

Effect of Delayed Endoscopic Retrograde Cholangiopancreatography after Diagnosis of Acute Cholangitis; A Real-life Experience

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ABSTRACT

Objective: Acute cholangitis is a potentially life-threatening condition. Its main treatments include antibiotics and biliary drainage, but longer waiting times for endoscopic biliary drainage may be unavoidable in some limited-resource settings.

Materials and Methods: All patients who presented with cholangitis and received ERCP during the 3-year study period were included. The associations between waiting time from the diagnosis of acute cholangitis to the endoscopic drainage and the clinical outcomes, including 30-day all-course mortality and 30-day rehospitalization rates, were compared in patients who received ERCP within 24 hours, 48 hours, 72 hours, 7 days, and later than 7 days.

Results: Overall, 300 patients were included. The 30-day all-course mortality rate was 5%, with 9% overall rehospitalization rate, and median waiting time for ERCP of 5 days (1 -50 days). There was no significant difference between 30-day mortality rates in patients who received ERCP within 24 hours, 48 hours, 72 hours and over 7 days ($p > 0.05$). The mortality rate was significantly higher in those with severe cholangitis and with pancreatobiliary malignancy ($p < 0.05$).

Conclusion: In real life situation when resources are limited, delayed ERCP did not increased the 30-day mortality rate in patients with cholangitis.

Keywords: Cholangitis; ERCP (Siriraj Med J 2024; 76: 209-215)

INTRODUCTION

Acute cholangitis is a common emergency condition in clinical practice, and it carries a high rate of morbidity and mortality if not properly treated. According to the Tokyo Guidelines (2018), patients who present with cholangitis should be classified into 3 levels of severity: mild, moderate, and severe.¹ Antibiotics and supportive care are recommended for all patients, but those with mild cases of the disease do not always require biliary drainage. On the other hand, patients with moderate forms of the

disease require early drainage, and severe cases need it urgently.² Unfortunately, some types of biliary drainage, such as endoscopic retrograde cholangiopancreatography (ERCP), require special expertise and equipment which are not available in every hospital in Thailand; in most of these cases, after initial treatment, patients are referred to a center in which the procedure is available, resulting in a delay in performance of the procedure. Several studies have recommended conducting ERCP within 24 hours of diagnosis of cholangitis^{3,4}, but others have

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shown no survival benefits of early endoscopic drainage.⁵ As a result, we conducted a retrospective study of the clinical impact of the timing of ERCP in patients with acute cholangitis and its clinical outcomes in settings with limited resources.

MATERIALS AND METHODS

We retrospectively reviewed all patients who were diagnosed with acute cholangitis and received ERCP in our institute between May 2018 and April 2021. Those with incomplete clinical information were excluded. Baseline characteristics, severity of cholangitis, etiology of biliary obstruction, and timing of ERCP after the diagnosis of cholangitis were analyzed. The waiting time in all patients were counted from the first presentation of acute cholangitis to the time of ERCP. The patients were classified in accordance with the physical status classification of the American Society of Anesthesiologists (ASA). The clinical outcomes, including 30-day mortality, 30-day rehospitalization rate, and length of hospital stay (LOS) were investigated. Unfortunately, information relating to length of hospital stay was missing for some patients who were referred from other hospitals specifically for ERCP. The study protocol was approved by local ethics committee.

Statistics or analysis or statistical analyses

The statistical software SPSS version 22.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses. All tests were two-tailed and $p < 0.05$ was considered significant. Descriptive analysis was presented as median (IQR), and categorical data, such as the correlation between timing of ERCP and 30-day mortality and rehospitalization, were analyzed using Chi-square test. Comparison of continuous data, such as LOS, was performed using Man-Whitney U- test. The univariate and multivariate analysis were calculated using logistic regression analysis.

RESULTS

After exclusion of those with incomplete data, a total of 300 patients were included and analyzed, and their baseline characteristics are shown in Table 1. The mean age was 61 years old, with equal proportions of females and males. The majority of the patients (58.3%) had comorbid diseases, with hypertension, diabetes mellitus and dyslipidemia being the three most common. All patients presented with clinical acute cholangitis and were diagnosed with cholangitis at the time of presentation and received standard care for acute cholangitis, such as intravenous antibiotics, intravenous fluid, and other supportive management.

TABLE 1. Baseline characteristics of the patients included in the study.

Characteristics	Total (n=300)	
	n	%
Sex		
Male	150	50.0%
Female	150	50.0%
Age (years) Mean±SD.	61.36 ±18.08	
<40	42	14.0%
40-49	38	12.7%
50-59	44	14.7%
60-69	63	21.0%
70-79	60	20.0%
≥80	53	17.7%
Comorbid Disease		
No	125	41.7%
Yes	175	58.3%
Hypertension	127	42.3%
Diabetes	90	30.0%
Dyslipidemia	31	10.3%
Coronary artery disease	12	4.0%
Chronic kidney disease	8	2.7%
Cerebrovascular disease	7	2.3%
Thalassemia	8	2.7%
Malignancy	6	2.0%
Other	26	8.7%
ASA score		
1	137	45.7%
2	124	41.3%
3	39	13.0%

Abbreviation: ASA = American Society of Anesthesiologists (ASA) physical status classification

The majority (58%) of the patients had mild cholangitis triggered by common bile duct stones (59.7%). The most common cause of malignant biliary obstruction was cholangiocarcinoma, followed by ampullary cancer. The mean interval for ERCP after the diagnosis of acute cholangitis was 8 days. Most of the patients were admitted with sepsis, and 7% developed septic shock. The incidence of 30-day mortality was 5%, mean length of hospital stay was 6 days, and the readmission rate was 9% (Table 2).

TABLE 2. Acute cholangitis presentation and complications according to each level of severity (n = 300).

	Total	Mild (%)	Moderate (%)	Severe (%)
Severity	300	174 (58.0%)	103 (34.3%)	23 (7.7%)
Malignant Obstruction				
No	238 (79.3%)	154	69	15
CBD stone	179 (59.7%)	117	51	11
Strictures	59 (19.7%)	37	18	4
Yes	62 (19.7%)	20	34	8
Cholangiocarcinoma	25 (8.3%)	6	14	5
Ampulla	20 (6.7%)	11	8	1
Pancreas	14 (4.7%)	2	10	2
Gallbladder	3 (1.0%)	1	2	0
Time to ERCP (days)				
Median (IQR)	5.0 (3-10)	7 (1 -50)	4 (1-47)	2 (1-22)
< 24 hours	33	16	11	6
24 -48 hours	39	14	16	9
48-72 hours	40	19	18	3
72 hours to 7days	83	43	37	3
> 7 days	105	82	21	2
Hospital Course				
Sepsis	199 (66.3%)	102	94	3
Septic shock	21 (7.0%)	1†	1	19
Respiratory failure	13 (4.3%)	1	1	11
Acute kidney injury	4 (1.3%)	0	0	4
DIC	2 (0.7%)	0	0	2
30-Day Mortality	15 (5.0%)	3 (1.7%)	5 (4.9%)	7 (30.4%)
Length of stay (Median±IQR)	5.0 (2-7)	4.0 (2-6.5)	6.0 (5-8)	10.0 (6-17)
Rehospitalization	27 (9.0%)	10	15	2

Abbreviations: IQR = interquartile range, SD = standard deviation, DIC = dissemination intravascular coagulation

†sepsis occurred as a consequence of hospital-acquired infection

Length of hospital stay was shorter than the waiting time from onset of cholangitis to ERCP, since most patients were diagnosed in other institutes and then referred to our hospital. Mortality occurred in 15 cases, a rate of 5%.

Table 3 shows the number of cases of 30-day mortality by each severity level and waiting time. There was significant correlation between the waiting time and 30-day mortality in patients with mild cholangitis ($P = 0.05$) but no significant difference mortality in overall severity was observed. Regarding other factors that relate to the mortality, the incidence of 30-day

mortality was significantly associated with the severity of cholangitis and the presence of malignant obstruction (p -value <0.05) but showed no significant correlation with age, ASA status, or total bilirubin, with p -values of 0.99, 0.7 and 0.2, respectively. There were 3 cases of mortality after mild cholangitis, and the causes of death were progression of underlying pancreatobiliary malignancy in 2 patients, and hospital-acquired infection after the treatment of acute cholangitis in one case. Table 4 showed the mortality rate when patients received ERCP according to each cut-off point. Overall, performance of ERCP within 7 days showed a difference in overall lower

TABLE 3. Association between 30-day mortality and waiting time for ERCP according to cholangitis severity.

Severity of cholangitis	Timing					P value
	< 24 hours	24 to 48 hours	48 to 72 hours	72 hours to 7 days	>7 days	
Mild (N = 174)	0	0	0	3	0	0.05
Moderate (N = 103)	0	0	1	2	2	0.66
Severe (N = 23)	2	2	1	2	0	0.55
Total (N = 300)	2	2	2	7	2	0.37

TABLE 4. Associations between 30-day mortality, rehospitalization rate, and waiting time for ERCP according to cholangitis severity at each cut-off point.

Severity of cholangitis	24 hours			48 hours			72 hours			>7 days		
	≤ 24 hours	>24 hours	P value	≤ 48 hours	>48 hours	P value	≤ 72 hours	>72 hours	P value	≤ 7 days	>7 days	P value
Mortality												
Mild	0/16 (0%)	3/158 (1.9%)	1.00	0/30 (0%)	3/144 (2.1%)	1.00	0/49 (0%)	3/125 (2.4%)	0.56	3/92 (3.3%)	0/82 (0%)	0.25
Moderate	0/11 (0%)	5/92 (5.4%)	1.00	0/27 (0%)	5/76 (6.6%)	0.32	1/45 (2.2%)	4/58 (6.9%)	0.38	3/82 (3.7%)	2/21 (9.5%)	0.27
Severe	2/6 (33.3%)	5/17 (29.4%)	1.00	4/15 (26.7%)	3/8 (37.5%)	0.66	5/18 (27.8%)	2/5 (40%)	0.60	7/21 (33.3%)	0/2 (0%)	1.00
Overall	2/33 (6.1%)	13/267 (4.9%)	0.77	4/72 (5.6%)	11/228 (4.8%)	0.80	6/112 (5.4%)	9/118 (4.8%)	0.83	13/195 (6.7%)	2/105 (1.9%)	0.07
Rehospitalization												
Mild	1/16 (6.3%)	9/158 (5.7%)	0.93	3/30 (10%)	7/144 (4.9%)	0.27	3/49 (6.1%)	7/125 (5.6%)	0.89	9/92 (9.8%)	1/82 (1.2%)	0.02
Moderate	1/11 (9.1%)	14/92 (15.2%)	0.59	2/27 (7.4%)	13/76 (17.1%)	0.22	5/45 (11.1%)	10/58 (17.2%)	0.38	13/82 (15.9%)	2/21 (9.5%)	0.46
Severe	1/6 (16.7%)	1/17 (5.9%)	0.46	1/15 (6.7%)	1/8 (12.5%)	1.00	2/18 (11.1%)	0/5 (0%)	1.00	2/21 (9.5%)	0/2 (0%)	1.00
Overall	3/33 (9.1%)	24/ 267 (9%)	0.99	6/72 (8.3%)	21/228 (9.2%)	0.82	10/112 (8.9%)	17/188 (9%)	0.97	24/195 (12.3%)	3/105 (2.9%)	0.01

mortality, but this did not reach statistical significance ($P = 0.07$). The Kaplan-Meier curve demonstrating cumulative 30-day survival according to each severity and waiting time for ERCP using 7 days at the cut-off point is demonstrated in Fig 1. Performance of ERCP within 7 days was associated with a significant difference in rehospitalization rate, especially in mild cases but with a higher rehospitalization rate in early procedure (Table 4). For all severity levels, shorter waiting times for ERCP reduced the length of hospital stay, especially for those who received ERCP early and in those with mild forms of the disease (Table 5). However, hospital stay in our center might not represent total treatment course since most cases of ERCP were performed as outpatient care and the patient were admitted after the procedure.

Considering the factors that associated with 30-day mortality, we performed the univariate and multivariate analysis (Table 6). The univariate analysis did not show clinical significance correlation between age, ASA status or the waiting time interval for ERCP but there was significant correlation with severe cholangitis and the presence of pancreatobiliary malignancy. There was marginal correlation between the waiting time when considered as a continuous data. When these parameters are calculated using multivariate analysis, there was no significant correlation between the waiting time before ERCP but still demonstrated significant correlation between the mortality rate and the presence of malignancy and severe cholangitis.

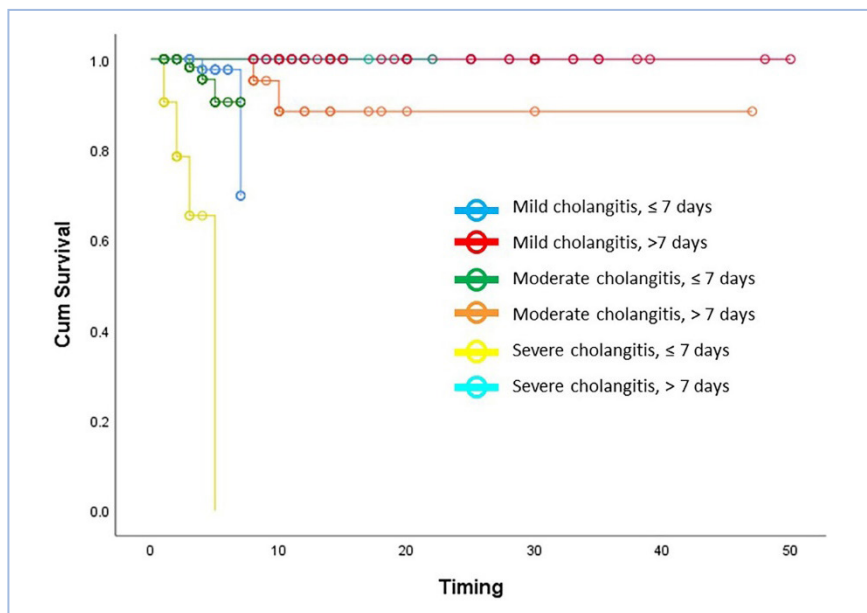


Fig 1. Kaplan-Meier curve demonstrating cumulative 30-day survival according to each severity and waiting time for ERCP using 7 days at the cut-off point.

TABLE 5. Associations between length of stay (data presented as median (IQR)) and waiting time for ERCP according to cholangitis severity.

Severity of cholangitis	Timing					Total	P value
	< 24 hours	24 to 48 hours	48 to 72 hours	72 hours to 7 days	>7 days		
Mild (N = 174)	6.00 (3.00-7.75)	5 (3.00-6.00)	5 (4.00-9.00)	6.00 (4.00-7.00)	2 (2.00-3.25)	4.00 (2.00-6.25)	< 0.05
Moderate (N = 103)	5.00 (5.00-6.00)	5.00 (5.00-7.00)	6.00 (5.75-8.25)	6.00 (5.00-7.50)	8.00 (4.50-12.50)	6.00 (5.00-8.00)	0.09
Severe (N = 23)	12.00 (6.75-24.00)	10.00 (4.50 -19.50)	6.00 (5.00-6.00)	9.00 (3.00-9.00)	6.00 (2.00-6.00)	10.00 (6.00-17.00)	0.39
Total (N = 300)	6.00 (4.50-7.50)	5.00 (4.00-8.00)	6.00 (4.00-8.75)	6.00 (4.00-8.00)	2.00 (2.00-7.00)	5.00 (2.00-7.00)	< 0.05

TABLE 6. Univariate and multivariate analysis predicting 30-day mortality.

Factors	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value
Age	1.03 (0.99-1.06)	0.137	-	
ASA score			-	
1	1			
2	1.11 (0.349 – 3.54)	0.860		
3	1.82 (0.43 – 7.63)	0.413		
Presence of Malignant obstruction	8.76 (2.87-26.68)	< 0.001	8.61 (2.43-30.52)	0.001
Severity				
Mild	1		1	
Moderate	2.91 (0.68-12.43)	0.150	1.34 (0.29-6.19)	0.707
Severe	24.94 (5.87 – 105.92)	< 0.001	14.47 (3.10 – 67.55)	0.001
Timing	0.91 (0.81 – 1.02)	0.099	0.93 (0.815 -1.05)	0.225
Time interval	0.85 (0.59- 1.23)	0.395	-	-

DISCUSSION

Acute biliary infection, particularly acute cholangitis, can cause rapid deterioration in a patient's condition, and it warrants prompt and proper treatment. In addition to appropriate administration of antibiotics, timely biliary drainage via endoscopic transpapillary biliary drainage is also important.

There have been several studies of the differences in outcomes achieved after different lengths of waiting times for performance of ERCP following the onset of cholangitis, and their results have varied. An older nationwide study of clinical outcomes of patients with cholangitis who were admitted during weekdays or at weekends and received delayed ERCP showed no differences in length of stay, mortality, or total cost of hospitalization⁶, underlining the importance of supportive treatment. More recently, another large nationwide retrospective study conducted in the USA found that performing ERCP within 48 hours lowered in-hospital mortality, 30-day mortality, and readmission rates for all levels of severity.⁷ On the other hand, research in Japan and Taiwan showed that ERCP within 48 hours after diagnosis lowered the incidence of mortality only in cases of moderate severity and did not affect mortality in mild or severe cases.¹ These data were included in a meta-analysis involving 7534 patients which demonstrated lower odds of 30-day mortality (OR,

0.39; 95% CI, 0.14-1.08) and organ failure (OR, 0.69; 95% CI, 0.33-1.46) when the patients received ERCP within 48 hours.⁸ Focusing only on severe cholangitis, two retrospective studies showed conflicting results. One study from China showed that performing ERCP later than 48 hours after diagnosis of severe acute cholangitis was associated with a longer ICU stay but not with in-hospital or 30-day mortality. In this report, performance of biliary drainage within 24 hours did not significantly reduce the mortality or shorten ICU stay.⁹ On the other hand, another retrospective study showed that biliary drainage within 12 hours was beneficial for patients with neurological or cardiovascular dysfunction, and the authors recommended complete biliary decompression within 24 hours of admission for severe acute cholangitis.¹⁰

However, ERCP, which is the method of choice for biliary drainage, requires special equipment and advanced technical skill on the part of the physician. In limited-resource situations, patients who are diagnosed with acute cholangitis need to be transferred to a center where ERCP is available; hence, the waiting time for this procedure might be different from that recommended in the treatment guidelines.

Our study investigated the effect of waiting time for ERCP in patients with cholangitis, a common occurrence in centers with limited resources. We analyzed the correlation

between waiting time and 30-day all-course mortality, length of hospital stay, and 30-day rehospitalization. Our results showed that the waiting time for ERCP did not affect 30-day mortality but shortened the length of hospital stay. Also, there was a significant difference in rehospitalization rate when ERCP was performed within 7 days but the number of those who received earlier ERCP showed a higher rehospitalization rate. Interestingly, the 30-day mortality rate in patients who received early ERCP was higher than delayed ERCP. The main reason is unknown but this might be due to the selection bias as attending physicians may decide to perform ERCP earlier in more severe cases or cases with comorbidity. Furthermore, our findings were slightly different from those of previous studies, as we had a low number of patients in the severe cholangitis group compared with those with mild or moderate forms of the disease. Considering the univariate and multivariate analysis for the factors that associated with 30-day mortality, there was no significant correlation between the waiting time for biliary drainage but significant mortality rate become high when a patient has severe cholangitis or has a pancreatobiliary malignancy. This analysis correlates with our finding that 2 out of 3 patient with mild cholangitis died from the underlying malignancy shortly after the procedure.

Our study had several limitations. Firstly, it included only those who received ERCP for biliary drainage. Patients with acute cholangitis who underwent other methods, such as percutaneous tube placement, or who died before the endoscopic procedure, were not included in the study. Secondly, the length of hospital stay in our study might not be accurate, since many patients were admitted from the primary care hospital specifically for the procedure or referred for the ERCP as an outpatient care. Thirdly, as this study is based on retrospective analysis, many missing data might be present. As our study showed many conflicting data, these findings should be confirmed in a larger study cohort.

CONCLUSION

In conclusion, in real life situation when resources are limited, delayed ERCP did not increase the 30-day mortality rate in patients with cholangitis. The 30-day mortality was higher with severe cholangitis and pancreatobiliary malignancy.

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None

Conflict of interest

None

Authors contribution

Study design: TC, Data gathering: PK, data source: TC, KL, AS, TR, Drafting the manuscript: TC, statistics: TC, Revision and comment: TC, KL, AS, TR.

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