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Editorial Board Member of *World Journal of Gastroenterology*, Nikolaos Papadopoulos, MD, PhD, Consultant, The First Department of Internal Medicine, 417 Army Share Fund Hospital, Monis Petraki 10-12, Athens 11521, Greece. nipapmed@gmail.com

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Retrospective Cohort Study

Optimal timing of biliary drainage based on the severity of acute cholangitis: A single-center retrospective cohort study

Zhao-Qing Lu, Han-Yu Zhang, Chen-Fen Su, Yue-Yan Xing, Guo-Xing Wang, Chun-Sheng Li

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Zhao-Qing Lu, Han-Yu Zhang, Chen-Fen Su, Yue-Yan Xing, Guo-Xing Wang, Department of Emergency Medicine, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

Chun-Sheng Li, Emergency and Critical Care Center, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

Corresponding author: Chun-Sheng Li, PhD, Professor, Emergency and Critical Care Center, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong'an Road, Xicheng District, Beijing 100050, China. lcscyy@163.com

Abstract

BACKGROUND

Biliary decompression is well known to greatly decrease the risks of mortality in acute cholangitis (AC). Although early biliary drainage is recommended by the treatment guidelines for AC, the best time for performing this procedure is yet to be established. Furthermore, since the clinical outcomes of patients with severe AC vary dramatically, screening for patients that could benefit the most from early drainage would be more beneficial than the drainage performed based on the severity grade criteria.

AIM

To investigate the optimal drainage timing for AC patients with each disease severity grade and organ dysfunction.

METHODS

In this retrospective monocenter cohort analysis, we reviewed 1305 patients who were diagnosed with AC according to the Tokyo guidelines 2018 at a Chinese tertiary hospital between July 2016 and December 2020. Demographic characteristics including age and sex, clinical and laboratory characteristics, and imaging findings of each patient were obtained from electronic medical records. We investigated the all-cause in-hospital mortality (IHM), hospital length of stay (LOS), and hospitalization costs associated with the timing of biliary drainage according to the severity grading and different dysfunctioning organs and predictors [age, white blood cell (WBC) count, total bilirubin, albumin, lactate, malignant obstruction, and Charlton comorbidity index (CCI)].

RESULTS

Biliary drainage within 24 or 48 h in Grade III AC patients could dramatically decrease IHM (3.9% *vs* 9.0%, $P = 0.041$; 4% *vs* 9.9%, $P = 0.018$, respectively), while increasing LOS and hospitalization costs. Multivariate logistic analysis revealed that neurological, respiratory, renal, and cardiovascular dysfunctions, hypoalbuminemia, and malignant obstruction were significantly associated with IHM (odds ratio = 5.32, 2.541, 6.356, 4.021, 5.655, and 7.522; $P < 0.001$, $P = 0.016$, $P < 0.001$, $P = 0.012$, $P < 0.001$, and $P < 0.001$; respectively). Biliary decompression performed within 12 h of admission significantly decreased the IHM in AC patients with neurological dysfunction (0% *vs* 17.3%, $P = 0.041$) or with serum lactate > 2 mmol/L (0% *vs* 5.4%, $P = 0.016$). In the subgroup of AC patients with renal dysfunction, abnormal WBC count, hyperbilirubinemia, or hypoalbuminemia, early drainage (< 24 h) reduced the IHM (3.6% *vs* 33.3%, $P = 0.004$; 1.9% *vs* 5.8%, $P = 0.031$; 1.7% *vs* 5.0%, $P = 0.019$; 0% *vs* 27%, $P = 0.026$; respectively). The IHM was lower in patients with AC combined with hepatic dysfunction, malignant obstruction, or a CCI > 3 who had undergone biliary drainage within 48 h (2.6% *vs* 20.5%, $P = 0.016$; 3.0% *vs* 13.5%, $P = 0.006$; 3.4% *vs* 9.6%, $P = 0.021$; respectively).

CONCLUSION

Biliary drainage within 12 h is beneficial for AC patients with neurological or cardiovascular dysfunction, while complete biliary decompression within 24 h of admission is recommended for treating patients with Grade III AC.

Key Words: Acute cholangitis; Endoscopic retrograde cholangiopancreatography; Mortality; Biliary drainage; Organ dysfunction

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Core Tip: This study aimed to investigate the optimal timing of drainage for patients with acute cholangitis (AC) with each grade and organ dysfunction. We first attempted to study whether AC patients with different organ dysfunction should undergo biliary drainage at distinct times. We believe that our study makes a significant contribution to the literature because we found that patients with severe AC should complete biliary decompression within 24 h of admission, while biliary drainage within 12 h was beneficial for AC patients with neurological or cardiovascular dysfunction.

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INTRODUCTION

Acute cholangitis (AC) is a life-threatening condition that occurs in the presence of biliary obstruction. Although growing evidence confirms that biliary decompression can dramatically decrease the mortality rates associated with AC, the optimal time for biliary drainage remains controversial[1-3]. Most experts agree that the timeframe for biliary decompression is distinct for different severity grades based on the Tokyo guidelines 2018/2013 (TG18/13), which recommend early biliary drainage for Grade II AC and urgent biliary drainage for Grade III AC; however, the exact timeframe is unclear[4]. Moreover, the 2019 European Society of Gastrointestinal Endoscopy guidelines recommend biliary drainage as soon as possible in patients with Grade III AC and within 12 h for patients with septic shock, while within 48–72 h for patients with Grade II AC[2]. Meanwhile, the 2021 American Society of Gastrointestinal Endoscopy (ASGE) guidelines suggest endoscopic retrograde cholangiopancreatography (ERCP) within 48 h in AC patients, regardless of severity[1]. Some studies have demonstrated a “the earlier, the better” approach for the management of AC cases[5-8]. They deemed urgent biliary decompression necessary in severe cases. However, other studies have shown that ERCP can be safely delayed to allow for sufficient resuscitation[9-11]. In our clinical experience, the severity of Grade III AC varies dramatically, and we have observed that the optimal timing of biliary decompression may vary for different organ injuries.

So far, no relevant study has determined whether the clinical outcomes of Grade III AC patients vary with different organ injuries and whether AC patients with different organ dysfunction should undergo biliary drainage at distinct times. Consequently, this single-center retrospective study aimed to

investigate the relationship between drainage timing and in-hospital mortality (IHM) in patients with AC of different severities, and attempted to stratify patients with AC to identify the best decompression time.

MATERIALS AND METHODS

Patients

Ethical compliance: This retrospective cohort study was conducted according to the tenets of the Declaration of Helsinki, and approved by the Bioethics Committee of Beijing Friendship Hospital, Capital Medical University (Certification No. 2020-P2-224-01). After the review conducted by the Ethics Committee, the need for informed consent was waived.

Sample size: Based on the pre-experimental results, which revealed a 0.87% and 3% mortality rates for patients who did and did not undergo biliary drainage, respectively, we calculated the sample size using PASS 15.0 with Power = 0.8, Alpha = 0.05, and N1 = N2. The resultant sample size was 1306. On this basis, we expanded the sample size by 15% to exclude the reduction caused by data deficiency or diagnostic errors.

Enrollment: We searched the electronic medical record database of the Beijing Friendship Hospital for all adult (> 18 years) non-pregnant patients visiting the Emergency Department (ED) between July 2016 and December 2020 who were discharged with a diagnosis of AC. A total of 1498 patients were included in the study. All the medical records were reviewed and a diagnosis of AC was confirmed according to the TG18 diagnostic criteria[12]. Besides pregnant women and patients aged < 18 years, we also excluded patients transferred to other hospitals or outpatient departments for treatment and patients whose medical data were incomplete or missing. Finally, 1305 patients were enrolled (Figure 1).

Data collection

Demographic data, including age and sex, were obtained for each patient. Clinical data, laboratory characteristics, and imaging findings were obtained from the electronic medical records. Clinical data included vital signs, fluid output, Glasgow coma score, the vasoactive drug dose, history of biliary disease, Charlton comorbidity index (CCI), etiology of AC, registration time at the ED, time and type of drainage, discharge time, complications of drainage, hospitalization cost, and IHM. Laboratory findings included white blood cell (WBC) count, platelet count, total bilirubin, albumin, aspartate transaminase, alanine transaminase, creatinine, amylase, prothrombin time-international normalized ratio, arterial blood oxygen pressure, and lactate. Computed tomography, magnetic resonance cholangiopancreatography, or ERCP findings were reviewed to determine the etiology of cholangitis. The time interval for biliary drainage was calculated as the difference between ED registration time and the time of ERCP or percutaneous transhepatic biliary drainage (PTBD). We used the TG18 severity criteria for grading the severity[12].

Definition and indications

Benign stenosis was defined as stenosis in the biliary ducts without radiological findings of metastasis or malignant cells on histological examination. The indications of ERCP were AC combined with persistent extrahepatic biliary obstruction, and cases of anatomical derangement, failed ERCP, intrahepatic biliary obstruction underwent PTBD. The contraindications of ERCP included acute coronary syndrome, acute heart failure (New York Heart Association class III-IV), acute stroke occurring within 2 wk prior to enrollment, and acute pulmonary embolism complicated with the arterial PaO₂ < 60 mmHg, while the contraindications of PTBD were platelet count < 50000/mm³ or prothrombin activity < 60%. The adverse effects after drainage were based on the lexicon guidelines of the ASGE[13]. The second treatment included a second ERCP and a second PTBD for stone removal or stent placement. The need for a second therapeutic ERCP was assessed per the discretion of the experienced operators who performed the intervention and based on 2018 ERCP Guidelines for China[14]. All of the endoscopists had independently completed 300 ERCP interventions per year for 3 years.

Study outcomes

Our primary outcome was IHM, and the secondary outcomes were hospital length of stay (LOS) and hospitalization costs. When analyzing the survivors' LOS and entailed cost, we excluded patients who died or were transferred to other hospitals. We investigated the primary and secondary outcomes relevant to the timing of biliary drainage according to severity grading and some predictors based on TG18 and other previous studies.

Statistical analysis

Continuous variables were reported as medians with interquartile ranges (IQR) for not normally distributed; categorical variables were expressed as numbers and percentages. Comparisons between

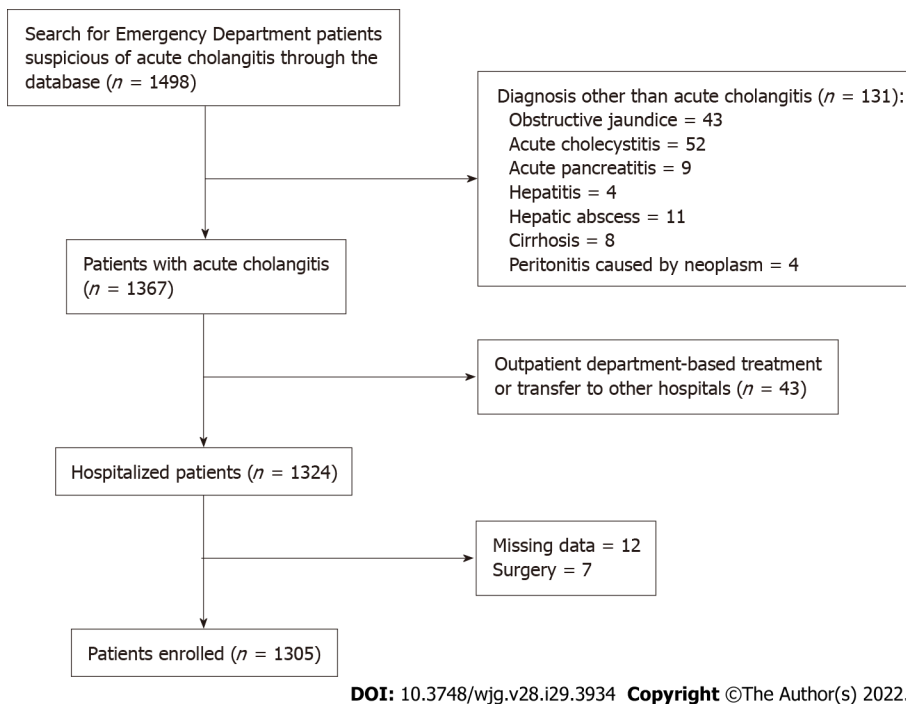


Figure 1 A flowchart of the study population.

groups for continuous variables were evaluated using the Kruskal-Wallis test and Mann-Whitney *U* test, and for categorical variables, Fisher's exact test was used. Univariate logistic regression analysis and multivariate logistic regression with stepwise variable selection were used to analyze the relationship between organ dysfunction or predictors and IHM. Odds ratios (ORs) and 95% confidence intervals were calculated. Statistical significance was set at $P < 0.05$. Statistical analyses were conducted using SPSS v22.

RESULTS

The characteristics of the study population are shown in Tables 1 and 2. This cohort included 1305 patients, the majority of whom were men (60%). The median age of the group was 74 years (IQR, 63-82 years), and patients with Grade I AC were significantly younger ($P < 0.001$). The CCI of individuals with Grade III cholangitis was significantly higher than that of patients with Grade I or II cholangitis ($P < 0.001$). Choledocholithiasis (69.4%) was the most common cause of cholangitis, followed by malignant obstruction (18.5%). Among patients with cholangitis caused by malignancy, the number of patients with Grade II cholangitis was higher than that of patients with Grade I or III cholangitis. More patients with Grade II AC underwent biliary decompression ($P = 0.006$), while the IHM and hospitalization costs were significantly higher in the Grade III AC group than in the Grade I and II AC groups (IHM: $P < 0.001$, hospitalization costs: $P < 0.001$). Deaths tended to occur earlier in the disease course in patients with Grade III AC (median time 6 d).

A total of 915 patients in this cohort (70.1%) underwent biliary decompression, most of whom underwent endoscopic interventions (90.7%), while more patients underwent PTBD in the severe AC groups (Grade II: 37 cases, Grade III: 35 cases *vs* Grade I: 13 cases, $P = 0.001$). One hundred and sixty patients with Grade III were treated with antibiotics and fluid infusion only (disagreement about procedures = 35 cases, including two of mortality; with contraindications = 24 cases, including five of death; not tolerable conditions = 14 cases, including eight of death; obstruction spontaneous relief = 67 cases, including seven of mortality; not persistent biliary obstruction with high risk to stone removal by ERCP = 15 cases without death; not persistent biliary obstruction with selective cholecystectomy = five cases without death). The median drainage time was 24 h. Nearly half of the patients underwent biliary drainage within 24 h (445/915, 48%), while 89 patients with Grade III underwent drainage within 12 h (29%), which was significantly higher than that in Grades I and II ($P = 0.04$). Among the patients who underwent biliary drainage, more patients in Grade III underwent biliary drainage outside regular working hours (31.9%) and 478 patients (52.2%) required a second intervention for stone removal or stent placement, which exhibited no relationship with severity ($P = 0.688$). Post-ERCP pancreatitis was the major adverse event (8.2%), and the incidence of adverse events was not significantly different among the three severity grades.

Table 1 Characteristics data for all patients

Characteristics, <i>n</i> (%)	Total (<i>n</i> = 1305)	Grade I (<i>n</i> = 433)	Grade II (<i>n</i> = 405)	Grade III (<i>n</i> = 467)	<i>P</i> value
Age (yr)-median (IQR)	74 (63-82)	66 (59-72.5)	79 (69-84)	77 (66-83)	< 0.001
Male, <i>n</i> (%)	783 (60)	276 (63.7)	240 (59.3)	267 (57.2)	0.123
CCI- median (IQR)	2 (1-4)	2 (1-3)	2 (1-4)	3 (1-5)	< 0.001
Etiology, <i>n</i> (%)					< 0.001
Cholelithiasis	906 (69.4)	315 (72.7)	252 (62.2)	339 (72.6)	
Malignant obstruction	242 (18.5)	73 (16.9)	97 (24.0)	72 (15.4)	
Benign stenosis	94 (7.2)	27 (6.2)	42 (10.4)	25 (5.4)	
Others	63 (4.8)	18 (4.2)	14 (3.5)	31 (6.6)	
Biliary drainage, <i>n</i> (%)	915 (70.1)	302 (69.7)	306 (75.6)	307 (65.7)	0.006
LOS (d)-median (IQR)	11 (8-14)	11 (8-14)	11 (7.5-14)	12 (7-15)	0.110
Hospitalization cost (CNY)-median (IQR)	38784.37 (22744.31-53278.63)	36536.36 (20851.37-47274.77)	38308.33 (23452.14-52847.29)	41832.19 (23355.98-58145.52)	< 0.001
IHM, <i>n</i> (%)	41 (3.1)	1 (0.2)	7 (1.7)	33 (7.1)	< 0.001
Survival time of dead (d)-median (IQR)	8 (3-23.5)	9	23 (13-46)	6 (3-17)	0.024
Organ dysfunction					
Neurological dysfunction	126	0	0	126	< 0.001
Respiratory dysfunction	227	0	0	227	< 0.001
Renal dysfunction	64	0	0	64	< 0.001
Cardiovascular dysfunction	39	0	0	39	< 0.001
Hematological dysfunction	149	0	0	149	< 0.001
Hepatic dysfunction	83	0	0	83	< 0.001
Temperature (°C)-median (IQR)	37.0 (36.6-38)	36.8 (36.6-37.8)	37 (36.6-38.25)	37.2 (36.6-38.3)	0.001
Laboratory values					
WBC (/mm ³)-median (IQR)	10560 (7705-14305)	9120 (7160-11165)	12700 (8897-18441)	11140 (7870-15810)	< 0.001
T-Bil (mg/dL)-median (IQR)	99.81 (62.43-155.76)	69.28 (49.625-120.975)	121.74 (88.97-184.41)	1041.2 (67.74-156.31)	< 0.001
Albumin (g/L)-median (IQR)	35.4 (31.2-39.2)	37.5 (34.2-40.4)	34.9 (30.8-38.1)	33.6 (29.2-37.8)	< 0.001
Lactate (mmol/L)-median (IQR)	2.15 (1.6-3.4)	1.8 (1.4-2.7)	2.1 (1.5-2.8)	2.4 (1.7-4.1)	< 0.001

IQR: Interquartile range; CCI: Charlton Comorbidity Index; LOS: Length of stay; CNY: Chinese Yuan; IHM: In-hospital mortality; WBC: White blood cell count; T-Bil: Total bilirubin.

The association of the IHM, LOS, and hospitalization costs with the timing of biliary drainage in each severity grade has been presented in [Table 3](#). Biliary drainage significantly decreased the IHM in all AC patients (13/915 *vs* 28/390, $P < 0.001$). Among individuals with Grade III cholangitis, the IHM rate was significantly decreased in patients who had biliary drainage within 24 h or 48 h ($P = 0.041$, $P = 0.018$), while the LOS was significantly increased among those patients who underwent drainage within 12 h, 24 h, or 48 h ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively). Hospitalization costs significantly increased for all patients with biliary drainage, regardless of severity criteria. For patients with Grade I AC, IHM was not affected by the timing of drainage and there was no relationship between LOS and the timing of biliary drainage for the survivors, but LOS was significantly extended in all the patients who underwent biliary drainage within 24 h or 48 h ($P = 0.004$, $P = 0.002$).

Univariate and multivariate analyses of predictors, including TG18 severity grading factors, lactate, CCI, and etiology of malignant obstruction, are shown in [Table 4](#). In the univariate analysis, organ dysfunction, abnormal WBC count, hypoalbuminemia, CCI > 3, and etiology of malignancy were significantly associated with IHM. In a multivariate analysis of organ dysfunction, only neurological, respiratory, renal, and cardiovascular dysfunction, hypoalbuminemia, and malignant obstruction were significantly positively associated with IHM (OR = 5.32, 2.541, 6.356, 4.021, 5.655, and 7.522; $P < 0.001$, $P = 0.016$, $P < 0.001$, $P = 0.012$, $P < 0.001$, and $P < 0.001$, respectively).

Table 2 Characteristics data for patients with drainage

Characteristics, <i>n</i> (%)	Total (<i>n</i> = 915)	Grade I (<i>n</i> = 302)	Grade II (<i>n</i> = 306)	Grade III (<i>n</i> = 307)	<i>P</i> value
Drainage method, <i>n</i> (%)					0.001
ERCP	830 (90.7)	289 (95.7)	269 (87.9)	272 (88.6)	
PTBD	85 (9.3)	13 (4.3)	37 (12.1)	35 (11.4)	
Timing of drainage (hours)- median (IQR), <i>n</i> (%)	24.0 (60.0)	26.4 (62.4)	26.4 (62.4)	21.6 (45.6)	0.001
Biliary drainage within, <i>n</i> (%)					0.001
12 h	212 (23.2)	54 (17.9)	69 (22.5)	89 (29.0)	
12-24 h	233 (25.5)	74 (24.5)	70 (22.9)	89 (29.0)	
24-48 h	172 (18.8)	71 (23.5)	54 (17.6)	47 (15.3)	
> 48 h	298 (32.6)	103 (34.1)	113 (36.9)	82 (26.7)	
Second intervention, <i>n</i> (%)	478 (52.2)	159 (52.6)	154 (50.3)	165 (53.7)	0.688
Drainage outside working hours, <i>n</i> (%)	207 (22.6)	49 (16.2)	60 (19.6)	98 (31.9)	< 0.001
Adverse events, <i>n</i> (%)					
Pancreatitis	75 (8.2)	23 (7.6)	23 (7.5)	29 (9.4)	0.643
Cholangitis	8 (0.9)	2 (0.7)	2 (0.7)	4 (1.3)	0.742
Perforation	7 (0.8)	1 (0.3)	2 (0.7)	0 (0)	0.440
Bile leak	4 (0.4)	2 (0.7)	1 (0.3)	1 (0.3)	0.701
Myocardial infarction	5 (0.5)	0 (0)	3 (1.0)	2 (0.7)	0.339

IQR: Interquartile range; ERCP: Endoscopic retrograde cholangiopancreatography; PTBD: Percutaneous transhepatic biliary drainage.

From the data presented in Table 4, the association between IHM and the timing of biliary drainage for each clinical predictor is reflected. Among patients with AC complicated with neurological dysfunction or hyperlactatemia, the IHM rate was significantly decreased in individuals who underwent biliary decompression within 12 h ($P = 0.041$, $P = 0.016$), while those patients complicated with neurological dysfunction who had drainage within 24 h or 48 h could not improve prognosis compared with those who underwent drainage after 24 or 48 h, as well as those who did not undergo biliary drainage after admission ($P = 0.175$, $P = 0.304$). In patients with renal dysfunction, abnormal WBC count, hyperbilirubinemia, hypoalbuminemia, or hyperlactatemia, who had biliary decompression within 24 h or 48 h, there were significantly lower IHM rates than those of the remaining patients in each subgroup. Among patients with AC complicated with hepatic dysfunction, higher CCI (> 3), or malignancy, a lower IHM rate was significantly associated with early drainage (< 48 h) ($P = 0.016$, $P = 0.006$, $P = 0.021$).

DISCUSSION

In this retrospective monocenter cohort analysis including 1305 AC patients stratified according to TG18 severity criteria, early drainage (< 24 h) in Grade III AC patients had the greatest benefit, which could significantly reduce the all-cause IHM. It is worth noting that, in this subgroup, patients complicated with neurological dysfunction should be drained as early as possible (< 12 h). Moreover, early drainage was also required for AC patients with lactate more than 2 mmol/L, abnormal WBC count, hyperbilirubinemia, or hypoalbuminemia. Although these patients may have no severe cholangitis, early drainage could significantly reduce IHM and benefit the most. However, it should be noted that our results did not prove that drainage reduced hospitalization costs compared to conservative treatment. Furthermore, early drainage increased hospitalization costs and LOS.

AC is a clinically heterogeneous disease with recent mortality rates ranging from 2.7% to 10%, which is considered as an improvement since these rates were as high as 50%-60% in severe cases[15,16]. Although it is well-accepted that biliary decompression can significantly decrease the mortality of AC, it is highly debatable as to what the optimal strategy is for performing biliary drainage procedures. Should drainage occur as early as possible or should the procedure be delayed until stabilization after adequate resuscitation, especially for Grade III AC patients? Our study showed that biliary drainage could significantly decrease the IHM of AC patients (1.4% *vs* 7.2%, $P < 0.001$), and AC patients of Grade

Table 3 Association of the clinical outcomes in relation to the timing of biliary drainage and severity grading by Tokyo guidelines 2018

Severity of AC	Characteristic-median (IQR)	Drainage	Absence of drainage	P value	Drainage < 12 h	Drainage > 12 h or absence	P value	Drainage < 24 h	Drainage > 24 h or absence	P value	Drainage < 48 h	Drainage > 48 h or absence	P value
Grade I	IHM	0/302	1/131	0.303	0/54	1/379	1.000	0/128	1/305	1.000	0/199	1/234	1.000
	LOS (d)	11 (9-15)	7 (4-10)	< 0.001	11 (8-13.25)	10 (8-14)	0.778	11 (8-14)	10 (7-14)	0.004	11 (8-14)	10 (6-14)	0.002
	Survivors' LOS (d) (<i>n</i> = 387)	12 (9-15)	8 (5-11)	< 0.001	11 (8-13.25)	11 (8-14)	0.794	11 (9-14)	11 (8-14)	0.065	11 (9-14)	10 (8-14)	0.101
	Hospitalization cost (CNY)	42845.67 (33734.18-52209.23)	15763.10 (7737.32-23680.31)	< 0.001	43328.59 (32863.61-49384.19)	35317.71 (18848.59-46850.08)	0.001	44154.19 (35638.76-52219.56)	31292.68 (16269.75-44599.67)	< 0.001	42908.34 (33358.44-50564.68)	25519.43 (12347.06-42424.96)	< 0.001
	Survivors' hospitalization cost (CNY) (<i>n</i> = 387)	42957.18 (33973.58-52224.73)	16596.85 (9096.73-24755.65)	< 0.001	43462.72 (36174.00-49384.19)	36604.86 (21962.98-47554.27)	0.003	44443.3 (35988.02-52237.14)	33492.6 (46019.17-18880.26)	< 0.001	43264.07 (34606.54-51093.62)	29762.32 (16376.75-44463.21)	< 0.001
Grade II	IHM	2/306	5/99	0.011	0/69	7/336	0.608	0/139	7/266	0.101	1/193	6/212	0.125
	LOS (d)	11 (9-15)	7 (4-12)	< 0.001	11 (8-14)	11 (7-14)	0.684	11 (9-14)	10 (7-14)	0.122	11 (8-14)	10 (7-14.8)	0.190
	Survivors' LOS (d) (<i>n</i> = 349)	12 (9-15)	7.5 (4.75-11.25)	< 0.001	11.5 (9-14)	11 (8-14)	0.367	12 (10-14)	11 (7-14)	0.024	12 (9-14)	11 (7-14)	0.050
	Hospitalization cost (CNY)	44033.13 (31071.05-56134.72)	17626.20 (10037.69-25587.43)	< 0.001	45832.44 (36061.53-56949.37)	36132.93 (21795.89-51453.62)	< 0.001	46789.09 (35989.59-57723.15)	31505.72 (19948.31-47463.61)	< 0.001	45489.74 (33858.99-57600.43)	29275.30 (16928.45-46255.47)	< 0.001
	Survivors' hospitalization cost (CNY) (<i>n</i> = 349)	45004.20 (32631.09-56660.62)	16342.15 (10300.68-25017.80)	< 0.001	47938.00 (37937.29-58046.02)	36629.15 (22828.93-51509.37)	< 0.001	48254.61 (37937.29-58929.51)	31589.96 (20386.80-47062.76)	< 0.001	46564.37 (36191.07-57998.63)	29338.38 (17687.02-45685.12)	< 0.001
Grade III	IHM	11/307	22/160	< 0.001	3/89	30/378	0.168	7/178	26/289	0.041	9/225	24/242	0.018
	LOS (d)	13 (9-17)	8 (3-12)	< 0.001	13 (11-19)	11 (6-15)	< 0.001	13 (10-17)	10 (6-14)	< 0.001	13 (9-17)	9.5 (5-14)	< 0.001
	Survivors' LOS (d) (<i>n</i> = 351)	13 (11-18)	9.5 (7-13.25)	< 0.001	13 (12-19)	12 (9-16)	0.001	13 (11-17.75)	12 (9-15)	< 0.001	13 (11-17.75)	11 (8-15)	< 0.001
	Hospitalization cost	51583.64 (38985.47-64886.01)	20183.58 (11317.37-29525.99)	< 0.001	56599.94 (43260.73-70300.00)	38527.58 (21034.79-55279.53)	< 0.001	55121.49 (40428.29-67707.01)	31832.99 (17933.81-50037.89)	< 0.001	54295.52 (39252.57-65638.57)	28165.23 (15708.29-45478.26)	< 0.001
	Survivors' hospitalization cost (CNY) (<i>n</i> = 351)	53507.33 (41027.94-65312.29)	22909.77 (15594.93-31845.39)	< 0.001	57976.4 (50131.44-70333.71)	43241.54 (28347.56-57860.29)	< 0.001	55873.84 (46654.40-69946.73)	38973.06 (24292.41-53090.85)	< 0.001	55782.38 (43994.26-66493.67)	34748.29 (21379.37-50147.24)	< 0.001

AC: Acute cholangitis; IQR: Interquartile range; IHM: In-hospital mortality; LOS: Length of stay; CNY: Chinese Yuan.

Table 4 Univariate and multivariate analysis of predictors of mortality, and relationship of mortality with the timing of drainage for each predictor

Predictors (<i>n</i> = 1305)	Univariate analysis		Multivariate analysis		Mortality to the timing of drainage								
	OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value	< 12 h	> 12 h or absence	<i>P</i> value	< 24 h	> 24 h or absence	<i>P</i> value	< 48 h	> 48 h or absence	<i>P</i> value
Neurological dysfunction	8.377 (4.384-16.007)	< 0.001	5.32 (2.373-11.931)	< 0.001	0/22	18/104	0.041	3/42	15/84	0.175	5/51	13/75	0.304
Respiratory dysfunction	2.886 (1.491-5.497)	0.003	2.541 (1.189-5.43)	0.016	1/44	14/183	0.314	4/91	11/136	0.414	6/117	9/110	0.428
Renal dysfunction	11.043 (5.402-22.573)	< 0.001	6.356 (2.623-15.397)	< 0.001	1/15	12/49	0.269	1/28	12/36	0.004	1/31	12/33	0.001
Cardiovascular dysfunction	11.569 (5.078-26.357)	< 0.001	4.021 (1.361-11.88)	0.012	0/7	9/32	0.169	2/16	7/23	0.262	2/18	7/21	0.139
Hematological dysfunction	2.611 (1.253-5.441)	0.02	N/A		2/37	8/104	1	3/61	7/88	0.527	3/74	7/75	0.327
Hepatic dysfunction	5.263 (2.484-11.152)	< 0.001	N/A		0/15	10/68	0.196	1/30	9/53	0.086	1/39	9/44	0.016
Age (≥ 75 yr)	1.432 (0.765-2.680)	0.261	N/A		2/88	21/531	0.759	4/196	19/423	0.172	7/267	16/352	0.284
Temperature (≥ 39 °C)	0.390 (0.093-1.631)	0.197	N/A		0/43	2/106	1	1/75	1/74	1	1/85	1/64	1
WBC (> 12000/mm ³ , < 4000/mm ³)	1.962 (1.043-3.688)	0.036	N/A		1/107	23/445	0.063	4/207	20/342	0.031	6/278	18/275	0.012
T-Bil (≥ 5 mg/dL)	1.711 (0.865-3.385)	0.123	N/A		3/143	26/626	0.333	5/292	24/477	0.019	8/407	21/362	0.007
Albumin (< STD*0.7)	10.715 (5.147-22.303)	< 0.001	5.655 (2.398-13.335)	< 0.001	0/8	12/51	0.188	0/15	12/44	0.026	1/24	11/35	0.018
Lactate (≥ 2 mmol/L)	1.450 (0.766-2.747)	0.254	N/A		0/105	16/298	0.016	2/186	14/217	0.008	4/227	12/176	0.018
Malignant obstruction	5.495 (2.924-10.325)	< 0.001	7.522 (3.504-16.149)	< 0.001	1/26	21/216	0.483	2/59	20/183	0.116	3/101	19/141	0.006
CCI (> 3)	4.080 (2.153-7.7340)	< 0.001	N/A		2/57	23/318	0.397	4/127	21/248	0.052	6/177	19/198	0.021

WBC: White blood cell count; T-Bil: Total bilirubin; STD: Lower limit of normal value; CCI: Charlton Comorbidity Index; OR: Odds ratio; CI: Confidence interval; N/A: Not applicable.

III underwent decompression within 24 h or 48 h had lower IHM (3.9% *vs* 9.0%, *P* = 0.041; 4% *vs* 9.9%, *P* = 0.018). These findings are in line with the results of a large sample size retrospective study, which showed that drainage within 48 h was associated with improved IHM (3.4% *vs* 10.2%, *P* = 0.019)[17], although it did not discuss drainage within 24 h. Another retrospective study of 6063 patients with AC conducted by Kiriya *et al*[3] reported a distinct result: decompression within 24 h or 48 h improved the 30-d mortality rate only among Grade II patients (drainage within 24 h *vs.* after 24 h or no drainage: 1.7% *vs* 3.4%, *P* < 0.05; drainage within 48 h *vs* after 48 h or no drainage: 2.0% *vs* 3.7%, *P* < 0.05), and the drainage timing did not influence 30-d mortality in patients with Grade I and Grade III. This dissimilarity may be because we reviewed the all-cause IHM, while Kiriya *et al*'s study observed 30-d cholangitis-caused mortality, and the mortality rate of Grade III AC patients was lower than that in our study (5.1% *vs* 9.4%), especially for subgroups of delayed decompression in which more patients died from malignancy[3]. In addition, as the number and grade of patients without drainage were not shown in the results of Kiriya *et al*[3], the proportion of patients without drainage in our study may be different from the group studied by Kiriya *et al*[3]. Since then, few researchers have tried to examine

the possibility of improving the prognosis of Grade III AC patients by undergoing biliary drainage more immediately [6,8]. Unfortunately, consistent with our results, there was no evidence that earlier decompression (within 12 h) benefited these severe patients.

Another multicenter retrospective net cohort study reported a novel finding in which delayed biliary decompression (> 12 h) was significantly associated with increased mortality in AC patients combined with septic shock [OR 3.40 (1.12-10.31)] [7]. These results suggest that it may be necessary to approach each organ's failure separately and that different types of organ dysfunction should be considered when determining the optimal drainage timing. This was verified by our multivariable analysis which showed that neurological, respiratory, renal, and cardiovascular dysfunction were significantly associated with IHM (OR = 5.32, 2.541, 6.356, 4.021, respectively), whereas hepatic and hematological dysfunction did not influence IHM. In addition to indicators affecting mortality recommended in TG18, we also analyzed CCI, malignancy, and lactate levels, which were previously reported to have an impact on the death rate [5,7,18]. Multivariate regression analysis showed that, in addition to organ dysfunction, hypoproteinemia and malignant obstruction significantly increased IHM. These outcomes were similar to those reported in a previous review [3].

In this study, we first attempted to stratify Grade III AC patients according to organ dysfunction to identify patients whose prognosis could most likely be improved by earlier decompression. According to our clinical experience, neurological dysfunction was the most severe complication and might affect drainage operation; therefore, AC patients with altered mental status require immediate biliary decompression. This was verified by our data that only undergoing drainage within 12 h could greatly improve IHM in this subgroup of individuals (0% *vs* 17.3%, $P = 0.041$). For AC patients with renal dysfunction, performing drainage within 24 h could decrease the IHM. As a result, the renal injury was not only caused by infection but also induced by hypovolemia, which was provoked by fever, decreased appetite, early initiation of antibiotics, and aggressive fluid resuscitation to improve renal flow were more valuable for these patients. Unlike previous studies [7], we did not observe an association between drainage and IHM in AC patients with cardiovascular dysfunction. This may be because only 39 patients were included in this subgroup. Drainage within 12 h significantly reduced mortality in AC patients with increased lactate levels (≥ 2 mmol/L), suggesting that decompression within 12 h might be beneficial for patients with cardiovascular dysfunction. Performing drainage within 48 h greatly reduced mortality in AC patients with hepatic dysfunction, because the amelioration of biliary stasis after drainage could directly rescue hepatic function and diminish inflammatory reaction, even if no significant association between hepatic injury and IHM was observed.

The influence of abnormal WBC count and hyperbilirubinemia on outcomes in AC has been previously described [9]. The underlying pathophysiologic mechanisms are known to result from sepsis; therefore, abnormal WBC count and hyperbilirubinemia are linked with an increased likelihood of poor prognosis. Hypoalbuminemia refers to malnutrition, which is linked to life-threatening infections and poor outcomes. For individuals in these subgroups, undergoing drainage within 24 h indicated a lower IHM.

Decompression within 12, 24, or 48 h in Grade III AC patients would extend the LOS, which was contrary to the findings of Aboelsoud *et al* [19] who demonstrated that drainage within 24 h or 48 h could decrease the LOS, compared with drainage after 24 h or 48 h (drainage within 24 h *vs* after 24 h: mean 7.71 *vs* 13.57 d, $P = 0.001$; drainage within 48 h *vs* after 48 h: mean 8.61 *vs* 14.24 d, $P = 0.002$). This was because their study only reviewed patients who underwent drainage, whereas our study included both patients who underwent drainage and those who did not. In addition, most of the Grade II and Grade III patients in this study received only endoscopic nasobiliary drainage or endoscopic retrograde biliary drainage treatment at the first ERCP intervention because of their serious condition, and 52.2% of them received a second endoscopic intervention for biliary stone removal or stent placement when their condition stabilized, thus increasing the LOS. Drainage within 12, 24, or 48 h was associated with increased hospital costs despite the severity of AC since endoscopic operation itself was expensive, and the delayed-drainage group contained non-drainage ones who spent little.

Limits of study

Our analysis had certain limitations. First, it was retrospective in design, and as such, was susceptible to record bias and incomplete data. Second, because it is a single-center study, the study results only reflect the clinical status of our center and cannot represent the situation of all hospitals. Third, due to the limited sample size, especially the limited number of patients with cardiovascular dysfunction who underwent drainage within 48 h, some results were not statistically significant. In addition, the time from onset to initial treatment and the antibiotics and fluid resuscitation before admission to our hospital were not evaluated, which may have an impact on the outcome. A prospective multicenter study will be conducted to further explore a precise stratified model to guide drainage timing rather than TG18.

CONCLUSION

To our knowledge, this is the first study to stratify patients with Grade III AC according to different organ dysfunctions and to recommend the optimal timing of biliary drainage accordingly. Biliary decompression significantly decreases the all-cause IHM rates in AC, and early biliary drainage (< 24 h) was shown to be beneficial for AC patients with Grade III severity. Severe cases with different organ dysfunctions have distinct prognoses, and cases complicated with either neurological or cardiovascular dysfunction should undergo drainage within 12 h of admission. For patients with mild or moderate cholangitis, early drainage increases the probability of a second treatment and increases the patients' injury, hospitalization cost, and LOS. A further multicenter prospective cohort study will be conducted to verify the result and investigate whether the optimal timing of drainage based on different organ dysfunctions can increase the 30-d mortality rates and decrease the readmission rate.

ARTICLE HIGHLIGHTS

Research background

Acute cholangitis (AC) is a life-threatening condition that occurs in the presence of biliary obstruction. Biliary decompression is well known to greatly decrease the risks of mortality in AC. Although early biliary drainage is recommended by the treatment guidelines for AC, the exact timeframe is yet to be established.

Research motivation

We have observed that the clinical outcomes of severe AC patients vary dramatically. So, we first attempted to study whether AC patients with different organ dysfunction should undergo biliary drainage at distinct times and try to screen out patients that could benefit the most from earlier drainage.

Research objectives

To investigate the optimal drainage timing for AC patients with each disease severity grade and organ dysfunction.

Research methods

In this retrospective monocenter cohort analysis, we reviewed 1305 patients who were diagnosed with AC according to the Tokyo guidelines 2018 at a Chinese tertiary hospital for four years. We investigated the all-cause in-hospital mortality (IHM), hospital length of stay (LOS), and hospitalization costs associated with the timing of biliary drainage according to the severity grading and different dysfunctioning organs and critical predictors [age, white blood cell (WBC) count, total bilirubin, albumin, lactate, malignant obstruction, and Charlton comorbidity index (CCI)].

Research results

Biliary drainage within 24 h in Grade III AC patients had the greatest benefit, which could significantly reduce the all-cause IHM, while increasing LOS and hospitalization costs. Multivariate logistic analysis revealed that neurological, respiratory, renal, and cardiovascular dysfunctions, hypoalbuminemia, and malignant obstruction were significantly associated with IHM. Furthermore, AC patients complicated with neurological dysfunction or with serum lactate > 2 mmol/L should be drained as early as possible (< 12 h) for it could significantly decrease the IHM. In the subgroup of AC patients with renal dysfunction, abnormal WBC count, hyperbilirubinemia, or hypoalbuminemia, drainage within 24 h reduced the IHM, while in the subgroup of AC patients with hepatic dysfunction, malignant obstruction, or a CCI > 3, biliary drainage should be performed within 48 h.

Research conclusions

Biliary drainage within 12 h is beneficial for AC patients with neurological or cardiovascular dysfunction, while complete biliary decompression within 24 h of admission is recommended for treating patients with Grade III AC.

Research perspectives

A further multicenter prospective cohort study will be conducted to verify the result and investigate whether the optimal timing of drainage based on different organ dysfunctions can increase the 30-d mortality rates and decrease the readmission rate.

FOOTNOTES

Author contributions: Li CS designed the research study and made critical revisions to the article; Lu ZQ, Zhang HY, Xing YY, Su CF, and Wang GX performed the research and analyzed the data; Lu ZQ drafted the article; all authors have read and approved the final manuscript.

Institutional review board statement: This retrospective cohort study was conducted according to the tenets of the Declaration of Helsinki, and approved by the Bioethics Committee of Beijing Friendship Hospital, Capital Medical University (Certification No. 2020-P2-224-01).

Informed consent statement: Since we conducted a retrospective review of patient data obtained from the electronic medical records of our hospital, and as stated by the ethical standards of China, the Ethics Committee exempted the need for obtaining informed consent.

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Country/Territory of origin: China

ORCID number: Zhao-Qing Lu 0000-0001-8895-1596; Han-Yu Zhang 0000-0001-5181-4619; Chen-Fen Su 0000-0002-7882-6975; Yue-Yan Xing 0000-0002-6162-3098; Guo-Xing Wang 0000-0003-1379-5749; Chun-Sheng Li 0000-0002-3161-4457.

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