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Evaluation of ASGE Criteria for Prediction of Choledocholithiasis: Can Early Endoscopic Ultrasound Utilization Make the Prediction More Accurate?

Amir Sadeghi[1], Hamid Asadzadeh Aghdaei[1], Pardis Ketabi Moghadam[1]*, Khaled Rahmani[2], Mohsen Rajabnia[1], Niloufar Salehi[3], Seyedayin Hosseini[3], Seyedeh Melika Fanaei[3]

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Abstract

Background: ASGE predictive model for the detection of choledocholithiasis is a reasonable approach for the management of patients with cholelithiasis. Surgeons do not pursue cholecystectomy without evaluation of the biliary system when laboratory tests and diagnostic imaging evidence show biliary duct involvement. Literature revisions reveal that the prediction of choledocholithiasis based on ASGE criteria suffers from poor accuracy which results in unnecessary ERCPs. We decided to estimate the sensitivity and specificity of the ASGE predictive model for the detection of choledocholithiasis with the hope that early EUS would obviate the need for unnecessary ERCPs among highly probable patients for choledocholithiasis based on ASGE criteria.

Methods: This is a prospective intervention and control study on the accuracy of ASGE criteria for the prediction of choledocholithiasis. To evaluate the sensitivity and specificity of ASGE criteria, patients were followed in two groups of controls who were treated based on ASGE guidelines and cases who underwent primary EUS. The clinical relevance of the ASGE criteria was estimated by sensitivity and specificity using SPSS Statistics 28 software. Then, absolute risk reduction utilizing primary EUS was also calculated.

Results: The sensitivity and specificity of the ASGE predictive guideline for choledocholithiasis were estimated to be 62.31% and 51.85%, respectively. Evaluation of the ASGE guideline also revealed that patients in the intermediate probability group who finally required ERCP based on EUS results (false-negatives) were estimated to be 49.1% and patients who were predicted to require ERCP but finally did not need ERCP (false positives) were estimated to be 37.68%. The comparison of the two groups revealed the need for ERCP in about 55.56% of the primary EUS group and 77.42% in the ASGE group. Utilization of primary EUS reduced the need for ERCP by an absolute risk reduction of 0.299. (Primary Endpoint)

Conclusion: ASGE guideline is associated with the overestimation of ERCP in cholelithiasis. The usage of primary EUS will reduce the need for ERCP.

Keywords: Cholelithiasis, Choledocholithiasis, Cholangiopancreatography, Endoscopic Retrograde (ERCP), Endoscopic Ultrasound (EUS), Pancreatitis, Cholangitis

Conflicts of Interest: *None declared*
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Corresponding author: *Dr Pardis Ketabi Moghadam, ketabimoghdam.p@sbmu.ac.ir*

1. Research Institute for Gastroenterology and Liver Diseases (RIGLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Liver and Digestive Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran
3. Medicine Faculty, Shahid Beheshti University of Medical Sciences, Tehran, Iran

↑What is "already known" in this topic:
The absence of choledocholithiasis is vital before pursuing cholecystectomy. ASGE guideline has been accepted to predict the probability of choledocholithiasis and suggest the best way of dealing with this problem based on laboratory tests and diagnostic imaging reports.

→What this article adds:
Evidence show that utilization of ASGE criteria would result in unnecessary ERCPs. This study has evaluated the sensitivity and specificity of this guideline. The results show that primary evaluation of patients suspicious of choledocholithiasis by EUS instead of ASGE guideline would obviate the need for ERCP by an absolute risk reduction of about 0.299.

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Introduction

Management of patients with choledocholithiasis is of clinical importance due to the fact that around 5-20% of patients with symptomatic cholelithiasis have choledocholithiasis at the time of cholecystectomy (1-4). The probability of choledocholithiasis in patients with cholelithiasis is suspected when a rise in serum bilirubin, alkaline phosphatase (ALP), Aspartate/Alanine aminotransferase (AST/ALT) with/without evidence of choledocholithiasis in ultrasound is detected (5). Presence of choledocholithiasis in symptomatic cholelithiasis harbors potential dangers like cholangitis and biliary pancreatitis indicating the significance of perfect evaluation of the biliary system before cholecystectomy (6-10). Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) are gold standards for the detection of choledocholithiasis (3). Edematous wall of duodenum and pancreas after pancreatitis, haemobilia, parasitic infection, neoplasms, and artifacts producing internal gallbladder echoes, bile duct dilatations following biliary abnormalities like sclerosing cholangitis, anomalous biliary system, and cholangiocarcinoma as well as biliary and duodenal air bubbles blur the trans-abdominal ultrasound and radiographic visualization of distal parts of CBD particularly for small stones and can interfere with a definite diagnosis of CBD stone (11). So, ERCP and EUS are more accurate for the diagnosis of choledocholithiasis in this group of patients (12, 13). Few guidelines are as acceptable as the American society for gastrointestinal endoscopy (ASGE) for prioritization of available methods in the detection of choledocholithiasis based on clinical, laboratory and ultrasound findings. Having reviewed ASGE guidelines (14), predictive risk factors for choledocholithiasis are stratified into three groups "very strong", "strong" and "moderate". "Very strong" predictive risk factors are cholangitis, serum bilirubin more than 4 mg/dl, and any observed common bile duct (CBD) stone in ultrasound. "Strong" predictive risk factors for choledocholithiasis are either CBD diameter of more than 6mm in patients without previous history of cholecystectomy or serum bilirubin level=1.8-4 mg/dl. Finally, "moderate" predictive risk factors of choledocholithiasis are abnormal liver function tests, age more than 55 years old and biliary pancreatitis. It is driven by the guideline that patients with one very strong predictive risk factor or two concomitant strong predictive risk factors are known high probable for choledocholithiasis and are selected to undergo ERCP which is a simultaneous diagnostic and therapeutic procedure. Patients with one strong predictive risk factor or one/more moderate predictive risk factors are allocated into the intermediate probability group. They are considered to proceed with an early EUS as a low-risk diagnostic procedure for evaluation of the biliary system (10). Patients without any predictive risk factor for choledocholithiasis will be sent for cholecystectomy without any further evaluation and actually were excluded from the present study. The design of the study is depicted in Figure 1. There are some evolving studies emphasizing the role of EUS before ERCP in patients with high probable suspicion of choledocholithiasis. The rationale for this decision is the rate of documented unnecessary ERCPs done based on ASGE guidelines (15-19). So, this is logical to widen indications for early EUS in the management of symptomatic cholelithiasis to choose more accurate patients for ERCP. Taleghani hospital is a tertiary referral center for patients with cholelithiasis. With this regard, we evaluated the accuracy of ASGE predictive risk factors for the detection of choledocholithiasis in the hope of a reduction in the number of unnecessary ERCPs by utilization of early EUS since performing an ERCP has the potential risk of serious post-ERCP pancreatitis, and other fatal complications and further cost (10). In the cases of the present study, only patients with cholangitis were sent directly for ERCP and the rest of them with very strong, strong and moderate risk factors for choledocholithiasis have initially been evaluated by EUS to make sure if ERCP was only allocated to the group of patients with definite choledocholithiasis. In contrast, the management of patients in the control group was based on ASGE guidelines. After evaluation of CBD and extraction of any stone or sludge, cholecystectomy was considered for every eligible patient as soon as possible. The number of patients in the high probable group who finally did not have choledocholithiasis based on EUS/ERCP results is representative of unnecessary ERCPs. The objection to this estimation is the probability of false negative results (patients with choledocholithiasis who are reported negative) using EUS in this study. To reduce the bias of this fact, we followed our patients over the next 6 months after cholecystectomy. Recurrence of symptoms in a duration less than 6 months from index cholecystectomy indicates a residual stone and therefore represents the inaccuracy of EUS in the detection of choledocholithiasis (20, 21). Although there are some studies emphasizing the fact that ASGE guideline needs revision. More studies are still required to show the best approach for the prediction of choledocholithiasis and narrow candidates for ERCP down in this group of patients (22). This study is looking forward to decreasing the number of unnecessary ERCPs among highly probable patients for choledocholithiasis based on ASGE guidelines by means of primary EUS before proceeding with ERCP.

Methods

This is a prospective intervention and control study on 216 patients referred to Taleghani hospital, a tertiary referral center for biliary diseases, with symptomatic cholelithiasis suspicious of choledocholithiasis. The design of the study is depicted in Figure 1. Patients were included in the study after acceptance and signing a written informed consent. This study has been registered in the research institute for gastroenterology and liver diseases under the supervision of Shahid Beheshti medical university with the code of medical ethics: IR.SBMU.MSP.REC.1400.803.

Patients older than 18 years with symptomatic cholelithiasis reported in transabdominal ultrasound including biliary pain and/or biliary pancreatitis suspected to CBD stone

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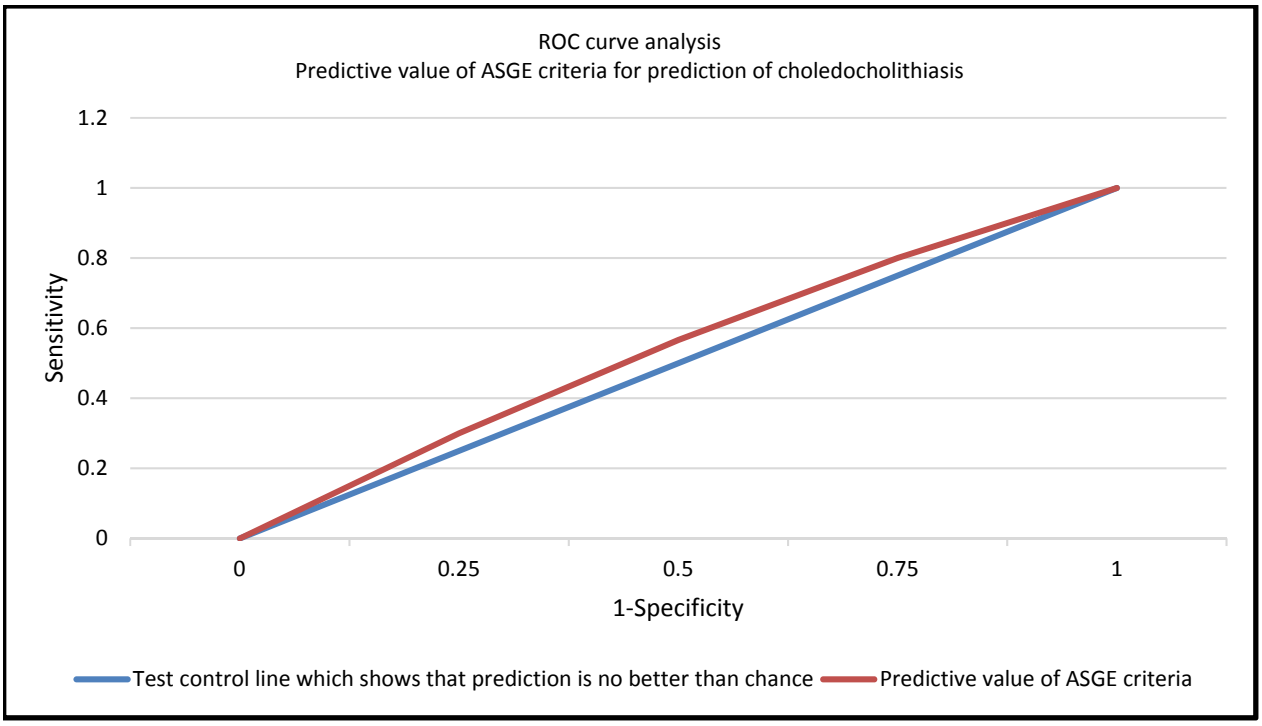

Figure 1. ROC curve analysis. The capacity of ASGE criteria for prediction of ERCP in patients with cholelithiasis (Red curve) is 0.5664 which shows that ASGE criteria are only a little better than the control line (Blue curve) with AUC equal to 0.5 which shows that performance of the diagnostic test is no better than chance. The Control line (Blue curve) shows the situation that the predictive model does not have any discrimination capacity for the prediction of ERCP in patients with cholelithiasis.

based on biochemical tests (elevation of AST/ALT/ALP/bilirubin) and/or ultrasound abnormalities (stone detection in CBD, CBD dilation) referred to hospital between 2020 July the first and 2021 July the first were included in the study. Pancreatitis is defined as the elevation of amylase and/or lipase more than 3-fold the upper limit of normal in a patient with abdominal pain consistent with pancreatitis or abdominal imaging suggestive of pancreatitis. Patients allocated to the low-risk group were sent for cholecystectomy without further evaluation and were excluded from the study. Patients with previous BillrothII, coagulopathy, cirrhosis, history of post-ERCP pancreatitis, non-biliary pancreatitis, pancreatobiliary malignancy, and cardiopulmonary or other systemic diseases were also excluded from the study. All eligible patients were admitted to the daycare or gastroenterology ward for further evaluation. One of the proposed efforts to lessen the bias of the study was choosing similar timing of lab tests for all patients due to the fact that fluctuation of liver enzymes would be probable during the time. On admission, patients who had high and intermediate probability for choledocholithiasis were divided into two groups of cases (who underwent primary EUS) and controls (who underwent EUS or ERCP based on ASGE guideline) by means of simple randomization using a random computer-generated number. Patients with cholangitis were sent for an early ERCP due to the risk of fatal complications in deferred drainage of the biliary system. Patients who required an ERCP after EUS proceeded with an ERCP in the same setting. Finally, we evaluated the accuracy of ASGE predictive risk factors for the detection of choledocholithiasis and then compared the need for ERCP in both groups. To evaluate and exclude patients with missed choledocholithiasis based on the EUS report, we followed patients 6 months after discharge. It is believed that CBD stones detected within 6 months from index cholecystectomy are supposed to be a recurrence of an already existing choledocholithiasis (residual stone), but stones detected after 6 months of surgery are considered new ones. Residual stones are indicative of missed stones by EUS (20-22). Missed stones were excluded from the analysis.

Statistical analysis

Data were inserted into the IBM SPSS software-Malaysia version 26 for the windows operating system. The sample size was calculated based on the relevant studies as indicated in references 16, 18, and 20 with a power level of 80% and a probability of type II error. The normal distribution of data was analyzed by the Shapiro-Wilk test. Qualitative variables for the two groups were presented by mean (standard deviation, SD) and quantitative variables were introduced by numbers (percentages). To report P-values, chi-square (for frequencies ≥ 5) and fissure exact tests (for frequencies less than 5) were used to determine whether or not there is a significant association between categorical variables. The sensitivity and specificity of the guideline and absolute risk reduction of the introduced method were calculated. To compare the mean age of the 2 groups, a t-test of independence was used.

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Results

216 patients referred to Taleghani hospital with symptomatic cholelithiasis with respect to the exclusion and inclusion criteria and, after signing a written informed consent, were divided into high, intermediate and low probable groups for choledocholithiasis. Then, highly probable patients for choledocholithiasis were randomly allocated to the control (ASGE) or case (Primary EUS) groups (Figure 2). Low-probable patients for choledocholithiasis were sent for cholecystectomy and did not enter the study. Two patients in the case group and nobody in the control group had a recurrence of the disease during 6-month follow-up. The mentioned two patients were indicative of the inaccuracy of EUS for the detection of choledocholithiasis and were excluded from the study. Finally, 124 patients were allocated to the ASGE group and 90 patients entered into the primary EUS. Patients with cholangitis urgently underwent ERCP regardless of patients' allocation to the case or control group. In the control group, 87 patients were females (70.16%) and 37 were males (29.84%). In the case group, 65 patients were females (72.22%) and 25 were males (27.78%). Demographic characteristics are shown in Table 1. Other variables are shown in Table 2. Pain severity was estimated based on Wong-Baker criteria to be mild, moderate and severe in 15 (12.1%), 39 (31.45%), and 70 (56.45%) patients in the control group, respectively and in 65 (14.44%), 25 (31.1%), 45 (54.44%) patients in the case group, subsequently. Prevalence of illicit drugs in controls was calculated to be 23.39%, 17.74%, 1.61% and 4.03% and 55%, 13.33%, 1.11% and 4.44% in the case group for tobacco, opioids, stimulants and alcohol, respectively. The proportion of subjects who reported having leukocytosis was estimated to be 14.52% versus 10% and thrombocytopenia was shown to be 4.03% versus 3.33% in case and control groups. In this study, abnormal AST and ALT were defined by an elevation of more than 25 U/L for women and 35 U/L for men based on AASLD guidelines. ALP of more than 400 U/L was considered to be higher than normal. Bilirubin level was stratified into 3 groups of less than 1.8 mg/dl, 1.8-4 mg/dl, and ≥ 4 mg/dl. A chi-square test of independence showed that with CI=95% there was no significant difference between variables in cases and controls.

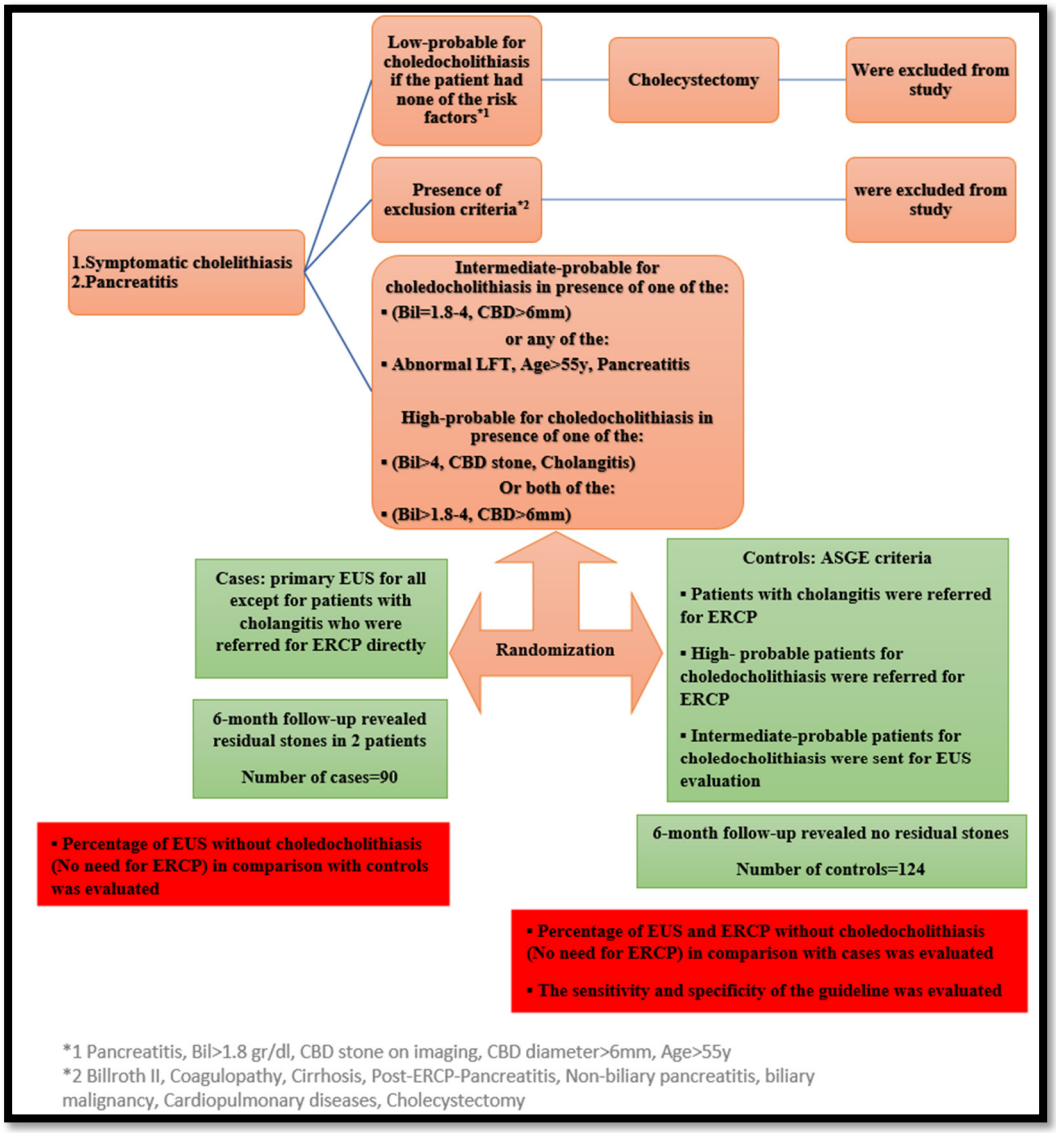

Figure 2. Design of study

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Percentages of patients with abnormal AST, ALT, ALP and Bilirubin were 81.45%, 80.65%, 45.16% and 55.64% respectively in controls and 80%, 8101%, 45.5% and 48.9% in relative manner for cases. Abnormal bilirubin levels were divided into 2 groups of 1.8-4 and ≥4 which were 33.87% and 21.77% in controls and 30% and 18.9%, correspondingly in cases. Prevalence of pancreatitis and cholangitis was estimated to be 12.9% and 6.49% in controls and 10% and 5.56% in cases which was not statistically different. Prevalence of CBD dilation and CBD stone reported in trans-abdominal ultrasound was 73.39% and 25.58% in controls and 66.67% and 11.11% among cases. As could be seen in Table 2, with CI=95%, the difference between ultrasound CBD stone findings was statistically significant between cases and controls. The purpose of this study was to have a comparison between ERCPs done in the ASGE group and the primary EUS group. As can be seen in Table 3, the prediction of choledocholithiasis based on ASGE guidelines regarding the final results of EUS/ERCP revealed a sensitivity of 62.31% which reveals the percentage of patients with definite choledocholithiasis who required ERCP based on the guideline. But we have to take into account the number of patients in the intermediate group who are not decided based on ASGE guidelines if they require ERCP or not. So, 37.68% of patients who were reported to need ERCP did not have choledocholithiasis and did not require ERCP. The reasons for misinterpretation of diagnostic criteria were found to be: 14 cases with passed stone, one case of Klatskin tumor, 3 cholangiocarcinomas, 3 pancreatic cancer, one choledochal cyst, 3 ampullary cancers and one fasciola hepatica. The estimated specificity of the guideline was 51.85% which shows the percentage of patients without choledocholithiasis who did not require ERCP based on the guideline. As illustrated in Figure 1, the quality of the ASGE guideline as a classifier was assessed on the basis of the (AUC) area under the receiver operating characteristic curve (ROC) which was calculated to be 0.566. This curve shows that the mentioned guideline has predicted the need for ERCP only a little better than a random decision. The percentage of patients who underwent an ERCP was found to be 77.42% and the percentage of patients who underwent an unnecessary ERCP was 20.97% based on the ASGE guideline. On the other hand, we have patients in the case group who did not have any unnecessary ERCP and the percentage of ERCPs in this group was 55.56%. So, we can calculate the absolute risk for ERCP as

Table 1. Demographic characteristics

Demographic characteristic		Control (n=124)	Case (n=90)	*P*-value
Gender	Female n (%)	87 (70.16%)	65 (72.22%)	0.742
	Male n (%)	37 (29.84%)	25 (27.78%)	
Age Mean (SD)		44.35± (17.9)	44.22 ± (13.7)	0.470

Table 2. Frequency of patients' characteristics required for prediction of need to ERCP based on ASGE criteria at admission

variable		Control (n=124)	Case (n=90)	*P*-value
Pain severity	Mild n (%)	15 (12.1%)	13 (14.44%)	0.878
	Moderate n (%)	39 (31.45%)	28 (31.1%)	
	Severe n (%)	70 (56.45%)	49 (54.44%)	
Illicit drugs	Tobacco n (%)	29 (23.39%)	23 (25.55%)	0.849
	Opioids n (%)	22 (17.74%)	12 (13.33%)	
	Stimulants n (%)	2 (1.61%)	1 (1.11%)	
	Alcohol n (%)	5 (4.03%)	4 (4.44%)	
Leukocytosis n (%)		18 (14.52%)	9 (10%)	0.304
Thrombocytopenia n (%)		5 (4.03%)	3 (3.33%)	0.790
Biochemical tests	Abnormal AST[1] n (%)	101 (81.45%)	72 (80%)	0.914
	Abnormal ALT[2] n (%)	100 (80.65%)	73 (81.1%)	
	Abnormal ALP[3] n (%)	56 (45.16%)	41 (45.5%)	
	Bil[4]<1.8 mg/dl n (%)	55 (44.35%)	46 (51.1%)	
	Bil=1.8-4 mg/dl n (%)	42 (33.87%)	27 (30%)	
	Bil≥4 mg/dl n (%)	27 (21.77%)	17 (18.9%)	
Pancreatitis		16 (12.9%)	9 (10%)	0.513
Cholangitis		8 (6.45%)	5 (5.56%)	0.786
CBD[5] dilation>6mm		91 (73.39%)	60 (66.67%)	0.245
CBD[5] stone in trans-abdominal ultrasound		28 (22.58%)	10 (11.11%)	0.030

[1]. AST: Aspartate aminotransferase
[2]. ALT: Alanine aminotransferase
[3]. ALP: Alkaline phosphatase
[4]. Bil: Bilirubin
[5]. CBD: Common bile duct

Table 3. Contingency table for prediction of choledocholithiasis in controls (ASGE guideline)

Controls		True class based on the final results		Total (n)
		Necessary ERCPs[1] n (%)	Unnecessary ERCPs[1] n (%)	
Prediction class based on the ASGE guideline	Necessary ERCPs[1] n (%)	43 (62.31%) Sensitivity=62.3%	26 (37.68%) Unnecessary ERCPs[1] (False Positive)	69
	Unnecessary ERCPs[1] n (%)	27 (49.1%) Patients with intermediate probability for choledocholithiasis who finally required ERCP[1] (So-called False Negative)	28 (51.85%) Specificity=51.85%	55
Total (n)		70	54	124

[1]. ERCP: Endoscopic retrograde cholangiopancreatography

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Table 4. The relationship between variables and the need for ERCP in the control group using the chi-square test

ERCP		Is required	Is not required	*P*-value
Sex	Female n (%)	48 (68.57%)	39 (72.22%)	0.660
	Male n (%)	22 (31.43%)	15 (27.78%)	
Age	<55years old n (%)	33 (47.14%)	31 (57.41%)	0.257
	≥55years old n (%)	37 (52.86%)	23 (42.59%)	
Pain severity	Mild n (%)	2 (2.86%)	13 (24.07%)	0.001
	Moderate n (%)	21 (30%)	18 (33.33%)	
	Severe n (%)	47 (67.14%)	23 (42.59%)	
Illicit drugs	Tobacco n(%)	17 (24.29%)	12 (22.22%)	0.788
	Opioids n (%)	15 (21.43%)	7 (12.96%)	0.221
	Stimulants n (%)	1 (1.43%)	1 (1.85%)	0.853
	Alcohol n (%)	4 (5.71%)	1 (1.85%)	0.278
Leukocytosis		11 (15.71%)	7 (12.96%)	0.666
Thrombocytopenia		2 (2.86%)	3 (5.56%)	0.449
Biochemical tests	Abnormal AST[1] n (%)	62 (87.14%)	39 (74.07%)	0.020
	Abnormal ALT[2] n (%)	59 (84.29%)	41 (75.93%)	0.243
	Abnormal ALP[3] n (%)	35 (50%)	21 (38.89%)	0.218
	Bil[4] <1.8 mg/dl n (%)	32 (45.71%)	23 (42.59%)	0.537
	1.8-4 mg/dl n (%)	21 (30%)	21 (38.89%)	
	≥4 mg/dl n (%)	17 (24.29%)	10 (18.52%)	
Pancreatitis		7 (10%)	9 (16.67%)	0.272
Cholangitis		8 (11.43%)	0 (0%)	0.010
CBD[5] dilation		58 (82.86%%)	33 (61.11%)	0.007
CBD[5] stone		23 (32.86%)	5 (9.26%)	0.002

[1]. AST: Aspartate aminotransferase
[2]. ALT: Alanine aminotransferase
[3]. ALP: Alkaline phosphatase
[4]. Bil: Bilirubin
[5]. CBD: Common bile duct

about 0.774 in the control group and approximately 0.555 in the case group. Comparison of these results between cases and controls indicates an absolute risk reduction (ARR) of about 0.774-0.555=0.219 using early EUS in this group of patients (NNT=4.6). The relationship between variables evaluated in the control group and the need to perform ERCP has been illustrated in Table 4. Based on the chi-square test of independence, the more these values are far from each other. They would be more likely to be related to the need for ERCP. As a result, patients with severe abdominal pain were more likely to need an ERCP than patients with mild abdominal pain. Furthermore, high levels of serum AST were more likely than other tests to show the high probability of choledocholithiasis and the need for a therapeutic procedure like ERCP. It is also indicated that two variables including dilation of CBD diameter>6mm and presence of CBD stone in trans-abdominal ultrasound, have a significant relationship with the need for ERCP. There was also a significant relationship between cholangitis and ERCP necessity which is derived from the fact that all patients with cholangitis had been sent for an urgent ERCP. In contrast to the mentioned variables, there was not found any statistically significant difference between other variables like sex, age, consumption of illicit drugs, High levels of serum ALT/ALP/Bilirubin, pancreatitis and ERCP necessity.

Discussion

A precise prediction of choledocholithiasis accompanied by an appropriate sweeping of CBD before cholecystectomy would be lifesaving in patients with symptomatic cholelithiasis. ASGE guideline is an acceptable decision-making approach for the prediction of choledocholithiasis. It seems that the sensitivity of this predictive value has been increased at the cost of utilization of more ERCPs which would be potentially life-threatening. The idea of performing early EUS for the detection of choledocholithiasis is derived from studies conducted on patients with suspected choledocholithiasis and introduced EUS as a very good diagnostic modality for choledocholithiasis with a sensitivity and specificity of approximately 100% and 92.8%, respectively (16). This is close to the sensitivity of EUS in our study which was estimated to be 100% in controls who did not show any recurrence of CBD stone within 6-month follow-up after cholecystectomy and about 97.6% in cases with 2 recurrences out of 90 patients during 6-month follow up from surgery. Distribution of sex, age, severity of pain, prevalence of consumption of illicit drugs, and laboratory tests were not statistically different between cases and controls using simple randomization. Evaluation of the ASGE guideline as a classifier using ROC and AUC illustrated an estimation of about 0.566. This estimation shows that the mentioned guideline has not been successful in an acceptable prediction of the need for ERCP. But it should be considered that the number of false negatives in this table demonstrates the number of patients allocated to the intermediate probability group for choledocholithiasis who finally required ERCP. So, it should be noted that defining strict indications for early usage of ERCP would result in more unnecessary ERCPs and more complications attributed to the overestimation of ERCP in this group of patients. The results show an ARR of about 0.219 by early evaluation of choledocholithiasis by an acceptable sensitive diagnostic procedure like EUS before the decision to proceed with a potentially dangerous procedure like ERCP. ARR=0.219 explains that utilization of 4-5 EUS would decrease 1 unnecessary ERCP in this group of patients (NNT=4.6). This is comparable to the studies that claim using early EUS in patients referred for symptomatic cholelithiasis would decrease the number of ERCPs by about 30%

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in two series of patients with pancreatitis suspected of biliary origin undergoing sequential EUS and ERCP. The sensitivity of these modalities was estimated to be 91-97% and 97-98%, respectively (7,8). These studies show the generalizability (external validity) of the presented study. There is another study on 219 patients who underwent ERCP for suspected choledocholithiasis in Cleveland clinic which demonstrated that ASGE high-risk criteria had only more than 50% accuracy for the prediction of probability in choledocholithiasis (14). There are also studies that show the poor diagnostic accuracy of ASGE clinical criteria leading to unnecessary ERCPs in (33.1%) of the high-probable group (16, 17). These studies also indicated that the results would be more accurate when lab tests are performed 24 hours after admission (23). Appropriate timing for laboratory tests would lessen the bias resulting from the stone passage (16). As derived from the present study, 14 patients of the ASGE group who were estimated to be high-probable for choledocholithiasis finally had normal ERCPs. This shows the inaccuracy of this guideline for the prediction of choledocholithiasis. Passed stones were found to be the main reason for this misinterpretation. Other reasons justifying the absence of choledocholithiasis were one Klatskin tumor, 3 other cholangiocarcinomas, 3 pancreatic cancers, one choledochal cyst, 3 ampullary cancers and one Fasciola hepatica. The probability of various reasons mimicking the signs and symptoms of choledocholithiasis shows the importance of a precise evaluation of the biliary system before proceeding with an ERCP. As illustrated in Table 4, the severity of abdominal pain, high levels of serum AST, dilation of CBD more than 6mm and observation of CBD stone via trans-abdominal ultrasound are variables that reject the null hypothesis and show a significant relationship with a need for ERCP (P-value<0.05). It is not surprising to see a significant relationship between cholangitis and the necessity for ERCP when we had sent all cases of cholangitis for an early ERCP. In keeping with the results, there are some studies introducing risk factors for the prediction of choledocholithiasis like R factor which is (patient's ALT/ALT the upper limit of normal)/(patient's ALP/ALP the upper limit of normal<2. But these models still need more evidence to be endorsed (14). This study magnifies the importance of early utilization of EUS in symptomatic cholelithiasis for the detection of choledocholithiasis (24-28).

Conclusion

Acknowledgments

This study has been designed and managed under the supervision of the research institute of Shahid Beheshti University of medical sciences and all expenses were supposed to be provided by the gastroenterology and liver diseases research institute budget of Shahid Beheshti Medical University. We show our sincere appreciation to the staff of the gastroenterology and liver diseases research Institute and gastroenterology and liver diseases ward of Taleghani hospital for their cooperation in the preparation of the required information and equipment for this study.

Ethical approval

This study has been submitted to the Research Institute for Gastroenterology and Liver Diseases under the supervision of Shahid Beheshti Medical University, Tehran, Iran. The ethical code of study is IR.SBMU.MSP.REC.1400.803 on March 8th 2022.

Authors' contributions

Concept – Amir Sadeghi, Hamid Asadzadeh Aghdaei; Design –Amir Sadeghi, Hamid Asadzadeh Aghdaei, Pardis Ketabi Moghadam; Supervision – Amir Sadeghi, Hamid Asadzadeh Aghdaei; Resources – Amir Sadeghi; Materials – Amir Sadeghi; Data Collection and/or Processing – Niloufar Salehi, Seyedayin Hosseini, Seyedeh Melika Fanaei, Mohsen Rajabnia; Analysis and/or Interpretation –Khaled Rahmani, Pardis Ketabi Moghadam; Literature Search – Pardis Ketabi Moghadam, Mohsen Rajabnia; Writing Manuscript – Pardis Ketabi Moghadam, Mohsen Rajabnia; Critical Review – Pardis Ketabi Moghadam.

Conflict of Interests

The authors declare that they have no competing interests.

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