Emergent versus urgent ERCP in acute cholangitis: a systematic review and meta-analysis

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Background and Aims: Acute cholangitis is characterized by abdominal pain, fever, and jaundice. Most patients respond to medical management with intravenous hydration and antibiotics. About 20% to 30% require biliary drainage, and ERCP is the procedure of choice. We conducted a systematic review and meta-analysis to evaluate the impact of emergent biliary drainage on patient outcomes.

Methods: A comprehensive literature review was conducted by searching the Embase and PubMed databases from inception to April 2019 to identify all studies that evaluated the impact of timing of ERCP on patient outcomes. Our primary outcome was in-hospital mortality (IHM), and secondary outcomes were length of stay (LOS), organ failure, and 30-day mortality. Fixed and random effects models were used to generate pooled measures of IHM, 30-day mortality, and LOS.

Results: Nine observational studies involving 7534 patients were included in the primary meta-analysis. IHM was significantly lower in patients who underwent emergent biliary drainage within 48 hours (odds ratio [OR], 0.52; 95% confidence interval [CI], 0.28-0.98). As a sensitivity analysis, we pooled the data from 2 population registry studies of 81,893 patients, which yielded consistent results for the main outcomes. LOS was also significantly lower in patients who underwent ERCP within 48 hours with a mean difference of 5.56 days (95% CI, 1.59-9.53). Patients who underwent emergent ERCP also had lower odds of 30-day mortality (OR, 0.39; 95% CI, 0.14-1.08) and organ failure (OR, 0.69; 95% CI, 0.33-1.46).

Conclusions: Our study reveals that performing emergent ERCP within 48 hours in patients with acute cholangitis is associated with lower IHM, 30-day mortality, organ failure, and shorter LOS. (Gastrointest Endosc 2020;91:753-60.)

Abbreviations: AC, acute cholangitis; CI, confidence interval; IHM, in-hospital mortality; LOS, length of stay; MD, mean difference; OR, odds ratio.

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INTRODUCTION

Acute cholangitis (AC) is an infection of the extrahepatic biliary system. First described by Charcot in 1877, it was clinically characterized by abdominal pain, fever, and jaundice alongside abnormal laboratory test results suggestive of infection and biliary obstruction.[1,2] Bile is normally a sterile substance with bacteriostatic properties. Infections result from ascending migration of pathogens or portal bacteremia.[2,3] Normal sphincter of Oddi pressure between 10 and 15 mm Hg provides a barrier to prevent bacterial migration into the biliary tree. With biliary obstruction, there is disruption of this normal flow and increase in pressure of the biliary tract. This leads to cholangiovenous reflux, allowing pathogens to have access to the biliary tree and cause cholangitis.[3] The most common cause is choledocholithiasis followed by additional pathologies that obstruct the extrahepatic biliary tree such as pancreatic cancer, ampullary adenoma or cancer, metastasis, parasitic infection, biliary stent obstruction, Lemmel syndrome, Mirizzi syndrome, and AIDS cholangiopathy.[2,3]

In its severe form, AC is a rapidly progressive infection with mortality as high as 30%.[1] Most patients respond to aggressive medical management comprising intravenous hydration and antibiotic therapy. About 20% to 30% fail to respond to medical management alone and require biliary drainage.[3,4] ERCP is the procedure of choice for biliary decompression. The current Tokyo guidelines recommend urgent biliary drainage depending on the severity without any specific timing.[5] Current literature is conflicting; some studies show improved outcomes with emergent biliary drainage, whereas others do not show any significant advantage of emergent ERCP in AC. We therefore conducted a systematic review and meta-analysis of the available literature to evaluate the impact of emergent biliary drainage within 48 hours on in-hospital mortality (IHM) and length of stay (LOS) compared with urgent ERCP after 48 hours.

METHODS

Search strategy and selection criteria

A systematic literature search was conducted in the PubMed and Embase databases to identify all original studies published from inception to April 2019 that evaluated the impact of timing of ERCP on IHM. A manual search through the bibliographies of the retrieved publications was conducted to increase the yield of potentially relevant articles. The systematic literature review was independently conducted by 2 investigators. Eligible studies were required to be observational studies that reported IHM or LOS or 30-day mortality in patients admitted with AC and received emergent ERCP within 48 hours, compared with patients who underwent urgent ERCP after 48 hours. Our primary outcome was IHM, and secondary outcomes were LOS, organ failure, and 30-day mortality. We did not restrict inclusion of studies based on the cause of AC, and therefore we included all the studies evaluating the timing of ERCP in patients with AC regardless of the cause. If 2 studies used a similar database, only 1 study was included to avoid patient overlap. The studies were also required to provide the effect estimates with the 95% confidence interval (CI) or sufficient raw data to calculate them. The sample size of a study did not restrict its inclusion. This study was conducted in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[6]

Quality assessment

The Newcastle-Ottawa quality assessment scale was used to evaluate the quality of cohort studies in 3 areas: the recruitment of cases and controls, the comparability of the 2 groups, and the outcome of interest of the cohort study. The results of the methodological quality assessment did not influence the eligibility of the studies.

Data extraction

A structured data collection form was used to extract the following data from each study: the title of the study, publication year, name of the first author, country where the study was performed, number of participants, characteristics of the participants, timing of ERCP, and outcomes of interest (IHM, LOS, 30-day mortality, and organ failure). To ensure accuracy, data extraction was independently performed by 2 investigators (U.I. and O.S.) and was reviewed by the third investigator (M.K.). Any disagreement was resolved by mutual consensus.

Statistical analyses

Meta-analyses were conducted for each outcome using fixed and random effects models. Odds ratios (ORs) and 95% CIs were calculated initially for binary outcomes from the studies. The pooled OR was considered statistically significant if the 95% CI did not span 1. Mean differences (MDs) with corresponding 95% CIs were estimated and considered statistically significant if the 95% CI did not cover 0. Each study's pooled estimates and measures of variability were used to generate forest plots. Publication bias was evaluated by the Egger test. Variability between studies was assessed by heterogeneity tests using the I^2 statistic. The I^2 statistic was calculated to quantify the proportion of between-study heterogeneity attributable to variability in the association rather than sampling variation. Jackknife sensitivity analysis was performed to evaluate the robustness of the results by omitting 1 study at a time and repeating the meta-analysis based on the rest of the data. Meta-regression was implemented to investigate the potential unaccounted heterogeneity from study-level factors, including age, in the outcome of interest across studies. All analyses were conducted using RStudio (Version 1.0.136) using the Metafor package.

RESULTS

The initial search revealed 1454 articles, 543 in PubMed and 911 in Embase. After removal of duplicates, review articles, and editorials, 789 articles underwent title and abstract review, and 30 articles were selected for full manuscript review. Articles were excluded if they did not report the IHM, 30-day mortality, or LOS outcomes. Nine studies involving 7534 patients were included in the final meta-analysis.[7,9-12,14-17] A sensitivity analysis of 2 national database studies with 81,893 patients was also performed.[8,13] Figure 1 presents the systematic literature review process of our study.

All the included studies were observational studies. Seven studies were of good quality, and 4 were fair quality. There

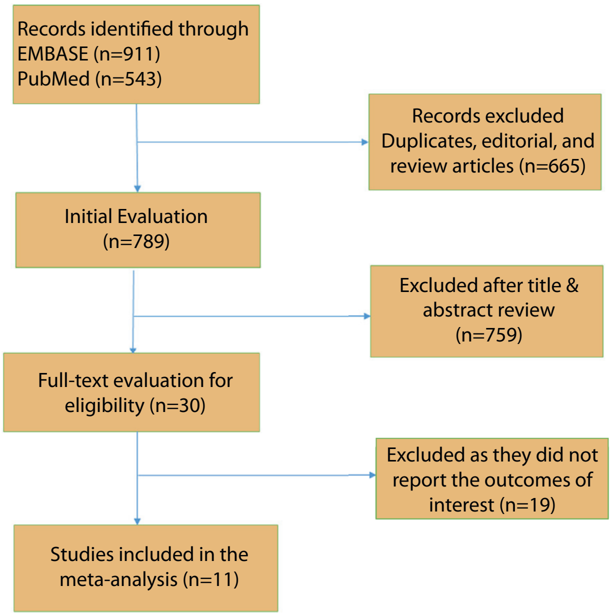

Figure 1. Literature review process.

were some differences in the baseline characteristics of the patients included in the studies. The prevalence of severe AC was higher in patients included in Aboelsoud et al's[7] study because this study was done on critically ill patients. This study also has more elderly patients compared with other studies. Hou et al's[9] study has more patients from Hispanic ethnicity compared with other studies that have a white majority.[9] Baseline characteristics of the studies are reported in Supplementary Table 1 (available online at www.giejournal.org). Choledocholithiasis was the most common cause of AC in the studies. Other causes included benign strictures, malignant strictures, and stent occlusion.

In-hospital mortality and 30-day mortality

Five observational studies including 762 patients compared IHM in patients who underwent emergent ERCP within 48 hours and urgent ERCP after 48 hours. Of these, 469 underwent emergent ERCP and 293 underwent urgent ERCP.[7,9-12] Mortality was significantly lower in patients who underwent biliary drainage within 48 hours (OR, 0.52; 95% CI, 0.28-0.98) without heterogeneity (I^2 = 0%, P = .62) (Fig. 2). We performed subgroup analysis of the 2 studies including 81,893 patients identified through national databases. IHM was significantly lower in patients who underwent emergent ERCP within 48 hours (OR, 0.58; 95% CI, 0.52-0.64) with no significant differences between the 2 subgroups as evaluated by test for subgroup differences (χ^2 = 0.12, P = .76, I^2 = 0). There was no statistical heterogeneity in the studies (I^2 = 0%, P = .47). The Egger test suggested that no potential publication bias for IHM (Egger P = .68) and LOS (Egger P = .27) existed among the studies.

Three observational studies including 6400 patients evaluated 30-day mortality in patients who underwent emergent ERCP within 48 hours and urgent ERCP after 48 hours.[7,10,17] Although 30-day mortality trended lower in patients who underwent ERCP within 48 hours, it was not statistically significant (OR, 0.39; 95% CI, 0.14-1.08) with heterogeneity (I^2 = 79%) (Fig. 3). However, in a subgroup analysis including a national database study with 4570 patients, patients who underwent emergent ERCP within 48 hours have significantly lower odds for 30-day mortality (OR, 0.44; 95% CI, 0.30-0.67).[13] We also performed a subgroup analysis to determine whether emergent ERCP has any mortality benefit in patients with mild to moderate AC. Only 2 studies reported 30-day mortality [13,17] and IHM mortality stratified according to severity of AC.[11,13] Severe AC is associated with end organ dysfunction, whereas mild to moderate AC is not associated with end organ dysfunction. Patients with mild to moderate AC who underwent ERCP within 48 hours have lower odds of IHM (OR, 0.51; 95% CI, 0.30-0.85) and 30-day mortality 0.59 (95% CI, 0.44-0.81). Patients with severe AC who underwent emergent ERCP within 48 hours also had lower odds of IHM (OR, 0.41; 95% CI, 0.17-0.98) and 30-day mortality (OR, 0.31; 95% CI, 0.25-0.39).

Length of stay

Three studies including 494 patients compared LOS in patients who underwent ERCP within 48 hours compared with ERCP done after 48 hours.[7,10,12] LOS was significantly lower in patients who underwent ERCP within 48 hours with MD of −5.56 (95% CI, −1.59 to −9.53) with heterogeneity (I^2 = 74%) (Fig. 4). In a subgroup analysis including a national database study involving 4570 patients, LOS was significant lower in patients who underwent emergent ERCP within 48 hours (MD, −2.40; 95% CI, −2.10 to −2.70) with heterogeneity (I^2 = 74%) (Fig. 4).[13] Four studies including 862 patients compare LOS in those who underwent ERCP within 24 hours and after 24 hours.[7,14-16] LOS was also significantly lower in patients who underwent ERCP within 24 hours with a pooled MD of −2.87 (95% CI, −1.55 to −4.18) with heterogeneity (I^2 = 47%).

Organ failure

Three studies including 546 patient reported persistent organ failure.[7,10,14] Although patients who underwent ERCP within 24 hours had lower odds of persistent organ failure (OR, 0.69; 95% CI, 0.33-1.46) with heterogeneity I^2 = 66%, this did not reach statistical significance. Table 1 summarizes the clinical outcomes of patients admitted with AC in the studies included in the analyses.

We performed the jackknife analysis to evaluate whether the findings of our meta-analysis were robust. The jackknife sensitivity results were consistent and valid,

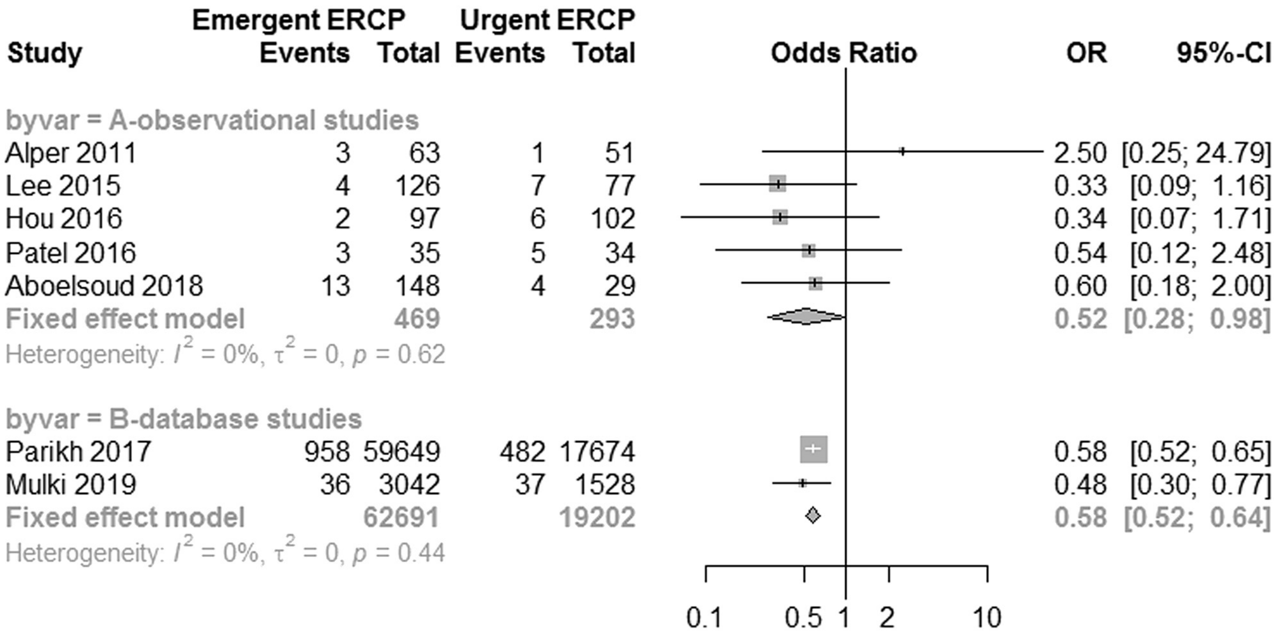

Figure 2. Forest plot for mortality of all the studies included in the analyses.

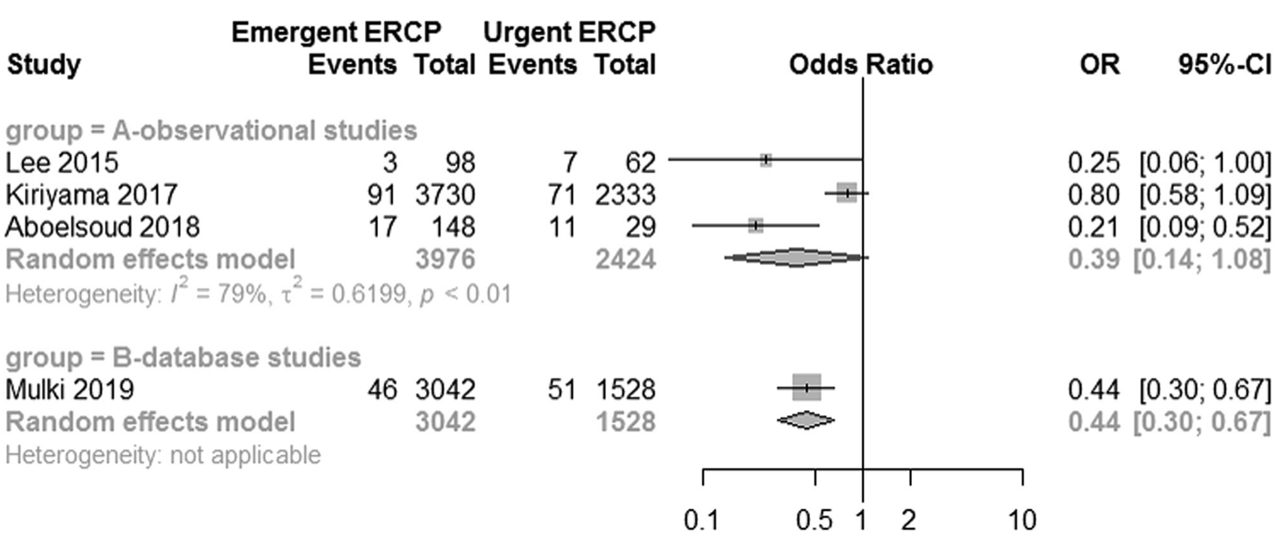

Figure 3. Forest plot for 30-day mortality.

when repeating the meta-analysis with 1 study omitted at a time for IHM and LOS outcomes. The jackknife sensitivity analysis of the OR of IHM was robust, with the point estimates varying from 0.50 to 0.58 and the corresponding 95% CIs remaining <1. Similarly, the jackknife sensitivity analysis of the MD in LOS was also robust, with the point estimates varying from −5.56 to −3.11, and the corresponding 95% CIs remaining <0. Detailed results are presented in the Appendix (available online at www.giejournal.org), Supplementary Table 2 for IHM (available online at www.giejournal.org), and Supplementary Table 3 for LOS (available online at www.giejournal.org).

We also performed a meta-regression to determine whether mean age was associated with effect sizes (IHM and LOS). Meta-regression linear prediction plots are presented in bubble plots, where each bubble represents each study, and the size of the bubbles is proportional to the contribution of the individual study measured by study weight (Fig. 5). The solid line in the bubble plot represents linear predictions for the effect sizes (log-transformed OR and MD) as a function

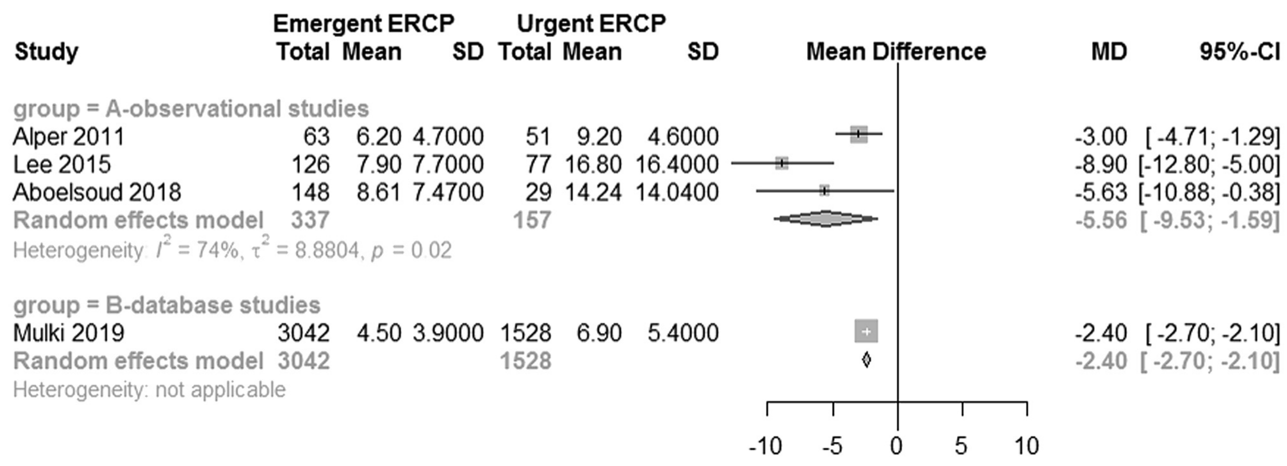

Figure 4. Forest plot for length of stay (<48 hours vs >48 hours).

TABLE 1. Clinical outcomes of patients with acute cholangitis in the studies included in the analyses

	In-hospital mortality (%)		Length of stay (days)				30-day mortality (%)	
Study	<48 hours	>48 hours	<24 hours	>24 hours	<48 hours	>48 hours	<48 hours	>48 hours
Aboelsoud et al[7]	8.78	13.8	7.71 ± 6.77	13.57 ± 11.9	8.61 ± 7.47	14.24 ± 14.04	11.49	17.24
Parikh et al[8,*]	1.6	2.72	5.0 ± 0.06	NR	NR	10.0 ± 0.16	NR	NR
Hou et al[9,†]	Patient who underwent ERCP >48 hours are at increased odds of mortality: OR, 3.2, 95 CI, 0.6-16; P = .17		6.5 (2.2-63.8)	9.1 (3.0-75.7)	NR	NR	NR	NR
Lee et al[10]	3.17	9.09	NR	NR	7.9 ± 7.7	16.8 ± 16.4	3	11
Patel et al[11,‡]	8.57	14.7	6	14	NR	NR	NR	NR
Alper et al[12]	4.76	1.96	NR	NR	6.2 ± 4.7	9.2 ± 4.6	NR	NR
Mulki et al[13]	1.2	2.4	NR	NR	4.5 ± 3.9	6.9 ± 5.4	3.4	13
Tan et al[14]	NR	NR	8 ± 8	12 ± 10	NR	NR	NR	NR
Jang et al[15]	NR	NR	6.1 ± 2.5	9.2 ± 4.5	NR	NR	NR	NR
Park et al[16]	NR	NR	7.0 ± 3.7	8.8 ± 5.8	NR	NR	NR	NR
Kiriyama et al[17]	NR	NR	NR	NR	NR	NR	2.4	3

Length of stay is presented as the mean ± standard deviation (SD) or median (range).
NR, Not reported.
*The study was not included in the meta-analysis of the pooled length of stay calculation because it did not report the pooled mean or SD for patients who had ERCP within 48 hours.
†The study was not included in the meta-analysis of the pooled length of stay calculation because the median rather than the mean or SD for length of stay was reported.
‡The study was not included in the meta-analysis of the pooled length of stay calculation because it did not report the SD for the mean length of stay.

of the mean age at the study level. Although there was a linear trend of mean age in predicting the log-transformed OR in IHM and the MD in LOS, changes in the mean age were not associated with changes in the effect sizes because the meta-regression results were not significant at the 0.05 significance level (P = .30 and P = .41, respectively).

DISCUSSION

Based on our knowledge and the literature search, this is the first systematic review and meta-analysis on evaluating the impact of timing of ERCP on patient outcomes in AC. Our meta-analysis revealed that emergent ERCP within 48 hours is associated with lower odds of IHM and shorter LOS. Our study also showed that emergent ERCP is not only beneficial in patients with severe AC but is associated with better outcomes in patients with mild to moderate AC.

Our findings are congruent with several high-impact studies that were not included in our meta-analysis, given that they reported composite outcomes or otherwise did not provide the explicit data needed for our specific research questions.[18-20] In a study by Chak et al,[18] patients who had ERCP within 24 hours had shorter LOS.

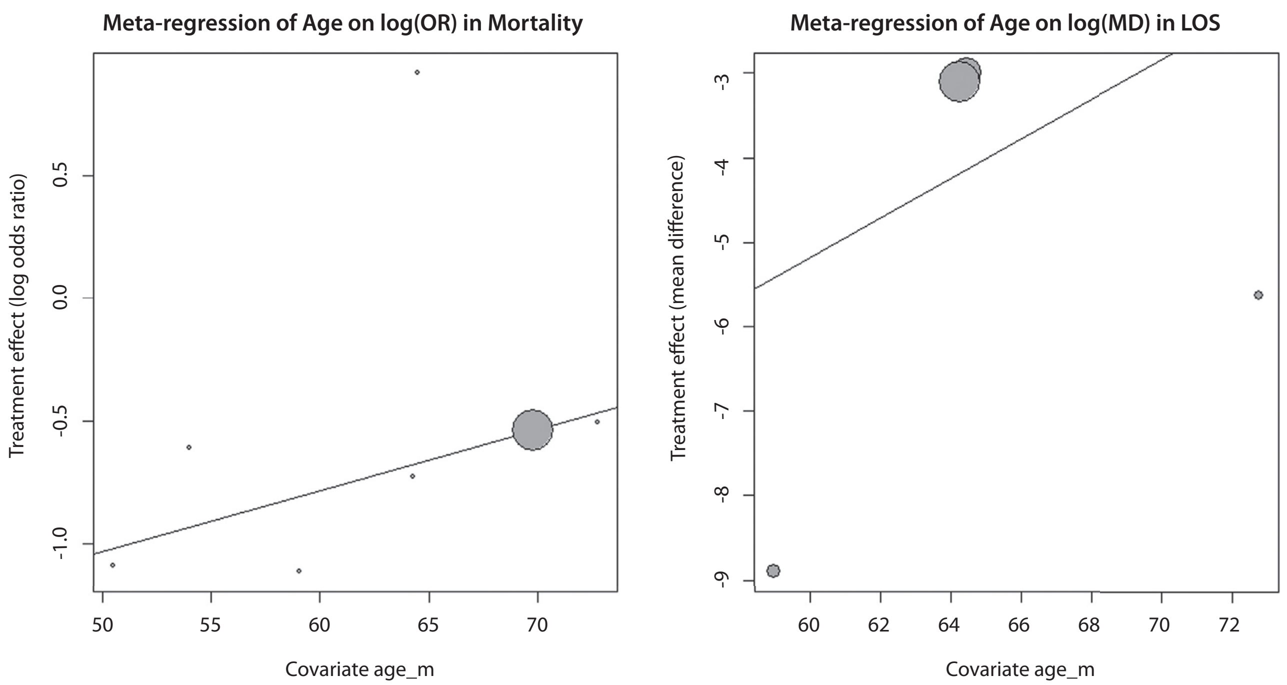

Figure 5. Bubble plot of the association between mean age and in-hospital mortality, and length of stay (<48 vs >48 hours).

The study was not included in our meta-analysis because it lacked sufficient data. Similarly, in a study by Khashab et al,[19] delay in ERCP for more than 72 hours was associated with prolonged LOS, increased cost of hospitalization, and composite outcome (IHM, persistent organ failure, and/or intensive care unit stay). This study was also not included in our meta-analysis because it reported IHM as a composite outcome rather than reporting it separately. In a study with 5340 patients by Navaneethan et al,[20] ERCP done later than 72 hours was associated with prolonged LOS and increased cost of hospitalization. The study was not included in our meta-analysis because if a lack of sufficient data to be analyzed meta-analytically.

The largest study on the topic, a large database study by Parikh et al,[8] identified patients with AC secondary to choledocholithiasis identified from the National Inpatient Sample database. This study revealed that IHM is highest in patients who had no ERCP, followed by patients who had ERCP after 48 hours. There was no statistically significant difference in IHM between the patients who had ERCP within 24 hours compared with those who had the procedure between 24 and 48 hours. In the same study, ERCP later than 48 hours was associated with higher hospitalization costs compared with patients who had a procedure within 24 hours (US$48,627 vs US$25,836). In a retrospective study by Aboelsoud et al,[7] IHM trended lower in patients who had ERCP within 24 or 48 hours but did not reach statistical significance. Although IHM did not reach statistical significance, LOS and persistent organ failure were significantly lower in patients who had emergent ERCP.[7] Similar results were seen in a study done by Lee et al[10] that showed early ERCP was associated with lower IHM, 30-day mortality, and persistent organ failure. Early ERCP has also been shown to decrease the 30-day readmission rate, which is considered a marker of poor health care quality and an increased burden on health care costs.[13,21] A retrospective study by Navaneethan et al[21] revealed that ERCP after 48 hours was associated with increased risk of 30-day readmission.[21] Similar results were seen by Mulki et al,[13] revealing that emergent ERCP was associated with lower risk of 30-day readmission.

Although most studies revealed better patient outcomes with emergent biliary drainage, some studies did not reveal any significant benefit of early biliary drainage on patient outcomes.[22-24] Inamdar et al[22] revealed no difference in IHM in 23,661 patients who were admitted on weekdays compared with patients admitted over the weekend. Patients admitted on weekdays underwent ERCP within 48 hours significantly more often compared with patients admitted over the weekend (70% vs 65.4%, $P = <.001$).[22] However, in this study, patients were identified via the National Inpatient Sample database from 2009 to 2012; in the larger study by Parikh et al[8] using the National Inpatient Sample data from 1998 to 2012, this trend was not apparent. This contradiction in outcomes is likely secondary to the larger sample size of our study to evaluate for any differences. Similarly, in a study by Tabibian et al,[23] no difference was seen in patient outcomes among those admitted on weekdays compared with weekend days. However, both groups had no statistically significant difference in time to biliary drainage, which may have contributed to their outcome.[23] In a study by Hakuta et al,[24] urgent biliary drainage within 12 hours had no difference on patient outcomes, including IHM, compared with elective biliary drainage. Again, 86% of the patients in the elective ERCP group underwent ERCP within 48 hours, which might explain no difference in mortality, as seen in our study.

The systematic literature search of our study is comprehensive, the sample size is large, and all the studies included are fair to good quality; however, we do acknowledge that there are some limitations to our meta-analysis. First, all of the studies are observational studies, which may have introduced bias. Therefore, there is a need for larger randomized controlled trials to evaluate the impact of timing of ERCP on outcomes of patients with AC. Second, one of the studies included in the analysis is in abstract form and has not been fully published yet.[12] We did stratify our meta-analysis based on the severity of AC, but only 2 studies reported mortality stratified based on the severity of AC. Although our meta-analysis revealed decreased odds of IHM and 30-day mortality for patients who underwent ERCP within 24 or 48 hours, we were unable to meta-analytically evaluate if there was a mortality difference in patients with AC who underwent ERCP within 24 hours and patients who underwent ERCP between 24 and 48 hours because the mortality data for patients who underwent ERCP between 24 and 48 hours was inconsistently reported in the studies. Also, the cause of the AC, especially the presence of malignant obstruction and comorbidities of the patients, were inconsistently reported in the studies. This may introduce bias in the study results because more patients who underwent urgent ERCP may have had higher comorbidities and malignant obstruction, which increases the risk of mortality. Last, a challenge that emerged was that we identified a number of granular cohort studies but also 2 large national database studies. Given that the overlap between these 2 types of data structures is impossible to rectify, we used the observational studies for our primary analysis and used the national database studies as a sensitivity analysis. We did not identify material differences between our assessment of the observational studies and the national databases for outcomes of IHM and LOS. However, for 30-day mortality, there is disagreement between the observational studies and the database study with 30-day mortality, although this trended lower in the observational studies and was not statistically significant. In a subgroup analysis including patients from the database study, 30-day mortality was significantly lower in patients who underwent emergent ERCP within 48 hours.

In summary, our study revealed that emergent biliary drainage within 48 hours in patients with AC is associated with lower odds of IHM, 30-day mortality, organ failure, and shorter LOS. Mortality benefit persisted in patients with mild to moderate and severe AC who underwent emergent ERCP. Larger randomized controlled trials are needed to further delineate the optimal timing of ERCP in patients with AC, stratified based on severity, to evaluate whether emergent ERCP is beneficial in patients with nonsevere AC.

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APPENDIX: SEARCH TERMS

PubMed

((("Cholangitis"[Mesh] OR cholangitis[tiab] OR cholangitides[tiab])) AND ("Cholangiopancreatography, Endoscopic Retrograde"[Mesh] OR "endoscopic retrograde cholangiopancreatography"[tiab] OR ERCP[tiab] OR "endoscopic retrograde cholangiopancreatographies"[tiab])) AND (early[tiab] OR late[tiab] OR "time factors"[mh])

Embase

'cholangitis'/exp OR cholangitis:ti,ab OR cholangitides:ti,ab AND 'endoscopic retrograde cholangiopancreatography'/exp OR 'endoscopic retrograde cholangiopancreatography':ti,ab OR 'endoscopic retrograde cholangiopancreatographies':ti,ab OR ercp:ti,ab AND 'time factor'/exp OR early:ti,ab OR late:ti,ab

Excluded studies after full text review

1. Khashab MA, Tariq A, Tariq U, et al. Delayed and unsuccessful endoscopic retrograde cholangiopancreatography are associated with worse outcomes in patients with acute cholangitis. Clin Gastroenterol Hepatol 2012;10:1157-61.

Reason: In-hospital mortality (IHM) was not reported. They reported differences in composite clinical outcome between early and delayed ERCP groups. We tried to reach the authors for the missing data but did not get any response. Insufficient data to be included in the meta-analysis.

2. Inamdar S, Sejpal DV, Ullah M, et al. Weekend vs. weekday admissions for cholangitis requiring an ERCP: comparison of outcomes in a national cohort. Am J Gastroenterol 2016;111:405-10.

Reason: This was a retrospective analysis on patients with acute cholangitis using the National Inpatient Sample (NIS) database from 2009 to 2012. We included Parikh et al. study in our analysis, which includes acute cholangitis patients from the NIS database 1998-2012. Therefore, the study was excluded to avoid overlap of the patients.

3. Chak A, Cooper GS, Lloyd LE, et al. Effectiveness of ERCP in cholangitis: a community-based study. Gastrointest Endosc 2000;52:484-9.

Reason: The study did not evaluate for IHM. They reported differences in length of hospital stay for patients who underwent early ERCP and delayed ERCP. However, lengths of stay were given as medians. Mean and standard deviations were not reported. Therefore, insufficient data to be included in the meta-analysis.

4. Schwed AC, Boggs MM, Pham X-BD, et al. Association of admission laboratory values and the timing of endoscopic retrograde cholangiopancreatography with clinical outcomes in acute cholangitis. JAMA Surg 2016;151:1039-45.

Reason: The definition of mortality is unclear in the study. Also, mortality differences between early and late ERCP were not included. The article reported differences in mortality between a validation cohort (2008-2015) and a derivation cohort (1995-2005) to evaluate for differences in outcomes of acute cholangitis over time.

5. Parikh ND, Issaka R, Lapin B, et al. Inpatient weekend ERCP is associated with a reduction in patient length of stay. Am J Gastroenterol 2014;109:465-70.

Reason: The article reported differences in length of stay between patients who underwent weekend ERCP and those who had delayed ERCP on Monday. Also, length of stay was stratified according to the timing of ERCP and mortality was not reported in the study.

6. Tabibian JH, Yang JD, Baron TH, et al. Weekend admission for acute cholangitis does not adversely impact clinical or endoscopic outcomes. Dig Dis Sci 2016;61:53-61.

Reason: Although the study reported in-hospital mortality, it evaluated the differences in outcome between patients admitted on weekdays compared with weekend admission. The article reported mortality in 2 groups: weekday admissions versus weekend. However, 77% of patients admitted over the weekend still underwent ERCP within 48 hours. Mortality was not reported stratified by timing of ERCP. Therefore, the study was excluded from the meta-analysis as we were unable to determine from the available data if there were any differences in mortality between patients who underwent ERCP within 24 to 48 hours versus delayed ERCP.

7. Navaneethan U, Njei B, Hasan MK, et al. Timing of ERCP and outcomes of patients with acute cholangitis and choledocholithiasis: a nationwide population based study [abstract]. Gastrointest Endosc 2015;81:AB354.

Reason: This was a cross-sectional study on patients with acute cholangitis using the National Inpatient Sample database from 2010. We included the study by Parikh et al in our analysis, which includes patients with acute cholangitis from the NIS database 1998-2012. Therefore, the study was excluded to avoid overlap of the patients.

8. Singh A, Gaetano JN. Impact of late ERCP on health outcomes in patients with acute biliary pancreatitis and cholangitis: results from Nationwide Inpatient Sample (NIS) analysis [abstract]. Gastrointest Endosc 2016;83:AB605.

Reason: This was a retrospective analysis on patients with acute cholangitis using the National Inpatient Sample database from 2008 to 2012. We included the study by Parikh et al in our analysis, which includes patients with acute cholangitis from the NIS database 1998-2012. Therefore, the study was excluded to avoid overlap of the patients.

9. Adebogun AO, Musa A, Kibreab A, et al. Timing of ERCP and inpatient mortality among patients hospitalized for cholangitis. Gastroenterology 2017;152:S504.

Reason: Although inpatient mortality was reported, there was insufficient data to be included in the meta-analysis. They study did not report differences in mortality among patients who underwent ERCP within 24 to 48 hours versus delayed ERCP after 48 to 72 hours. Therefore, the study was excluded after mutual consensus given the lack of reported data regarding differences in in-hospital mortality outcomes stratified by timing of ERCP. The data on the length of stay outcome were also insufficient to be included in the meta-analysis

10. Hakim S, Aneese AM, Edhi A, et al. Reduction in length of stay, hospital costs and hospital charges for all-cause ERCPs performed over the weekend versus ERCPs that were postponed to the first available weekday [abstract]. Gastrointest Endosc 2018;87:AB587-8.

Reason: The study evaluated hospital costs and hospital charges between weekend and weekday ERCP groups. The primary outcomes of interest, ie, in-hospital mortality or LOS, were not reported in the study.

11. Rustagi T, Njei B. Timing of ERCP and outcomes of patients with acute gallstone pancreatitis: a nationwide population based study [abstract]. Gastrointest Endosc 2015;81:AB405.

Reason: This was a cross-sectional study on patients with acute cholangitis using the National Inpatient Sample database from 2010. We included the study by Parikh et al in our analysis, which includes patients with acute cholangitis from the NIS database 1998-2012. Therefore, the study was excluded to avoid overlap of the patients.

12. Hakuta R, Hamada T, Nakai Y, et al. No association of timing of endoscopic biliary drainage with clinical outcomes in patients with non-severe acute cholangitis. Dig Dis Sci 2018;63:1937-45.

Reason: The study evaluates differences in outcomes between urgent (within 12 hours) versus elective ERCP (>12 hours). It is unclear from the study how many patients underwent ERCP within 24 hours or within 48 hours and how many underwent ERCP after 48 hours. This distinction is important because >12 hours includes a broad range of timings, including <24 hours, >24 hours, >48 hours, and >72 hours. Therefore, the study was excluded after mutual consensus due to lack of data regarding the exact number of patients who underwent ERCP within and after 24 to 48 hours. Also, in-hospital mortality was 0.33% (1/299). The study also could not be included in the sub-group analysis because there no other studies evaluating patient outcomes <12 versus >12 hours.

13. Sinha A, Le M, Sivaraman A, et al. Early intervention lowers morbidity and mortality in severe and moderate acute cholangitis [abstract]. Gastrointest Endosc 2017;85:AB616.

Reason: The study used the NIS database 2011 to evaluate differences in outcomes between early and delayed ERCP. We included the study by Parikh et al in our analysis, which includes patients with acute cholangitis from the NIS database 1998-2012. Therefore, the study was excluded to avoid overlap of the patients.

14. Parikh MP, Wadhwa V, Lopez R, et al. National trends of endoscopic retrograde cholangiopancreatography (ERCP) usage for management of in-patients with cholangitis due to choledocholithiasis [abstract]. Gastrointest Endosc 2017;85:AB227-8.

Reason: They study is the poster form of the Parikh et al. study. The full text version of the study was already included in the meta-analysis.

15. Navaneethan U, Gutierrez NG, Jegadeesan R, et al. Factors predicting adverse short-term outcomes in patients with acute cholangitis undergoing ERCP: a single center experience. World J Gastrointest Endosc 2014;6:74-81.

Reason: The article did not report our primary outcome of interest, which is in-hospital mortality. Also, insufficient data for the length of stay outcome. Therefore, the study was excluded from our meta-analysis.

16. Craft B, Cotton P, Hawes R, et al. Does timing/delay of ERCP affect outcomes in patients with cholangitis? Am J Gastroenterol 2011;106:S56.

Reason: In-hospital mortality or length of stay was not reported stratified by timing of ERCP.

17. Schepers NJ. Early endoscopic retrograde cholangiography with biliary sphincterotomy or conservative treatment in predicted severe acute biliary pancreatitis (APEC): a multicenter randomized controlled trial. UEG Week 2018 Oral Presentations. United European Gastroenterol J 2018;6(8 suppl):A1-134.

Reason: The study evaluated the impact of early ERCP on severe acute biliary pancreatitis without cholangitis. The study was therefore excluded from the meta-analysis.

18. Mulki R, Shah R, Qayed ES. Outcomes of early versus late ERCP in hospitalized patients with acute cholangitis: a nationwide analysis [abstract]. Gastrointest Endosc 2018;87:AB58-9.

Reason: The study included patients identified through the National Readmission Database (NRD) 2010-2014. In our meta-analysis, we included 2 studies: 1 including patients identified through the NIS database 1998-2012 and 1 with patients from the NRD 2014 database. Also, there is a possibility that this study is the abstract form of the study by Mulki et al included in our meta-analysis. Therefore, study was excluded to avoid patient overlap.

19. Navaneethan U, Gutierrez NG, Jegadeesan R, et al. Delay in performing ERCP and adverse events increase the 30-day readmission risk in patients with acute cholangitis. Gastrointest Endosc 2013;78:81-90.

Reason: The study did not report in-hospital mortality, which is an inclusion criterion. They reported 30-day readmission risk and the difference in 1-year mortality between early and delayed ERCP groups. Although length of stay outcome was reported, mean and standard deviations were not given. Therefore, the study was excluded due to missing data. We also attempted to reach the authors to get the missing data but were unsuccessful.

SUPPLEMENTARY TABLE 1. Baseline characteristics of the studies included in the analyses

Reference, year, country	Sample size	Study population	Design of the study	Baseline characteristics	Quality assessment	Outcomes
Alper et al, 2011,[12] Turkey	114	Patients with AC diagnosed with laboratory and screening methods applied with Charcot triad between May 2008 and May 2010	PCS	Early ERCP: mean age 68 ± 15 years; late ERCP: mean age 70 ± 13 years; 46 males	Fair	No significant difference in IHM but LOS was shorter
Lee et al, 2015,[10] USA	203	Consecutive patients who received ERCP for AC between 2005-2013	RCS	Mean age 59 ± 19 years; 45% male; 65% white; CBD stone, 163	Good	IHM and LOS were lower in early ERCP group
Hou et al, 2017,[9] USA	199	Patients with AC who received ERCP from 2010-2013	PCS	Age 50.5 ± 16.5 years; 83 male; 40 grade I; 87 grade II; 72 grade III; 2 whites; 15 Asians; 170 Hispanics	Fair	IHM and LOS was lower in early ERCP group
Patel et al, 2016,[11] USA	69	Patients with AC who underwent ERCP between January and August 2012	RCS	46 grade I, age 50 ± 19 years; 13 grade II, age 54 ± 24 years; 10 grade III, age 73 ± 17 years; 28 males; 44 CBD stone/ sludge	Fair	No significant difference in IHM but LOS was shorter
Parikh et al, 2018,[8] USA	77,323	AC secondary to choledocholithiasis identified by NIS from 1998 to 2012	RCS	ERCP <24 hours: age 69.1 ± 0.23, 45.7% male, 63.8% white; ERCP >48 hours: age 72.0 ± 0.36, 45.8% male, 65.1% white	Good	IHM and LOS was significantly lower in early ERCP group
Mulki et al, 2019,[13] USA	4570	AC patients identified by NRD 2014	RCS	Early ERCP: age 63.6 ± 18.1 years, 48.8% male, 7.7% severe cholangitis; late ERCP: age 65.1 ± 18.3 years, 46.9% male, 7.1% severe cholangitis	Good	IHM, LOS, 30-day mortality, and 30-day readmission was significantly lower in early ERCP group
Aboelsoud et al, 2018,[7] USA	177	Patients with AC admitted to the ICU identified using MIMIC-III database between 2001 and 2012	RCS	Median age 75 years (62-84 years), 23 mild, 19 moderate, 135 severe, 50% male	Good	No significant difference in IHM although trended lower in early ERCP group; LOS significantly low in early ERCP group
Jang et al, 2013,[15] South Korea	212	Patients with mild to moderate AC who underwent ERCP from January 2006 to August 2010	RCS	Early ERCP: age 66.3 ± 14.6 years, 63.1% male; late ERCP: age 64.6 ± 17.4 years, 54.9% male	Good	Shorter LOS in early ERCP group
Tan et al, 2018,[14] Denmark	166	Patients with AC who underwent ERCP from March 2009 to September 2016	RCS	Median age 71 ± 9 years, 55% male	Good	Lower 30-day mortality and shorter LOS in early ERCP group
Park et al, 2016,[16] Korea	331	Patient >75 year of age admitted to the hospital for calculous AC from 2009 to 2014	RCS	Mean age: elderly (n = 156) 77.2 ± 1.8 years, very elderly (n = 175) 85.1 ± 3.3 years; 158 males; 52 severe AC	Fair	Early ERCP is associated with shorter LOS
Kiriyama et al, 2017,[17] Japan and Taiwan	6063	Patients admitted with AC		Mean age 72.2 ± 13.6, 3581 males; 25.1% severe AC	Good	30-day mortality was lower in early ERCP group

AC, Acute cholangitis; *PCS*, prospective cohort study; *IHM*, in-hospital mortality; *LOS*, length of stay; *RCS*, retrospective cohort study; *CBD*, common bile duct; *NIS*, National Inpatient Sample, *NRD*, National Readmission Database; *ICU*, intensive care unit; *MIMIC-III*, Medical Information Mart for Intensive Care III.

SUPPLEMENTARY TABLE 2. Jackknife analysis for mortality outcome

Study	Odds ratio	95% Confidence interval	Weight (%)	I^2 (%)	*P* value
All studies	0.57	0.52-0.64	–	0	.76
Alper et al, 2011[12]	0.57	0.51-0.64	0.20	0	.88
Lee et al, 2015[10]	0.58	0.52-0.64	0.70	0	.76
Hou et al, 2017[9]	0.58	0.52-0.64	0.40	0	.71
Patel et al, 2016[11]	0.57	0.52-0.64	0.50	0	.65
Parikh et al, 2018[8]	0.50	0.34-0.72	92.0	0	.75
Mulki et al, 2019[13]	0.58	0.52-0.65	5.20	0	.73
Aboelsoud et al, 2018[7]	0.57	0.52-0.64	0.80	0	.65
Parikh[8] and Mulki[13]	0.51	0.28-0.98	–	0	.62

SUPPLEMENTARY TABLE 3. Jackknife analysis for length of stay (<48 hours vs >48 hours)

Study	Mean difference	95% confidence interval	Weight (%)	I^2 (%)	*P* value
All studies	−4.06	−6.16 to −1.95	–	68	.03
Alper et al, 2011[12]	−5.33	−9.86 to −0.79	31.8	78	<.01
Lee et al, 2015[15]	−3.11	−3.45 to −2.76	16.90	0	.64
Mulki et al, 2019[13]	−5.56	−9.53 to −1.59	39.90	74	.02
Aboelsoud et al, 2018[7]	−4.05	−6.05 to −2.05	11.50	76	.01