Digestive Diseases and Sciences (2018) 63:1937–1945
https://doi.org/10.1007/s10620-018-5058-8

ORIGINAL ARTICLE

No Association of Timing of Endoscopic Biliary Drainage with Clinical Outcomes in Patients with Non-severe Acute Cholangitis

Ryunosuke Hakuta[1] · Tsuyoshi Hamada[1,2] · Yousuke Nakai[1] · Hirofumi Kogure[1] · Rie Uchino[1] · Naminatsu Takahara[1] · Suguru Mizuno[1] · Tatsunori Suzuki[1] · Tatsuya Sato[1] · Tsuyoshi Takeda[1] · Kazunaga Ishigaki[1] · Kei Saito[1] · Tomotaka Saito[1] · Minoru Tada[1] · Hiroyuki Isayama[1,3] · Kazuhiko Koike[1]

Received: 20 January 2018 / Accepted: 5 April 2018 / Published online: 16 April 2018

Abstract

Background Biliary drainage via endoscopic retrograde cholangiopancreatography (ERCP) is the first-line treatment for acute cholangitis. Despite the established effectiveness of urgent biliary drainage in patients with severe acute cholangitis, the indication of this procedure for non-severe acute cholangitis is controversial.

Aims To assess the safety of elective drainage (≥ 12 h of admission) for non-severe acute cholangitis.

Methods We retrospectively identified 461 patients with non-severe acute cholangitis who underwent endoscopic biliary drainage. Using linear regression models with adjustment for a variety of potential confounders, we compared elective versus urgent biliary drainage (< 12 h of admission) in terms of clinical outcomes. The primary outcome was the length of stay.

Results There were 98 and 201 patients who underwent elective and urgent biliary drainage, respectively. The median length of stay was 11 days in both groups ($P = 0.52$). The timing of ERCP was not associated with length of stay in the multivariable model ($P = 0.52$). Secondary outcomes including in-hospital mortality and recurrence of cholangitis were not different between the groups.

Conclusions Elective biliary drainage was not associated with worse clinical outcomes of non-severe acute cholangitis as compared to urgent drainage. Further investigation is warranted to justify the elective drainage for non-severe cholangitis.

Keywords Drainage · Cholangitis · Endoscopic retrograde cholangiopancreatography · Length of stay

Introduction

Acute cholangitis is an inflammatory process due to bacterial infection of the bile duct and can be potentially fatal. In most patients, cholestasis is an underlying etiology of bacterial overgrowth in the biliary system and can cause the cholangiovenous reflux and resultant sepsis. In addition to fluid resuscitation and administration of antibiotics as initial therapy, emergent biliary decompression is required to improve clinical outcomes of patients with severe acute cholangitis. Endoscopic retrograde cholangiopancreatography (ERCP) with biliary stent placement is currently performed as a first-line biliary drainage method for patients with acute cholangitis [1–8]. The current version of the Tokyo Guidelines for management of acute cholangitis and cholecystitis (TG13, Japanese Society of Hepato-Biliary-Pancreatic Surgery) [9, 10] recommends urgent biliary drainage within 24 h of admission for severe acute cholangitis, but the role of urgent

Ryunosuke Hakuta and Tsuyoshi Hamada contributed equally as co-first authors.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10620-018-5058-8) contains supplementary material, which is available to authorized users.

✉ Yousuke Nakai
ynakai-tky@umin.ac.jp

[1] Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

[2] Department of Oncologic Pathology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA

[3] Department of Gastroenterology, Graduate School of Medicine, Juntendo University, Tokyo, Japan

biliary drainage in non-severe acute cholangitis remains to be determined [11, 12].

Clinical outcomes including mortality among patients with acute cholangitis may worsen due to delays in biliary interventions [13–16]. Observational studies suggest weekend effects in a variety of acute diseases: i.e., worse clinical outcomes associated with weekend admissions compared with weekday admissions [17–25], which can be attributed to delayed intensive treatments owning to unavailability of expertized medical staff or specialized procedures. On the other hand, drawbacks of urgent biliary drainage may include personnel burden, referral to a tertiary care center, and a potentially higher rate of procedure-related adverse events such as aspiration pneumonia due to non-fasting endoscopic procedures and post-ERCP pancreatitis due to the lack of experienced endoscopists. Few studies have examined the association of the timing of endoscopic biliary drainage with clinical outcomes of patients who are admitted for non-severe acute cholangitis [16, 26].

Therefore, we conducted a retrospective single-center study to compare clinical outcomes between elective and urgent endoscopic biliary drainage for patients with non-severe acute cholangitis.

Patients and Methods

Study Design

This study was designed as a retrospective study to compare the clinical outcome of elective drainage (time from admission to ERCP $\geq$ 12 h) for non-severe acute cholangitis with that of urgent drainage (time from admission to ERCP < 12 h) [3, 11, 27]. Using the electronic medical records and our prospectively maintained endoscopy database, data on consecutive patients who underwent biliary stent placement via ERCP for acute cholangitis at The University of Tokyo Hospital (Tokyo, Japan) were retrospectively studied. The medical records also included times of admission and ERCP on a minute basis. Written informed consent for ERCP procedures was obtained from all patients before the procedure. This study was approved by the ethical committee at the University of Tokyo Hospital and was conducted in accordance with the Helsinki Declaration.

Patients

We retrospectively collected data on consecutive adult patients (20 years or older) who underwent ERCP for acute cholangitis between August 2010 and July 2017. For patients who underwent multiple ERCP procedures for the same indication during the study period, the initial procedure was included in the analysis. The exclusion criteria were as follows: (1) patients who underwent subsequent procedures such as surgery and chemotherapy during the index hospitalization (considering the substantial influence of the care on length of stay [LOS]), (2) patients who had a percutaneous transhepatic biliary catheter in situ, and (3) patients with unsuccessful endoscopic biliary drainage.

ERCP Procedures

Antibiotics were administered to all patients intravenously after blood culture was obtained. All ERCP procedures were performed on an inpatient basis in our hospital using a side-viewing duodenoscope (JF-260V or TJF-260V; Olympus, Tokyo, Japan), or a balloon-assisted endoscope (EI-530B or EI-580BT; Fujifilm, Tokyo, Japan) in cases with a surgically altered upper gastrointestinal anatomy, under moderate intravenous sedation using pethidine hydrochloride or pentazocine hydrochloride, and diazepam or midazolam. Biliary cannulation was achieved via wire-guided cannulation or contrast-assisted cannulation at the endoscopists' discretion. We used a standard ERCP cannula (ERCP catheter; MTW Endoskopie, Wesel, Germany) or a sphincterotome (CleverCut3, Olympus; Autotome, or Truetome; Boston Scientific Japan, Tokyo, Japan) with a 0.035-inch angle-tip guidewire (RevoWave; Piolax, Kanagawa, Japan or Jagwire; Boston Scientific Japan) or a 0.035-inch angle-tip hydrophilic guidewire (Radifocus; Terumo, Tokyo, Japan). Bile for culture was obtained before cholangiogram through the catheter. A 5-F or 7-F endoscopic nasobiliary drainage (QuickPlace V; Olympus, or Nasal Biliary Drainage Catheter; Cook Japan, Tokyo, Japan) or a 5-F, 7-F, or 8.5-F endoscopic biliary stenting (Geenen, Cook Japan or Flexima, Boston Scientific Japan) was placed at the discretion of endoscopists. All patients were hospitalized at least 36 h after the procedure.

Diagnosis and Severity of Acute Cholangitis

Acute cholangitis was diagnosed and graded according to the TG13 guidelines for acute cholangitis and cholecystitis (Supplementary Table 1) [10]. In brief, the diagnostic criteria for acute cholangitis were as follows: (1) fever or evidence of inflammatory response, (2) jaundice or abnormal liver function tests, (3) biliary dilation or evidence of the etiology (e.g., stricture, stone, stent) on imaging. For patients with leukopenia or thrombocytopenia due to chemotherapy, or prolonged prothrombin time due to liver cirrhosis or anticoagulants, these items were excluded from the severity grading to avoid overestimation.

Study Outcomes

The primary outcome of this study was LOS. The secondary outcomes included in-hospital mortality, admission

to intensive care unit (ICU), organ failure, recurrence of cholangitis within 30 days of discharge, readmission within 30 days of discharge, and early adverse events associated with ERCP. Organ failure was defined as hypotension requiring vasopressor, need for mechanical ventilation, or acute kidney injury (1.5-fold increase in the serum creatinine level from baseline or need for dialysis), which lasted more than 48 h [15]. Early adverse events of ERCP (e.g., pancreatitis, cholecystitis, or cholangitis) were defined and the severity was graded according to the lexicon guidelines of American Society for Gastrointestinal Endoscopy [28].

Definitions

Time to ERCP was defined as the time from patient arrival at the hospital to the initiation of ERCP. Weekends were defined as Saturday, Sunday, and public holidays in Japan (approximately 21 days annually). Night time was defined from 5 p.m. to 9 a.m. during which outpatient clinic service was not available at our hospital. American Society of Anesthesiologists Physical Status (ASA-PS) score [29] was as follows: (1) a normal healthy patient, (2) a patient with a mild systemic disease, (3) a patient with a severe systemic disease, (4) a patient with a life-threatening systemic disease, (5) a moribund patient who is not expected to survive without the operation, and (6) a declared brain-dead patient whose organs are removed for donor purposes.

Statistical Analysis

Continuous variables were compared using the Wilcoxon rank sum test, and categorical variables were compared using the Chi-square test or the Fisher's exact test, as appropriate.

Uni- and multivariable linear regression models were used to assess the association between the timing of ERCP (elective vs. urgent) and LOS (a continuous outcome variable). To avoid a bias due to arbitrary cutoff points, we analyzed LOS as a continuous variable. LOS was log-transformed taking its skewed distribution into account. Beta coefficients and 95% confidence intervals (CIs) were calculated. In addition to the timing of ERCP, variables with a P value < 0.1 in univariable analyses were further analyzed in the multivariable linear regression model. We assigned a missing category for cases who did not undergo blood and bile cultures (23 and 12%, respectively). Using the Wald test on the cross-product, we also assessed a potential interaction between the timing of ERCP and each of the following covariates which were considered as clinically relevant: age > 80 years, male gender, ASA-PS score > 2, Charlson comorbidity index > 2 [30], admission at night time, admission on weekends, etiology of cholangitis, hilar biliary stricture, severity of cholangitis, balloon endoscopy-assisted ERCP, chemotherapy, history of cholangitis, positive bile culture, and positive blood culture. In these analyses, we evaluated 14 covariates for subgrouping and therefore adjusted α level to 0.004 ($= 0.05/14$). For secondary outcomes, we did not perform multivariable analyses considering the small number of each event.

All statistical analyses were performed using the EZR software (Saitama Medical Center, Jichi Medical University), which was a modified version of R software (version 3.3.2, R Development Core Team: http://www.r-project.org) [31]. A two-sided P value < 0.05 was considered statistically significant in all analyses.

Results

A total of 461 patients were admitted for acute cholangitis during the study period of 7 years (Fig. 1). We included the initial admission for the analysis when patients underwent multiple hospitalizations during the study period. We excluded 162 patients, leaving 299 patients as the study population (98 and 201 patients for elective and urgent drainage groups, respectively). The baseline characteristics of the

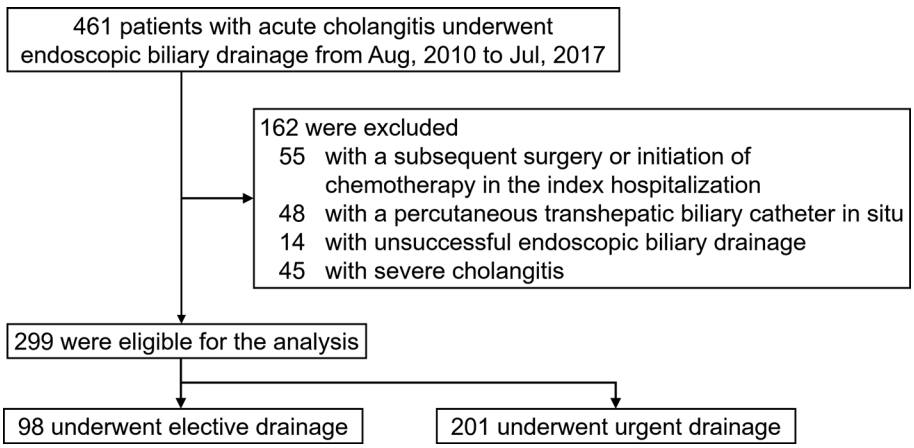

Fig. 1 Flowchart of patient selection for the elective and urgent drainage groups of patients who were admitted with mild or moderate cholangitis and underwent endoscopic biliary drainage

study population are summarized in Table 1. Patients in the urgent drainage group were more likely to have stent occlusion as a cause of acute cholangitis, and higher levels of total bilirubin. Balloon endoscopy-assisted ERCP was more likely to be carried out electively. In the elective drainage group, 57% underwent ERCP within 24 h of admission.

Table 2 summarizes clinical outcomes of patients with acute cholangitis who underwent endoscopic biliary drainage according to the timing of ERCP. The median LOS was 11 days (IQR, 9–15 days), for both the elective and urgent drainage groups ($P = 0.52$). In our primary hypothesis test using multivariable linear regression models, elective drainage was not associated with LOS compared to urgent drainage (beta coefficient, 0.019; 95% CI, −0.039 to 0.077; $P = 0.52$; Table 3 and Supplementary Table 2). The variables which were associated with longer LOS included ASA-PS > 2, positive blood culture, and higher levels of total bilirubin. Weekend admissions were not associated with LOS. When we categorized LOS into short (≤ 10 days) vs. long (≥ 11 days) at the median value in the total study population, long LOS was observed in 58 and 57% patients who underwent elective and urgent drainage, respectively. In a multivariable logistic regression model, the rate of long LOS did not differ by the timing of ERCP, either (Supplementary Table 3). The odds ratio for long LOS comparing elective to urgent drainage was 0.98 (95% CI, 0.56–1.79).

Subgroup analyses of LOS are shown in Table 4. There were no statistically significant modified effects on the association between the timing of ERCP and LOS by covariates (P for interaction > 0.007 with the adjusted α level of 0.004). Given inconsistent definitions of urgent biliary drainage across the prior studies [3, 9, 10, 14–16], we conducted a sensitivity analysis using the cutoff of 24 h and observed similar results (Supplementary Table 4).

We did not observe any differences in other clinical outcomes including in-hospital mortality, recurrence of cholangitis and readmission within 30 days of discharge, and early adverse events associated with ERCP between the elective and urgent drainage groups (Table 2). In-hospital mortality was not observed in the elective drainage group. Two patients in the urgent drainage group were initially scheduled to receive elective drainage at their admission, but underwent urgent drainage due to the deterioration of cholangitis. Excluding these two patients would not change our findings substantially (data not shown).

Discussion

We conducted this retrospective single-center study to compare clinical outcomes between elective and urgent biliary drainage for patients with non-severe acute cholangitis. LOS did not differ significantly between the elective and urgent drainage groups. Adjustment with a variety of confounders did not materially alter our findings. In addition, we found no between-group differences in the rates of in-hospital mortality, ICU admission, recurrence of cholangitis, or early adverse events associated with ERCP. Despite the undoubted necessity of urgent endoscopic biliary drainage for severe acute cholangitis, our findings do not support this emergent procedure for patients with mild or moderate acute cholangitis.

Delayed biliary drainage may lead to worse clinical outcomes of patients with acute cholangitis, as undrained infectious bile can cause sepsis and organ failure through the cholangiovenous reflex. Several studies indicated the association between the delay in ERCP and worse clinical outcomes, including longer LOS and higher rates of organ failure and recurrence of cholangitis [13–16, 25, 30–35]. In a retrospective study of 90 patients at a single referral center in the USA, delayed and unsuccessful ERCP procedures were associated with longer LOS (OR for long LOS, 19.8 [95% CI, 2.18–178] and 52.5 [95% CI, 4.0–681], respectively) [14]. In contrast to the prior studies, our study focused on patients with non-severe acute cholangitis and found no association of the timing of ERCP and LOS. The severity criteria of the TG13 guidelines have been shown to be useful to stratify patients with acute cholangitis, and our previous study showed a significant increase in plasma levels of procalcitonin (as an indicator of systemic bacterial inflammation) according to the severity of acute cholangitis defined by the TG13 guidelines [3]. Effective risk stratification of patients with acute cholangitis might have allowed us to identify a subgroup of patients who were less likely to benefit from urgent biliary drainage. Various definitions of urgent biliary drainage used in previous studies, i.e., 12–48 h [9, 10, 13–16, 28] and relatively earlier ERCP in the elective drainage group (57% within 24 h from admission), might explain the inconsistency of our data with previous studies.

Disadvantages of urgent biliary drainage should be taken into account when discussing the timing of ERCP for acute cholangitis. Urgent biliary drainage, particularly when performed at night or weekends, requires medical resources including personnel costs for specialized staff (e.g., expertized endoscopists, technicians, and nurses) and patient transfer to tertiary care centers. Furthermore, urgent biliary drainage may lead to a higher rate of procedure-related adverse events. Less expertise of endoscopists and unprepared patient conditions potentially increase the risks of unsuccessful biliary drainage, post-ERCP pancreatitis, and aspiration pneumonia. In our institution, at least one experienced endoscopist was present during both urgent and elective biliary drainage in this study, which might be associated with comparable adverse events between urgent and elective biliary drainage groups at the cost of personnel burden. Given these potential drawbacks, substantial evidence

Table 1 Baseline characteristics of patients who underwent elective or urgent biliary drainage for non-severe acute cholangitis

Characteristic[a]	All cases ($n=299$)	Endoscopic biliary drainage		*P* value
		Elective ($n=98$)	Urgent ($n=201$)	
Age, years	72 (65–82)	74 (66–80)	73 (65–83)	0.69
Sex				0.90
Male	184 (58%)	61 (62%)	123 (61%)	
Female	115 (42%)	37 (38%)	78 (39%)	
ASA-PS score				0.73
1	32 (11%)	10 (10%)	22 (11%)	
2	225 (75%)	72 (74%)	153 (76%)	
3	42 (14%)	16 (16%)	26 (13%)	
Charlson comorbidity index				0.08
0	39 (13%)	10 (10%)	29 (14%)	
1	44 (15%)	10 (10%)	34 (17%)	
2	70 (23%)	22 (22%)	48 (24%)	
≥3	146 (49%)	56 (58%)	90 (45%)	
Concomitant disease				
Acute pancreatitis	12 (4.0%)	2 (2.0%)	10 (5.0%)	0.35
Liver abscess	4 (1.3%)	0	4 (2.0%)	0.31
Acute cholecystitis	9 (3.0%)	4 (4.1%)	5 (2.5%)	0.48
Time of admission				
Night time	106 (35%)	35 (36%)	71 (35%)	0.99
Weekends	66 (22%)	21 (21%)	45 (22%)	0.88
History of cholangitis	106 (35%)	34 (35%)	72 (36%)	0.90
Etiology of acute cholangitis				0.001
Bile duct stone	165 (55%)	56 (57%)	109 (54%)	
Stent occlusion	101 (34%)	23 (24%)	78 (39%)	
Others	33 (11%)	19 (19%)	14 (7.0%)	
Presence of hilar biliary stricture	77 (26%)	32 (33%)	45 (22%)	0.07
Severity of acute cholangitis				0.06
Mild	178 (60%)	66 (67%)	112 (56%)	
Moderate	121 (40%)	32 (33%)	89 (44%)	
Balloon endoscopy-assisted ERCP	28 (9.4%)	19 (19%)	9 (4.5%)	< 0.001
Chemotherapy	81 (27%)	23 (24%)	58 (29%)	0.41
Time from admission to ERCP				
< 12 h	201 (67%)	0	201 (100%)	
12–24 h	56 (19%)	56 (57%)	0	
24–48 h	28 (9.4%)	28 (29%)	0	
≥48 h	14 (4.7%)	14 (14%)	0	
Positive culture[b]				
Bile culture	235 (79%)	65 (86%)	170 (91%)	0.27
Blood culture	89 (30%)	29 (35%)	60 (41%)	0.57
Laboratory data				
White blood cells (10^4/μL)	8.9 (6.7–12.6)	8.7 (6.8–11.9)	9.0 (6.7–13.2)	0.31
C-reactive protein (mg/dL)	4.4 (1.2–8.9)	3.1 (0.8–7.4)	5.3 (1.6–9.7)	0.02
Procalcitonin (ng/mL)[c]	0.96 (0.31–5.15)	0.96 (0.35–2.67)	0.96 (0.27–5.82)	0.91
Total bilirubin (mg/dL)	2.3 (1.4–4.0)	1.9 (1.1–3.1)	2.5 (1.4–4.5)	0.002
Albumin (mg/dL)	3.5 (3.0–3.8)	3.5 (3.1–3.9)	3.5 (3.0–3.7)	0.51

ASA-PS American Society of Anesthesiologists Physical Status, *ERCP* endoscopic retrograde cholangiopancreatography

[a]Data are expressed as number (percentage) of patients within a given group or as median (interquartile range)

[b]Bile and blood cultures were not obtained in 36 and 70 patients, respectively

[c]Procalcitonin was not measured in 179 patients

Table 2 Clinical outcomes of patients who underwent elective or urgent endoscopic biliary drainage for non-severe acute cholangitis

Outcome[a]	Endoscopic biliary drainage		*P* value
	Elective ($n=98$)	Urgent ($n=201$)	
Length of stay, days	11 (9–15)	11 (9–15)	0.52
In-hospital mortality	0	1 (0.5%)	0.99
Admission to intensive care unit	0	0	NA
Organ failure	1 (1.0%)	0	0.33
Recurrence of cholangitis within 30 days of discharge	16 (16%)	28 (14%)	0.60
Readmission within 30 days of discharge	24 (25%)	49 (24%)	0.99
Early adverse events associated with ERCP	7 (7.1%)	17 (8.5%)	0.82
Pancreatitis	3 (3.1%)	4 (2.0%)	0.69
Cholecystitis	1 (1.0%)	8 (4.0%)	0.28
Others	2 (2.0%)	7 (3.5%)	0.72

ERCP endoscopic retrograde cholangiopancreatography, *NA* not available

[a]Data are expressed as number (percentage) of patients within a given group or as median (interquartile range)

Table 3 Linear regression analyses to assess the association of the timing of ERCP (elective versus urgent) and length of stay (LOS)

	No. of cases	Univariable		Multivariable[a]	
		Beta coefficient for LOS (95% CI)[b]	*P* value	Beta coefficient for LOS (95% CI)[b]	*P* value
Timing of ERCP					
Urgent drainage	201	1 (reference)		1 (reference)	
Elective drainage	98	0.022 (−0.029 to 0.073)	0.40	0.019 (−0.039 to 0.077)	0.52

ASA-PS American Society of Anesthesiologists Physical Status, *CI* confidence interval, *ERCP* endoscopic retrograde cholangiopancreatography, *LOS* length of stay

[a]Multivariable liner regression model was adjusted for variables with a *P* value < 0.1 in univariable analyses among the following: age, sex, ASA-PS score, Charlson comorbidity index, concomitant acute pancreatitis, admission at night time, admission on weekends, history of cholangitis, etiology of cholangitis, presence of hilar biliary stricture, severity of acute cholangitis, balloon endoscopy-assisted ERCP, chemotherapy, history of cholangitis, positive bile culture, positive blood culture, and total bilirubin. The full model is described in Supplementary Table 2

[b]LOS was log-transformed to increase its normality

on the effectiveness of urgent biliary drainage is required before this procedure is justified for patients with non-severe acute cholangitis.

There are some limitations to be acknowledged in this study. First, a retrospective study design at a single referral center might have led to selection biases of treatments and patients. Nonetheless, we included all eligible patients who were consecutively identified during the study period, and our detailed electric medical records and endoscopy database allowed us to comprehensively examine the association of the timing of ERCP with clinical outcomes while adjusting for potential confounders. However, our findings require an external validation by studies at multiple hospitals in different settings. Second, a relatively small sample size was another limitation in that null findings in LOS might be due to limited statistical power. Finally, we only included cases where endoscopic biliary drainage was successfully carried out, and therefore, we did not evaluate technical success rate or other biliary drainage procedures (e.g., endoscopic ultrasound-guided biliary drainage, percutaneous transhepatic biliary drainage).

In conclusion, urgent biliary drainage for non-severe cholangitis was not necessarily associated with short LOS or other clinical outcomes compared to elective biliary drainage. Further investigation is warranted to evaluate the trade-off of potentially higher morbidities due to the delay in ERCP and medical resources associated with urgent biliary drainage.

Table 4 Linear regression analyses to assess the association of the timing of ERCP (elective vs. urgent) and length of stay (LOS), stratified by covariates

Subgroup	Elective drainage		Urgent drainage		Beta coefficient for LOS comparing elective versus urgent drainage (95% CI)[a]	*P* for interaction[b]
	n	LOS (IQR), days	n	LOS (IQR), days		
Age						0.11
> 80 years	23	13 (10–20)	59	11 (9–15)	−0.119 (−0.359 to 0.121)	
≤ 80 years	75	11 (9–14)	142	11 (8–15)	0.017 (−0.124 to 0.157)	
Sex						0.72
Male	61	11 (10–14)	123	14 (9–14)	−0.070 (−0.224 to 0.085)	
Female	37	11 (9–16)	78	11 (9–15)	0.073 (−0.120 to 0.267)	
ASA-PS score						0.66
> 2	16	13 (11–19)	26	14 (10–21)	−0.019 (−0.308 to 0.270)	
≤ 2	82	11 (9–14)	175	11 (9–14)	−0.006 (−0.138 to 0.126)	
Charlson comorbidity index						0.20
> 2	56	13 (10–17)	90	12 (9–15)	0.044 (−0.031 to 0.118)	
≤ 2	42	10 (8–12)	111	11 (8–15)	−0.022 (−0.090 to 0.046)	
Admission at night time						0.57
Yes	35	11 (9–14)	71	11 (9–15)	0.002 (−0.088 to 0.092)	
No	63	12 (10–16)	130	11 (9–15)	0.033 (−0.029 to 0.095)	
Admission on weekends						0.008
Yes	21	11 (8–15)	45	13 (9–18)	−0.063 (−0.184 to 0.058)	
No	77	12 (10–15)	156	11 (9–14)	0.046 (−0.010 to 0.101)	
Etiology of acute cholangitis						0.85
Bile duct stone	56	11 (10–15)	109	11 (8–15)	0.039 (−0.021 to 0.099)	
Stent occlusion	23	12 (10–13)	78	12 (9–14)	0.028 (−0.078 to 0.134)	
Hilar biliary stricture						0.22
Present	32	12 (8–16)	45	13 (9–17)	−0.033 (−0.139 to 0.074)	
Absent	66	11 (10–17)	156	11 (9–14)	0.037 (−0.021 to 0.095)	
Severity of acute cholangitis						0.46
Mild	66	11 (9–14)	112	11 (8–14)	0.016 (−0.052 to 0.083)	
Moderate	32	13 (11–19)	89	12 (9–15)	0.055 (−0.021 to 0.131)	
Balloon endoscopy-assisted ERCP						0.66
Yes	19	10 (8–15)	9	10 (8–12)	0.064 (−0.097 to 0.225)	
No	79	11 (10–15)	192	11 (9–15)	0.025 (−0.030 to 0.080)	
Chemotherapy						0.33
Yes	23	12 (10–17)	58	12 (9–14)	0.066 (−0.034 to 0.167)	
No	75	11 (9–15)	143	11 (8–15)	0.008 (−0.051 to 0.067)	
History of cholangitis						0.52
Yes	34	11 (8–13)	72	12 (9–14)	−0.001 (−0.090 to 0.089)	
No	64	12 (10–16)	129	11 (9–15)	0.034 (−0.028 to 0.096)	
Bile culture						0.34
Positive	65	12 (10–16)	170	11 (9–15)	0.023 (−0.035 to 0.081)	
Negative	11	12 (10–15)	17	11 (7–16)	0.105 (−0.095 to 0.306)	
Blood culture						0.18
Positive	29	13 (12–18)	60	12 (9–17)	0.072 (−0.018 to 0.163)	
Negative	52	11 (9–14)	88	11 (8–15)	−0.008 (−0.082 to 0.066)	

ASA-PS American Society of Anesthesiologists Physical Status, *CI* confidence interval, *ERCP* endoscopic retrograde cholangiopancreatography, *IQR* interquartile range, *LOS* length of stay

[a]LOS was log-transformed to increase its normality. Beta coefficients were calculated using univariable linear regression models

[b]*P* for interaction was calculated using the Wald test on the cross-product of timing of ERCP (elective vs. urgent) and each of the covariates

Author's contribution RH, TH, and YN contributed to conception and design of the study, analysis and interpretation of the data, and drafting of the article. HK, RU, NT, SM, TS, TS, TT, KI, KS, TS, MT, HI, YN, and KK contributed to critical revision of the article for important intellectual content. All authors contributed to the final approval of the article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Kogure H, Tsujino T, Yamamoto K, et al. Fever-based antibiotic therapy for acute cholangitis following successful endoscopic biliary drainage. *J Gastroenterol*. 2011;46:1411–1417.
2. van Santvoort HC, Besselink MG, de Vries AC, et al. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. *Ann Surg*. 2009;250:68–75.
3. Umefune G, Kogure H, Hamada T, et al. Procalcitonin is a useful biomarker to predict severe acute cholangitis: a single-center prospective study. *J Gastroenterol*. 2017;52:734–745.
4. Salek J, Livote E, Sideridis K, et al. Analysis of risk factors predictive of early mortality and urgent ERCP in acute cholangitis. *J Clin Gastroenterol*. 2009;43:171–175.
5. Pang YY, Chung YA. Predictors for emergency biliary decompression in acute cholangitis. *Eur J Gastroenterol Hepatol*. 2006;18:727–731.
6. Tsujino T, Sugita R, Yoshida H, et al. Risk factors for acute suppurative cholangitis caused by bile duct stones. *Eur J Gastroenterol Hepatol*. 2007;19:585–588.
7. Ramchandani M, Pal P, Reddy DN. Endoscopic management of acute cholangitis as a result of common bile duct stones. *Dig Endosc*. 2017;29(Suppl 2):78–87.
8. Tsuchiya T, Sofuni A, Tsuji S, et al. Endoscopic management of acute cholangitis according to the TG13. *Dig Endosc.*. 2017;29(Suppl 2):94–99.
9. Okamoto K, Takada T, Strasberg SM, et al. TG13 management bundles for acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci*. 2013;20:55–59.
10. Kiriyama S, Takada T, Strasberg SM, et al. New diagnostic criteria and severity assessment of acute cholangitis in revised Tokyo Guidelines. *J Hepatobiliary Pancreat Sci*. 2012;19:548–556.
11. Miura F, Takada T, Strasberg SM, et al. TG13 flowchart for the management of acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Sci*. 2013;20:47–54.
12. Miura F, Okamoto K, Tokyo Takada T, Takada T, Tokyo Guidelines, et al. Iinitial management of acute biliary infection and flowchart for acute cholangitis. *J Hepatobiliary Pancreat Sci*. 2018;. https://doi.org/10.1002/jhbp.509.
13. Navaneethan U, Gutierrez NG, Jegadeesan R, et al. Delay in performing ERCP and adverse events increase the 30-day readmission risk in patients with acute cholangitis. *Gastrointestl Endosc*. 2013;78:81–90.
14. Khashab MA, Tariq A, Tariq U, et al. Delayed and unsuccessful endoscopic retrograde cholangiopancreatography are associated with worse outcomes in patients with acute cholangitis. *Clin Gastroenterol Hepatol*. 2012;10:1157–1161.
15. Lee F, Ohanian E, Rheem J, et al. Delayed endoscopic retrograde cholangiopancreatography is associated with persistent organ failure in hospitalised patients with acute cholangitis. *Aliment Pharmacol Ther*. 2015;42:212–220.
16. Jang SE, Park SW, Lee BS, et al. Management for CBD stone-related mild to moderate acute cholangitis: urgent versus elective ERCP. *Dig Dis Sci*. 2013;58:2082–2087.
17. Shaheen AA, Kaplan GG, Myers RP. Weekend versus weekday admission and mortality from gastrointestinal hemorrhage caused by peptic ulcer disease. *Clin Gastroenterol Hepatol.*. 2009;7:303–310.
18. Palmer WL, Bottle A, Davie C, et al. Dying for the weekend: a retrospective cohort study on the association between day of hospital presentation and the quality and safety of stroke care. *Arch Neurol*. 2012;69:1296–1302.
19. Ananthakrishnan AN, McGinley EL, Saeian K. Outcomes of weekend admissions for upper gastrointestinal hemorrhage: a nationwide analysis. *Clin Gastroenterol Hepatol*. 2009;7:296–302e291.
20. Gallerani M, Imberti D, Ageno W, et al. Higher mortality rate in patients hospitalised for acute pulmonary embolism during weekends. *Thromb Haemost*. 2011;106:83–89.
21. Kostis WJDK, Marcella SW, Shao YH, et al. Weekend versus weekday admission and mortality from myocardial infarction. *N Engl J Med*. 2007;356:1099–1109.
22. Hamada T, Yasunaga H, Nakai Y, et al. No weekend effect on outcomes of severe acute pancreatitis in Japan: data from the diagnosis procedure combination database. *J Gastroenterol*. 2016;51:1063–1072.
23. Inamdar S, Sejpal DV, Ullah M, et al. Weekend vs. weekday admissions for cholangitis requiring an ERCP: comparison of outcomes in a national cohort. *Am J Gastroenterol*. 2016;111:405–410.
24. Tabibian JH, Yang JD, Baron TH, et al. Weekend admission for acute cholangitis does not adversely impact clinical or endoscopic outcomes. *Dig Dis Sci*. 2016;61:53–61.
25. Parikh ND, Issaka R, Lapin B, et al. Inpatient weekend ERCP is associated with a reduction in patient length of stay. *Am J Gastroenterol*. 2014;109:465–470.
26. Hou LA, Laine L, Motamedi N, et al. Optimal timing of endoscopic retrograde cholangiopancreatography in acute cholangitis. *J Clin Gastroenterol*. 2017;51:534–538.
27. Mok SR, Mannino CL, Malin J, et al. Does the urgency of endoscopic retrograde cholangiopancreatography (ercp)/percutaneous biliary drainage (pbd) impact mortality and disease related complications in ascending cholangitis? (deim-i study). *J Interv Gastroenterol*. 2012;2:161–167.
28. Cotton PB, Eisen GM, Aabakken L, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc*. 2010;71:446–454.
29. Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. *Anesthesiology*. 1978;49:239–243.
30. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
31. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013;48:452–458.
32. Tan M, Schaffalitzky de Muckadell OB, Laursen SB. Association between early ERCP and mortality in patients with acute cholangitis. *Gastrointest Endosc*. 2017;. https://doi.org/10.1016/j.gie.2017.04.009.
33. Isayama H, Yasuda I, Tan D. Current strategies for endoscopic management of acute cholangitis. *Dig Endosc*. 2017;29(Suppl 2):70–77.
34. Kiriyama S, Takada T, Hwang TL, et al. Clinical application and verification of the TG13 diagnostic and severity grading criteria

for acute cholangitis: an international multicenter observational study. *J Hepatobiliary Pancreat Sci*. 2017;24:329–337.
35. Kiriyama S, Kozaka K, Takada T, et al. Diagnostic and severity grading criteria for acute cholangitis in the Tokyo Guidelines 2018. *J Hepatobiliary Pancreat Sci*. 2017;. https://doi.org/10.1002/jhbp.512.