Impact of endoscopic retrograde cholangiopancreatography (ERCP) timing on clinical outcomes in acute cholangitis associated with common bile duct stones

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Summary

Objective: To evaluate the association between the timing of ERCP and clinical outcomes in patients with acute cholangitis (AC) of varying severities caused by common bile duct (CBD) stones patients. *Subject and method:* 227 acute cholangitis patients caused by CBD stones who underwent ERCP at the Department of Emergency Gastroenterology, 108 Military Central Hospital from February 2021 to April 2024 were retrospectively identified. Efficacy was compared between early ERCP (≤ 24 hours) and delayed ERCP (> 24hours) group concerning clinical characteristics, length of hospital stays (LOHS), and mortality rate. *Result:* The patient cohort was stratified by severity: 43.6% Grade III AC, 39.2% Grade II, and 17.2% Grade I. ERCP ≤ 24h was performed in 44.1% of cases. The early ERCP group exhibited significantly lower platelet counts and prothrombin levels, and higher INR compared to the delayed group. LOHS was significantly longest in the severe AC group (8.28 ± 6.30 days) compared to the moderate and mild groups (p=0.017), demonstrating direct proportionality to disease severity. Furthermore, the complete stone removal rate was significantly lower in the severe AC group (34.3%) compared to Grade I (71.0%) and Grade II (60.6%) groups (p<0.001). Crucially, early ERCP significantly reduced the median LOHS compared to the delayed group 5 days vs. 7 days, (p=0.003), although the difference in overall mortality rate (4.0% vs. 3.15%) was not statistically significant (p>0.05). *Conclusion:* Severe acute cholangitis is directly proportional to the LOHS and increases the risk of mortality. Early ERCP demonstrated a significant reduction in the progression of organ failure and shortened the LOHS, with no statistically significant change in mortality.

Keywords: Acute cholangitis, Common bile duct stones, ERCP.

I. BACKGROUND

Acute cholangitis due to common bile duct stones may progress to septicemia and organ failure resulting in mortality without treatment. ERCP has been accepted as a first-line treatment for AC. According Tokyo Guidelines 2018 (TG18)[1] moderate and severe AC should be treated with early or urgent biliary drainage, although early biliary drainage does not prevent complications from ERCP but avoiding persistent organ failure or septic shock. Despite consensus on the need for biliary drainage, the timing of ERCP is controversial. Numerous studies have shown that emergency ERCP intervention should be performed in high-risk patients including elderly patients, initial intensive care unit, severe cholangitis, patients with a prolonged international normalized ratio (INR) and thrombocytopenia. Delaying ERCP is associated with risk of progressive organ failure, prolonged hospital stays, mortality and an increased financial burden[1,2,3].

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Therefore, this study aims to identify whether the timing of ERCP is associated with improved outcomes in AC due to CBD stones patients. .

II. SUBJECT AND METHODS

2.1. Subject

227 acute cholangitis due to CBD stones were diagnosed and underwent ERCP at the Department of Emergency Gastroenterology, 108 Military Central Hospital from February 2021 to April 2024.

Inclusion criteria:

AC due to CBD stones based on the 2018 Tokyo Guidelines[1].

Exclusion criteria:

Obstructive biliary malignancy.

Failed ERCP intervention.

2.2. Methods

Patient demographics, clinical symptoms and data laboratory were collected through retrospective review of medical records. The severity of AC and the timing of ERCP intervention was recorded. outcomes were hospital stays and mortality rates.

Patient demographics:

Age, gender, body temperature and comorbidities. Comorbidities included diabetes mellitus, hypertension, stroke, heart failure disease, obstructive pulmonary and disease multiple underlying diseases at the same time.

White blood cell (WBC) count, Platelet count, Alanine aminotransferase (ALT); Aspartate aminotransferase (AST); bilirubin total, Prothrombin time (PT), international normalized ratio (INR), creatinine, albumin. The diagnostic criteria for AC were based on the 2018 Tokyo Guidelines[1] including systemic inflammation, cholestasis and imaging findings. Systemic inflammation included fever and/or shaking chills or evidence of an inflammatory response. Cholestasis included jaundice or abnormal liver function tests. Imaging findings included bile duct dilatation and imaging stones.

AC severity was divided into three grades based on the 2018 Tokyo Guidelines (1): Grade III (severe) AC is defined as AC that is associated with the onset of dysfunction at least in any one of the following organs/systems: neurological, cardiovascular, respiratory, renal, hepatic and hematological dysfunction. Grade II (moderate) AC is associated with any two of the following conditions: Abnormal WBC count >12,000/mm^3 or < 4,000/mm^3; High fever ≥ 39°C; Age ≥75 years; total bilirubin ≥ 5mg/dL, albumin < 24.5g/L. Grade I (mild) AC does not meet the criteria of "Grade III or "Grade II" AC at initial diagnosis.

ERCP intervention: Stent insertion and stone retrieval. The timing of ERCP was defined as the interval between the patient's arrival at the emergency department and the initiation of the procedure. Patients were subsequently stratified into two groups based on this interval: Early ERCP (≤ 24h) and Delayed ERCP(> 24h).

Outcome assessments: clinical symptoms, data lab, complication, length of hospital stays, mortality.

Statical analysis: SPSS software (version 25.0).

III. RESULT

A total 227 AC due to CBD stones patients who fulfilled the eligibility criteria were included in the study.

The baseline characteristics of the patients are presented in (Table 1): The median age (IQR) age was 74 years (22-96); Males comprised 48.9% of the cohort; The median body temperature was 37.8°C (37.0 - 38.5°C) and 64.8% exhibited an abnormal White Blood Cell (WBC) count; The median serum levels for AST and ALT were 98U/L and 107.7U/L, respectively. The median serum bilirubin level was 72.1µmol/L (37.8-118), the median serum creatine level was 76µmol/L (58.7-106.7) and the median serum albumin was 30g/dL (27-35).

Table 1. Characteristics of patients

Patient characteristics	Total n (%)	Time to ERCP divided by 24 h		P value
		ERCP ≤ 24h n (%)	ERCP > 24h n (%)	
	227	100 (44.1)	127(55.9)	
Age in year	74 (22-96)	74 (62-82)	73 (62-82)	0.896
Male sex	111 (48.9)	48 (48)	63 (50)	0.810
Body temperature in °C	37.8 (37.0-38.5)	37.8 (37.0-38.5)	37.8 (36.9-38.5)	0.316
Abnormal WBC count, n (%)	147 (64.8)	86 (86)	61 (48)	0.051
Platelet count as /µL	166 (111- 270)	138 (68-228)	207 (131-296)	<0.001
AST in U/L	98.0 (530-234.5)	104.5 (51.2-226.7)	94.3 (53.1-247.4)	0.738
ALT in U/L	107.7 (54.6-231.7)	109.5 (61.9-247.7)	104.1 (51.1-218.4)	0.278
Bilirubin in µmol/L	72.1 (37.8-118.0)	87.1 (42.4-119.0)	67.3 (31.8-117.6)	0.212
Prothrombin	81.8 (67.2-97.2)	77 (58-90)	87 (73-103)	<0.001
INR	1.00 (0.99- 1.19)	1.19 (1.07-1.43)	1.09 (0.99-1.20)	<0.001
Creatinine in µmol/L	76.0 (58.7-106.7)	80 (63-114)	75 (57-100)	0.052
Albumin in g/dL	30 (27-35)	30 (28-35)	31 (26-35)	0.780
Cardiovascular dysfunction, n (%)	33 (14.5)	22 (22)	11 (8.7)	0.005
Neurological disturbance, n (%)	11 (4.8)	8 (8)	3 (2.4)	<0.001
Respiratory dysfunction, n(%)	72 (31.7)	43 (43)	29 (22.8)	0.01

Comparisons between early ERCP and delayed ERCP groups (Table 1): The ERCP ≤ 24h group demonstrated several statistically significant differences when compared to the ERCP > 24h group: Platelet count was significantly lower in the early group (median, 138x10^3/ µL *vs* 207x 10^3/ µL. *p*-0.001) and prothrombin (median, 77% *vs.* 87%; p-0.001); significantly higher INR (1.19 vs. 1.09; p-0.001); significantly higher proportions of cardiovascular dysfunction (22% *vs.* 8.7%; *P*-0.005), neurological disturbance (8% *vs* 2.4%. p-0.001) and respiratory dysfunction (43% *vs* 22.8%. p=0.01).

Table 2. The relationship between AC severity, intervention procedures and hospital length of stays

	Grade I AC	Grade II AC	Grade III AC	P value
Number of patients	**39**	**89**	**99**	
Treatment during ERCP, n(%)				
Stent	7 (6.6)	35 (33.0)	64 (60.4)	<0.001
Stone retrieval	32 (26.4)	54 (44.6)	35 (29.0)	
Death, n (%)	0	2 (2.2)	6(6.1)	**0.15**
Mean time of hospital stay (Mean ± SD)	5.64 ± 2.39	6.65 ± 3.77	8.28 ± 6.30	**0.017**

There were 99 (43.6%) grade III AC patients, 89 grade II AC patients (39.2%) and 39 (17.2%) grade I AC patients (Table 2). In therapeutic ERCP: Biliary stent placement was performed in 60.4% severe AC patients, while 71% of patients with mild to moderate cholangitis underwent complete stone removal, with a statistically significant difference, p< 0.001. Comparison of mortality rate: The grade III AC group (6.1%) was higher than the grade I and II AC groups (2.2%), but the difference was not statistically significant (p=0.15). Comparison of LOHS: The grade 3 AC had the longest (8.28 ± 6.30 days), followed by grade II AC (6.65 ± 3.77 days), and grade 1 grade I AC (5.64 ± 2.39 days), the difference was statistically significant, p=0.017.

The characteristics of ERCP (Table 3): Patients with Grade III AC was 43.6%, ERCP ≤ 24h was performed 57.6%, 65.7% stent placement, the mortality rate was 6.1%, the median LOHS was 7 days (5-11). Comparisons between early and delayed ERCP groups revealed significant differences in LOHS, but not in mortality among severe AC cases. The early ERCP group demonstrated a significantly shorter median LOHS compared to the delayed group (6 days *vs.* 8 days; p-0.009); Mortality in Grade III AC: the mortality rate was higher in the delayed ERCP (4 patients, 66.7%) compared to the early ERCP group (2 patients, 33.3%). However, the difference did not achieve statistical significance (p-0.493).

Patients with Grade II AC was 39.2%, ERCP ≤ 24h was performed 37.1%. Compared with ERCP > 24h, ERCP ≤ 24h had lower median LOHS (5 vs 6 days. p-0.102) and lower death of patients (0 vs 2; p-0.528), the difference did not reach statistical significance.

Patients with grade I AC was 17.2%; only 25.6% patients were performed ERCP ≤ 24h. the stone retrieval was74.4% which had higher than stent placement. Compared with ERCP>24h, ERCP ≤ 24 h had significance lower the median LOHS in ERCP the ERCP >24 h (4 *vs* 6 days; p-0.003).

Table 3. Outcomes of ERCP

Outcome	Total, n (%) n= 227	Time to ERCP divided by 24 h		P value
		ERCP≤24h, (n = 100)	ERCP>24h, (n = 127)	
Grade III AC	99 (43.6)	57 (57.6)	42 (42.4)	
Treatment during ERCP, n (%)				0.624
Stent	65 (65.7)	38 (59)	26 (41)	
Stone retrieval	34 (34.3)	19 (54)	16 (46)	
Length of hospital stay	7 (5-11)	6 (4-8)	8 (6-12)	0.009
Death, n (%)	6 (6.1)	4 (66.7)	2 (33.3)	0.493
Grade II AC	89 (39.2)	33 (37.1)	56 (62.9)	
Treatment during ERCP, n (%)				0.992
Stent	34 (38.2)	13 (37)	22 (63)	
Stone retrieval	55 (61.8)	20 (37)	34 (63)	
Length of hospital stay	6 (4-8)	5 (4-7)	6 (5-8)	0.102
Death, n (%)	2 (2.2)	0	2 (100)	0.528
Grade I AC	39 (17.2)	10 (25.6)	29 (74.4)	
Treatment during ERCP, n (%)				0.845
Stent	7 (25.6)	2 (29)	5 (71)	
Stone retrieval	32 (74.4)	8 (25)	24 (75)	

Outcome	Total, n (%) n= 227	Time to ERCP divided by 24 h		P value
		ERCP≤24h, (n = 100)	ERCP>24h, (n = 127)	
Length of hospital stay	6(3-7)	4(3-5)	6(5-8)	0.003
Death, n (%)	0	-	-	-
Hospitalize time	5(5-9)	5 (4-8)	7 (5-9)	0.003
Death, n (%)	8	4 (4)	4(3.15)	0.493

Compared with ERCP > 24h, ERCP ≤ 24 h had significance lower median LOHS (5 *vs* 7 days; p-0.003) Hower, there was no statistical significance in mortality rates between early and delayed ERCP group (4% vs 3.15%; p-0.493).

IV. DISCUSSION

Acute Cholangitis constitutes a significant gastrointestinal emergency that necessitates timely management. The optimal timing for biliary intervention is contingent upon the severity of clinical symptoms and the progression of the disease. Previous studies[3,4] showed that failure or delay ERCP after 48 hours was increased the risk of prolonged vasopressor use, the persistent organ failure and the long of hospital stays. In our study, we found that platelet count, prothrombin time, INR, cardiovascular dysfunction, respiratory dysfunction and neurological disturbance were the determinants that require us to intervene with urgent or early ERCP. Comparisons between early and delayed ERCP groups (Table 1): Compared with ERCP > 24h, ERCP ≤ 24 h had significantly lower platelet count (median, 138x103/ µL *vs* 207x 10^3/ µL; p - 0.001) and prothrombin (median, 77% *vs* 87%; p - 0.001); significantly higher INR (1.19 *vs* 1.09; p-0.001); significantly higher proportions of cardiovascular dysfunction (22% *vs* 8.7%; *P*-0.005), neurological disturbance (8% vs 2.4%. p<0.001) and respiratory dysfunction (43% *vs* 22.8%; p-0.01).

In 2012, Khashab et al[5] reported that failure or delay ERCP after 72 hours was associated with the long of hospital stay in intensive care and the burden of medical cost. In a meta-analysis published in 2020, Du et al[6] reported that urgent or early ERCP reduced in-hospital mortality regardless of whether it was defined as < 24h, < 48h or < 72h. Kiriyama et al[1] reported that AC due to CBD stones patients should undergo emergency or early intervention within 24 hours to reduce the rate of organ failure complications, shorten hospital stays, and decrease 30-day mortality[1,2,7,8]. In the present study, we found that the median LOHS for the ERCP ≤ 24h group was 5 days, which had lower significance than ERCP > 24h group with p=0.003. A comparison of the overall mortality rate between the early and delayed ERCP groups revealed no statistically significant difference (p-0.493). Although the early ERCP group exhibited a numerically higher mortality rate (4.0%) compared to the delayed group (3.15%), this difference was not statistically.

According to the TG18 guidelines[1], moderate and severe acute cholangitis indicates biliary drainage for decompression and broad-spectrum antibiotics. The American Society for Gastrointestinal Endoscopy guidelines 2021[7] recommend ERCP within 48 hours in acute cholangitis patients, but these guidelines specify that for grade III AC, it improves treatment effectiveness and shortens the LOHS. In our study, depending on the severity of cholangitis, the level of difficult and the risk of complications ERCP intervention, we selected biliary stent placement or complete stone removal methods. Results in (Table 2) showed that Grade III AC, grade II AC and grade I AC were 43.6%, 39.2% and 17.2%, respectively. Stent placement in the severe AC group was 60.4 %, which was higher compared to the moderate and mild cholangitis groups, at 33% and 6.6%, respectively. In contrast, the complete stone removal rate showed

an inverse relationship with disease severity. As detailed in Table 3, the complete stone removal rates were significantly higher in the Grade I and Grade II cholangitis groups (74.4% and 61.8%, respectively) compared to the severe cholangitis group (34.3%), a difference that was statistically significant ($p<0.001$. Zhu et al. (10, 11) reported that while stent placement in severe AC patients (70.8%) helped to control the acute phase and reduce mortality, the hospital stay in this severe group remained the longest compared to those with mild and moderate cholangitis. Consistently, our study demonstrated that the median LOHS was longest in the Grade III AC and directly proportional to the severity of cholangitis, with a statistically significant difference of $p= 0.017$. This reinforces the notion that disease severity is a major determinant of post-procedure recovery time, even with successful intervention.

V. CONCLUSION

Severe AC associated with CBD stones is directly correlated with prolonged Length of Hospital Stay and increased mortality rate. The implementation of early ERCP significantly reduces the median LOHS and mitigates progressive organ dysfunction, though a statistically significant difference in overall mortality was not observed. Early ERCP should be established for patients with AC, regardless of initial severity.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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