 8 MeSH descriptor: [Stents] explode all trees No. 9 MeSH descriptor: [Drainage] explode all trees No. 10 MeSH descriptor: [Plastics] explode all trees No. 11 MeSH descriptor: [Prosthesis Implantation] explode all trees No. 12 MeSH descriptor: [Prostheses and Implants] explode all trees No. 13 MeSH descriptor: [Sphincterotomy, Endoscopic] explode all trees No. 14 MeSH descriptor: [Sphincterotomy, Transduodenal] explode all trees No. 15 MeSH descriptor: [Cholangiopancreatography, Endoscopic Retrograde] explode all trees No. 16 MeSH descriptor: [Catheterization] explode all trees No. 17 MeSH descriptor: [Catheters] explode all trees No. 18 MeSH descriptor: [Decompression] explode all trees No. 19 drain* No. 20 stent* No. 21 Endoscopic Retrograde Cholangiopancreatograph* No. 22 ERCP No. 23 Sphincterotom* No. 24 Papillotom* No. 25 Sphincteroplast* No. 26 nasobiliary catheter* No. 27 Decompression No. 28 percutaneous transhepatic cholangiograph*

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

Database	Search criteria
	No. 29 no. 8 or no. 9 or no. 10 or no. 11 or no. 12 or no. 13 or no. 14 or no. 15 or no. 16 or no. 17 or no. 18 or no. 19 or no. 20 or no. 21 or no. 22 or no. 23 or no. 24 or no. 25 or no. 26 or no. 27 or no. 28 No. 30 no. 7 and no. 29
Database name: Web of Science Core Collection Database vendor: Clarivate Analytics Database coverage: Science Citation Index Expanded (1900 to present) Social Sciences Citation Index (1900 to present) Arts & Humanities Citation Index (1975 to present) Conference proceedings Citation Index–Science (1990 to present) Conference Proceedings Citation Index–Social Science & Humanities (1990 to present) Book Citation Index–Science (2005 to present) Book Citation Index–Social Sciences & Humanities (2005 to present) Emerging Sources Citation Index (2015 to present) Current Chemical Reactions (1985 to present) Index Chemicus (1993 to present) Date last searched: July 15, 2019	(Cholangitis OR Cholangitides OR angiocholitis OR cholangeitis OR cholangiitis) AND (drain* OR stent* OR Endoscopic Retrograde Cholangiopancreatograph* OR ERCP OR Sphincterotom* OR Papillotom* OR Sphincteroplast* OR nasobiliary catheter* OR Decompression OR percutaneous transhepatic cholangiograph*)
Database name: Clinicaltrials.gov Database vender: U.S. National Library of Medicine Date last searched: July 15, 2019 Database name: Google Scholar Date last searched: July 15, 2019	*Advanced search* *In condition or disease search box:* Cholangitis OR Cholangitides OR angiocholitis OR cholangeitis OR cholangitis *In intervention/treatment search box:* drain OR drainage OR stent OR stenting OR Endoscopic Retrograde Cholangiopancreatography OR ERCP OR Sphincterotomy OR Papillotomy OR Sphincteroplasty OR Decompression OR percutaneous transhepatic cholangiography Cholangitis (drain OR drainage OR stent OR stenting OR Endoscopic Retrograde Cholangiopancreatography OR ERCP OR Sphincterotomy OR Papillotomy OR Sphincteroplasty OR Decompression OR percutaneous transhepatic cholangiography)

SUPPLEMENTARY TABLE 2. Search strategy for population, intervention, comparator, and outcomes 3

Database	Search criteria
Database name: Medline [MEDLINE(R) ALL] Database vendor: Ovid SP Database coverage: 1946 to present Date last searched: February 28, 2019	(exp Cholangitis/ OR Cholangitis OR Cholangitides OR angiocholitis OR cholangeitis OR cholangitis) OR ((Biliary OR "bile duct") ADJ8 (inflammat* OR infection)) AND (exp Stents/ OR exp Drainage/ OR exp Plastics/ OR exp Prosthesis Implantation/ OR exp "Prostheses and Implants"/ OR drain* OR stent*)
Database name: Embase & Embase Classic Database vendor: Elsevier Database coverage: 1947 to present Date last searched: February 28, 2019	('cholangitis'/exp OR Cholangitis OR Cholangitides OR angiocholitis OR cholangeitis OR cholangiitis) OR ((biliary OR "bile duct") NEAR/8 (inflammat* OR infection)) AND ('biliary tract drainage'/exp OR 'biliary drain'/exp OR 'stent'/exp OR drain OR stent*)
Database name: Cochrane Library Database vendor: Wiley Database coverage: Cochrane Database of Systematic Reviews (2005 to present) Cochrane Central Register of Controlled Trials (1898 to present) Database of Abstracts of Reviews of Effects (1994 to present) Cochrane Methodology Register (1951 to present) Health Technology Assessment Database (1989 to present) National Health Service Economic Evaluation Database (1968 to present) Date last searched: February 28, 2019	ID Search No. 1 MeSH descriptor: [Cholangitis] explode all trees No. 2 Cholangitis No. 3 Cholangitides No. 4 angiocholitis No. 5 cholangeitis No. 6 cholangiitis No. 7 no. 1 OR no. 2 OR no. 3 OR no. 4 OR no. 5 OR no. 6 No. 8 biliary No. 9 "bile duct" No. 10 no. 8 OR no. 9 No. 11 inflammat* No. 12 infection No. 13 no. 11 OR no. 12 No. 14 no. 10 AND no. 13 No. 15 no. 7 OR no. 14 No. 16 MeSH descriptor: [Stents] explode all trees No. 17 MeSH descriptor: [Drainage] explode all trees No. 18 MeSH descriptor: [Plastics] explode all trees No. 19 MeSH descriptor: [Prosthesis Implantation] explode all trees No. 20 MeSH descriptor: [Prostheses and Implants] explode all trees No. 21 drain* No. 22 stent* No. 23 no. 16 OR no. 17 OR no. 18 OR no. 19 OR no. 20 OR no. 21 OR no. 22 No. 24 no. 15 AND no. 23
Database name: Web of Science Core Collection Database vendor: Clarivate Analytics Database coverage: Science Citation Index Expanded (1900 to present) Social Sciences Citation Index (1900 to present) Arts & Humanities Citation Index (1975 to present) Conference Proceedings Citation Index–Science (1990 to present) Conference Proceedings Citation Index–Social Science & Humanities (1990 to present) Book Citation Index–Science (2005 to present) Book Citation Index–Social Sciences & Humanities (2005 to present) Emerging Sources Citation Index (2015 to present) Current Chemical Reactions (1985 to present) Index Chemicus (1993 to present) Date last searched: February 28, 2019	Cholangitis OR Cholangitides OR angiocholitis OR cholangeitis OR cholangiitis) OR ((biliary OR "bile duct") NEAR/8 (inflammat*OR infection)) AND (drain* OR stent*)

(*continued on the next page*)

SUPPLEMENTARY TABLE 2. Continued

Database	Search criteria
Database name: Clinicaltrials.gov Database vender: U.S. National Library of Medicine Date last searched: February 28, 2019	*In expert search:* (Cholangitis OR Cholangitides OR angiocholitis OR cholangeitis OR cholangiitis OR biliary inflammation OR biliary infection OR bile duct inflammation OR bile duct infection) AND (drain OR drainage OR stent OR stenting)
Database name: Google Scholar Date last searched: February 28, 2019	(Cholangitis OR Cholangitides OR angiocholitis OR cholangeitis OR cholangiitis) AND (drain OR drainage OR stent OR stenting)

SUPPLEMENTARY TABLE 3. Trials directly comparing ERCP versus (PTBD) for Cholangitis

First Author, Year	ERCP (n)	PTBD (n)	Success ERCP (n)	Success PTBD (n)	ERCP adverse events (n)	PTBD adverse events (n)	ERCP mortality (n)	PTBD mortality (n)	Mean (SD) ERCP length of stay (days)	Mean (SD) PTBD length of stay (days)
Sugiyama 1997[10]	77	58	77	53	6	8	1	2	14.5 (4.1)	30.5 (7.2)
Bin 2012[19]	22	15	19	15	*	*	*	*	*	*
Mok 2012[33]	230	20	227	12	*	*	*	*	*	*
Park 2016[9]	293	23	284	23	*	*	*	*	6.9 (4.0)	12.1 (5.1)
Karvellas 2016[26]	107	113	81	90	*	*	*	*	*	*
Kumar 2016[34]	16	15	11	15	0	5	1	2	14.1 (9.8)	28.3 (30.2)

PTBD, Percutaneous transhepatic biliary drainage.
*Comparative data unavailable.

SUPPLEMENTARY TABLE 4. Outcomes of ERCP versus PTBD in cholangitis from noncomparative observational cohorts

	ERCP				PTBD			
	Pooled proportion	95% Confidence interval	No. of cases	I^2 (%)	Summary proportion	95% Confidence interval	No. of cases	I^2 (%)
Successful decompression	.97	.96-.98	73	83	.94	.88-.98	17	85
Mortality	.04	.02-.05	42	80	.06	.03-.10	8	12.3
Total adverse events	.05	.04-.07	48	81	.10	.07-.14	8	17
Bleeding	.03	.02-.04	32	37	.08	.05-.13	4	20
Pancreatitis	.03	.02-.05	39	79	.02	.02-.12	1	—
Bile leak	.01	0-.06	1	—	.02	0-.06	4	0
	Pooled mean	95% Confidence interval		I^2 (%)	Pooled mean	95% Confidence interval		I^2 (%)
Length of hospitalization, day	10.4	9.0-11.8	19	99	23.2	(8-38.4)		75

PTBD, Percutaneous transhepatic biliary drainage; —, insufficient information.

SUPPLEMENTARY TABLE 5. ERCP versus PTBD Outcomes Stratified by Cholangitis Severity from Comparative and Noncomparative Observational Studies

	ERCP				PTBD			
	Nonsevere proportion (95% confidence interval)	No. of studies	Severe proportion (95% confidence interval)	No. studies	Nonsevere proportion (95% confidence interval)	No. of studies	Severe proportion (95% confidence interval)	No. of studies
Successful decompression	.98 (.95-.99)	8	.96 (.92-.99)	12	1.0 (.68-1)	1	.98 (.85-1.0)	5
Mortality	.02 (0-.04)	4	.04 (.02-.06)	8	0 (0-18)	1	.14 (.01-.35)	2
Total adverse events	.06 (.03-.11)	6	.04 (.03-.06)	5	—	—	.33 (.15-.58)	1
Postintervention pancreatitis	.04 (.02-.08)	6	.02 (.01-.05)	4	—	—	—	—
Bile leak	—	—	—	—	—	—	—	—
Bleeding	0.02(.01-0.04)	3	0.03(.01-0.04)	4	—	—	—	—
	Pooled mean	No. of studies	Pooled mean	No. of studies	Pooled mean	No. of studies	Pooled mean	No. of studies
Length of hospitalization, days	10 (7.7-12.4)	5	17.5 (11.8-23.2)	2	—	—	28.3(13-43.5)	1

PTBD, Percutaneous transhepatic biliary drainage; —, insufficient information.

SUPPLEMENTARY TABLE 6. Quality parameters (Newcastle-Ottawa scale tool) of studies of endoscopic vs percutaneous drainage for cholangitis

First author	Year	Journal	Study type	Selection	Comparability	Exposure/outcome
Sugiyama[10]	1997	Arch Surg	Cohort	****	**	***
Bin[19]	2012	Hepato-Gastroenterology	Cohort	***#	*#	***
Karvellas[26]	2016	Aliment Pharmacol Ther	Cohort	****	*##	***
Park[9]	2016	Hepatobiliary Pancreat Dis	Cohort	***###	*###	***
Kumar[34]	2016	Gastrointest Endosc	Cohort	****	**	***
Mok[33]	2012	J Interv Gastreonterol	Cohort	****	####	**

*, **, ***, **** as defined by Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON), Canada: Ottawa Hospital Research Institute; 2016.

#Although groups had comparable biochemical profiles, those in the percutaneous group had undergone prior bowel surgery.

##Percutaneous vs endoscopic populations not clearly defined although all severe.

###Similar severity, although PTBD (percutaneous transhepatic biliary drainage) included failed ERCP.

####Comparison information for PTBD vs ERCP not provided.

SUPPLEMENTARY TABLE 7. Quality parameters (Newcastle-Ottawa scale tool) of studies of ERCP at ≤48 versus >48 h

Study	Selection	Comparability	Outcomes	Total score
Aboelsoud et al	**	*	**	5
Hou et al	***	*	**	6
Lee et al	***	*	***	7
Patel et al	***		**	5
Alper et al	***		**	5
Tan et al	***	*	**	6
Jang et al	****	*	**	7
Park et al	**	*	**	5
Kiriyama et al	***	*	***	7

SUPPLEMENTARY TABLE 8. Additional studies of ERCP timing in cholangitis

Author Year	Time to ERCP	Outcomes
Parikh 2018[13]	<24 h 24-48 h >48 h	Shorter length of stay for ERCP <24 h, 4.5 (95% CI, 4.4-4.7) than 24-48 h, 5.8 (95% CI, 5.6-5.9), and >48 h, 9.3 (9.1-9.5 days). No different in inpatient mortality for <24 h, 1.7%, vs 24-48 h, 1.2%; both less than ERCP >48 hours 2.7%.
Mulki 2019[14]	<24 h 24-48 h >48 h	Lower inpatient mortality, OR .5 (95% CI, .76-0.83), 30-day mortality, OR .5 (95% CI, .3-.7), and 30-day readmission, OR .6 (95% CI, .5-.7). The length of stay, 4.5 ± 3.9 vs 6.8 ± 5.4 days and for ERCP <48 vs >48 h. No difference in outcomes for ERCP 0-24 vs 24-48 h.
Navaneethan 2013[21]	>48 h after admission	OR of 30-day readmission 2.5 (95% CI, 1.0-6.1) for ERCP >48 h after admission.
Khashab 2012[15]	Delayed ERCP >72 h after admission	Multivariate OR 19.8 for >90th percentile hospital stay. OR 7.8 (95% CI, 1.1-58) for composite outcome of death, intensive care unit stay, persistent organ failure for ERCP >72 h.
Chak 2000[35]	>24 h after admission	ERCP <24 h shortens median length of hospitalization 5 vs 9.5 days.
Tabibian 2016[36]	Weekend vs weekday admission	Weekend admission does not confer higher mortality, 1.9% vs 4.7%, organ failure, 13.5% vs 14.7%, or length of stay, 4.6 ± 4.0 days vs 4.3 ± 2.4 days, than weekday admission.
Hakuta 2018[22]	< 12 h vs ≥12 h	Nonsevere cholangitis same median length of stay, 11 days (interquartile range, 9-15), for both group with no difference in mortality, organ failure, or 30-day readmission.
Inamdar 2016[16]	Weekend vs weekday admission	Weekend ERCP for cholangitis has comparable mortality, 2.9% vs 2.6 % and length of stay, 7.0 (95% CI, 6.89-7.04) vs 6.9 (95% CI, 6.8-7.0) days as weekday ERCP.
Mok, 2012[33]	>22 h >42 h	Hospital readmission more likely if ERCP after >22 h and mortality more likely if >42 h than before 11 h.
Karvellas, 2016[26]	>12 h*	Severe cholangitis, ERCP >12 h associated with increased mortality, OR 3.4 (95% CI, 1.1-10.3).

OR, Odds ratio; *CI*, confidence interval.
*After 12 hours of septic shock defined as hypotension requiring pressors despite 2 L of fluid resuscitation.

SUPPLEMENTARY TABLE 9. clinical outcomes for combined endoscopic therapy versus decompression alone in cholangitis

Author and year	Combined therapy	Stent alone	Combined therapy success	Stent alone success	Combined therapy hospital stay	Stent alone hospital days	Combined therapy mortality
Sugiyama 1997[10]	73	93	67 (91.8)	89 (95.7)	10.4 ± 3.6	15.8 ± 4.2	0
Hui 2003[28]	37	37	33 (89.2)	32 (86.5)	6.5 (7)*	7 (7)*	1 (2.7)
Zhang 2014[29]	36	36	36 (100)	36 (100)	—	—	
Ueki 2009[27]	63	64	—	—	11.8 ± 8.0	16.2 ± 6.8	
Park 2008[30]	55	25	55 (100)	25 (100)			
Jin 2018[37]	44	61	44 (100)	61 (100)	7.3 ± 2.2	9.1 ± 3.6	0
Yamamiya 2017[11]	19	12	19 (100)	12 (100)	10 (6)	17 (16)	0
Ito 2016[31]	59	28	32 ?	25 ?	13.2 ± 7.5	21.8 ± 14.1	
Morikawa 2012[38]	99	62	—	—	—	—	

—, Insufficient data available.
Values are n or mean ± standard deviation, unless otherwise defined.
*Median (interquartile range).

SUPPLEMENTARY TABLE 9. Continued

Stent alone mortality	Combined therapy adverse events	Stent alone adverse events	Combined therapy bleeding	Stent alone bleeding	Combined therapy post-ERCP pancreatitis	Stent alone post-ERCP pancreatitis
0	8 (11)	2 (2.2)	3 (4.1)	0	1 (1.4)	1 (1.1)
2 (5.4)	4 (10.8)	1 (2.7)	3 (8.1)	0	1 (2.7)	1 (2.7)
	9 (25)	7 (19.4)	5 (13.9)	0	2 5.6)	5 (13.9)
	10 (15.9)	4 (6.3)	8 (12.7)	3	2 (3.2)	1 (1.6)
	—	—	8 (14.5)	0 (4.7)	2 (3.6)	0
0	3 (6,8)	4 (6.6)	—	—	—	—
0	0	1 (8.3)	0	1 (8.3)	0	0
	0 (?)	1 ?	0	0	0	1 (3.5)
	—		—	—	7 (7.1)	0

SUPPLEMENTARY TABLE 10. Outcomes of combined endoscopic therapy vs decompression alone by disease severity

	All cholangitis			Severe cholangitis			Nonsevere cholangitis		
	No. of studies	Odds ratio (95% confidence interval)	I^2 (%)	No. of studies	Odds ratio (95% confidence interval)	I^2 (%)	No. of studies	Odds ratio (95% confidence interval)	I^2 (%)
Successful treatment	8	1.0 (.4-2.3)	0	1	1.3 (.3-5.2)	—			
Mortality	5	.5 (0-5.6)	—	1	.5 (0-5.6)	—			
Overall adverse events	5	2.0 (1.0-3.9)	7.8	1	4.4 (.5-41.1)	—	3	1.7 (.8-3.4)	0
Post-ERCP pancreatitis	8	1.0 (.4-2.6)	0	2	1.5 (.2-11.8)	0	2	.7 (.1-3.6)	23.7
Bleeding	7	3.9 (1.5-10.1)	0	2	8.4 (1.0-67.0)	0	2	3.9 (1.1-13.4)	0
		Standardized mean difference (95% confidence interval)			**Standardized mean difference (95% confidence interval)**			**Standardized mean difference (95% confidence interval)**	
Length of hospitalization	6	–.8 (–.4 to –1.2)	80.6	1	–.1 (–.6 to .4)	—	—	–.6 (–.9 to –.3)	0

—, Insufficient data available.

SUPPLEMENTARY TABLE 11. Quality parameters of studies of combined therapy vs stent alone for cholangitis

First author	Year	Journal	Study type	Newcastle Ottawa scale		
				Selection	Comparability	Exposure/outcome
Sugiyama[10]	1997	Am J Gastroenterol	Cohort	****	**	***
Hui[28]	2003	Gastrointest Endosc	Cohort	****	**	***
Ueki[27]	2009	J Gastroenterol	Cohort	* ***	*†	***
Park[30]	2008	Gastrointest Endosc	Cohort	****	*‡	***
Jin[37]	2018	Int J Clin Exp Med	Cohort	****	*§	***
Yamamiya[11]	2017	World J Clin Cases	Cohort	***‖	***‖	***
Ito[31]	2016	World J Gastrointest Endosc	Cohort	***¶	***¶	***
Morikawa[38]	2012	Gastrointest Endosc	Cohort	****	*‡	***

				Cochrane tool					
				Random sequence generation	Concealed allocation	Blinding Participants	Blinding Outcome Interpretation	Incomplete Outcome	Selective Reporting
Zhang[29]	2014	J Dig Dis	Randomized controlled trial	+	+	–	–	+	

*Excluded coagulopathy.
†Higher white blood cell and bilirubin in patients managed by decompression alone.
‡No report of comparison of treatment arms.
§Difference in proportion with single stone.
‖More severe cases and antithrombotic use in decompression alone arm.
¶More anticoagulant use, thrombocytopenia, coagulopathy in decompression alone arm.

SUPPLEMENTARY TABLE 12. Severity, etiology, and reporting of adverse outcome of cholangitis, adjudication of outcomes by first vs all procedures

Authors Year	Severe cholangitis (%)	Etiology			Reported subsequent ERCP (%)	Adverse events for subsequent ERCP
		Stones (%)	Benign stricture (%)	Malignant stricture (%)		
Sugiyama 1997[10]	20	71	7	22	32	0
Hui 2003[28]	100	100	0	0	100	—
Zhang 2014[29]	10	100	0	0	—	—
Ueki 2009[27]	0	127	0	0	100	—
Park 2008[30]	—	92.5	6.2		—	—
Jin 2018[37]	0	105	0	0	—	—
Yamamiya 2017[11]	0	100	0	0	*	—
Ito 2016[31]	—	87	0	0	—	0
Morikawa 2012[38]	17.2	65.9	3.6	29.9	—	—

—, Insufficient data available.
*Percentage of ERCP not reported but median of 1 (interquartile range, 1-1) for combination group vs 2 (interquartile range, 2-2) for decompression only group.

SUPPLEMENTARY TABLE 13. Definition and management of hemorrhage

Author	Definition		Management			
	Overt bleeding (procedural, melena, or hematochezia)	Decrease in hemoglobin >2 g/dL	Total	Conservative	Transfusion	Endoscopic therapy
Sugiyama 1997[10]	X	X	3	1	2	2
Hui 2003[28]	X	X	3	1	—	2
Zhang 2014[29]	X		5	3	—	2*
Ueki 2009[27]	X	X†	11	11		
Park 2008[30]	X	X†	8	6		2
Jin 2018[37]	—	—	?			
Yamamiya 2017[11]		X†	1	1		
Ito 2016[31]	X	X	0	—	—	—
Morikawa 2012[38]	—	—	0	—	—	—

—, Insufficient data available.
*IR embolization and endoscopic therapy for 1 patient.
†Transfusion or endoscopic therapy also included in bleeding definition.