Choledocholithiasis in acute calculous cholecystitis: guidelines and beyond

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Abstract

Background Acute calculous cholecystitis (ACC) is the most frequent complication of gallstones requiring cholecystectomy. These patients may have coexisting choledocholithiasis. We aimed to evaluate the role of current guidelines for choledocholithiasis in patients with ACC.

Methods In this retrospective study, we included all patients diagnosed with ACC between December 2018 and May 2019. These patients were substratified according to the guidelines of the American and European Societies of Gastrointestinal Endoscopy (ASGE and ESGE) as having high, intermediate, or low likelihood of choledocholithiasis, and the diagnostic performance was measured. Binomial logistic regression analysis was applied to ascertain independent risk factors for choledocholithiasis.

Results A total of 173 patients with ACC, mean age (±standard deviation) 49.89±15.74 years and 60.1% male, were included. Sixty-three (36.4%) had confirmed choledocholithiasis. ASGE high likelihood criteria had sensitivity and specificity of 61.9% (95% confidence interval [CI] 48.8-73.9) and 83.4% (95%CI 75.4-90.0) for predicting choledocholithiasis. ESGE high likelihood criteria had sensitivity and specificity of 49.2% (95%CI 36.4-62.1) and 87.3% (95%CI 79.6-92.9). On logistic regression analysis, an alkaline phosphatase level above the upper limit of normal (P=0.003; odds ratio [OR] 4.26, 95%CI 1.66-10.96) and a dilated common bile duct on ultrasound (P=0.001; OR 9.97, 95%CI 4.65-21.36) were independent positive predictors for choledocholithiasis, while acute biliary pancreatitis was an independent negative predictor (P=0.030; OR 0.36, 95%CI 0.14-0.91).

Conclusions The performance of the ASGE and ESGE guidelines' risk stratification criteria is inadequate in patients with ACC. We suggest the utilization of a separate predictive model for suspected choledocholithiasis in these patients.

Keywords Acute calculous cholecystitis, choledocholithiasis, predictors, gallstones, risk

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Introduction

Acute calculous cholecystitis (ACC) is the most frequent complication of gallstones, accounting for 14-30% of

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cholecystectomies [1,2]. Patients with symptomatic gallstones carry more risk for the development of ACC than patients without symptoms [3]. Symptomatic gallstones also increase the risk for other complications, such as gallstone pancreatitis and choledocholithiasis. ACC is diagnosed according to the Tokyo guidelines with a combination of clinical, laboratory, and imaging findings [4,5]. Initial investigations include liver function tests (LFTs), hemogram and abdominal ultrasound (US). A dilated common bile duct (CBD) on US and/or alerted LFTs should raise the suspicion for choledocholithiasis. Coexisting choledocholithiasis needs to be recognized early as it may lead to jaundice and/or cholangitis, the incidence of which is reported to be 13.7% (range 3.36-25%) in a meta-analysis [6].

The American and European Societies of Gastrointestinal Endoscopy (ASGE and ESGE) have recently updated their guidelines for the management of choledocholithiasis [7,8]. These guidelines stratify patients with suspected choledocholithiasis

into high, intermediate and low likelihood groups, depending on the presence of clinical cholangitis, LFTs, and US findings (Table 1). However, these guidelines do not mention their clinical application in the presence of ACC. ACC *per se* is associated with an alteration of LFTs, irrespective of choledocholithiasis, which may decrease the clinical utility of these guidelines in this subset of patients. In the current study, we aimed to evaluate the diagnostic performance of the ASGE and ESGE guidelines for the prediction of choledocholithiasis in patients with ACC.

Patients and methods

Institutional Review Board approval was obtained. In this single-center retrospective study of prospectively maintained data we included all consecutive patients diagnosed with ACC between December 2018 and May 2019. ACC was diagnosed as per Tokyo guidelines [5,9]. Patients with underlying liver disease, alcohol consumption, prior biliary surgery, prior endoscopic retrograde cholangiopancreatography (ERCP), biliary stricture, or primary sclerosing cholangitis were excluded. All included patients were stratified as having a high, intermediate or low likelihood of choledocholithiasis, as per ASGE and ESGE criteria. Coexisting acute pancreatitis was diagnosed according to the revised Atlanta classification [10]. The diagnosis of acute cholangitis in the presence of ACC is clinically difficult: we diagnosed acute cholangitis in patients who had confirmed CBD stones on ERCP and clinical improvement after CBD stone clearance or biliary stenting.

The data were collected in a standardized data collection sheet, which included demographic data such as age, sex, LFTs at admission, serum amylase or lipase whenever indicated, US findings including presence of CBD dilatation, CBD stone/sludge, signs of ACC, and pancreatitis. For confirmation of CBD stones, details of endoscopic procedures endoscopic US and ERCP, and the radiological procedure magnetic resonance cholangiopancreatography (MRCP) were noted whenever they were performed. Patients in whom CBD stones were not detected during an initial presentation but were detected within 6 months of follow up were considered as having a missed CBD stone.

The categorical data were presented as proportions. The continuous data were presented as mean and standard deviation (SD). The diagnostic performance of the ASGE and ESGE criteria was presented as sensitivity, specificity, positive and negative predictive value, likelihood ratio + and – along with respective 95% confidence interval (CI). Clopper-Pearson

CIs were calculated for sensitivity and specificity. The log method was used to calculate the CIs for the likelihood ratio, and standard logit was used to obtain CIs for the predictive values. Binominal logistic regression analysis using a forward conditional method was carried out to ascertain independent predictors of CBD stones among the variables that were significant in univariate analysis. Acute cholangitis was not included in the analysis, as it was diagnosed only in patients with confirmed CBD stones. A P-value <0.05 was considered as statistical significance. SPSS version (IBM Corp., Armonk, New York, USA) and MedCalc version 19.1.3 (MedCalc Software bv, Ostend, Belgium) were used for the statistical analysis.

Results

A total of 173 patients with ACC, mean age (±SD) 49.89±15.74 years and 60.1% male, were included in the analysis; of these 43 (24.9%) had coexisting acute pancreatitis and 15 (8.67%) had cholangitis. There were 63 (36.4%) confirmed cases of choledocholithiasis. Other baseline characteristics of the study population are summarized in Table 2.

After analysis of clinical, laboratory and US findings, patients were stratified according to the ASGE criteria as follows: high likelihood of choledocholithiasis 57 (32.9%), intermediate likelihood 105 (60.7%) and low likelihood 11 (6.4%); and according to ESGE criteria as follows: 45 (26%) high, 109 (63%) intermediate and 19 (11%) low likelihood. Of the patients who satisfied the ASGE and ESGE high likelihood criteria, 39/57 (68.4%) and 31/45 (68.9%) had choledocholithiasis respectively. In the ASGE and ESGE intermediate likelihood group, 24/105 (22.85%) and 31/109 (28.44%) had choledocholithiasis, respectively. Only one patient in the ESGE low likelihood group had choledocholithiasis. The diagnostic performance of the ASGE and ESGE guidelines is summarized in Table 3. ASGE high likelihood criteria had sensitivity and specificity of 61.9% (95%CI 48.8-73.9) and 83.4% (95%CI 75.4-90.0) for predicting choledocholithiasis. ESGE high likelihood criteria had sensitivity and specificity of 49.2% (95%CI 36.4-62.1) and specificity 87.3% (95%CI 79.6-92.9). The risk of undergoing diagnostic ERCP according to the high likelihood ESGE and ASGE criteria is 31.1% and 31.6%, respectively.

On univariate analysis, we found that elevated bilirubin and alkaline phosphatase (ALP) levels, dilated CBD on US, CBD stone on US, and acute biliary pancreatitis were significant risk factors for choledocholithiasis in patients with ACC (P<0.05). On logistic regression analysis using a forward conditional

Table 1 American and European Societies of Gastrointestinal Endoscopy risk stratification criteria

Society	High likelihood	Intermediate likelihood	Low Likelihood
ESGE ASGE	Cholangitis or CBD stone on US	Abnormal LFT and/or CBD dilatation on US	Normal LFT and US
	Combination of Serum Bilirubin >4 mg/dL and CBD dilatation on US	Age >55 years	

ESGE, European Society of Gastrointestinal Endoscopy; ASGE, American Society of Gastrointestinal Endoscopy; US, ultrasound; CBD, common bile duct; LFT, liver function test

method, ALP elevated above the upper limit of normal (P=0.003; odds ratio [OR] 4.26, 95%CI 1.66-10.96) and dilated CBD on US (P=0.001; OR 9.97, 95%CI 4.65-21.36) were independent positive predictors for choledocholithiasis, while acute biliary pancreatitis was an independent negative predictor (P=0.030; OR 0.36, 95%CI 0.14-0.91) (Table 4). The predictive score was calculated by allotting +1 score for each positive predictor and -1 for each negative predictor, giving a range from -1 to +2. Using ≥1 as cutoff, sensitivity and specificity for predicting choledocholithiasis were 95.24% (95%CI 86.71-99.01) and 51.82% (95%CI 42.09-61.45). When the score was -1 or 0, 95% of patients did not have choledocholithiasis. When the score was 1, 28/68 (41.17%) had choledocholithiasis, and when the score was 2, 32/45 (71.11%) had choledocholithiasis.

Discussion

ACC is the most common complication of symptomatic gallstones [1]. In a significant proportion of patients with ACC other complications, such as choledocholithiasis, cholangitis, or biliary pancreatitis, may coexist [4]. Current guidelines for the management of choledocholithiasis do not separately address the evaluation and management of coexisting ACC and choledocholithiasis [7,8].

In the current study, we evaluated the diagnostic utility of ASGE and ESGE algorithms for diagnosing choledocholithiasis in patients with ACC. The sensitivity and specificity of the ASGE high likelihood criteria were 61.9% and 83.4%, while the ESGE high likelihood criteria's sensitivity and specificity were 49.2% and 87.3%, respectively. The sensitivity and specificity of the ASGE high likelihood criteria were 74.64% and 96.87%, respectively in all patients with symptomatic cholelithiasis who had suspected cholelithiasis, irrespective of the presence of ACC, while for the ESGE high probability criteria the sensitivity and specificity were 74.28% and 98.96%, respectively [11]. Thus, the sensitivity and specificity of current guidelines to predict choledocholithiasis appear suboptimal in the presence of ACC compared to the overall population. However, the diagnostic performance of these guidelines in the intermediate likelihood group of patients with ACC appeared to be comparable or slightly superior to that in the overall population [11]. These differences underline the need to re-stratify patients who have ACC with suspected choledocholithiasis. This difference could be explained by frequent alterations of LFTs due to non-specific hepatitis in ACC and significant pericholecystic edema and/or inflammatory changes along the cystic duct and CBD, irrespective of choledocholithiasis [12-15]. This study showed that there is a need to develop other predictive clinical tools to rule out choledocholithiasis on patients with ACC.

We evaluated independent predictive factors for choledocholithiasis using logistic regression analysis with a forward conditional method. Elevated ALP above the upper limit of normal (OR 4.26, 95%CI 1.66-10.96) and dilated CBD on US (OR 9.97, 95%CI 4.65-21.36) were independent positive predictors, whereas coexisting acute biliary pancreatitis was an independent negative predictor (OR 0.36, 95%CI 0.14-0.91). Previous studies have shown good sensitivity and specificity of raised ALP and γ-glutamyl transpeptidase, and dilated CBD on US, for predicting choledocholithiasis [15-17]. Acute biliary pancreatitis is considered to be a negative predictor for choledocholithiasis, demonstrated by various studies in the past [18,19]. This is possibly because acute biliary pancreatitis is caused by small stones or sludge that may pass the papilla

Table 2 Baseline characteristics of the study population (n=173)

Parameter	Mean ± SD
Age in years	49.89 ± 15.74
Sex, male (%)	104 (60.1%)
Acute biliary pancreatitis, n (%)	43 (24.9%)
Dilated CBD on US, n (%)	72 (41.6%)
CBD stone/sludge on US, n (%)	36 (20.8%)
Serum bilirubin	3.93 ± 5.12
ALT	101.09 ± 128.58
ALP	212.01 ± 149.72
Confirmed choledocholithiasis, n (%)	63 (36.4%)

SD, standard deviation; CBD, common bile duct; US, ultrasonography; ALT, alanine aminotransferase; ALP, alkaline phosphatase

Table 3 Diagnostic performance of ESGE and ASGE criteria for prediction of choledocholithiasis in acute calculous cholecystitis

Society	True Positive/ Total Positive	True Negative/ Total Negative	Sensitivity	Specificity	PPV	NPV	LR+	LR-
			% (95% confidence interval)					
ASGE High	39/57	92/116	61.9 (48.8- 73.9)	83.4 (75.4- 90.0)	68.4 (57.7-77.5)	79.3 (73.5- 84.2)	3.78 (2.38- 6.02)	0.46 (0.33-0.63)
ASGE Intermediate	24/105	29/68	38.1 (26.2- 51.2)	26.4 (18.4- 35.6)	22.9 (17.5-29.3)	42.7 (33.9- 51.8)	0.52 (0.37- 0.72)	2.35 (1.63-3.39)
ESGE High	31/45	96/128	49.2 (36.4- 62.1)	87.3 (79.6- 92.9)	68.9 (56.1- 79.4)	75.0 (69.9- 79.4)	3.87 (2.23- 6.70)	0.58 (0.45-0.75)
ESGE intermediate	31/109	32/64	49.2 (36.4- 62.1)	29.1 (20.8- 38.5)	28.4 (23.1- 34.4)	50.0 (40.6- 59.4)	0.69 (0.53- 0.92)	1.75 (1.19-2.55)

ASGE, American Society of Gastrointestinal Endoscopy; ESGE, European Society of Gastrointestinal Endoscopy; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio plus; LR-, likelihood ratio minus

Table 4 Univariate and multivariate analysis for predictors of choledocholithiasis in acute calculous cholecystitis

Parameters	Univariate		Multivariate	
	n (%)	P-value	AOR (95%CI)	P-value
Age > 55 years				
Yes	29/69	0.211		
No	34/104			
Sex				
Male	36/104	0.546		
Female	27/69			
Bilirubin > 1.8 mg/dL				
Yes	42/94	0.014		
No	21/79			
ALT > 3x ULN				
Yes	18/45	0.561		
No	45/128			
ALP > ULN				
Yes	55/124	0.001	4.26 (1.66-10.96)	0.003
No	8/49			
Dilated CBD on USG				
Yes	47/72	0.001	9.97 (4.65-21.36)	0.001
No	16/101			
CBDS on USG				
Yes	24/36	0.001		
No	39/137			
Acute biliary pancreatitis				
Yes	10/43	0.039	0.36 (0.14-0.91)	0.030
No	53/130			

AOR, adjusted odds ratio; CI, confidence interval; CBD, common bile duct; CBDS, choledocholithiasis; USG, ultrasonography; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ULN, upper limit of normal

spontaneously [18]. In the APEC study of urgent ERCP in severe acute biliary pancreatitis, a total of 30.9% (71/230) patients had CBD stones or sludge in both study groups [20]. The remaining 69.1% (159/230) did not have CBD stones, indicating that in a majority of patients a CBD stone passes the papilla spontaneously.

Taking the above into account, we propose a new algorithm, depicted in Fig. 1. Patients having score -1 or 0 should be directly referred for cholecystectomy. Those who have a score of 2 can be referred for preoperative ERCP or an intraoperative cholangiogram. Patients with a score of 1 should undergo endoscopic US or MRCP for confirmation of the CBD stone. Using this approach, 5% of patients will undergo cholecystectomy despite choledocholithiasis, an acceptable rate as per the previous literature [21]. However, 29% of patients are at risk of undergoing diagnostic ERCP, slightly higher than the acceptable rate of 25% [22,23]. Using the ESGE and ASGE high likelihood criteria, the proportion of patients at risk of undergoing diagnostic ERCP is 31.1% and 31.6%, respectively.

Chisholm *et al* developed a model using an increase in alanine aminotransferase to more than 3 times the upper limit of normal, raised ALP more than the upper limit of normal and dilated CBD on US. The authors showed that the presence of 0 or 1 risk factors rules out CBD stones in 98.6% of cases, and when the score was 3, 77.8% of patients with ACC had

choledocholithiasis [23]. This earlier predictive model appears better than the current study in the validation cohort. However, it was based on the odds ratio calculated from the univariate analysis [23] and did not evaluate the independence of each predictive factor by multivariate analysis.

Apart from being a retrospective study, the current study had a few other limitations. Our patients with ACC included a higher proportion of patients with coexisting choledocholithiasis (36%) and acute biliary pancreatitis (25%) [15]. This could be due to referral bias at a highly specialized endoscopic center. However, the suboptimal performance of current guidelines for predicting choledocholithiasis in ACC and the proposed model for evaluation can be utilized in general gastroenterology practice. We have used parameters for analysis at admission and have not studied the utility of serial LFT monitoring. However, previous studies have shown conflicting results regarding the role of serial LFT monitoring [18,24,25] and the current guidelines do not recommend it.

To conclude, a significant proportion of patients with ACC have concomitant choledocholithiasis. The performance of the ASGE and ESGE guidelines' risk stratification criteria is inadequate in patients with ACC. We suggest the utilization of a separate predictive model for suspected choledocholithiasis in these patients. However, these findings need to be validated prospectively in the future.
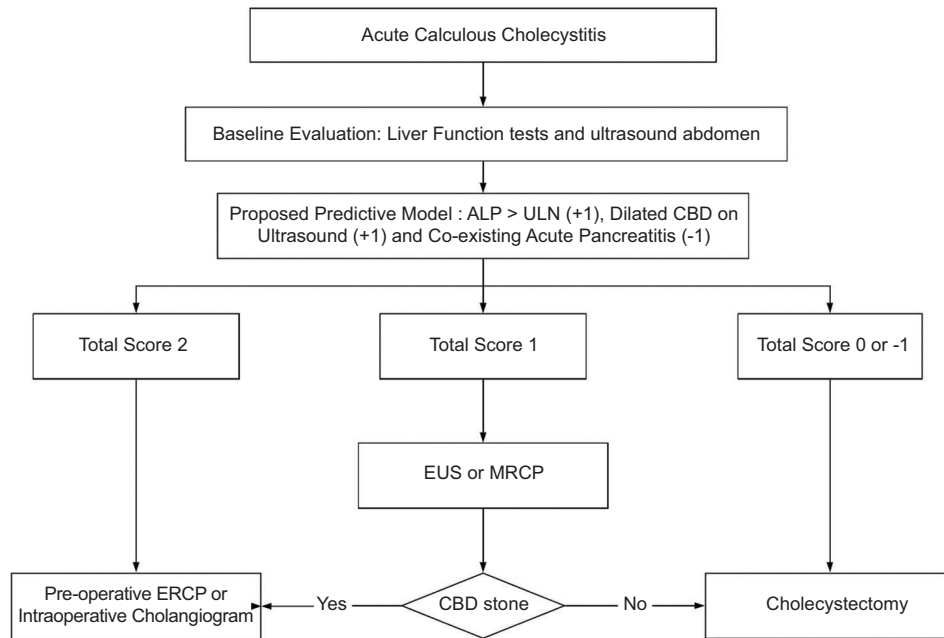
Figure 1 A proposed predictive model for choledocholithiasis in acute calculous cholecystitis
ALP, alkaline phosphatase; ULN, upper limit of normal; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound

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Summary Box

What is already known:

- Patients with acute calculous cholecystitis (ACC) can have coexisting choledocholithiasis
- Current guidelines for the evaluation of choledocholithiasis do not mention its application in patients with ACC

What the new findings are:

- ASGE and ESGE risk stratification algorithms are suboptimal in predicting choledocholithiasis in patients with ACC
- A separate predictive model can be used for the prediction of choledocholithiasis in ACC

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