Association between early ERCP and mortality in patients with acute cholangitis

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Background and Aims: Acute cholangitis (AC) is associated with high mortality of up to 10%. The association between timing of ERCP and mortality in patients with AC remains unclear. The aim of this study was to investigate whether early ERCP within 24 hours was associated with improved survival.

Methods: All patients who underwent ERCP at Odense University Hospital, Denmark, between March 2009 and September 2016 were identified using a prospective ERCP database. Clinical data were collected from medical records. Patients fulfilling the Tokyo Guidelines 2013 criteria and for whom a detailed review of medical records revealed evidence of AC were included. We investigated the association between ERCP within 24 hours and 30-day mortality using logistic regression analysis with adjustment for confounding factors.

Results: A total of 4066 consecutive patients underwent ERCP during the study period, and 166 patients fulfilled the inclusion criteria. Forty-eight patients (29%) underwent ERCP within 24 hours from the time of hospitalization, and 118 patients (71%) underwent later ERCP. Patients undergoing ERCP within 24 hours were younger (medians: 65 vs 73 years; $P = .01$) and had a higher heart rate (medians: 95 vs 90 beats/minute; $P = .02$). Overall 30-day mortality was 16% (n = 27). Mortality was 8% (n = 4) among patients undergoing early ERCP and 19% (n = 23) among patients undergoing later ERCP ($P = .10$). After adjustment for confounding factors, performance of ERCP within 24 hours was associated with lower 30-day mortality (odds ratio, 0.23; 95% confidence interval, 0.05-0.95; $P = .04$).

Conclusion: Our results indicate that early ERCP within 24 hours is associated with lower 30-day mortality in patients with AC. (Gastrointest Endosc 2018;87:185-92.)

INTRODUCTION

Acute cholangitis (AC) is a serious condition involving bacterial infection in the bile duct, facilitated by an obstruction in the biliary tract. Without treatment, the obstruction is followed by an increase in intraductal pressure, which can lead to an ascending spread of infection resulting in septicemia and organ failure. Thus, AC requires emergent treatment because it is associated with high mortality rates up to 10% despite proper treatment,[1,2] and above 50% without treatment.[3,4] The treatment of choice for AC is biliary decompression, preferably through ERCP, combined with antibiotics.[1,3] Although ERCP is regarded as the cornerstone in the treatment of AC, only a few studies have been conducted to investigate the optimal timing of ERCP, none of which were able to show a significant impact on mortality.

The international Tokyo Guidelines 2013 (TG13), based on expert opinions, recommend early biliary drainage for cases of moderate AC[5,6] without clearly defining any

Abbreviations: AC, acute cholangitis; ASA, American Society of Anaesthesiologists; CCI, Charlson comorbidity index; CI, confidence interval; ICU, intensive care unit; INR, international normalized ratio; LOS, length of hospital stay; OR, odds ratio; OUH, Odense University Hospital; SBP, systolic blood pressure; TG13, Tokyo Guidelines 2013.

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timeframe. In the literature, early ERCP has been defined as ERCP performed within 24 to 72 hours from hospital admission.[1,2,7,8] The recommendation is supported by previous studies, generally indicating that early ERCP is associated with better overall outcomes for patients with AC, including shorter length of hospital stay (LOS), reduced rates of persistent organ failure, and lower incidence of 30-day readmission.[2,8-11] However, a lack of evidence on the impact of early ERCP on compelling outcomes such as mortality may undermine the importance of the recommendation. In a recent study with 196 patients, it was suggested that the timing recommendation for ERCP in TG13 should be re-evaluated because that particular study was unable to determine any association between early ERCP and an impact on mortality (both as an isolated outcome and in combination with organ failure).[12] In contrast, another recent study concluded that early ERCP within 12 hours was associated with reduced in-hospital mortality in 260 patients with cholangitis-associated septic shock,[13] suggesting there might be a corresponding association in unselected AC patients. From a clinical perspective, it would be of great interest to clarify any association between timing of ERCP and mortality in patients with AC.

Based on the findings of previous studies, and on the recommendations of AC management guidelines (eg, TG13),[1,4,5] we hypothesized that early ERCP performed within 24 hours from hospital admission might be associated with reduced mortality. The aim of this study was to investigate the relationship between early ERCP and mortality in patients with AC when adjusted for potential confounding factors.

METHODS

Study setting

The study was conducted as a retrospective registry study at the Department of Medical Gastroenterology S, Odense University Hospital (OUH), a 1000-bed tertiary referral center performing more than 600 ERCP procedures yearly. Data collection and storage were performed with the consent and approval of the Danish patient safety agency and the Danish data protection agency.

Study population

Using an internal ERCP database, we identified consecutive patients with AC who underwent ERCP from March 1, 2009 to September 30, 2016 at OUH. The database contains records of 4066 consecutive ERCP procedures performed during the study period. Each AC diagnosis in the database was made prospectively by a highly experienced endoscopist performing the ERCP. Data from the Danish Patient Registry were used to obtain information on comorbidities. In addition, data on clinical parameters and laboratory values were obtained from the medical records.

Inclusion criteria

We included all patients who had received an AC diagnosis during ERCP by the endoscopist (prospectively registered directly in the database) and fulfilled the TG13 criteria for AC evaluated during a retrospective examination of medical records. In TG13, diagnosis of AC is based on the presence of the following criteria:[5,14] (A) systemic inflammation (fever or laboratory evidence), (B) cholestasis (jaundice or laboratory evidence), (C) imaging (biliary dilatation or evidence of the cause). The presence of one item from A plus one from either B or C fulfills the "suspicion criteria" for AC, whereas one item from each of A, B, and C fulfills the "definitive diagnosis criteria." Patients fulfilling either the suspicion criteria or the definite diagnosis criteria at the time of admission were included in this study, provided that an AC diagnosis had also been given at the time of ERCP by the endoscopist.

Patients were excluded from the study if either of the following was applicable: (1) the primary indication for ERCP was not AC, (2) the patient was initially admitted at another hospital and was transferred to OUH for the purpose of ERCP.

For patients readmitted with AC during the study period, we only included the first hospital admission and ERCP procedure.

Data collection and storage

Relevant laboratory values and clinical findings were obtained by examination of the medical records. Registered laboratory values included the following: hemoglobin, B-leukocytes, C-reactive protein, platelet count, international normalized ratio (INR), pancreatic amylase, plasma albumin, plasma creatinine, plasma alanine aminotransferase, plasma alkaline phosphatase, plasma bilirubin, plasma γ-glutamyl transferase. Registered clinical findings included the following: vital parameters (body temperature, systolic blood pressure, heart rate, saturation, and respiratory frequency), cause of obstruction (eg, stone, malignant stricture, or stent dysfunction), and the presence of bacteremia. In addition, the time of hospital admission and time of ERCP were extracted from the medical records and used to determine the exact timing of ERCP.

Data on procedures performed during ERCP were obtained from the ERCP database, and diagnosis codes for comorbidities (International Classification of Diseases ICD-8/ICD-10) were extracted from the Danish Patient Registry.

All collected data were registered and stored via Research Electronic Data Capture, provided by Odense Patient Data Explorative Network, Institute of Clinical Research, University of Southern Denmark.

Definition of outcomes

The primary outcome measure was 30-day mortality, defined as death occurring within 30 days from the date of admission to hospital. Secondary outcomes were organ failure, LOS, and intensive care unit (ICU) stay. Organ failure was defined as the occurrence of any of the following: renal failure (increase in serum creatinine to $\geq$1.5 times upper baseline value), ventilatory failure (requirement of intubation or noninvasive ventilation), or cardiovascular failure (systolic blood pressure [SBP] <90 mm Hg or mean arterial pressure <65 mm Hg) during the hospitalization period. LOS was measured as the duration of the hospitalization for the treatment of AC in days. ICU stay was defined as any admission to the ICU during the hospitalization.

Statistical analysis

Basic statistics. For each continuous variable, a normality test was performed using the Shapiro-Wilk test. Considering the asymmetrical distribution for most of the clinical data, each variable was described by calculating the median and the 2.5 and 97.5 percentiles, equivalent to the mean and 95% confidence interval (CI) for normal distributions but robust to skewed distribution forms. Medians and the 2.5 and 97.5 percentiles were calculated for each continuous variable for all samples and for samples grouped by ERCP or mortality status. Difference in distribution of each clinical variable in patients grouped by time to ERCP was tested by the Fisher exact test for discrete variables and by the Mann-Whitney-Wilcoxon test for continuous variables.

Univariable regression analysis. The association of each clinical variable with mortality was assessed by fitting logistic regression models that regress mortality on the clinical factor. The Wald test was used to evaluate the statistical significance of the corresponding coefficient in the model with a null hypothesis that the estimated coefficient in the model was not different from zero.

Multivariable regression analysis. Multiple logistic regression models were fitted by regressing mortality status on multiple clinical variables. Considering the large number of clinical variables included in the study, we chose a stepwise regression approach using backward elimination. The order of elimination was based on clinical importance and *P* value. Similar to the univariable models, the significance of each variable was tested by the Wald test. The *P* value cut-off for exclusion of clinical variables during the stepwise procedure was .1.

Candidate variables for the stepwise regression model were as follows: age (continuous variable, years), gender (categorical variable, male/female), body temperature (continuous variable, degrees Celsius), hypotension (categorical variable, defined as SBP <90 mm Hg, yes/no), heart rate (continuous variable, beats/minute), respiratory rate (continuous variable, breaths/minute), hemoglobin (continuous variable, mmol/L), leukocytosis (categorical variable, defined as B-leukocytes $>12 \times 10^9$/L, yes/no), plasma albumin (continuous variable, g/L), INR (continuous variable), plasma alanine aminotransferase (continuous variable, U/L), plasma alkaline phosphatase (continuous variable, U/L), hyperbilirubinemia (categorical variable, defined as plasma bilirubin >100 μmol/L, yes/no), plasma γ-glutamyl transferase (continuous variable, U/L), American Society of Anesthesiology (ASA) physical classification score (continuous variable), Charlson Comorbidity Index (CCI) (continuous variable), and malignant cause of AC (categorical variable, yes/no). ERCP <24 hours was used as a mandatory variable in all models.

We performed 2 sensitivity analyses: (1) evaluation of the association between performance of ERCP within 48 hours and 30-day mortality; and (2) evaluation of the association between performance of ERCP within 72 hours and 30-day mortality. The appropriateness of the underlying assumptions (collinearity, linearity of independent variables, and log odds) was examined graphically and statistically. Goodness of fit was evaluated using the Hosmer-Lemeshow test.

Using interaction terms, we performed post hoc analyses of potential interaction between performance of early ERCP and competing risk factors.

RESULTS

Patient characteristics

We identified 244 cases of AC registered in the ERCP database during the study period. After applying the TG13 inclusion criteria, one patient did not fulfill the criteria and was excluded. Of the remaining 243 patients with AC, 77 were excluded for the following reasons: (1) AC was not the primary indication for ERCP (n = 30), or (2) the patient was transferred from another hospital for the sole purpose of ERCP (n = 47). In total, 166 patients with AC were eligible for inclusion in the study.

Of the 166 patients with AC, 48 (29%) underwent ERCP within 24 hours from the time of admission, and 118 (71%) underwent ERCP after 24 hours. The median age was 71 ± 9 years; 103 of 153 patients (67%) showed evidence of systemic inflammatory response syndrome (SIRS) and 77 of 137 patients (56%) had bacteremia. Antibiotic treatment was given to 161 patients (97%) in combination with ERCP. Patients receiving early ERCP were younger (medians: 65 versus 73 years, *P* = .01) and had a higher heart rate (medians: 95 versus 90 beats/minute, *P* = .02) than patients who underwent later ERCP. Baseline characteristics are presented in Table 1.

ERCP characteristics and causes of AC

The median time to ERCP was 38 hours. When stratified into intervals, the distribution of time to ERCP was as follows: 48 patients (29%) within 24 hours, 102 patients (61%) within 48 hours, and 123 patients (74%) within 72 hours. Four patients (2%) had undergone a previous failed ERCP during the same admission. During ERCP, 83 patients (50%) underwent endoscopic biliary sphincterotomy and 11 (7%) underwent pre-cut sphincterotomy. Sixty-two patients (37%) underwent stone extraction and 11 patients

TABLE 1. Baseline characteristics

	All patients (n = 166)	ERCP <24 hours (n = 48)	ERCP ≥24 hours (n = 118)	*P* value
Patient characteristics				
Age (years), median	71 ± 9	65 ± 11	73 ± 8	.01
Male gender	92 (55)	25 (52)	67 (57)	.61
ASA score, mean	2.7 ± 0.73	2.7 ± 0.75	2.8 ± 0.72	.27
CCI, mean	1.8 ± 1.7	1.4 ± 1.6	2 ± 1.8	.09
Change in mental status	10/164 (6.1)	5/47 (11)	5/117 (4.3)	.15
Pain in right upper quadrant	65 (39)	25 (52)	40 (34)	.04
Acute pancreatitis (pre-ERCP)	11 (6.6)	4 (8.3)	7 (6.0)	.73
Antibiotics	161 (97)	46 (96)	115 (97)	.63
Clinical parameters (medians)				
Body temperature (°C)	37.6 ± 0.85	38.1 ± 0.9	37.5 ± 0.8	.05
Systolic blood pressure (mm Hg)	126 ± 14	122 ± 14	126 ± 14	.70
Heart rate (beats/minute)	92 ± 11	95 ± 13	90 ± 11	.02
Saturation (%)	96 ± 1	97 ± 2	96 ± 2	.59
Respiratory rate (breaths/minute)	18 ± 2	20 ± 2	18 ± 2	.12
Laboratory values at hospital admission (medians)				
Hemoglobin (mmol/L)	7.6 ± 1.1	8 ± 0.9	7.3 ± 0.9	.01
WBC >12 × 10^9/L	94 (57)	27 (56)	67 (57)	1
C-reactive protein (mg/L)	94 ± 54	100 ± 66	93 ± 51	.65
Platelet count (×10^9/L)	218 ± 68	247 ± 88	213 ± 68	.57
INR	1.2 ± 0.2	1.1 ± 0.1	1.2 ± 0.2	.16
Pancreatic amylase (U/L)	20 ± 10	17 ± 7	21 ± 11	.37
Albumin (g/L)	34 ± 4	34 ± 5	33 ± 4	.10
Creatinine (μmol/L)	86 ± 28	85 ± 27	86 ± 27	.98
pH	7.45 ± 0.04	7.47 ± 0.03	7.44 ± 0.05	.08
Liver function tests (medians)				
Alanine aminotransferase (U/L)	152 ± 87	164 ± 88	148 ± 89	.27
Alkaline phosphatase (U/L)	408 ± 186	368 ± 145	432 ± 198	.67
Bilirubin >100 μmol/L	58 (35)	20 (42)	38 (32)	.28
γ-Glutamyl- transferase (U/L)	704 ± 369	728 ± 398	666 ± 342	.79
Acute cholangitis presentation				
Bacteremia	77/137 (56)	22/38 (58)	55/99 (56)	.85
Malignant obstruction	72 (43)	15 (31)	57 (48)	.06
SIRS	103/153 (67)	31/45 (69)	72/108 (67)	.85

Data are presented as number of patients (%) unless otherwise stated. Median and mean values are presented as median or mean ± SD.
ASA, American Society of Anesthesiologists; *CCI*, Charlson comorbidity index; *WBC*, white blood cell count; *INR*, international normalized ratio; *SIRS*, systemic inflammatory response syndrome.

(7%) underwent lithotripsy/stone crushing; 108 patients (65%) had a biliary stent inserted. Rates of post-ERCP adverse events, defined as occurrence of either bleeding or fever (within 1 week), perforation or post-ERCP pancreatitis, and/or cholangitis, were low (combined adverse event rate of 6%, n = 10). An overview of the ERCP characteristics is presented in Table 2.

The cause of AC was benign in 94 patients (57%) and malignant in 72 patients (43%). The most frequent benign causes for AC were as follows: common bile duct stone (n = 74), accounting for 45% of the overall causes for AC, and benign stent dysfunction (stent dysfunction occurring as a result of benign pathologies) (n = 13) accounting for 8% of all AC causes in the study sample. The most frequent malignant cause was malignant stent dysfunction (stent dysfunction occurring as a result of other, simultaneously registered, malignant pathologies) (n = 50), accounting for 30% of overall causes of AC, followed by

TABLE 2. Characteristics of ERCP

	All patients (n = 166)	ERCP <24 hours (n = 48)	ERCP ≥24 hours (n = 118)	*P* value
ERCP characteristics				
Delay to ERCP (hours), median	38 ± 19	17 ± 4	51 ± 23	–
Previous failed ERCP	4 (2)	1 (2)	3 (3)	1
Procedures during ERCP				
Endoscopic sphincterotomy	83 (50)	23 (48)	60 (51)	.86
Pre-cut sphincterotomy	11 (7)	4 (8)	7 (6)	.83
Stone extraction	62 (37)	17 (35)	45 (38)	.88
Stone crushing	11 (7)	3 (6)	8 (7)	1
Remaining stone after ERCP	28 (17)	10 (21)	18 (15)	.37
Endoprosthesis applied	108 (65)	27 (56)	81 (69)	.18
Endoprosthesis removal	67 (40)	15 (31)	52 (44)	.18
Balloon dilatation	30 (18)	8 (17)	22 (19)	.93
Pancreatic duct stent applied	6 (4)	2 (4)	4 (3)	1
Pancreatic duct stent removal	5/6 (83)	1/2 (50)	4/4 (100)	.33
Post-ERCP adverse events				
Pancreatitis	3 (2)	1 (2)	2 (2)	1
Bleeding	4 (2)	1 (2)	3 (3)	1
Perforation	1 (1)	1 (2)	0 (0)	.64
Fever within 1 week	7 (4)	2 (4)	5 (4)	1
Acute cholangitis	1 (1)	0 (0)	1 (1)	1
None	156 (94)	44 (92)	112 (95)	.66
Combined incidence of post-ERCP adverse events	10 (6)	4 (8)	6 (5)	.66

Data are presented as number of patients (%) unless otherwise stated. Median and mean values are presented as median or mean ± SD.

pancreatic cancer (n = 36) and cholangiocarcinoma (n = 20), accounting for 22% and 12% of all causes, respectively. Distribution of the causes of AC is presented in Table 3.

Outcome distribution

Overall 30-day mortality was 16% (n = 27). When comparing the 2 groups, 30-day mortality was 8% (n = 4) in the <24-hour group, and 19% (n = 23) in the ≥24-hour group (P = .10). The overall rate of organ failure (defined as post-ERCP organ failure, including renal failure, cardiovascular failure, and ventilatory failure) was 26% (n = 43). Rates for organ failure were 31% (n = 15) in the <24-hour group and 24% (n = 28) in the ≥24-hour group (P = .33). The most frequent type of organ failure was renal failure with an overall incidence of 23% (n = 39), followed by cardiovascular failure 12% (n = 20), and ventilatory failure 10% (n = 16). There were no differences in the incidence of each type of organ failure or incidence of ICU stay between groups (P > .1, respectively). LOS was significantly shorter in the <24-hour group compared with the ≥24-hour group (mean LOS, 8 days vs 12 days; P = .01). An overview of outcome distribution is presented in Table 4.

Regression analyses

Univariable and multivariable regression analyses for predictors of 30-day mortality are presented in Table 5. After adjustment for confounding factors, ERCP within 24 hours was associated with a significant reduction in 30-day mortality (odds ratio [OR], 0.23; 95% confidence interval [CI], 0.05-0.95; P = .04).

The sensitivity analyses showed no indication of any association between performance of ERCP within 48 hours (OR, 0.71; 95% CI, 0.25-1.99; P = .51) or within 72 hours (OR, 0.55; 95% CI, 0.19-1.63; P = .28) and 30-day mortality, when adjusted for the same covariates.

There were no signs of interaction between performance of ERCP within 24 hours and malignant cause of AC, age, or hemoglobin level.

DISCUSSION

The current study investigated the association between performance of early timing of ERCP and 30-day mortality, taking other competing clinical risk factors into account. Our results indicate that performance of ERCP within 24 hours from the time of admission is associated with a significant reduction in 30-day mortality. In previous studies, early

TABLE 3. Causes of acute cholangitis

	All patients (n = 166)	ERCP <24 hours (n = 48)	ERCP ≥24 hours (n = 118)	*P* value
Benign cause				
Common bile duct stone	74 (45)	24 (50)	50 (42)	.47
Common bile duct stent dysfunction	13 (8)	5 (10)	8 (7)	.64
Chronic pancreatitis	3 (2)	3 (6)	0 (0)	.04
Other	4 (2)	1 (2)	3 (3)	1
Total cases with benign cause	94 (57)	33 (69)	61 (52)	.06
Malignant cause				
Pancreatic cancer	36 (22)	6 (13)	30 (25)	.10
Cholangiocarcinoma	20 (12)	5 (10)	15 (13)	.88
Liver metastases*	10 (6)	3 (6)	7 (6)	1
Other	6 (4)	1 (2)	5 (4)	.83
Stent dysfunction (malignant)†	50 (30)	11 (23)	39 (33)	.27
Total cases with malignant cause	72 (43)	15 (31)	57 (48)	.06

Data are presented as number of patients (%) unless otherwise stated.
*Liver metastases from primary cancer outside the pancreatic/biliary region.
†Stent dysfunction occurring as a result of other, separately registered, malignant pathologies.

TABLE 4. Outcome distribution

Outcome	Total (n = 166)	ERCP <24 hours (n = 48)	ERCP ≥24 hours (n = 118)	*P* value
30-day mortality	27 (16)	4 (8)	23 (19)	.10
Organ failure	43 (26)	15 (31)	28 (24)	.33
Length of hospital stay (days), mean	11 ± 10	8 ± 8	12 ± 10	.01
Intensive care unit stay	21 (13)	9 (19)	12 (10)	.2

Data are presented as number of patients (%) unless otherwise stated. Mean values are presented as mean ± SD.

ERCP was shown to be associated with improved overall outcomes for patients with AC, including reduced LOS, reduced rates of persistent organ failure, as well as reduced rates of different composite endpoints (eg, combination of 30-day mortality and organ failure). The present study is the first to show a significant association between early ERCP and 30-day mortality as an isolated endpoint. Partially inconsistent findings and different definitions for early ERCP had left the definition of "early" ERCP rather unclear; early ERCP has been defined as being within 24 to 72 hours from admission in previous studies and AC management guidelines.[1,2,8] Our results support the statement on use of early ERCP in patients with AC from the TG13 and indicate that 24 hours is the best timeframe for defining early ERCP.

In general, our study population was older and had a higher proportion with malignant causes of AC (43%) compared with populations investigated previously (all below 30%). To control for comorbidities, most studies adjusted for either the CCI or ASA classification. To maintain optimal comparability and model fit, we included both CCI and ASA in our data collection. CCI was excluded during the variable selection process in the multivariable analysis ($P > .1$) because ASA was more closely associated with mortality in our dataset. Similarly, both age and malignant cause of AC were nonsignificant when included in the multivariable regression model (both $P > .1$).

In a retrospective study of 90 patients with AC, ERCP within 72 hours was associated with improved overall outcome, defined as reduced overall rates of composite outcome: death, persistent organ failure, and/or ICU stay.[8] Given that the defined outcomes are closely correlated to 30-day mortality, the results strongly support a likely association between early ERCP and reduced 30-day mortality. The overall mortality rate was lower in the previous study compared with ours: 9% (in-hospital mortality) versus 16% (30-day mortality). Differences in overall mortality may be attributed to major differences in age (mean 60 years vs median 71 years), cause of AC (malignant cause, 26% vs 43%), and time to follow-up in the 2 study populations. Similar findings were reported in a retrospective study with 172 patients with AC, in which ERCP within 72 hours was associated with reduced LOS and reduced rate of adverse clinical outcomes (30-day

TABLE 5. Univariable and multivariable regression analysis of predictors for 30-day mortality

Variable	Univariable, OR (95% CI)	Multivariable, OR (95% CI)	Multivariable, *P* value
Time to ERCP			
ERCP <24 hours	0.38 (0.12-1.15)	0.23 (0.05-0.95)	.04
Patient characteristics			
Age (years)	1.02 (0.99-1.05)		
Male gender	0.84 (0.37-1.92)		
ASA score	11.69 (4.45-30.70)	14.66 (4.8-44.77)	<.00001
Charlson comorbidity index	1.15 (0.89-1.49)		
Change in mental status	2.32 (0.56-9.61)		
Pain in right upper quadrant	0.49 (0.19-1.23)		
Acute pancreatitis (pre-ERCP)	0.5 (0.06-4.04)		
Antibiotics	0.77 (0.08-7.17)		
Vital parameters			
Body temperature (°C)	0.48 (0.31-0.73)		
Systolic blood pressure (mm Hg)	0.99 (0.97-1.00)		
Heart rate (beats/minute)	0.98 (0.95-1.00)		
Saturation (%)	0.93 (0.85-1.03)		
Respiratory rate (breaths/minute)	0.87 (0.76-1)		
Laboratory values at hospital admission			
Hemoglobin (mmol/L)	0.67 (0.48-0.92)		
WBC >12 ($\times 10^9$/L)	3.16 (1.20-8.32)	3.19 [0.99-10.3]	.05
C-reactive protein (mg/L)	1.00 (1-1.01)		
Platelet count ($\times 10^9$/L)	1.00 (1-1.00)		
INR	2.41 (1.15-5.08)		
Pancreatic amylase (U/L)	1.00 (1-1.00)		
Albumin (g/L)	0.84 (0.77-0.91)		
Creatinine (μmol/L)	1.00 (1-1.01)		
pH	0.01 (0-3.71)		
Liver functions tests			
Alanine aminotransferase (U/L)	1 (1-1.00)		
Alkaline phosphatase (U/L)	1.00 (1.00-1.00)		
Bilirubin (μmol/L)	1.00 (1.00-1.01)		
Bilirubin >100 μmol/L	2.33 (1.01-5.36)	2.82 [1.00-7.91]	.05
γ-Glutamyl transferase (U/L)	1.00 (1.00-1.00)		
SIRS	0.56 (0.23-1.34)		
Acute cholangitis presentation			
Bacteremia	1.15 (0.46-2.91)		
Malignant obstruction	3.15 (1.32-7.51)		

OR, Odds ratio; *CI*, confidence interval; *ASA*, American Society of Anesthesiologists; *WBC*, white blood cell count; *INR*, international normalized ratio; *SIRS*, systemic inflammatory response syndrome.

mortality or persistent organ failure),[9] whereas a recent study of 199 patients showed that ERCP within 48 hours was also associated with reduced LOS.[15] Although these results link early ERCP with favorable clinical outcomes that may correlate with a reduced death rate, the current study explicitly shows that only ERCP within 24 hours is directly associated with 30-day mortality.

In another retrospective study of 203 patients with AC, ERCP within 48 hours from admission was associated with a reduced rate of persistent organ failure.[2] These findings further support the hypothesis that early ERCP may be associated with reduced mortality. The study population was very similar to ours with regard to the timing of ERCP (mean delay, 40 vs 38 hours), comorbidities among patients (mean CCI, 2.5 vs 1.8), and incidence of organ failure (22% vs 26%). In contrast, a study of 196 patients with AC did not find any association between the timing of ERCP and adverse outcomes (defined as either in-hospital mortality or organ failure).[12] However, that study did not adjust for differences in comorbidities. The impact of early ERCP on clinical outcomes may have been undermined because of an uneven distribution of comorbidities among patients, which could have served as an important confounding factor. Finally, in a recent study of 260 patients with cholangitis-associated septic shock, it was found that early biliary drainage (with ERCP, percutaneous drainage, or surgical intervention) and antibiotic treatment within 12 hours from admission was associated with reduced in-hospital mortality, after adjustment for comorbidities (CCI and APACHE II).[13] Although septic cholangitis is undoubtedly a more serious presentation of AC, this does support a reduced risk of death associated with early biliary drainage.

Despite its limitations in having a retrospective design, a major strength of our study is the consecutive inclusion of all cases of AC. Each AC diagnosis was prospectively made and registered in the database. By excluding patients transferred from other hospitals, it was ensured that all patients with AC were admitted under relatively similar conditions, optimizing the comparability of the admission process. Potential confounders were the severity of AC and potential comorbidities during the time of admission, which could have influenced the timing of ERCP. To minimize confounding, we adjusted for the selected prognostic factors: ASA score (marker for comorbidities and disease severity), leukocytosis, and hyperbilirubinemia (markers for the severity of AC infection and biliary obstruction, respectively). The fact that patients undergoing ERCP 24 hours or later after presentation to hospital were older, had a lower hemoglobin level, and a trend toward a higher rate of underlying malignant cause compared with patients undergoing early ERCP, does indicate problems with confounding by severity. We performed supplementary interaction analyses that indicated that the effect of early ERCP on mortality was also valid for older patients and patients with malignant biliary obstruction. Although the association identified between early ERCP and reduced mortality was only marginally statistically significant (OR, 0.23; 95% CI, 0.05-0.95; $P = .04$), our data indicate that early ERCP within 24 hours is an important goal in all patients with AC. Even though a prospective randomized controlled trial would have been the optimal way to minimize confounding, it would have been unethical to conduct a study where patients are randomized to late ERCP, as previous studies have shown that early ERCP is associated with better outcomes.

The data from the present and previous studies indicate that early ERCP is a crucial part of the treatment of patients with AC. This raises the question whether patients with AC should be treated in hospitals without access to ERCP within 24 hours. Such a decision would naturally present many challenges for remote regions without optimal access to an experienced endoscopist. However, in some health care systems, it would make sense to consider centralizing treatment of patients with AC to regional referral centers with access to high-quality ERCP within 24 hours also on weekends.

In conclusion, our data indicate that early ERCP performed within 24 hours from hospital admission is associated with lower 30-day mortality, after adjusting for prognostic factors. The association between early ERCP and improved outcome is supported by previous studies, although they differ somewhat in endpoints and timeframe for defining early ERCP. Therefore, early ERCP within 24 hours from admission should be considered in patients with AC to reduce mortality.

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