

Early Endoscopic Retrograde Cholangiopancreatography Versus Conservative Management in Acute Biliary Pancreatitis Without Cholangitis

A Meta-Analysis of Randomized Trials

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Background: Early endoscopic retrograde cholangiopancreatography (ERCP) should be performed in all patients with acute biliary pancreatitis (ABP) and coexisting acute cholangitis. In patients without cholangitis and predicted mild ABP it is generally accepted that early ERCP should not be performed. Nevertheless, there is a controversy regarding the role of early ERCP in the treatment of patients with predicted severe ABP without cholangitis. We reviewed randomized trials on early ERCP versus conservative management in patients with ABP without acute cholangitis.

Methods: Relevant publications in 3 electronic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials) were systematically reviewed and meta-analyzed.

Results: Seven randomized trials on ERCP in acute pancreatitis were found, of which 3 including a total of 450 patients (230 in the invasive arm and 220 in the control arm) qualified for a meta-analysis according to predefined criteria. In all patients with ABP (predicted mild and severe), early ERCP was associated with a nonsignificant reduction in overall complications [risk ratio (RR) 0.76; 95% confidence interval (CI) 0.41–1.04; $P = 0.38$] and a nonsignificant increase in mortality (RR 1.13; 95% CI 0.23–5.63; $P = 0.88$). Subgroup analysis based on predicted severity did not affect these outcomes (overall complications: predicted mild: RR 0.86; 95% CI 0.62–1.19; $P = 0.36$; predicted severe: RR 0.82; 95% CI 0.32–2.10; $P = 0.68$; mortality: predicted mild: RR 1.90; 95% CI 0.25–14.55; $P = 0.53$; predicted severe: RR 1.28; 95% CI 0.20–8.06; $P = 0.80$).

Conclusion: In this meta-analysis, early ERCP in patients with predicted mild and predicted severe ABP without acute cholangitis

did not lead to a significant reduction in the risk of overall complications and mortality.

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Acute biliary pancreatitis (ABP) is the most frequent form of acute pancreatitis in Western countries.^{1,2} There are 2 mechanisms generally accepted regarding the pathogenesis of ABP: reflux of bile into the pancreatic duct and transient ampullary obstruction caused by sludge or an impacted stone in the ampulla.^{3,4} Patients with small gallstones and sludge are particularly at risk for acute pancreatitis.⁵ By early endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) bile-duct stones and sludge can be removed, and obstruction released with potentially improved outcome. Nevertheless, despite technical improvements shown in recent years and an increased experience of endoscopists, there is a documented risk of procedure-related complications.^{6–8} In addition, it is well recognized that most small gallstones pass spontaneously without causing further harm.^{4,9}

Indisputable benefits of endoscopic biliary drainage in patients with acute cholangitis have been stressed in the recent Tokyo Guidelines.¹⁰ It is generally accepted that patients with predicted mild ABP without signs of acute cholangitis do not benefit from early ERCP.¹ Controversy persists, however, whether patients with predicted severe ABP in absence of acute cholangitis should undergo early ERCP.^{11–13} The 2005 UK guidelines on acute pancreatitis state that all patients with predicted severe ABP (irrespective of the presence of acute cholangitis) should undergo early ERCP,¹⁴ whereas the recent guidelines of the American College of Gastroenterology recommend that early ERCP is performed only in patients with acute cholangitis and severe acute pancreatitis (organ failure).¹ The 2007 guidelines of the American Gastroenterology Association state that early ERCP in patients with predicted severe ABP without

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signs of acute cholangitis is controversial and the available data are not uniform in support of this practice.¹⁵

Indeed, several randomized controlled trials (RCTs) that compared early ERCP, with or without ES, to conservative treatment with selective ERCP, with or without ES, have shown conflicting results.^{16–19} The first meta-analysis on this subject did not provide a definite answer.²⁰ The second meta-analysis aimed to control for a possible modifying effect of acute cholangitis and showed that early ERCP decreased complications in all patients with predicted severe ABP, regardless of the presence of cholangitis.²¹ However, this meta-analysis included a RCT in which 35% of patients suffered from acute pancreatitis of a nonbiliary cause.¹⁷ Finally, 1 new RCT has been published since that time.¹⁹ Therefore, the present meta-analysis aims to compare early ERCP, with or without ES, with conservative management in patients with ABP without signs of cholangitis. A predefined subgroup analysis on patients with predicted severe and predicted mild ABP will be performed.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

A systematic literature search with predefined search terms was carried out in the MEDLINE, EMBASE, and Cochrane databases for articles published until March 1, 2007 (Fig. 1). All identified articles and review articles were screened for cross-references of articles that included information on ERCP in acute pancreatitis. Language restrictions were not applied.

The title and abstract of all identified articles were screened for the following inclusion criteria:

1. Study population: patients with ABP without signs of acute cholangitis. Acute cholangitis should be either an exclusion criterion or separate data on patients without acute cholangitis should be presented.
2. Intervention: early ERCP (ie, within 72 hours after admission) with or without ES.
3. Comparison: conservative treatment with selective ERCP with or without ES.
4. Study outcomes: mortality and overall complications.
5. Study design: participants were assigned to either ERCP or comparator by random allocation.

Data Extraction and Quality Assessment

Titles and abstracts of all retrieved records and subsequently full-text articles were examined independently by 2 authors (MSP, HCvS) to identify trials that satisfied the inclusion criteria. Discrepancies in selection were resolved by discussion between the authors of this meta-analysis.

The Jadad scale was used to grade the methodological quality of the trials included.²² This scale consists of 3 items regarding: (1) random allocation, (2) masking of patients, (3) dropouts and withdrawals. The quality scale ranges from 0 to 5 points, with 2 or less indicating low quality and 3 or higher indicating high quality. In addition, 3 other criteria were applied regarding: (4) allocation concealment (yes or no), (5) blinding of end point assessment (yes or no, irrespective of

Database	Search strategy
PubMed	("acute pancreatitis" [Title/Abstract] OR "pancreatitis" [Title/Abstract]) AND ("gallstone" [Title/Abstract] OR "gallstones" [Title/Abstract] OR "biliary" [Title/Abstract]) AND ("ERCP" [Title/Abstract] OR "endoscopic retrograde cholangiopancreatography" [Title/Abstract] OR "sphincterotomy" [Title/Abstract] OR "papillotomy" [Title/Abstract]) AND ("conservative" [Title/Abstract])
Embase	"pancreatitis" AND ("ERCP" OR "endoscopic retrograde cholangiopancreatography" OR "Vater papillotomy" OR "sphincterotomy") AND [humans]/lim
Cochrane library	pancreatitis AND ("endoscopic retrograde cholangiopancreatography" OR "papillotomy" OR "sphincterotomy")

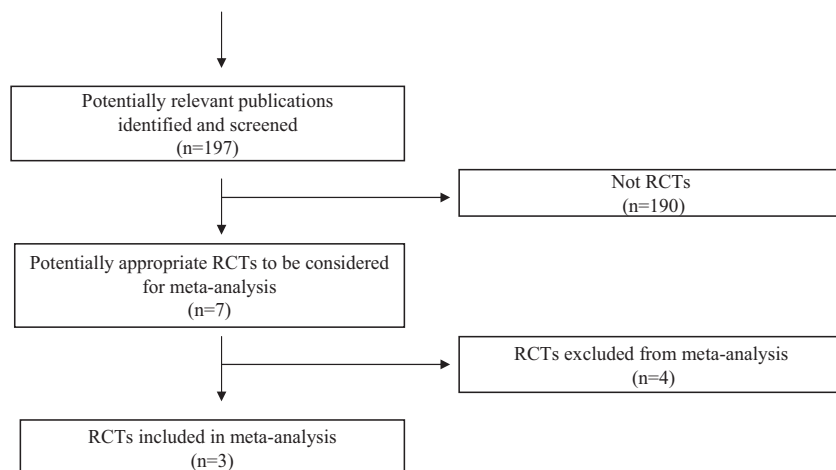


FIGURE 1. Flow chart illustrating the details of the search and study selection process.

blinding of treatment for patient and physician), and (6) missing data (at least 90% of the data reported).

Data with regard to the reported group size, baseline characteristics, and numbers of events for each end point were extracted and documented independently by 2 authors (MSP, HCvS).

Statistical Analysis

The data analysis was performed with the meta-analysis software Comprehensive Meta-Analysis (Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis Version 2, Biostat, Englewood, NJ, 2005). From the pooled data, the risk ratio (RR) and risk difference (RD) with the 95% confidence interval (CI) were calculated for the following end points: mortality and overall complications. The Mantel-Haenszel method was used for the pooled analysis of included trials. When no events were observed in both treatment groups of a particular trial, we added an event fraction (0.001) to the ERCP group to allow inclusion of such trials in the pooled data analysis. Funnel plots were created to explore possible biases (ie, reporting, publication and reviewer bias).

RESULTS

The literature search yielded 197 publications. The details of the literature search and selection of studies are shown in Figure 1. Seven potentially eligible RCTs on ERCP in acute pancreatitis were identified and 4 studies were excluded. The first excluded trial¹⁷ studied all patients with acute pancreatitis, irrespective of the cause, instead of only ABP. Moreover, neither patients with acute cholangitis were excluded nor was data for this subgroup presented separately. Patients in the second excluded RCT²³ were randomized to early ERCP, with or without ES, only in the case of persisting ampullary obstruction (based on clinical, biochemical, and imaging criteria) during more than 24 hours. Consequently, ERCP was performed only in 47% of patients in the intervention arm. The third excluded RCT²⁴ aimed to study exclusively patients with severe nonbiliary pancreatitis. The fourth trial²⁵ was excluded because patients undergoing duodenoscopy for suspected ABP were subsequently random-

ized to ES or no ES (ie, a RCT with different intervention and comparison than the current meta-analysis). Moreover, the last 2 studies^{24,25} were only published in abstract form.

In the 3 RCTs satisfying the inclusion criteria, patients with acute cholangitis were either excluded specifically,^{18,19} or outcome of patients without acute cholangitis was presented separately.¹⁶ With funnel plots publication bias for the different outcomes could not be detected (data not shown). The study characteristics for the 3 trials, including their definition of acute cholangitis, are shown in Table 1. A total of 450 patients were included: 230 were allocated to early ERCP with or without ES; 220 were allocated to conservative treatment with elective ERCP with or without ES. In the early ERCP groups of the 3 trials altogether, ERCP was successful in 214 of 230 patients (93%). In these 214 patients, ES was performed in 114 patients (53%) and a common bile duct stones were removed in 111 patients (52%). ERCP procedure-related complications occurred in 5 patients (2%). In the conservative treatment groups of the 3 trials altogether, 33 of the 220 patients (15%) underwent ERCP, of which 30 (91%) were successful. In addition, 14 patients underwent ES (47%), common bile duct stones were removed in 33 patients (43%), and ERCP procedure-related complications did not occur.

Two of 3 RCTs had a Jadad quality score²² grade 2 (Table 2). The demographic data of patients are summarized in Table 3. Complications and mortality were reported in all 3 trials. The results of the meta-analysis of the included trials for complications and mortality are presented in Table 4.

Early ERCP reduced the risk for overall complications (pooled RR for all ABP patients: 0.76; 95% CI 0.41–1.40) (Fig. 2) while it increased the risk of mortality (pooled RR for all ABP patients: 1.13; 95% CI 0.23–5.63) (Fig. 3). These results did, however, not reach statistical significance. Because of the low absolute risks for mortality and complications, these RRs translate in a very small reduction in the absolute risk for complications (pooled RD for all ABP patients: –0.08; 95% CI –0.22 to 0.07) and a very small increase in the absolute risk for mortality (pooled RD for all ABP patients 0.001; 95% CI –0.08 to 0.09).

TABLE 1. Summary of Study Characteristics for the Included Trials

Study	No. Patients		Time to ERCP	Definition of Cholangitis	Criteria of Predicted Severe ABP	No. Patients with Predicted Severe ABP		Criteria of ABP
	Early ERCP Group	Conservative Treatment Group				Early ERCP Group (%)	Conservative Treatment Group (%)	
Neoptolemos et al ¹⁶	53	57	<72 h of admission	Not stated	Glasgow ≥ 3	20 (38)	25 (44)	Gallstones on US or cholestatic laboratory abnormalities
Fölsch et al ¹⁸	126	112	<72 h of onset	Bilirubin >5 mg/dl (90 μ mol/L)*	Glasgow ≥ 3	26 (23) [†]	20 (18) [†]	Gallstones on US or CT or cholestatic laboratory abnormalities
Oria et al ¹⁹	51	51	<48 h of onset	Charcot's triad	APACHE II ≥ 6	17 (33)	21 (41)	Gallstones on US or CT
Total	230	220	—	—	—	63 (27)	66 (30)	—

*Twelve patients had serum bilirubin concentrations higher 5 mg/dL (90 μ mol/L) but were analyzed on an intention-to-treat basis.

[†]Patients were assigned severity score post hoc.

ERCP indicates endoscopic retrograde cholangiopancreatography; ABP, acute biliary pancreatitis; US, ultrasound; CT, computed tomography.

TABLE 2. Quality Assessment of Trials Included in the Meta-Analysis

Study	Primary End Point	Double Blinding	Randomization	Withdrawals*	Jadad Score	Allocation Concealment	Blinded End Point Assessment	Missing Data*
Neoptolemos et al ¹⁶	Mortality	No	Not stated	6/4	2	Unclear	No	0/0
Fölsch et al ¹⁸	Mortality	No	Not stated	0/0	2	Unclear	Yes	16/16 [†]
Oria et al ¹⁹	Organ failure	No	Sealed envelope	0/1	3	Potentially manipulable	No	0/0

*Early ERCP group/conservative treatment group.

[†]Patients with undefined severity.**TABLE 3.** Baseline Characteristics of Patients

Study	Setting	Centers	Female		Age in Years	
			Early ERCP Group (%)	Conservative Treatment Group (%)	Early ERCP Group	Conservative Treatment Group
Neoptolemos et al ¹⁶	UK	1	34 (58)*	35 (56)*	55 (20 to 86)/74 (38 to 85)* ^{†‡}	67.5 (30 to 87)/76.5 (37 to 96)* ^{†‡}
Fölsch et al ¹⁸	Germany	22	66 (52)	76 (68)	63 (24 to 90) [‡]	63 (15 to 93) [‡]
Oria et al ¹⁹	Argentina	1	35 (69)	38 (75)	49.9 ± 17.4 [§]	44 ± 17.7 [§]

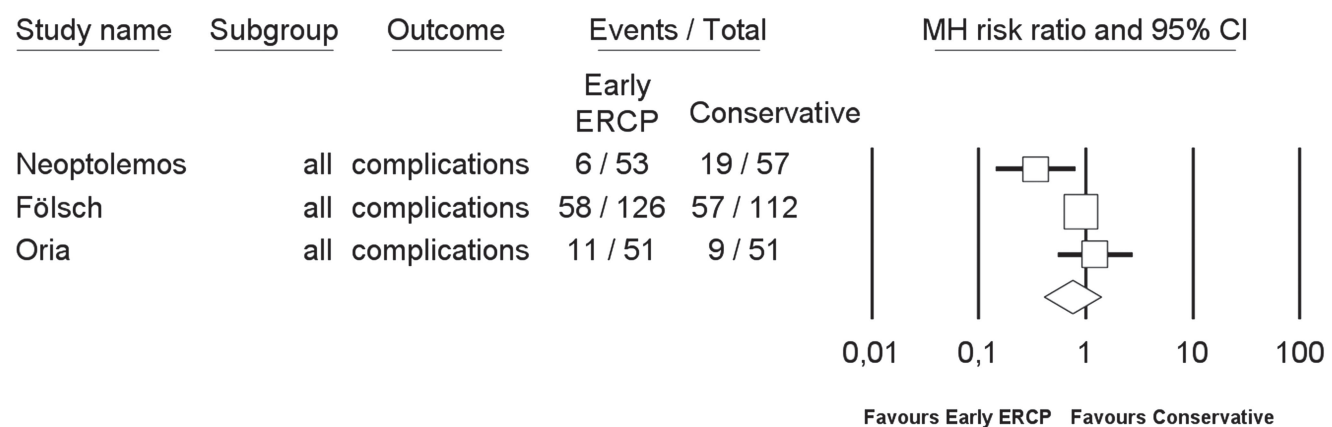
*Including patients with acute cholangitis.

[†]Predicted mild/predicted severe groups.[‡]Values are median (range).[§]Values are mean ± SD.**TABLE 4.** Meta-Analysis for Overall Complications and Mortality Comparing Early ERCP With Conservative Treatment

	Risk Ratio (95% Confidence Interval)	P	Risk Difference (95% Confidence Interval)	P
Overall Complications				
Predicted mild and severe ABP	0.76 (0.41 to 1.40)	0.38	−0.08 (−0.22 to 0.07)	0.29
Predicted mild ABP	0.86 (0.62 to 1.19)	0.36	−0.05 (−0.13 to 0.04)	0.32
Predicted severe ABP	0.82 (0.32 to 2.10)	0.68	−0.09 (−0.49 to 0.30)	0.64
Mortality				
Predicted mild and severe ABP	1.13 (0.23 to 5.63)	0.88	0.001 (−0.08 to 0.09)	0.97
Predicted mild ABP	1.90 (0.25 to 14.55)	0.53	0.01 (−0.02 to 0.04)	0.40
Predicted severe ABP	1.28 (0.20 to 8.06)	0.80	0.01 (−0.22 to 0.24)	0.91

ABP indicates acute biliary pancreatitis.

Effect of early ERCP on complications (all patients)

**FIGURE 2.** Forest plot for overall complications associated with early ERCP with or without ES compared with conservative management in all patients with acute biliary pancreatitis.

(Table 4). These results did, however, not reach statistical significance.

Based on the reported data the meta-analysis was stratified for predicted severe and predicted mild ABP. For this analysis additional unpublished data were provided by Oria et al.¹⁹ It should be noted that Fölsch et al¹⁸ failed to report the disease severity for 32 patients due to post hoc classification of their data. Consequently, the data on these 32 patients could not be analyzed. The stratification for severity did not result in significant differences for the risk of complications (Figs. 4, 5) and mortality (Figs. 6, 7) between the ERCP group and the conservative treatment group in both patients with predicted mild and predicted severe ABP.

DISCUSSION

In this meta-analysis of RCTs comparing early ERCP, with or without ES, with conservative treatment in patients with ABP without signs of acute cholangitis, no beneficial effect of early ERCP on mortality and overall complications was observed both in patients with predicted mild and patients with predicted severe ABP.

These results suggest that early ERCP in patients with ABP without coexisting cholangitis is an unnecessary invasive procedure. Notably, in the included RCTs, only about half the patients that underwent a successful ERCP were found to have common bile duct stones. This finding is in accordance with the recent study by Acosta et al,²³ in which

Effect of early ERCP on mortality (all patients)

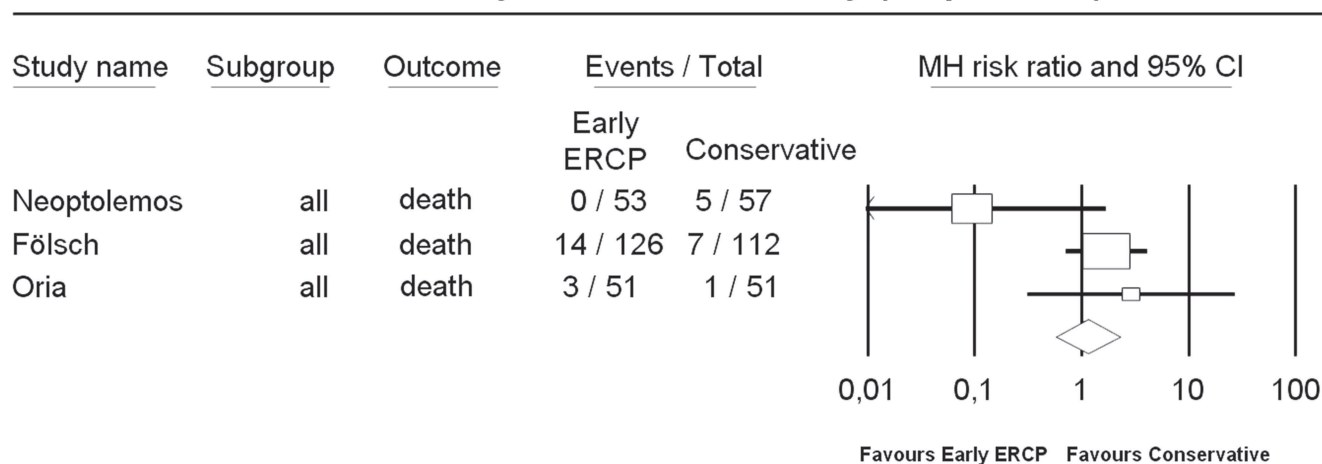


FIGURE 3. Forest plot for mortality associated with early ERCP with or without ES compared with conservative management in all patients with acute biliary pancreatitis.

Effect of early ERCP on complications (predicted mild patients)

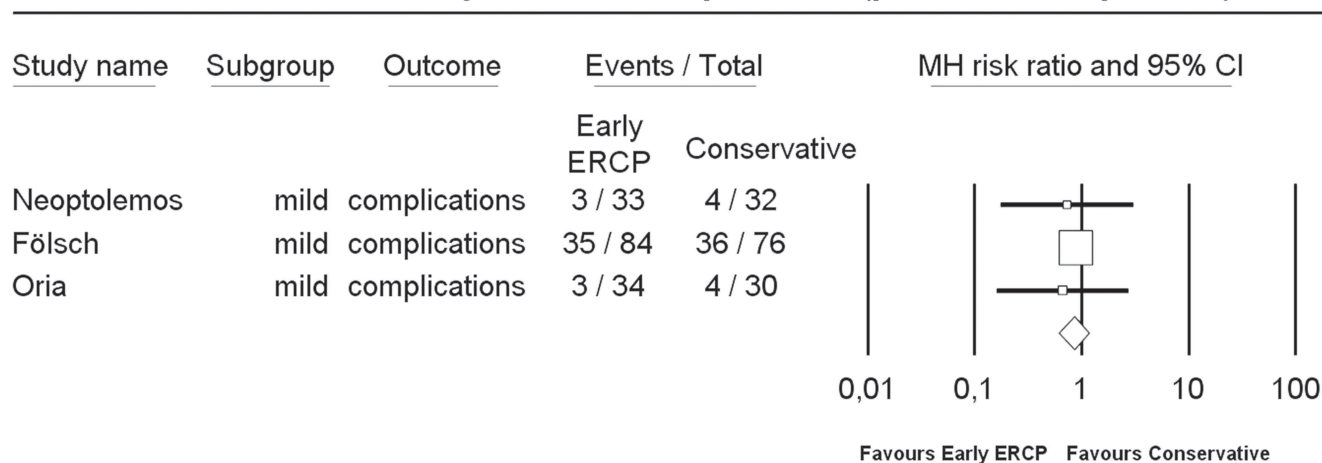


FIGURE 4. Forest plot for overall complications associated with early ERCP with or without ES compared with conservative management in patients with predicted mild acute biliary pancreatitis.

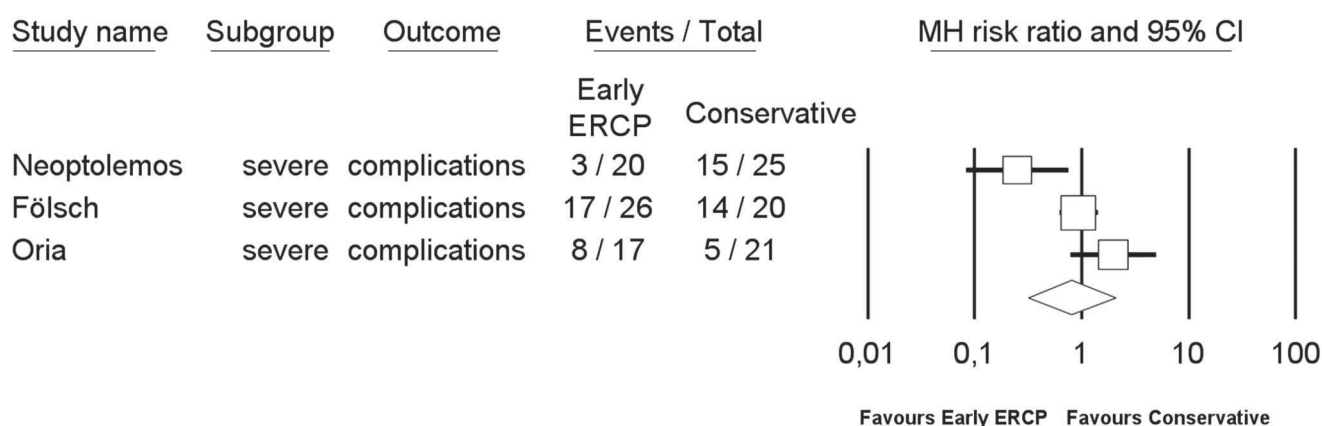
Effect of early ERCP on complications (predicted severe patients)

FIGURE 5. Forest plot for overall complications associated with early ERCP with or without ES compared with conservative management in patients with predicted severe acute biliary pancreatitis.

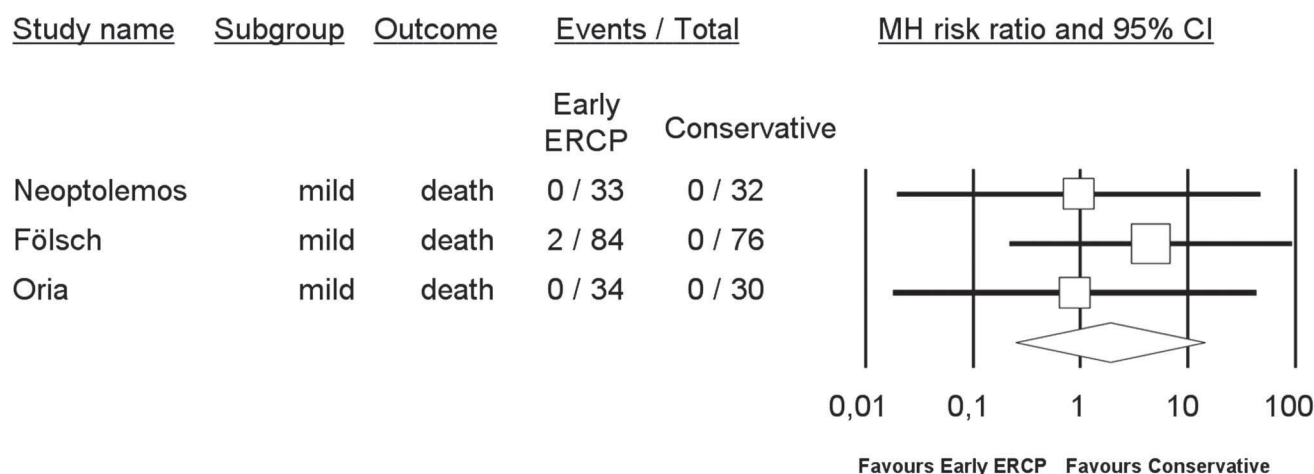
Effect of early ERCP on mortality (predicted mild patients)

FIGURE 6. Forest plot for mortality associated with early ERCP with or without ES compared with conservative management in patients with predicted mild acute biliary pancreatitis.

62% of patients with ABP and ampullary obstruction (defined in this study as severe and continuous epigastric pain, bile-free gastric aspirate, and elevated serum bilirubin level) showed spontaneous relief of obstruction within 48 hours from the onset of symptoms. In the RCTs included in this meta-analysis, ES was performed only when common bile duct stones were visualized during ERCP. In daily clinical practice, however, ES is often also performed in the absence of common bile duct stones because of a potential false-negative ERCP in case of sludge, microlithiasis or missed common bile duct stones.

The design of an optimal strategy in biliary pancreatitis is frustrated by a low sensitivity of pre-ERCP diagnostic tools to confirm the presence of common bile duct

stones. To increase on this sensitivity several studies with new imaging modalities have been performed. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS) have been proposed as minimal invasive diagnostic techniques to identify common bile duct stones, to further reduce the number of unnecessary ERCPs.^{26–30} A recent RCT comparing EUS (with selective ERCP and ES in case of common bile duct stones) with ERCP and selective ES in 140 patients with ABP showed a higher success rate for examination rate of the biliary tree with a comparable morbidity and mortality risk in patients undergoing EUS with selective ERCP.³¹ On the other hand, MRCP is known to miss small gallstones (<6 mm),³² while these are associated with the risk

Effect of early ERCP on mortality (predicted severe patients)

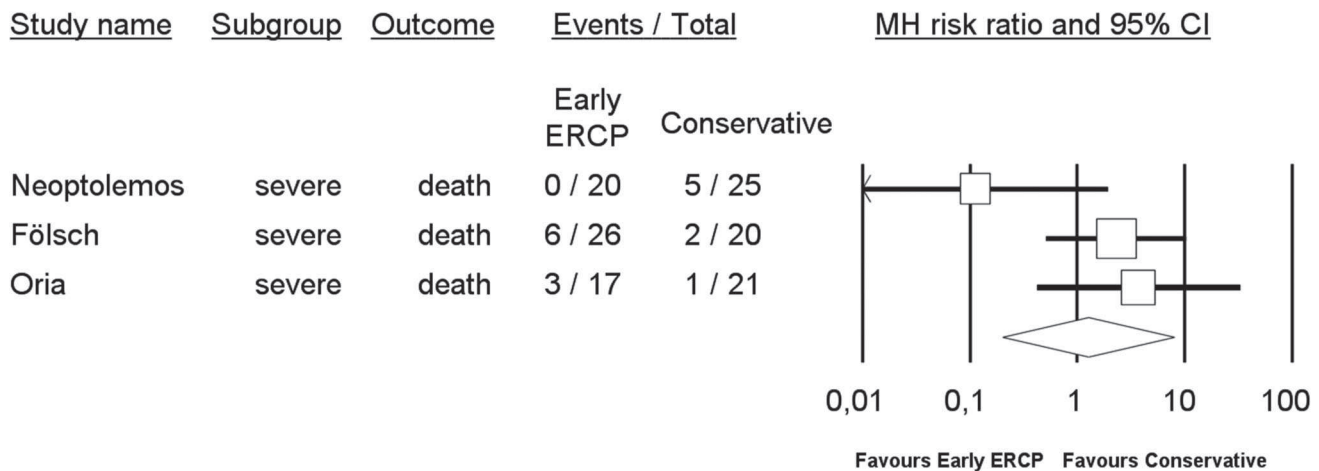


FIGURE 7. Forest plot for mortality associated with early ERCP with or without ES compared with conservative management in patients with predicted severe acute biliary pancreatitis.

for acute pancreatitis.⁵ Moreover, both MRCP and EUS are not yet widely available and because experience is scant, EUS may be technically difficult to perform in the early stage of ABP.

In the interpretation of the present meta-analysis the following aspects deserve attention. Firstly, the methodological quality of the included trials was relatively low (ie, Jadad score²² below 3 for 2 of the 3 included trials). However, these data are still the best available.

Secondly, the included trials used different definitions with respect to acute cholangitis, and included different subgroups of patients with ABP (Table 1). Neoptolemos et al¹⁶ included all patients with ABP and presented separate data on patients without acute cholangitis. Oria et al¹⁹ included only patients with ABP and clinical evidence of biliopancreatic obstruction without acute cholangitis. Fölsch et al¹⁸ excluded all patients with a bilirubin >5 mg per deciliter (90 μ mol per liter), thereby expelling a proportion of patients with acute cholangitis, but also likely excluding some patients with biliopancreatic obstruction without acute cholangitis. Furthermore, the incidence of cholestasis varied among the 3 included RCTs as a consequence of the different eligibility criteria of these trials. Although focus has historically been on acute cholangitis rather than cholestasis (without cholangitis), the presence of cholestasis alone might also be of influence on the clinical impact of early ERCP.

Thirdly, the 3 studies used different definitions for “early” ERCP. Neoptolemos et al¹⁶ considered early ERCP as within 72 hours after admission, regardless of duration of symptoms at time of admission. The 2 other trials^{18,19} defined early as within 48 to 72 hours after onset of symptoms.

Fourthly, there was considerable variation among the 3 trials in the definition of “overall complications” as outcome (eg, gallbladder empyema, recurrent pancreatitis, respiratory insufficiency, ascites, lumbar osteitis, infected

pancreatic necrosis). As a likely result of this variation, the incidence of complications in the patients treated conservatively varied from 19%¹⁹ to 51%.¹⁸ The above mentioned differences in patient populations and definitions on intervention and outcome might explain the different outcomes of various trials.

Fifthly, based on the individual findings of the performed RCTs^{16–19} and previous meta-analyses,^{20,21} the role of early ERCP is most controversial in the subgroup of patients suffering from a predicted severe attack of ABP without signs of acute cholangitis. Although in the current meta-analysis patients with predicted severe ABP did not benefit from early ERCP, it should be noted that the number of patients with predicted severe APB included was relatively small ($n = 129$). Moreover, the accuracy of current clinical scores for predicting severity is known to be quite poor. Oria et al¹⁹ used quite a low cutoff level (APACHE II ≥ 6) for “predicted severe” ABP. As a result, few patients identified as predicted severe eventually did suffer from clinically severe pancreatitis, as shown by low rates of organ failure and limited pancreatic necrosis (a low computed tomography severity index).¹⁹ Fölsch et al¹⁸ defined severity post hoc which resulted in a failure to define severity in 13% of randomized patients.

Finally, the results of this meta-analysis conflict with those of a previous Cochrane meta-analysis,²¹ which, unlike this study, included the trial by Fan et al¹⁷. We excluded the trial of Fan et al because this study included patients with a nonbiliary cause of acute pancreatitis and included patients with acute cholangitis, without presenting separate data for patients without acute cholangitis. However, when we provisionally included trial by Fan et al in the calculations, the pooled estimates of this meta-analysis did not principally change (data not shown).

In conclusion, the present meta-analysis does not demonstrate a beneficial effect of early ERCP, with or without ES, in both patients with predicted mild and severe ABP without cholangitis. There is, however, a lack of data on the subgroup of patients with predicted severe ABP. Therefore, a new adequately powered RCT in this setting may be justified. In the future study, patients with acute cholangitis should be excluded, timing after onset of the disease should be clearly defined, and stratification for the presence or absence of cholestasis (biochemical and radiologic) seems appropriate.

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