OPEN ACCESS

Saudi Journal of Medicine
Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) | ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Diagnostic and Therapeutic Value of ERCP in Acute Severe Cholangitis: Experience of a Moroccan Endoscopic Center

Inssaf Akoch[1*], Nada Lahmidani[1], Asmae Maktoub[1], Maria. Lahlali[1], Asmae. Lamine[1], Hakima Abid[1], Mounia Elyousfi[1], Mohammed El Abkari[1], Adil Ibrahimi[1], Dafrallah Benajeh[1]

[1]Department of Hepato-Gastroenterology of CHU Hassan II Fès Sidi Mohamed Ben Abdellah Fès University, Morocco

DOI: 10.36348/sjm.2022.v07i05.011 | **Received:** 01.04.2022 | **Accepted:** 05.05.2022 | **Published:** 26.05.2022

***Corresponding Author:** Inssaf Akoch
Department of Hepato-Gastroenterology of CHU Hassan II Fès Sidi Mohamed Ben Abdellah Fès University, Morocco

Abstract

Severe cholangitis is an urgent indication for endoscopic treatment, represented by endoscopic retrograde pancreatography (ERCP) and endoscopic sphincterotomy. It ensures good bile drainage, and improves patient morbidity and mortality. ***Materials and methods:*** This is a retrospective study carried out within our department between January 2010 and April 2018. All patients with severe cholangitis who benefited from therapeutic ERCP were enrolled. We analyzed the epidemiological data of the patients, the results of the ERCP, as well as the post-sphincterotomy mortality. We also performed multivariate analysis for predictive factors for mortality. ***Results:*** 88 patients were enrolled. The average age of the patients was 60.14 years [17-102 years], with a female predominance (n = 45, 51.1%). Twelve patients (13.6%) underwent a cholecystectomy. Almost 68, 18% patients (n = 60) had obstructive choledocholithiasis, fifteen patients (17,04%) had o cyst hydatic and 13 patients (14,77%) had tumor obstruction. Successful catheterization of the main bile duct was reported in 60 patients (68.18%), and failure in 28 cases (31.81%). The use of precut was performed in 28 cases (31.81%), which enabled successful access to main bile duct in 24 patients (85.71%). Failure of catheterization after a precut concerned 4 patients (14.28%): 3 patients (75%) benefited from a resumption of ERCP with success, and only one patient (25%) was proposed for surgery. fifty-five patients (91,66%) underwent stone evacuation (Figure 1). For 5 patients (8, 33%), failure of stone extraction was followed by successful surgery. Twenty-one patients benefited from successful implementation of a biliary prosthesis were objectified in 21 patients (25%). 5 patients (23.80%) failed. Among them, percutaneous drainage was done 4 patients (80%) and 1 patient (20%) was operated. The main post-ERCP complications were represented by: 5 cases (5.7%) of papillary bleeding, and 1 case of acute pancreatitis. The overall death rate was 11,36% (n=10). The course was marked by clinical and biological remission in the other patients with successful endoscopic drainage. The main predictors of mortality in multivariate analysis were impaired of consciousness upon admission (p = 0.023, OR=4, 5678 [2,678-10, 7890]), and the presence of renal failure (p = 0.001, OR=6, 4809 [2,089-15,781]). ***Conclusion:*** Endoscopic treatment is the gold standard for the treatment of severe cholangitis. Its results are satisfactory, with a lower mortality compared to surgical treatment with fewer hospitalizations.

Keywords: Severe cholangitis, cholelithiasis, ERCP, precut, mortality.

I. INTRODUCTION

Acute cholangitis is a bacterial infection of the main bile duct (VBP) or intrahepatic bile ducts (VBIH), usually due to the isolation of a calculus in the vater's bulb. Cholangitis can sometimes be due to migrant parasites such as roundworm or fluke, stenosis of the bile duct by a tumor or by lymphadenopathy or rarely chronic pancreatitis.

It is clinically reflected in the successive appearance within 48 hours of three clinical symptoms which are biliary pain, fever and jaundice constituting the Charcot triad [1].

The prevalence of chole lithiasis varies by ethnicity. Gallstones are found in 10 to 15% of the white population in the United States, it is much more common in Hispanics but less common in Asians and African Americans [2]. The incidence of severe cholangitis is very difficult to estimate in Morocco in the absence of a national and regional registry for the collection of pathologies treated at the University Hospital. The underestimation of the incidence may be

due to the lack of national consensus on the definition of severe forms of acute cholangitis.

The severity of cholangitis is linked to the spread of the infection with a risk of shock and multi visceral failure with neuropsychic disorders. Mortality can be high in case of delayed diagnosis. The clinical definition of severe cholangitis in clinical trials was the existence of septic shock, the persistence of septic syndrome despite antibiotic therapy and confusion. This severe form is observed in 10 to 15% of patients [3]. Since 2007, an expert group *"The Tokyo Guidelines Working Group"* has established regular recommendations updated in 2018 [4, 5]. The Tokyo 2018 guideline is the third revised version. The initial management of suspect patients according to this director begins with the measurement of vital parameters to assess whether the situation is urgent or not, and if the case is deemed urgent, medical treatment must be started immediately, including management respiratory and circulatory without waiting for a definitive diagnosis, and the severity must be assessed according to the criteria for classification of the severity of cholangitis [5].

Biliary drainage is essential in the treatment of severe cholangitis. Emergency surgical treatment is burdened with high mortality (20 to 40%) [6] and endoscopic treatment is currently recommended. The randomized study by Lai *et al*. [7] compared surgical treatment and endoscopic drainage in 82 patients with severe cholangitis defined by the existence of septic shock or the persistence of a septic state despite appropriate antibiotic treatment. The results showed significant differences in favor of endoscopic treatment with regard to morbidity (34 versus 66%) and mortality (10 versus 32%). Thus, endoscopic treatment has since become the standard method of biliary drainage in patients with severe cholangitis.

The main purpose of our study is to evaluate at the University Hospital Hassan II the clinical presentation of severe cholangitis, the outcome of ERCP in this setting and the main mortality causes severe cholangitis in the emergency department, and analyze the factors associated with mortality.

II. MATERIALS AND METHODS

We performed retrospective data analysis and reviewed data files of 88 patients recruited at the Endoscopic Emergency Unit at the university Hospital Hassan II Fez, either admitted through the emergency unit or intensive care unit between January 2010 and April 2018 who performed Therapeutic ERCP.

We included all patients over the age of 16 with severe cholangitis. The diagnosis of acute cholangitis was based on clinical, biological and radiological arguments according to the updated Tokyo guidelines 2018 defined by any acute cholangitis associated with at least one organ failure and / or particular terrain was considered serious.

The data were collected from the ERCP unit register and then completed from the computerized medical records of patients. The parameters collected were demographic, clinical, diagnostic, laboratory and radiological findings with ERCP performances and outcomes.

We also performed multivariate analysis for predictive factors of mortality. SPSS version 25 was used to analyze data.

III. RESULTS

III.1. Population Characteristics (Table 1)

During the study period, 88 patients with severe cholangitis were admitted to the endoscopic emergency unit representing 12, 5% of admitted patients for cholangitis and 1.25% of all hospitalization in GI unit during this period of time. The average age of patients was 60.14 years with extremes ages ranging from 17 to 102 years with a slight female predominance (n = 45, 51.1%), the sex ratio F / M was 1.04.

Comorbidities in our population were mainly diabetes mellitus in 25 cases (28.40%), high blood pressure in 20 patients (22.72%) and cardiovascular diseases in 10 cases (11.36%). Regarding clinical presentation, biliary pain and jaundice were present in more than 80% of the cases. Impaired consciousness was reported among 13.6% of admitted patients laboratory findings revealed a thrombocytopenia in 65% of patients with severe thrombocytopenia less than 50000 among 21% of patients and renal impairment in 25%. Past history of biliary pathology are resumed in Table 2:

Table-1: Clinical biological and radiological characteristics of patients admitted for acute severe cholangitis

Variables	Number (n)	Percentage %
Middle Age (an	60,14 (17-102)	-
Femal sex	45	51,13
Comorbidity:		
Diabetes	25	28,40
High blood pressure	20	22,72
Heart disease	10	11,36
Clinical finding:		
liver pain	88	100
Cholestatic jaundice	86	97,72
Fever	87	98,86
Vomiting	30	34,09
Wight loss and asthenia	15	17,04
Impaired consciousness	12	13,63
Average time for admission	8 days (Extremes 1- 15 days)	
Laboratory finding (Biologic):		
Leukocytes ≥10,000	80	90,90
Thrombopénie< 150000/mm3	65	73,86
TP<50%	40	45,45
CRP ≥ 10	88	100
Renal failure	22	25
Radiological finding US +/- CT scan:		
Cholelithiasis	60	68.18
gallbladder Lithiasis	50	56.81
Hydatic liver cyst rupture	15	17.04
Tumor obstruction:		
Pancreas head	9	10.22
Ampulloma	3	3.41
Cholangiocarcinoma	1	1.13

Table-2: History of biliary disease

Variables	Number (n)	Percentage %
History of choledocholithiasis	20	22,72
Cholecystectomy	12	13,63
Chydatic liver cyst	5	5,68%
Cholangiocarcinoma	1	1,13

Choledocholithiasis was the major cause of acute cholangitis in more than two third of patients followed by biliary rupture of hydatic liver cyst 17% of cases and tumor obstruction in 15% of cases.The radiological characteristics are shown in Table 1.

Concerning the severity scores, a SIRS was objectified in 80 cases (90.90%), and for the Tokyo criteria, 10 patients (11.36%) were classified grade I, 45 (51.13%) grade II and 33 (37.5%) grade III.

III.2. Medical Management

Therapeutic management was based on three components: Resuscitation measures and the treatment of organ failures, antibiotic therapy and endoscopic biliary drainage. All patients received intravenous antibiotic therapy upon admission and according to severity grade. Vit K also was delivered to all patients with prothrombine impairment and platelets perfusion in case of severe thrombocytopenia with hemorrhagic manifestations. The average delay in biliary drainage was 3 days with extremes ranging from 1 to 6 days.

III.3. Treatment techniques depending on the etiology (Table 3)

Successful catheterization of the main bile duct was reported in 60 patients (68.18%), and failure in 28 cases (31.81%). The use of precut was performed in 28 cases (31.81%), which enabled successful access to main bile duct in 24 patients (85.71%). Failure of catheterization after a precut concerned 4 patients (14.28%): Three patients (75%) benefited from a resumption of ERCP with success, and only one patient (25%) was proposed for surgery. fifty-five patients (91,66%) underwent stone extraction (Figure 1). For 5 patients (8,33%), failure of stone extraction was followed by successful surgery. Twenty-one patients benefited from successful implementation of a biliary stent (25%). Five patients (23.80%) failed. Among

them, percutaneous drainage was done 4 patients (80%) and 1 patient (20%) was operated.

Table-3: Treatment techniques depending on the etiology

Diseases / Techniques	Lithiasis (n=60)	Hydatic cyst (n=15)	Tumor pathology (n=13)
Successful main bile duct catheterization	n= 46/76,66%	n= 10/66,66%	n= 4/30,76%
Sphincterotomy	n= 58/96,66%	n= 15/100%	n= 12/80 %
Precut	n= 18/30%	n= 2/13,33%	n= 8/61,53%
Choledocholithiasis extraction: Dormia Balloon Failure	 n= 18/30% n= 37/ 61.66% n= 5/8,33%	 -	
Membrane extraction **• Dormia** Balloon Failure		 n= 15, 100%	
Stent Plastic Metallic Failure	 n= 6, 10% n= 1, 1,66%		 n= 6, 46,15% n= 9, 69,23% n= 4, 30,76%

The main post-ERCP complications were represented by: Five cases (5.7%) of papillary bleeding, and 1 case of acute pancreatitis. The overall death rate was 11, 36% (n=10). The course was marked by clinical and biological remission in the other patients with successful endoscopic drainage.

The main predictors of mortality in multivariate analysis were disturbances of consciousness on admission (p = 0.023, OR=4, 5678 [2,678-10, 7890]), and the presence of renal failure (p = 0.001, OR=6, 4809 [2,089-15,781]) and initial SIRS (p = 0.02 OR=1, 5 [1,340-4,033]).

The other variables studied were not predictive for mortality including: Age> 75 years ,co-morbidities (p = 0.13), tumor origin (p = 0.21), septic shock on admission (p = 0.11), leukocytes on admission (p = 0.11) and CRP level on admission (p = 0.11) (Table 4).

Table-4: Factors associated with mortality in multivariate analysis

Variables	OR	CI 95%	p
Impaired consciousness	4.567	[2,678-10,7890]	0.023
Renal failure	6.480	[2,089-15,781]	0.001
Delay in biliary drainage	1.03	[0,549-1,102]	0.25
Initial SIRS	1.5	[1,340-4,033]	0.02

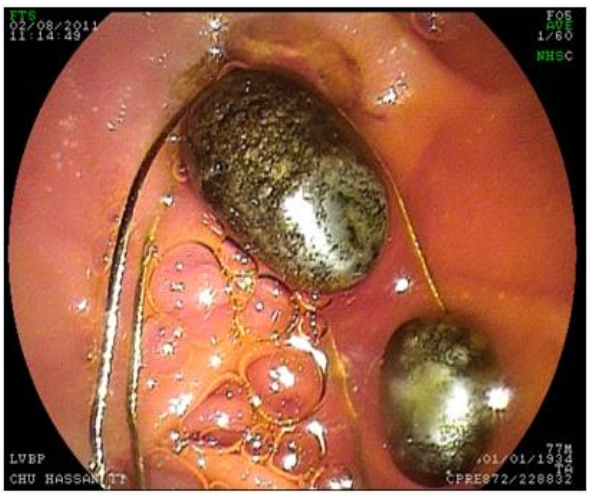

Fig-1: Endoscopic drainage procedure with stone evacuation [8].

DISCUSSION

Acute cholangitis is a bile duct infection with high mortality and morbidity. The organisms isolated during this infection are E. Coli, klebsiella, enterococcus, streptococcus, enterobacter and pseudomonas aeriginosa [9-11]. Although digestive endoscopy reduces mortality and morbidity rates, there are authors who indicate that these procedures can themselves cause bile contamination, hence the incidence of cholangitis [12, 13]. Drainage should not be delayed especially in fragile patients with co-morbidities. In the case of delay, mortality is between 17 and 40%. The mortality rate reduced to 3% in patients who underwent elective drainage after hemodynamic and circulatory restoration.

We have collected 88 cases of severe cholangitis over a 10-year period. This impact is probably underestimated. This may be due to the

absence of a national or even regional register for the collection and referencing of pathologies treated at the Hassan II University Hospital. No national study has looked at severe cholangitis; the majority of studies are the theses of Medicine. A 10-year retrospective study of cases of severe cholangitis admitted to the intensive care unit showed a prevalence of 1.92% [14].

In our series, 69, 18% patients (n = 60) had a lithiasic pathology. The prevalence of lithiasis pathology increases steadily with age. This is also found in the various national series focusing exclusively on lithiasic pathology [14, 15].

The Tokyo Guidelines Working Group has established diagnostic criteria where the diagnosis of cholangitis requires a criterion in one of the following 3 diagnostic categories: A/ Systemic inflammation (Fever / chills or biological evidence of a systemic inflammatory response), B / Cholestasis (Jaundice and Total Bilirubin ≥ 20 mg / l or other disturbed liver tests), C / Imaging (dilation of the bile ducts or etiological evidence of obstruction) [5]. These criteria were derived from a vast review of the literature of the most sensitive and specific clinical, biological and radiological manifestations and they are regularly updated since the year 2007. All our patients have spread to these criteria since we are based on it to include cases of acute cholangitis in our study.

As soon as the diagnosis of acute cholangitis is confirmed, the evaluation of the severity is essential because it makes it possible to stratify the multidisciplinary therapeutic attitude, according to the risk.

According to the Tokyo 2018 criteria**,** the severity of acute cholangitis is classified into three grades based on the following criteria: Organ failure inspired by the SOFA score widely used in resuscitation, SIRS, age, hyper bilirubinemia, hypo albuminemia. Grade II is characterized by the presence of an SIRS without organ failure but is at risk of progression to organ failure and grade III in the absence of urgent or early drainage.

Biliary drainage is recommended in acute cholangitis regardless of the degree of severity. Recent studies have demonstrated an obvious advantage to early drainage in terms of intra-hospital mortality, 30-day mortality and hospital costs, particularly within 48 hours of admission and regardless of severity [16, 17]. A retrospective study of 172 patients with acute cholangitis revealed that biliary drainage within 72 hours is associated with an increased risk of persistent organic failure and / or 30-day mortality (OR 3.36, 95% CI 1.12-10.20)**.** In the literature, there is no clear definition of "early" ERCP, which was defined between 24 and 72 h after admission.

Therefore, it is recommended to perform biliary drainage immediately after resuscitation measures without delay, within 12 hours if the response to antibiotics is not optimal in less severe cases and urgently within 24 to 48 hours for all other cases [18]. Endoscopic drainage is less invasive and compatible with a better quality of life (no bile leak compared to external drainage), and is the first choice technique despite the risk of acute pancreatitis post ERCP. In our series, endoscopic treatment was the reference treatment; surgical treatment is an alternative if the endoscopic treatment fails.

The sphincterotomy associated with instrumental maneuvers to extract stones is the usual endoscopic method of biliary obstruction proposed initially by the Anglo-Saxon authors as a treatment for severe lithiasic angiochitis [19]. In our series, fifty-five patients underwent stone evacuation. However, Chinese and Japanese authors favor biliary drainage with or without sphincterotomy by placing a nasobiliary drain or prosthesis.

In our series, three factors were predictive of mortality: impaired Consciousness upon admission, the presence of renal failure and initial SIRS which is consistent with several studies**.**

V. CONCLUSION

Severe acute cholangitis, a real medical and surgical emergency, requires close collaboration between hepatobiliary endoscopists, radiologists, surgeons, microbiologists and anesthetists.

The challenge for any clinician is to identify potentially serious forms in order to initiate appropriate therapeutic management as soon as possible. Early recognition, antibiotics, resuscitation and minimally invasive biliary drainage have improved patient outcomes although there is still room for improvement. Endoscopic treatment is the gold standard for the treatment of severe cholangitis. Its results are satisfactory, with a lower mortality compared to surgical treatment with and less hospitalizations.

In addition, since multiple organ failure is often associated with mortality from severe acute cholangitis, the risk factors predicting organ failure should be further investigated as part of more robust methodology.

Abbreviations

ERCP: Endoscopic Retrograde Pancreatography
VBP: Main bile duct
VBIH: Intrahepatic bile ducts

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