

ORIGINAL ARTICLE

Acute Cholangitis: Does the Timing of ERCP Alter Outcomes?

Harish Patel¹, Vinaya Gaduputi², Haritha Chelimilla³, Jasbir Makker¹, Hafiz Hashmi¹, Mahesh Irigela¹, Anil Dev¹, Sridhar Chilimuri¹

¹Bronx Lebanon Hospital Center, Department of Medicine, 1650 Selwyn Ave, Suite #10C, Bronx, New York 10457

²SBH Health System, Department of Medicine, 4422 3rd Ave, Bronx, New York 10457

³Parkway Endoscopy Center, 488 East Valley Parkway, Suite 110, Escondido, CA 92025

ABSTRACT

Introduction Ascending cholangitis is a life threatening condition whose treatment includes fluid resuscitation, antibiotic therapy and definitive decompression of biliary tree. Timing of endoscopic retrograde cholangiopancreatography can be influenced by multiple factors including resuscitation period and coagulation abnormalities. This in turn can affect outcomes such as mortality and length of stay. **Methods** Patients who underwent endoscopic retrograde cholangiopancreatography for cholangitis between January 2009 and August 2012 were included in the study. Patients were grouped into one of the three study groups based on timing endoscopic retrograde cholangiopancreatography - patients who underwent endoscopic retrograde cholangiopancreatography within 24 hours, between 24 to 48 hours, and beyond 48 hours. Outcome measures of mortality and length of stay were observed in the three groups. **Results** A total 69 patients were included in the study. The mean age of the study population was 54 years (20±SD). 68% (n= 47) and 16% (n=11) of the study population were of Hispanic and African American ethnicities respectively. 68% (n=46) had grade-I severity of cholangitis, 19% (n=13) had grade-II severity and 13% (n=10) had grade-III severity. Timing of endoscopic retrograde cholangiopancreatography was as follows: within 24 hours in 33% (n=23), between 24 hours and 48 hours in 18% (n=12), and beyond 48 hours in 49% (n=34). The all cause in hospital mortality for patients with acute cholangitis include in this study was 11% (n=8). Mortality did not correlate with the timing of endoscopic retrograde cholangiopancreatography. There was difference in the lengths of hospital stay- 7 days for endoscopic retrograde cholangiopancreatography within 24 hours group, 6 days for 24 to 48 hours group and 14 days for beyond 48 hours group. **Conclusion** Therapeutic endoscopic retrograde cholangiopancreatography must be expediently pursued in all cases of acute cholangitis whenever feasible. However, we observed that timing of endoscopic retrograde cholangiopancreatography in cholangitis did not correlate with mortality but did significantly influence the length of stay.

INTRODUCTION

Ascending cholangitis is a life threatening condition that occurs in the presence of biliary obstruction. It can present with variable severity with symptoms being fever, abdominal pain and jaundice. Initial treatment includes adequate fluid resuscitation and administration of broad-spectrum antibiotics. Early stabilization followed by decompression of the biliary system is required. It has been observed that surgical management of acute cholangitis is associated with substantial morbidity and mortality [1]. On the contrary, non-surgical drainage seems to be effective in relieving the biliary obstruction. This is most

frequently achieved through Endoscopic Retrograde Cholangiopancreatography (ERCP).

Severity of acute cholangitis is based on the initial response to antibiotics and presence of organ dysfunction [2] (**Table 1**). Timing of ERCP depends on the presence of organ dysfunction, response to antibiotics and other comorbid conditions [3]. In patients presenting with acute cholangitis, ERCP could be delayed because of initial resuscitation efforts, coagulation abnormalities and other comorbid conditions [4]. In our experience, unavailability of consent accounted for delays in performing ERCP. Studies have also shown that outcomes of acute cholangitis not only depend on the time taken to decompress the biliary system but also on etiology, presence of organ dysfunction and comorbid conditions [5].

We investigated the outcomes amongst patients with cholangitis of varying degrees of severity, based on 'Door to ERCP' time. The primary objective of the study was to observe the correlation between in-hospital mortality and 'Door to ERCP time', after controlling for severity of acute cholangitis. Secondary objectives included analyzing- the factors affecting the severity of cholangitis and the correlation between length of hospital stay and 'Door to ERCP time'.

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Keywords Cholangitis; Cholangiopancreatography, Endoscopic Retrograde
Abbreviations ERCP Endoscopic Retrograde Cholangiopancreatography
Correspondence Vinaya Gaduputi
SBH Health System
Department of Medicine
4422 3rd Ave
Bronx, New York 10457
Phone + 718-960-3730
E-mail VGADUPUTI@sbnhy.org

Table 1. Characteristics including demographic variables, etiologies, comorbid medical conditions, 'Door to ERCP times' and ERCP findings in patients stratified by varying severity of cholangitis.

	Severity of Acute Cholangitis			
	Grade - I (N = 46)	Grade - II (N = 13)	Grade - III (N = 10)	
Total Number of patients	46	13	10	
Age	50±19	54±24	73±17	0.002
Gender				0.336
Female (%)	26 (56.5)	10 (76.9)	5 (50)	
Male (%)	20 (43.5)	3 (23.1)	5 (50)	
Mortality (%)	5 (10.8)	0	3 (30)	0.081
Length of stay (%)	12±10	10±5	8±4	0.184
Etiology				
CBD stone/ Sludge (%)	29 (63)	9 (69.2)	6 (60)	0.225
Benign Stricture (%)	4 (8.7)	2 (15.4)	4 (40)	0.039
Malignant Stricture (%)	11 (23.9)	0	0	0.038
Stent Occlusion (%)	2 (4.4)	2 (15.4)	0	0.225
CO-morbidities				
DM-II (%)	13 (28.8)	2 (15.4)	4 (40)	0.416
ESRD (%)	2 (4.3)	0	0	0.598
CAD (%)	1 (2.2)	2 (15.4)	3 (30)	0.12
Fever (%)	18 (39.1)	5 (38.5)	7 (70)	0.187
Positive Blood culture (%)	4 (8.7)	1 (7.7)	3 (30)	0.144
Duration of symptoms before presentation (%)	3±1	2±1	2±1	0.022
Door to ERCP time				0.082
Less than 24 hours (%)	12 (26.1)	6 (46.2)	5 (50)	
24 to 48 hours (%)	12 (26.1)	0	0	
More than 48 hours (%)	22 (47.8)	7 (53.8)	5 (50)	
ERCP findings				
Pus discharge (%)	6 (13)	0	2 (20)	0.288
Peri-Ampullary diverticulum (%)	6 (13)	1 (7.7)	7 (70)	0.001

METHODS

Study Population: Inclusion and Exclusion Criteria

Our study was a retrospective review of patients who underwent ERCP for cholangitis during the study period between January 2009 and August 2012. The parameters included within the Tokyo Consensus for Cholangitis (2007) [2] were assessed for all the study subjects. Only those patients who fulfilled the criteria towards the diagnosis of cholangitis were included in the study. The patient with cholangitis who did not undergo ERCP were excluded from the study. The protocol for the study was reviewed and approved by the Institutional Review Board (IRB) at Bronx Lebanon Hospital Center.

Data Extraction and Tabulation

Demographic data including age, gender and ethnicity were extracted from medical records. Routine laboratory parameters including serum liver chemistry, complete blood count and coagulation profile were reviewed for all the patients. The medical charts were reviewed for symptoms, vital signs, physical examination findings, etiology of cholangitis and other comorbid medical conditions. The time (in hours) that elapsed between the presentation to Emergency Room (ER) and completion of ERCP was defined as 'Door to ERCP time'. It was calculated from review of electronic medical records. Death during the index admission for acute cholangitis was considered

as in-hospital mortality. Length of hospital stay was defined as the time period (in days) between presentation to ER and hospital discharge. Lengths of hospitalization in patients who expired were not included towards calculation of this variable. Recovery period for a patient was defined as the number of days of hospitalization after ERCP was performed. Patients were stratified into three different groups based upon 'Door to ERCP time' - patients who underwent ERCP within 24 hours, between 24 to 48 hours, and more than 48 hours respectively. Mortality was assessed in these three groups after controlling for severity of presentation. The lengths of stay amongst these three groups were also observed.

STATISTICAL ANALYSIS

Unpaired student t-test was used for continuous variables that were normally distributed. Non-parametric rank (Wilcoxon) sum was used for continuous variables that were not normally distributed. The association between two variables with removal of the set of random controlling variable was achieved by the Partial correlation test. SPSS version 20 was used for performing all statistical analyses.

RESULTS

A total of 301 patients underwent ERCP procedures during the study period. Amongst these, only 69 patients were diagnosed as having acute cholangitis as per the

diagnostic criteria included within the Tokyo Guidelines. All patients who underwent ERCP had successful biliary cannulation. The mean age of patients with cholangitis was 54 years (20±SD). 68% (n= 47) of the study population were of Hispanic ethnicity while 16% (n=11) was of African American ethnicity. Underlying etiology of cholangitis was choledocholithiasis in 63.8%, malignant stricture in 15.9%, benign stricture in 14.5% and stent occlusion in 4%. 68% (n=46) of patients presented with grade-I severity (without end organ dysfunction and responded to initial resuscitation), 19% (n=13) with grade-II severity (without end organ dysfunction and but did not respond to initial resuscitation) and 13% (n=10) with grade-III severity (with organ dysfunction).

Older individuals were more likely to present with increased severity of cholangitis. The mean age of individuals presenting with grade-III severity was 73(±17) years which was significantly higher than those presenting with less severe disease (p=0.002). Univariate analysis revealed that both mortality and length of stay were not significantly different across groups with varying severity of cholangitis. Patients with benign strictures were more likely to have severe cholangitis (grade-III) while those with malignant strictures were more likely to present with grade-I cholangitis. Patients with peri-ampullary diverticulae had more severe presentation (grade-III). The 'Door to ERCP time' was not significantly different amongst the three groups. 50% (n=5) of patients with the Grade-III cholangitis underwent ERCP within 24 hours of presentation, whereas the rest (n=5) had delayed ERCP (beyond 48 hours from the time of presentation) (**Table 1**). Of the five patients with delayed ERCP, three patients had to wait until compensation of an underlying cardiac condition, one had to be resuscitated from severe shock and one patient underwent Interventional Radiology guided cholecystectomy as first line of therapy as per family's wishes.

Thirty three percent (n=23) of study population underwent ERCP within 24 hours of presentation, 18% (n=12) underwent ERCP between 24 hours and 48 hours of presentation and 49% (n=34) had ERCP after 48 hours of presentation. Presentation on a particular day of the week (weekend including Friday or weekday) was not a deciding factor in 'Door to ERCP time'. All the three study groups were similar in terms of age, gender, laboratory parameters and comorbid conditions (**Table 2**).

Forty Nine percent (n=34) of patients included in the study, underwent endoscopic biliary decompression after 48 hours of initial presentation. The delays for ERCP were multifactorial including- time taken for management of the comorbid conditions, early interventional radiology assisted decompression, time taken for correction of coagulopathy, time taken for management of shock, refusal of consent and initial resuscitation with antibiotics. These factors however differed amongst patients with varying severity of cholangitis (**Table 3**).

The all cause in hospital mortality for patients with acute cholangitis include in this study was 11% (n=8). Mortality did not correlate with 'Door to ERCP time', even after controlling for the severity of the acute cholangitis at the time of presentation (**Table 4**). Fifty percent (n=4) of these patients died from cholangitis related complications, one patient died from end stage liver disease with Hepatocellular carcinoma while the remaining died from hospital acquired infections . Patient with grade-III cholangitis who expired and had the ERCP after 48 hours of presentation- underwent an early cholecystostomy.

The mean lengths of stay for patients with 'door to ERCP time' of less than 24 hours, between 24 to 48 hours and more than 48 hours was 7 days, 6 days and 14 days respectively. The difference in the lengths of stay was statistically significant amongst these groups (**Figure 1a**). Recovery time, as calculated by the number of days of hospitalization after ERCP, was not significantly different amongst the three groups (**Figure 1b**).

DISCUSSION

Acute cholangitis is infection arising from the hepatobiliary system due to biliary obstruction and bactibilia. Severity of cholangitis helps in guiding the management and predict the outcomes. Based on review of literature and expert opinion, a severity grading for the acute cholangitis was proposed in 2007 at the Tokyo consensus [2]. The stratification of severity of acute cholangitis was done based upon presence of organ dysfunction and response to initial resuscitation. This severity grading was revised in the 2013 Tokyo consensus to include laboratory parameters. This aided in triaging the patients who require urgent biliary intervention [6]. In view of the retrospective nature of the study, all the patients in the study were graded for severity as per the Tokyo classification of 2007.

Cholangitis in elderly tends to be severe and have poor outcomes due to presence of other comorbid conditions and atypical clinical presentation [7]. In our study, the patients with grade-III cholangitis were significantly older (mean age of 73 years) than patients with grade-1 (mean age of 50 years) and grade-II (mean age of 50 years) cholangitis (p=0.002). There was no significant difference in the distribution of etiologies, barring biliary strictures, across the three groups with varying severity of cholangitis. Multiple sources [8, 9] have reported that malignant strictures tend to present with severe acute cholangitis. However, we noticed in our study population that patients with malignant strictures presented with lower grade of severity. Majority of these patients were already aware of their diagnosis of a hepatobiliary malignancy and hence were more likely to seek early medical intervention. Patients who had a peri-ampullary diverticulum were more likely to fail initial resuscitative measures (70% in grade-III cholangitis). Impaired sphincter of Oddi [10] with resultant increase in retrograde biliary infection [11] has been reported in patients with duodenal diverticulae.

Table 2. Characteristics including demographic variables, etiologies, day of presentation, comorbid medical conditions, laboratory parameters and ERCP interventions/findings in patients stratified by 'Door to ERCP times'.

	Less than 24 hours (N=23)	Between 24 to 48 hours (N=12)	More than 48 hours (N=34)	p-value
Age	60±25	41±18	55±17	0.538
Gender				0.795
Male (%)	9 (39.1)	4 (33.3)	15 (44.1)	
Female (%)	14 (60.9)	8 (66.7)	19 (55.9)	
Day of presentation				0.152
Weekday (%)	21 (91.3)	8 (66.7)	26 (76.5)	
Weekend (%)	2 (8.7)	4 (33.3)	8 (23.5)	
Laboratory parameter (Units)				
WBC (k/uL)	12±5	11±3	13±6	0.317
Neutrophil Percentage (%)	83±14	80±9	72±27	0.062
Bilirubin (mg/dL)	6±5	5±5	6±6	0.581
ALT(U/L)	172±148	224±190	128±116	0.208
Alkaline Phosphatase(Unit/ L)	255±130	367±333	413±404	0.359
Amylase (U/L)	39±58	37±54	80±107	0.216
Lipase (U/L)	84±121	12± 297	104±191	0.052
Platelet Count (k/ul)	196±100	262±99	276±94	0.004
Pro thrombin time (seconds)	11±4	12±2	12±2	0.233
S.creatinine (mg/dL)	1±1	1±1	1±1	0.889
Co-morbidities				
DM-II (%)	5 (21.7)	2 (16.7)	12 (35.3)	0.346
ESRD (%)	0 (0)	1 (8.3)	1 (2.9)	0.378
CAD (%)	2 (8.7)	0 (0)	4 (11.8)	0.462
Etiology				
CBD stone/ Sludge (%)	17 (73.9)	8 (66.7)	19 (55.9)	0.371
Benign Stricture (%)	2 (8.7)	2 (16.7)	6 (17.6)	0.624
Malignant Stricture (%)	4 (17.4)	1 (8.3)	6 (17.6)	0.73
Stent Occlusion (%)	0 (0)	1 (8.3)	3 (8.9)	0.345
Endoscopic Intervention				
Sphincterotomy (%)	14 (60.1)	10 (83.3)	18 (52.9)	0.179
Balloon Sweep (%)	14 (60.1)	10 (83.3)	16 (47.1)	0.086
Stent Placement (%)	15 (65.2)	7 (58.3)	25 (73.5)	0.414
Clinical / Endoscopic parameter				
Pus discharge on ERCP (%)	2 (8.7)	2 (16.7)	4 (11.8)	0.782
Per-ampullary diverticulum (%)	6 (26.1)	2 (16.7)	6 (17.6)	0.697
Fever (%)	9 (39.1)	4 (33.3)	17 (50)	0.53
Chills (%)	2 (8.7)	1 (8.3)	1 (2.9)	0.606
Jaundice (%)	20 (87)	11 (91.7)	29 (85.3)	0.853
Abdominal pain (%)	23 (100)	11 (91.7)	32 (94.1)	0.428

Table 3: Factors affecting the 'Door to ERCP times' in patients stratified by varying severity of cholangitis.

Total number of patient with ERCP after 48 hours		49% (34)
Grade – III severity		10
	ERCP done Before 48 hours	5
	Management of cardiac condition	3
	Resuscitation of the sever shock	1
	Interventional Radiology guided cholecystostomy	1
Grade- II severity		13
	ERCP done Before 48 hours	6
	Awaiting response to initial antibiotics	4
	Patient on Plavix – awaiting initial antibiotic response	1
	Correction of coagulopathy (cirrhosis related)	1
	Management of pneumonia	1
Grade- I severity		46
	ERCP done Before 48 hours	24
	Initial resuscitation with antibiotics	15
	Patient on Coumadin /Plavix	3
	Management of DKA, COPD, Hepatic Encephalopathy	3
	Refusal of consent	1

Table 4: Mortality among patients stratified by severity of cholangitis and timing of ERCP.

Severity of Cholangitis	Door to ERCP time	Mortality		p-value
		No Mortality	Mortality	
Grade I	Less than 24 hours	11	1	0.252
	Between 24 to 48 hours	12	0	
	More than 48 hours	18	4	
Grade II	Less than 24 hours	6	0	N/A
	Between 24 to 48 hours	0	0	
	More than 48 hours	7	0	
Grade III	Less than 24 hours	3	2	0.49
	Between 24 to 48 hours	0	0	
	More than 48 hours	4	1	

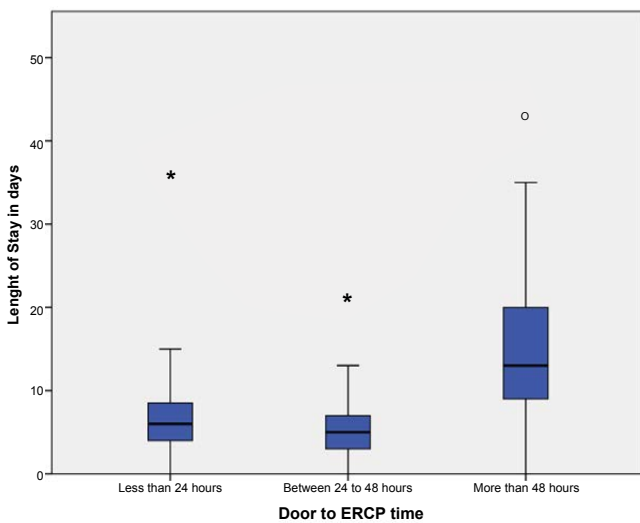


Figure 1a. Box-plot comparing the means of lengths of hospital stay (in days) amongst the three study groups stratified by timing of ERCP.

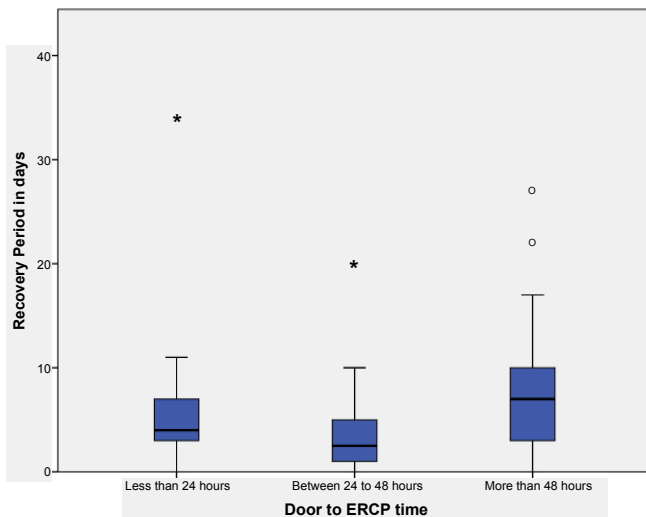


Figure 1b. Box-plot comparing the means of recovery times (in days) amongst the three study groups stratified by timing of ERCP.

The timing of the ERCP for decompression of the biliary system has been controversial [12, 13]. The mortality was reported to be high (17%-40%) if ERCP was delayed due to advanced age or underlying comorbid conditions [14]. The presence of comorbid conditions had been proposed for usage towards grading the severity of cholangitis but was deemed impractical due to the complexity [6]. However, in patients with cholangitis the ‘Door to ERCP time’ may

be prolonged for management of decompensated comorbid conditions [4]. We observed that 49% of our study population had ERCP performed after 48 hours. There was no difference in mortality between the groups which had biliary decompression within 24 hours, between 24 to 48 hours and beyond 48 hours. There were no difference in the baseline characteristics such as age, gender, etiology of cholangitis, clinical presentation, laboratory parameters, ERCP findings and interventions performed amongst these groups. As seen in other studies [15] we did not observe any weekday versus weekend variation.

The severity of cholangitis does affect mortality and other outcomes such as length of stay [4]. Good predictive models have been designed to triage the patients who need earlier intervention [6, 16]. Despite severe presentation of cholangitis, decompensated comorbid conditions often curtail an early ERCP. This was demonstrated in our study when almost half of patients with severe cholangitis, who constituted up to 11% of total study population, ended up getting ERCP beyond 48 hours of presentation. There was no observed difference in mortality amongst the three groups stratified as per the ‘Door to ERCP time’ even after controlling for the severity of cholangitis. The length of stay was prolonged in patients with delayed ERCP but the recovery time, as noted by number of days of hospitalization after ERCP was not different amongst the three groups. The prolonged length of stay in patients with delayed ERCP could be attributed to the time spent for management of underlying decompensated medication condition.

In conclusion, decompression of biliary tract should be attempted on expedited basis in every patient with acute cholangitis. However, we noted no difference in mortality for patients who underwent delayed ERCP. We did observe that the delay in ERCP contributed to increase in the length of hospital stay and thereby could possible lead to increased morbidity.

Conflict of Interest

The authors declare that there is no conflict of interests.

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