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ERCP within 6 or 12 h for acute cholangitis: a propensity score-matched analysis

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Abstract

Background The optimal timing of biliary drainage by endoscopic retrograde cholangiopancreatography (ERCP) for patients with acute cholangitis remains controversial. The aim of our study was to determine if ERCP performed within 6 or 12 h of presentation was associated with improved clinical outcomes.

Methods Medical records for all patients with acute cholangitis who underwent ERCP at our institution between 2009 and 2018 were reviewed. Outcomes were compared between those who underwent ERCP within or after 12 h using propensity score framework. Our primary outcome was length of hospitalization. Secondary outcomes included in-hospital mortality, adverse events, ERCP failure, length of ICU stay, organ failure, recurrent cholangitis, and 30-day readmission. In secondary analysis, outcomes for ERCP done within or after 6 h were also compared.

Results During study period, 487 patients with cholangitis were identified, of whom 147 had ERCP within 12 h of presentation. Using propensity score matching, we selected 145 pairs of patients with similar characteristics. Length of hospitalization was similar between ERCP within or after 12 h (135.9 vs 122.1 h, *p* 0.094). No difference was noted in mortality, ERCP failure, adverse events, need and length of ICU stay, and recurrent cholangitis. However, 30-day readmission rates were lower when ERCP within 12 h (7.6 vs 15.2, *p* 0.042). No significant difference was noted in aforementioned outcomes between ERCP performed within or after 6 h.

Conclusions ERCP performed within 6 h or 12 h of presentation was not associated with superior clinical outcomes, however, may result in reduced re-hospitalization.

Keywords ERCP · Cholangitis · Tokyo score · Length of hospitalization · Timing

Acute cholangitis is associated with substantial morbidity, mortality and healthcare costs [1, 2]. [3, 4]. In 2019, the American Society for Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE) published guidelines on the role of endoscopy in the management of choledocholithiasis [5, 6]. The international Tokyo guidelines, published in 2013 and revised in 2018 address the assessment of the severity of acute cholangitis and its subsequent management [7, 8]. These guidelines have established the current standard of care for management of choledocholithiasis and ascending cholangitis.

While the role of endoscopic retrograde cholangiopancreatography (ERCP) in the management of patients with choledocholithiasis and ascending cholangitis is well established, the optimal timing of biliary drainage remains controversial. Current European guidelines suggest that the timing for ERCP should be based on the severity of the cholangitis: within 12 h for severe cholangitis that is accompanied by septic shock, within 48 to 72 h for moderate cholangitis, and elective ERCP for mild cholangitis [6]. The 2013 Tokyo guidelines also recommended 'early' or 'urgent' (as soon as possible) drainage depending on the severity of the

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cholangitis, but did not make any recommendations regarding specific timing [8]. The ASGE guidelines also do not specifically address the issue of timing of ERCP [5]. Several studies have compared the outcomes between ERCP's done within 24, 48 and 72 h and have shown that earlier ERCP is associated with better outcomes. It is, therefore, possible that ERCP done even before 24 h of presentation may further improve outcomes, however, outcomes of ERCP when done within 6 or 12 h of presentation has not been fully studied.

The aim of this study was to assess if ERCP performed within 12 h of presentation in patients with acute cholangitis was associated with improved clinical outcomes. A priori, we determined that we would also analyze outcomes of ERCPs done within 6 h of presentation with acute cholangitis.

Patients and methods

All patients with acute cholangitis who underwent ERCP at our institution between 2009 and 2018 were identified using a database maintained by our advanced endoscopy group. Cholangitis was defined as a combination of the following per Tokyo guidelines: (1) Fever and/or right upper quadrant pain; (2) Elevated white blood count (WBC) and/or C-reactive protein (CRP); (3) Positive blood cultures and/or pus extraction from the common bile duct (CBD) and/or signs of cholangitis on cross section imaging. Patients who had previously undergone ERCP within the last year, presented to another hospital and then transferred to our institution for ERCP, and patients with modified upper gastrointestinal anatomy (e.g. gastric bypass or Whipple's procedure) were excluded. ERCP procedures and clinical management of cholangitis were done according to standard clinical practice. The study was approved by our Institutional Review Board.

The following variables were collected: patient demographics, comorbidities, ASA score, vital signs, symptoms, and medications. Routine blood tests including cell count, liver and pancreatic enzymes, and kidney function tests were also collected. Hypoalbuminemia was defined as serum albumin < 3.5 g/L and positive blood cultures as at least two bottle showing growth of same bacterial species. The cause and severity of cholangitis was determined using Tokyo guidelines grading system for cholangitis. We used the following definitions to characterize organ dysfunction: renal dysfunction as creatinine > 2 mg/dl, neurological dysfunction as presence of altered mental status or confusion, and hepatic dysfunction as INR > 1.5. The following variables pertinent to the ERCP procedures were collected: ERCP timing, sphincterotomy, biliary stent placement, type of stent, pancreatic stent, post-ERCP adverse events, and ERCP failure (defined as inability to achieve adequate biliary drainage). The timing of ERCP was defined as time of presentation to the emergency department or hospital to the ERCP starting time. We also collected the following outcome variables: length of hospitalization, length of intensive care unit (ICU) stay, presence of organ failure, post-ERCP adverse events, cholangitis recurrence within 30 days of discharge, 30-day readmission rate, and in-hospital mortality. The post-ERCP length of hospitalization was calculated from date of ERCP until date of discharge. Cholangitis recurrence was defined as repeat biliary drainage procedure and/or a repeat course of antibiotics in patients with new-onset cholangitis symptoms. All the data were collected by the investigators using an a priori designed study instrument.

The primary outcome of the study was the post-ERCP length of hospitalization in patients who underwent ERCP within 0 to 12 h of presentation (referred to in this manuscript as ERCP < 12 h group) compared with those who underwent ERCP after 12 h of presentation (referred to in this manuscript as ERCP > 12 h group). The secondary outcomes included in-hospital mortality, post-ERCP adverse events, ERCP failure, post-ERCP length of ICU stay, organ failure, cholangitis recurrence, 30-day readmission. We also compared post-ERCP length of hospitalization as well as aforementioned clinical outcomes in patients who underwent ERCP within 0 to 6 h of presentation (referred to in this manuscript as ERCP < 6 h group) and any time after 6 h of presentation (referred to in this manuscript as ERCP > 6 h group). Finally, we performed a sub-group analysis for patients with severe cholangitis (Tokyo cholangitis score of 3).

Continuous variables are expressed as means ± standard deviations and were compared with Student's t test or Mann–Whitney U test, as appropriate. Categorical variables are expressed as percentages and were compared using chi-squared tests or Fisher exact tests, depending on the sample size. Clinical endpoints were compared between ERCP within and after 12 h of presentation using propensity score (PS) framework. The PS approach aims at creating a new dataset in which the probability to have ERCP within or after 12 h of presentation is equal (as in a pure randomized trial) to balance patients' baseline characteristics. First, a multivariable logistic regression was used to predict the probability of ERCP within 12 h (i.e., the estimated propensity score), controlling for the following pre-specified covariates: age, past medical history of cholangitis, cholecystectomy, prior outside hospital ERCP, comorbidities, acute dysfunction, required ICU stay, total bilirubin, cause of cholangitis and Tokyo score. ERCP within and after 12 h of presentation patients were matched using a 1:1 nearest neighbor matching algorithm without replacement, with a caliper of 0.2 of the standard deviation of the PS on the logit scale [15]. An absolute standardized difference less than 0.1 was considered as evidence of covariate balance (Austin PC 2011

Multivariate Behav Res) (see Supplementary Figures). Then, clinical endpoints were compared between the two groups within the matched dataset. Post ERCP length of hospitalization was compared by the log rank method. Kaplan–Meier survival curves were constructed to analyze the time until hospital discharge, with censoring of data for patients who had died in the hospital. The Hazard Ratio (HR) was estimated using a Cox proportional hazards regression model. Finally, factors associated with a longer post ERCP length of hospitalization were assessed within the whole unmatched cohort using an univariate Cox regression model. Hazard-ratios and their 95% confidence interval were calculated. A *p* value < 0.05 was considered statistically significant. In a secondary analysis, the same PS matching approach was used to select unique pairs of patients with ERCP performed within or after 6 h. Finally, risk factors of longer length of hospitalization were assessed within the whole unmatched cohort using univariate cox regression models. Statistical analyzes were conducted with SPSS v23 and R software 3.6.2 for Mac.

Results

Patients

A total of 1597 patients who underwent ERCP for cholangitis were screened between September 2009 and March 2018. Overall, 508 were excluded because of prior ERCP at our institution; 33 because of altered anatomy, 397 because they did not meet our strict criteria for cholangitis, and 165 because they had first presented to another institution. A total of 487 patients were included for analysis amongst whom 147 had an ERCP within 12 h of presentation, and 340 after 12 h of presentation. The mean age was 73.03 (± 0.74) years-old, 42.92% of patients were female, 77% of patients had choledocholithiasis related cholangitis, the mean ASA score was 3.06 (± 0.029), and the mean timing of ERCP was 26.52 (± 2.31) hours. Severity of cholangitis was categorized using Tokyo guidelines and the distribution was as follows: score 1 = 26.70%, score 2 = 44.15% and score 3 = 28.54%.

Detailed baseline patient characteristics before and after propensity matching are shown in Table 1. In the unmatched cohort, patients with ERCP < 12 h had significantly more cardiovascular dysfunction (26% vs 14%, *p* 0.002) and more commonly had choledocholithiasis associated cholangitis (87% vs 73%, *p* 0.001). Matching on the propensity score allowed the selection of 145 pairs of patients with similar characteristics (Flow Chart 1, Table 1, Supplemental Figures 1 and 2). Amongst the 487 patients, 61 had an ERCP within 6 h of presentation (ERCP < 6 h group), and 426 after 6 h of presentation (ERCP > 6 h group). A second matching on the propensity score allowed the selection of 60 pairs of patients with similar characteristics (Table 2).

Post-ERCP length of hospitalization

Our primary outcome was post-ERCP length of hospitalization, and this outcome did not significantly differ between the ERCP < 12 h and ECRP > 12 h groups (135.9 vs 122.1 h, *p* 0.094) in the propensity score-matched population (Table 3A and Fig. 1A).

The main variables independently associated with a longer post-ERCP length of hospitalization according to Cox univariate regression on the whole unmatched cohort were: ASA score (HR 1.6; CI 1.4–1.8, *p* 001), Tokyo score of 2 (HR 1,3; CI 1.0–1.6, *p* 0.043), Tokyo score 3 (HR 2.1; CI 1.6–2.7, *p* 0.001), ERCP < 24 h (HR 1.3; CI 1.1–1.6, *p* 0.006), and required ICU stay (HR 2.0; CI 1.6–2.4, *p* 0.001).

ERCP < 12 h was not associated with a shorter post-ERCP length of hospitalization (HR 1.2; CI 1.0–1.4, *p* 0.096). In addition, post-ERCP length of hospitalization (HR 1.0; CI 0.8–1.3, *p* 0.687) was not associated with an increase in the 30-day readmission rate. Conversely, endoscopic sphincterotomy (HR 0.8; CI 0.6–0.9, *p* 0.004), stone extraction (HR 0.7; CI 0.6–0.9, *p* 0.002) and absence of post-ERCP adverse event (HR 0.5; CI 0.4–0.8, *p* 0.004) were associated with a shorter post-ERCP length of hospitalization (Table 4).

We also found that the post-ERCP length of hospitalization did not significantly differ between the ERCP < 6 h and ECRP > 6 h groups in the second propensity score-matched population of patients (142.9 vs 141.5 h, *p* 0.650) (Table 3B and Fig. 1B).

Secondary clinical outcomes

Mortality (2.8% vs 4.1%, *p* 0.520), ERCP failure (6.2% vs 10.3%, *p* 0.201), post-ERCP pancreatitis (2.1% vs 0%, *p* 0.247), bleeding (6.2% vs 3.5%, *p* 0.273), perforation (0.7% vs 0%, *p* 1.000), required ICU stay (48.3% vs 43.4%, *p* 0.409), post-ERCP length of hospitalization in ICU (1.3 vs 1.5 days, *p* 0.796), and cholangitis recurrence (4.8% vs 3.5%, *p* 0.555) did not differ between the ERCP < 12 h and ECRP > 12 h groups in the propensity score-matched population. However, the 30-day readmission rate was lower in the ERCP < 12 h group (7.6% vs 15.2%, *p* 0.042) (Table 3A).

We found similar results in the second propensity score-matched population of patients with ERCP < 6 h and ECRP > 6 h ($n = 120$). Mortality (3.3% vs 6.7%, *p* 0.679), ERCP failure (10% vs 8.3%, *p* 0.752), post-ERCP pancreatitis (1.7% vs 1.7%, *p* 1.000), bleeding (8.3% vs 6.7%, *p* 1.000), perforation (1.7% vs 0%, *p* 1.000), required ICU stay (43.3% vs 40.0%, *p* 0.711), post-ERCP length of ICU stay

Table 1 Characteristics of the cohort before and after propensity-score matching analysis

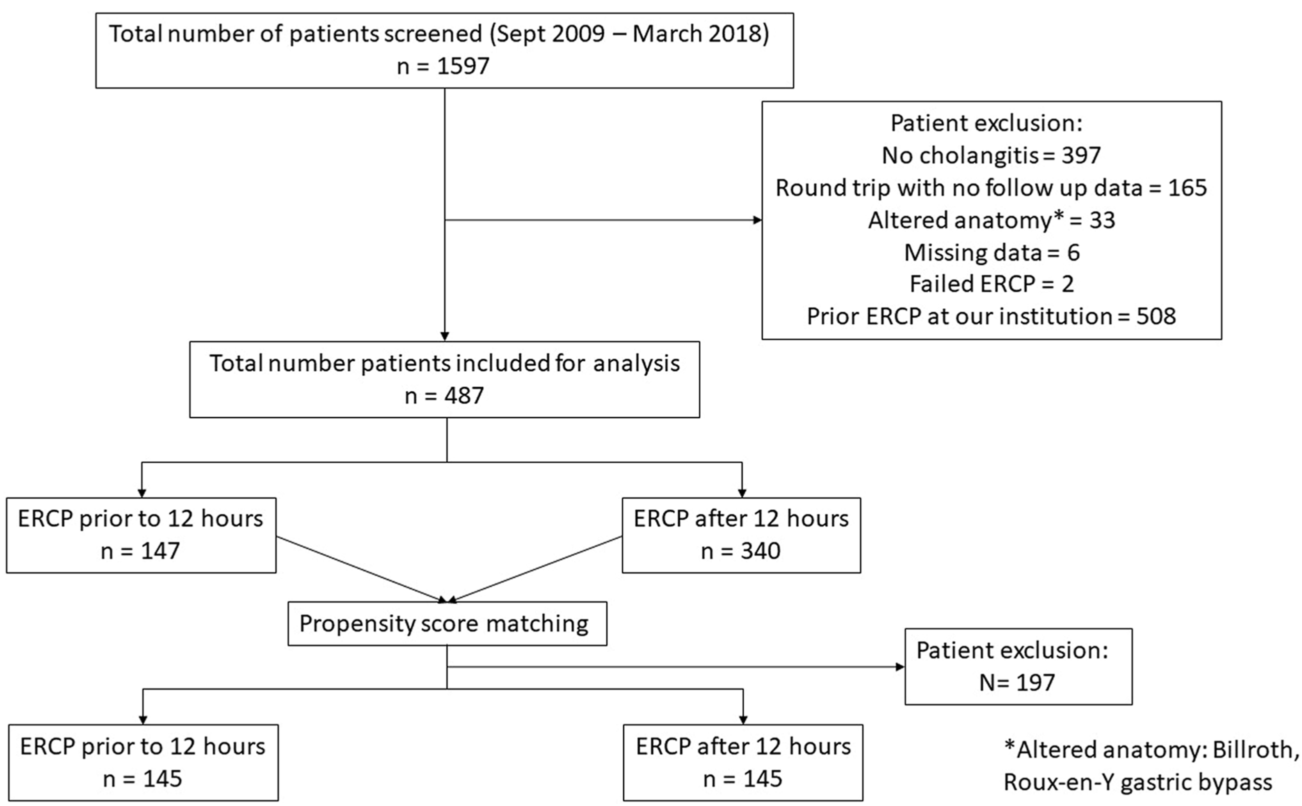
	Before matching			After matching			SMD
	ERCP < 12 h	ERCP > 12 h	*p* value	ERCP < 12 h	ERCP > 12 h	*p* value	
	n = 147	*n* = 340		*n* = 145	*n* = 145		
Age, years	73.9 (± 15.5)	72.66 (± 16.7)	0.556	73.71 (15.5)	73.5 (± 15.8)	0.963	0.0116
Female	68 (46)	141 (41)	0.327	66 (46)	54 (37)	0.153	
BMI	29.4 (± 7.9)	28.0 (± 6.1)	0.186	29.3 (± 8.0)	28.5 (± 5.3)	0.930	
ASA score	3.1 (± 0.7)	3.1 (± 0.6)	0.011	3.2 (± 0.7)	3.1 (± 0.6)	0.148	
Past Medical History							
Cholangitis	6 (4)	21 (6)	0.354	6 (4)	6 (4)	1.000	0.0000
Cholecystectomy	35 (24)	64 (19)	0.209	35 (24)	33 (23)	0.782	0.0323
Prior OSH ERCP	15 (10)	44 (13)	0.395	15 (10)	15 (10)	1.000	0.0000
Stent in situ	6 (4)	25 (7)	0.120	6 (4)	7 (5)	0.777	0.0347
Comorbidities							
CAD	43 (29)	100 (30)	0.972	43 (30)	46 (32)	0.702	0.0453
COPD	21 (14)	46 (14)	0.824	21 (14)	20 (14)	0.866	0.0196
CKD	32 (22)	65 (19)	0.501	31 (21)	32 (22)	0.887	0.0167
DM	47 (32)	107 (31)	0.913	47 (32)	41 (28)	0.443	0.0884
Clinical presentation							
Temperature	100.3 (± 2.2)	99.9 (± 99.7)	0.146	100.3 (2.2)	100.0 (± 2.1)	0.265	
SBP	116.5 (± 26.9)	120.8 (± 26.8)	0.077	116.4 (27.1)	116.6 (± 29.5)	0.941	
Heart Rate	89.6 (± 21.0)	91.2 (± 20.8)	0.282	89.3 (± 20.8)	92.6 (± 21.1)	0.112	
Right upper quadrant pain	132 (90)	281 (83)	0.044	131 (90)	120 (83)	0.058	
AMS	23 (16)	47 (14)	0.599	22 (15)	25 (17)	0.633	
Blood thinner	21 (14)	74 (22)	0.056	20 (14)	28 (19)	0.206	
Acute dysfunction							
Cardio-vascular	38 (26)	49 (14)	0.002	36 (25)	31 (21)	0.486	0.0785
Neurological	17 (12)	26 (8)	0.162	16 (11)	15 (10)	0.849	0.0215
Respiratory	17 (12)	38 (11)	0.901	16 (11)	17 (12)	0.853	0.0215
Renal	26 (18)	46 (14)	0.235	25 (17)	28 (19)	0.649	0.0540
Hepatic	6 (4)	25 (7)	0.175	6 (4)	4 (3)	0.520	0.0695
Blood coagulation	12 (8)	28 (8)	0.979	11 (8)	12 (8)	0.828	0.0251
Lab values							
WBC	15.7 (± 7.6)	15.9 (± 8.3)	0.935	15.6 (± 7.4)	15.4 (± 8.4)	0.449	
TB	4.7 (± 3.3)	5.3 (± 5.4)	0.849	4.7 (± 3.3)	4.7 (± 3.4)	0.951	0.0080
AST	312.0 (± 322.8)	296.8 (± 364.2)	0.185	313.4 (± 324.6)	291.8 (± 356.3)	0.296	
ALT	286.6 (± 252.9)	257.3 (± 243.7)	0.052	288.3 (± 254.0)	259.1 (± 239.0)	0.156	
AP	296.3 (± 210.3)	342.1 (± 288.5)	0.106	296.7 (± 211.4)	310.9 (± 244.6)	0.767	
Lipase	755.42 (± 2875.0)	726.2 (± 2481.7)	0.847	767.5 (± 2897.0)	1016.4 (± 3230.5)	0.464	
Hypoalbuminemia	71 (48)	151 (44)	0.429	69 (5)	66 (5)	0.724	
Positive blood cultures	56 (38)	122 (36)	0.642	56 (4)	67 (5)	0.904	
Cause of cholangitis							
Choledocholithiasis	128 (87)	247 (73)	0.001	126 (87)	128 (88)	0.722	0.0410
Stent occlusion	2 (1)	11 (3)	0.239	2 (1)	2 (1)	1.000	0.0000
Other*	17 (12)	82 (24)	0.002	17 (12)	15 (10)	0.708	0.0430
Tokyo Score							
1	36 (24)	97 (29)	0.054	36 (25)	38 (26)	0.755	0.0715
2	58 (39)	157 (46)		58 (40)	62 (43)		
3	53 (36)	86 (25)		51 (35)	45 (31)		
ERCP procedure							
Door to ERCP time	6.3 (4.1)	35.3 (59.0)	0.001	6.3 (4.1)	29.8 (26.3)	0.001	

Table 1 (continued)

	Before matching			After matching			SMD
	ERCP < 12 h	ERCP > 12 h	*p* value	ERCP < 12 h	ERCP > 12 h	*p* value	
	n = 147	*n* = 340		*n* = 145	*n* = 145		
Stent removal	7 (5)	25 (7)	0.289	7 (5)	9 (6)	0.607	
Sphincterotomy	91 (62)	188 (55)	0.176	89 (61)	87 (60)	0.810	
Pus at the papilla	59 (40)	118 (35)	0.253	57 (39)	55 (38)	0.809	
Stone extraction	82 (56)	159 (47)	0.068	81 (56)	81 (56)	1.000	
Remaining stone	45 (31)	88 (26)	0.282	45 (31)	44 (30)	0.899	
Stent placement	84 (57)	211 (62)	0.308	84 (58)	85 (59)	0.905	
Plastic	81 (55)	186 (55)	0.124	81 (56)	75 (52)	0.450	
Metal	4 (3)	25 (7)		4 (3)	8 (6)		
Pancreatic stent placement	2 (1)	18 (5)	0.045	2 (1)	6 (4)	0.282	

SMD Standardized Mean Difference, calculated for covariates used in the propensity score matching, *BMI* Body Mass Index, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *OSH* outside hospital, *ERCP* endoscopic retrograde cholangiopancreatography, *SBP* systolic blood pressure, *WBC* white blood count, *TB* total bilirubin, *AST* Aspartate transaminase, *ALT* alanine transaminase, *AP* alkaline phosphatase, *AMS* altered mental status

*Malignant obstruction, benign stricture, malignant stricture, PSC



Flow Chart 1 Caption comes here

(1.2 vs 1.5 days, *p* 0.749), cholangitis recurrence (8.3% vs 3.3%, *p* 0.439) and 30-day readmission (10% vs 11.7%, *p* 0.769) did not differ between the ERCP < 6 h and ECRP > 6 h groups (Table 3B).

Sub-group analysis of patients with Tokyo score of 3

In the primary propensity score-matched population, 96 patients had a severe cholangitis with a Tokyo score of 3.

Table 2 Characteristics after propensity-score matching analysis with à 6-h cutoff

	ERCP < 6 h $n=60$	ERCP > 6 h $n=60$	*p* value	SMD
Age, years	71.47 (16.6)	73.12 (±16.3)	0.532	0.0987
Female	27 (45.0)	27 (45.0)	1.000	
BMI	30.1 (±8.3)	27.9 (±6.3)	0.266	
ASA score	3.13 (±0.7)	3.13 (±0.6)	0.718	
Past Medical History				
Cholangitis	3 (5.0)	1 (1.7)	0.619	0.1291
Cholecystectomy	14 (23.3)	14 (23.3)	1.000	0.0001
Prior OSH ERCP	7 (11.7)	4 (6.7)	0.529	0.2515
Stent in situ	2 (3.3)	1 (1.7)	1.000	0.1291
Comorbidities				
CAD	18 (30.0)	21 (35.0)	0.559	0.1071
COPD	12 (20.0)	13 (21.7)	0.822	0.4155
CKD	14 (23.3)	15 (25.0)	0.831	0.0384
DM	16 (26.7)	15 (25.0)	0.835	0.0369
Clinical presentation				
Temperature	100.4 (±2.3)	99.9 (±2.0)	0.303	
SBP	128.1 (±28.1)	112.0 (±29.2)	0.003	
Heart Rate	85.57 (±17.9)	90.2 (±20.7)	0.300	
Right Upper Quadrant	51 (85.0)	56 (93.3)	0.142	
AMS	10 (16.7)	12 (20.0)	0.637	
Blood thinner	9 (15.0)	11 (18.3)	0.624	
Acute dysfunction				
Cardio-vascular	15 (25.0)	14 (23.3)	0.831	0.0376
Neurological	6 (10.0)	8 (13.3)	0.570	0.111
Respiratory	8 (13.3)	10 (16.7)	0.609	0.0979
Renal	10 (16.7)	12 (20.0)	0.637	0.0893
Hepatic	2 (3.3)	2 (3.3)	1.000	0.0001
Blood coagulation	3 (5.0)	3 (5.0)	1.000	0.2198
Lab values				
WBC	14.3 (±7.2)	16.3 (±8.3)	0.178	
TB	5.1 (±4.0)	5.3 (±4.8)	0.682	0.0373
AST	319.0 (±402.2)	250.5 (±201.0)	0.992	
ALT	291.4 (±277.3)	234.0 (±204.3)	0.188	
AP	288.7 (±185.8)	356.0 (±411.6)	0.587	
Lipase	643.0 (±1251.3)	714.8 (±1042.5)	0.871	
Hypoalbuminemia	28 (46.7)	29 (48.3)	0.855	
Positive blood cultures	22 (36.7)	25 (41.7)	0.575	
Cause of cholangitis				
Choledocholithiasis	52 (86.7)	52 (86.7)	1.000	0.0001
Stent occlusion	0 (0.0)	0 (0.0)		
Other*	8 (13.3)	8 (13.3)	1.000	0.0001
Tokyo Score				
1	17 (28.3)	12 (20.0)	0.448	0.0841
2	22 (36.7)	28 (46.7)		
3	21 (35.0)	20 (33.3)		
ERCP procedure				
Door to ERCP	1.9 (±2.1)	20.1 (±13.1)	0.001	
Stent removal	2 (3.3)	2 (3.3)	1.000	
Sphincterotomy	37 (61.7)	34 (56.7)	0.577	
Pus at the papilla	20 (33.3)	19 (31.7)	0.845	

Table 2 (continued)

	ERCP < 6 h $n = 60$	ERCP > 6 h $n = 60$	p value	SMD
Stone extraction	35 (58.3)	29 (48.3)	0.272	
Remaining stone	18 (30.0)	17 (28.3)	0.841	
Stent placement	34 (56.7)	35 (58.3)	0.853	
Plastic	33 (55.0)	32 (53.3)	0.388	
Metal	1 (1.7)	4 (6.7)		
Pancreatic stent placement	2 (3.3)	2 (3.3)	1.000	

SMD Standardized Mean Difference, calculated for covariates used in the propensity score matching, *BMI* Body Mass Index, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *OSH* outside hospital, *ERCP* endoscopic retrograde cholangiopancreatography, *SBP* systolic blood pressure, *WBC* white blood count, *TB* total bilirubin, *AST* Aspartate transaminase, *ALT* alanine transaminase, *AP* alkaline phosphatase, *AMS* altered mental status

*Malignant obstruction, benign stricture, malignant stricture, PSC

Amongst these patients, 51 had an ERCP within 12 h of presentation and 45 had an ERCP after 12 h of presentation. We then considered only patients with Tokyo score 3 cholangitis and compared outcomes for the ERCP < 12 h group with ERCP > 12 h group. The post-ERCP length of hospitalization did not significantly differ between these two subgroups (135.9 vs 122.1 h, p 0.094) (Table 3C and Fig. 1C). Furthermore, mortality (5.9% vs 6.7%, p 1.000), ERCP failure (11.8% vs 15.6%, p 0.588), post-ERCP pancreatitis (2% vs 0%, p 0.1.000), bleeding (2% vs 2.2%, p 1.000), perforation (0% vs 0%, p N/A), required ICU stay (84.3% vs 88.9%, p 0.513), post-ERCP length of ICU stay (2.8 vs 3.2 days, p 0.306), and cholangitis recurrence (7.8% vs 0%, p 0.120) also did not differ between the two subgroups. Similar to results for the entire patient cohort, in patients with Tokyo score 3 cholangitis, 30-day readmission rate was lower in the ERCP < 12 h group (3.9% vs 20.0%, p 0.014) (Table 3C).

Discussion

Using a large cohort of patients with acute cholangitis, we investigated the influence of the timing of ERCP on clinical outcomes. In our propensity-score matched population, we found that ERCP within 12 h of presentation did not result in a decreased post-ERCP length of hospitalization (135.9 vs 122.1 h, p 0.094) compared to when ERCP was performed after 12 h of presentation. We also found that ERCP < 6 h also did not shorten the post-ERCP length of hospitalization. The univariable analysis on unmatched cohort showed similar results (HR 1.182, CI 0.694–1.030, p 0.096). Other clinical outcomes including mortality, adverse events, and ICU stay were not significantly different between the two groups, with the notable exception of the 30-day readmission rate. The 30-day readmission rate was lower when the ERCP was performed within 12 h of presentation (7.6% vs 15.2%, p 0.042). This association appeared to be driven mostly by patients with severe cholangitis as we also found a lower rate of 30-day readmission in the subgroup of patients with Tokyo score of 3 but not Tokyo score 1 or score 2 patients.

Most previous reports have studied the impact of delaying ERCP by 24 h or longer in patients with acute cholangitis. A retrospective study including 90 patients showed that a delayed ERCP (> 72 h) was associated with a prolonged length of hospitalization (Odds ratio (OR), 19.8; p 0.008) and an increased hospitalization cost (OR, 11.3; p 0.03) [9]. In a study including 5340 patients, ERCP performed > 72 h after presentation was associated with prolonged length of hospitalization and increased cost of hospitalization [10]. In a cohort study including 166 patients, ERCP within 24 h was associated with a lower 30-day mortality rate (OR 0.23; 95% CI 0.05–0.95; p 0.04) [11]. In a 199 patient cohort study, length of hospitalization was significantly longer for patients undergoing ERCP > 48 h vs < 48 h (median 9.1 vs 6.5 days, p 0.004) even though the former were less sick (less ICU admission). Comparison of ERCP > 72 h vs < 72 h showed higher vasopressor requirement (OR 2.6, 95% CI, 1.0–7.0, p 0.05) and mortality (OR 3.6, 95% CI, 0.8–15.9 p 0.08) in the former [12]. In a cohort study including 203 patients, ERCP > 48 h was associated with persistent organ failure, and ERCP < 48 h with a lower in-hospital mortality and length of hospitalization [13]. Conversely, in another study, there was no difference in terms of ERCP timing between patients who did and did not have an adverse outcome (8 vs 16.5 h, p 0.99), even when stratified by cholangitis severity [14]. Recent larger studies using population-based databases have also been published. In the largest cohort study published, including 77,323 patients, ERCP > 72 h yielded significantly longer length of hospitalization than early (24 to 48 h) and < 24 h ERCP ($p < 0.001$). In-hospital mortality was higher in the > 72 h ERCP group ($p < 0.001$) but there was no difference in mortality between < 24 h ERCP and 24 to 48 h ERCP groups [15]. In another large cohort study including

Table 3 ERCP timing-related outcomes in the propensity matched population

A. 12 h from presentation ERCP cutoff

	ERCP < 12 h $n = 145$	ERCP > 12 h $n = 145$	*p* value
Post-ERCP LOS (h)	135.9 (± 127.6)	122.1 (± 143.5)	0.094
Mortality	4 (2.8)	6 (4.1)	0.520
ERCP failure	9 (6.2)	15 (10.3)	0.201
Adverse events			
PEP	3 (2.1)	0 (0.0)	0.247
Bleeding	9 (6.2)	5 (3.5)	0.273
Perforation	1 (0.7)	0 (0.0)	1.000
Required ICU stay	70 (48.3)	63 (43.4)	0.409
Post-ERCP LOS in ICU (d)	1.3 (± 2.9)	1.5 (± 3.3)	0.796
Cholangitis recurrence	7 (4.8)	5 (3.5)	0.555
30-day readmission	11 (7.6)	22 (15.2)	0.042

B. 6 h from presentation ERCP cutoff

	ERCP < 6 h $n = 60$	ERCP > 6 h $n = 60$	*p* value
Post-ERCP LOS (h)	142.9 (± 114.6)	141.5 (± 170.2)	0.650
Mortality	2 (3.3)	4 (6.7)	0.679
ERCP failure	6 (10.0)	5 (8.3)	0.752
Adverse events			
PEP	1 (1.7)	1 (1.7)	1.000
Bleeding	5 (8.3)	4 (6.7)	1.000
Perforation	1 (1.7)	0 (0.0)	1.000
Required ICU stay	26 (43.3)	24 (40.0)	0.711
Post-ERCP LOS in ICU (d)	1.2 (± 2.4)	1.5 (± 3.1)	0.749
Cholangitis recurrence	5 (8.3)	2 (3.3)	0.439
30-day readmission	6 (10.0)	7 (11.7)	0.769

C. Tokyo score 3 subgroup

	ERCP < 12 h $n = 51$	ERCP > 12 h $n = 45$	*p* value
Post-ERCP LOS (h)	189.3 (± 177.1)	156.2 (± 140.8)	0.126
Mortality	3 (5.9)	3 (6.7)	1.000
ERCP failure	6 (11.8)	7 (15.6)	0.588
Adverse events			
PEP	1 (2.0)	0 (0.0)	1.000
Bleeding	1 (2.0)	1 (2.2)	1.000
Perforation	0 (0.0)	0 (0.0)	_
Required ICU stay	43 (84.3)	40 (88.9)	0.513
Post-ERCP LOS in ICU (d)	2.8 (± 4.3)	3.2 (± 4.8)	0.306
Cholangitis recurrence	4 (7.8)	0 (0.0)	0.120
30-day readmission	2 (3.9)	9 (20.0)	0.014

SD standard deviation, *ERCP* Endoscopic retrograde cholangio pancreatography, *LOS* Length of hospitalization, *PEP* Post-ERCP pancreatitis, *ICU* Intensive care unit, *h* Hours, *d* Days

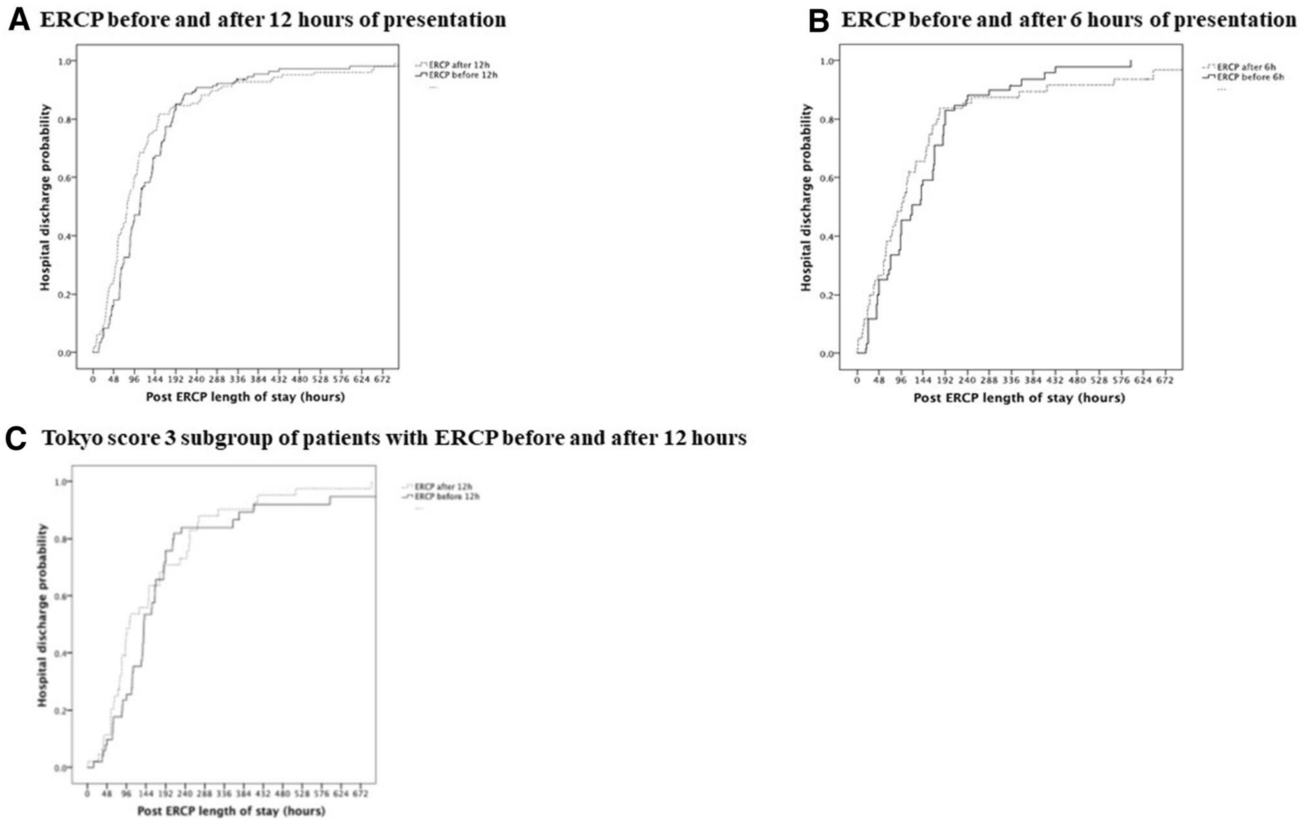


Fig. 1 Kaplan–Meier survival estimates in the propensity score matched populations. **A** ERCP before and after 12 h of presentation. **B** ERCP before and after 6 h of presentation. **C** Tokyo score 3 subgroup of patients with ERCP before and after 12 h

4570 patients, ERCP < 48 h was associated with lower in-hospital mortality (1.2% vs 2.4%, p 0.001) and mean length of hospitalization (4.5 vs 6.9 days, $p < 0.0001$) compared to ERCP > 48 h [16]. Finally, a meta-analysis published in 2019 included nine observational studies (including most of the above) to evaluate the impact of ERCP < 48 h or > 48 h on patient outcomes. This was the first meta-analysis evaluating ERCP timing in cholangitis. In-hospital mortality was significantly lower in patients who underwent ERCP within 48 h (OR, 0.52; 95% CI, 0.28–0.98). Length of hospitalization was significantly lower with a mean difference of 5.56 days (95% CI, 1.59–9.53) [17]. Overall, the available literature suggests that ERCP should be performed within 72 h and that it is probably best within 48 h.

Based upon available evidence noted above, most experts now agree that ERCP should probably be performed within 24–48 h of presentation with acute cholangitis. However, the ESGE guidelines recommend that for patients with severe cholangitis, ERCP should be performed as soon as possible and within 12 h of presentation. The evidence that very early ERCP within 12 h of presentation improves outcomes is based mostly on two studies. An analysis of 260 patients with acute cholangitis and septic shock found that delaying biliary decompression > 12 h was associated with increased mortality (OR 3.40, 95% CI, 1.12–10.31; $p < 0.04$) [18]. The overall mortality in this study was 37%. Interpretation of the results of this study are limited by the fact that > 50% of patients underwent biliary decompression by either PTC or surgery, and almost 20% failed any type of biliary decompression. In another study of 250 patients with moderate to severe ascending cholangitis, the authors reported that patients undergoing ERCP < 11 h had lower mortality when compared with those who underwent ERCP > 42 h, but not when compared with those who underwent ERCP within 11–21 h or 21–42 h [19]. We caution against adopting this standard without more supporting evidence. We have noted in our clinical practice that patients with pus in the biliary tree can develop hypotension after even a limited cholangiogram. We have hypothesized that this may be from increased biliary pressure that results in translocation of bacteria from the biliary tree into the rich blood supply of the liver, and that 12 to 24 h of antibiotics such as quinolones, which have excellent biliary penetration, may reduce biliary bacterial counts and minimize procedure-related bacteremia.

To overcome the limitation of previous studies, we elected to use propensity matching in creating two comparable

Table 4 Univariable analysis of factors associated with longer post-ERCP LOS

	Univariable cox regression analysis	
	HR (95% CI)	*p* value
Age, years	1.0 (0.9–1.0)	0.566
Female	1.1 (0.9–1.4)	0.112
BMI	1.0 (0.9–1.0)	0.292
ASA score	1.6 (1.4–1.8)	0.001
Past Medical History		
Cholangitis	1.2 (0.8–1.8)	0.403
Cholecystectomy	0.7 (0.6–0.9)	0.002
Prior OSH ERCP	0.9 (0.7–1.2)	0.461
Stent in situ	1.0 (0.7–1.4)	0.908
Comorbidities		
CAD	1.0 (0.8–1.2)	0.879
COPD	1.5 (1.1–2.0)	0.003
CKD	1.3 (1.0–1.6)	0.021
DM	1.0 (0.8–1.2)	0.947
Clinical presentation		
Temperature	1.0 (0.9–1.0)	0.197
SBP	1.0 (1.0–1.0)	0.007
Heart Rate	1.0 (1.0–1.0)	0.006
RUQ pain	0.9 (0.7–1.1)	0.292
AMS	1.3 (1.0–1.7)	0.036
Blood thinner	1.1 (0.8–1.3)	0.635
Acute dysfunction		
Cardio-vascular	1.8 (1.4–2.4)	0.001
Neurological	1.7 (1.2–2.3)	0.003
Respiratory	2.1 (1.5–2.8)	0.001
Renal	1.8 (1.4–2.3)	0.001
Hepatic	2.0 (1.3–2.9)	0.001
Blood coagulation	1.9 (1.4–2.7)	0.001
Lab values		
WBC	1.0 (1.0–1.0)	0.001
TB	1.0 (1.0–1.0)	0.011
AST	1.0 (1.0–1.0)	0.674
ALT	1.0 (1.0–1.0)	0.014
AP	1.0 (1.0–1.0)	0.171
Lipase	1.0 (1.0–1.0)	0.17
Hypoalbuminemia	1.5 (1.2–1.8)	0.001
Positive blood cultures	1.4 (1.2–1.7)	0.001
Cause of cholangitis		
Choledocholithiasis	0.9 (0.7–1.1)	0.314
Stent occlusion	0.8 (0.5–1.4)	0.385
Other*	1.2 (0.9–1.5)	0.178
Tokyo score		
1	Ref	
2	1.3 (1.0–1.6)	0.043
3	2.1 (1.6–2.7)	0.001
ERCP timing		
ERCP < 6 h	1.2 (0.9–1.6)	0.152
ERCP < 12 h	1.2 (1.0–1.4)	0.096
ERCP < 24 h	1.3 (1.1–1.6)	0.006
ERCP procedure		
Stent removal	0.9 (0.6–1.2)	0.405
Sphincterotomy	0.8 (0.6–0.9)	0.004
Pus at the papilla	1.1 (0.9–1.4)	0.162
Stone extraction	0.7 (0.6–0.9)	0.002
Remaining stone	1.2 (1.0–1.5)	0.061
Stent placement	1.5 (1.3–1.8)	0.001
Type of stent	1.4 (1.2–1.7)	0.001
Pancreatic stent placement	0.7 (0.4–1.1)	0.110
Outcomes		
Adverse events		
None	0.5 (0.4–0.8)	0.004
PEP	1.5 (0.7–3.2)	0.228
Bleeding	1.8 (1.1–3.0)	0.017
Perforation	20.4 (0.0–13.157.9)	0.362
Failed ERCP	1.6 (1.1–2.2)	0.010
Required ICU stay	2.0 (1.6–2.4)	0.001
Post-ERCP LOS in ICU (d)	1.2 (1.1–1.2)	0.001
Cholangitis recurrence	1.0 (0.7–1.5)	0.882
30 days readmission	1.1 (0.8–1.3)	0.687

HR Hazard Ratio, *BMI* Body Mass Index, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *OSH* outside hospital, ERCP endoscopic retrograde cholangiopancreatography, *SBP* systolic blood pressure, *WBC* white blood count, *TB* total bilirubin, *AST* Aspartate transaminase, *ALT* alanine transaminase, *AP* alkaline phosphatase, *AMS* altered mental status

*Malignant obstruction, benign stricture, malignant stricture, PSC

groups of patients who underwent ERCP < 12 and > 12 h and < 6 h and > 6 h after presentation to out institution. We only enrolled patients who presented directly to our institution with cholangitis and used a strict definition for cholangitis. We anticipated that mortality would be low in both groups, and therefore chose to use length of hospitalization as our primary outcome. Our results do not show any difference in outcomes when ERCP is done early, including within 6 h of presentation. Our results are supported by a study by Inamdar et al. which showed patients admitted with acute cholangitis on weekdays were more likely to get early ERCP when compared to those admitted on weekends [20]. However, no significant differences between clinical outcomes like length of hospitalization or mortality were noted between the weekday and weekend groups. Performing ERCP as soon as possible or within 12 h of presentation poses several practical challenges. Some smaller hospitals do not have ERCP facilities and routinely transfer patients to other regional referral centers for ERCP. Furthermore, very rapid ERCP for patients who present on evenings or weekends, would require an ERCP team on call and able to perform procedures 24 h a day and 7-days a week. Such a team could not only need to have physicians, but also nurses, ERCP technicians and anesthesiologists, and may pose a substantial burden to even high-volume centers.

In the propensity-matched groups, the 30-day readmission rate was significantly higher in patients with ERCP > 12 h (15.2% vs 7.6% *p* 0.042). The rate of cholangitis recurrence was similar so it is unclear why this difference was seen. In subgroup analysis in patients with severe cholangitis (Tokyo score of 3) the 30-day readmission rate was also significantly higher in patients with ERCP > 12 h (20% vs 3.9% *p* 0.014). Since this was a secondary analysis, this should be explored further by others.

In conclusion, we found that ERCP within 12 h or within 6 h did not result in a shorter post-ERCP hospital stay. It also did not result in reduced mortality, adverse events, length of ICU stay and cholangitis recurrence rates. However, in patients with severe cholangitis, ERCP within 12 h of presentation may reduce rates of 30-day readmission. Our results show that ERCP performed within 6 or 12 h of presentation is not associated with superior clinical outcomes, and that the optimal ERCP timing is likely between 12 and 48 h of presentation.

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Author contributions AB, AB, MC, SB, JC, MG, TB, DP and MS: Conception and study design, data collection, drafting and revising of the manuscript. AN: Analysis.

Declarations

Disclosures Drs Aymeric Becq, Madhuri Chandnani, Anthony Bartley, Alexandre Nuzzo, Mohammad Bilal, Shishira Bharadwaj, Jonah Cohen, Moamen Gabr, Tyler M. Berzin, Douglas K. Pleskow and Mandeep S. Sawhney have no conflicts of interest or financial ties to disclose.

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