

Use of Liver Function Tests as First-line Diagnostic Tools for Predicting Common Bile Duct Stones in Acute Cholecystitis Patients

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Abstract

Background Prior studies have examined the use of liver function tests (LFT) for predicting the presence of common bile duct (CBD) stones in chronic cholecystitis (CC) patients. It is currently unclear whether LFT are also useful for predicting CBD stones in patients with acute cholecystitis (AC).

Methods Of 1059 patients who visited an emergency room with gallbladder-related symptoms between March 2004 and December 2009, 854 patients were analyzed, and were divided into three groups (556 AC patients without CBD stones (AC – CBD), 98 AC patients with CBD stones (AC + CBD), and 200 CC patients without CBD stones). We compared the LFT values at admission and the changes in LFT values over time following admission among the three groups.

Results The LFT values were significantly greater in the AC + CBD group than in the AC – CBD groups. Of all the LFT variables analyzed, γ -glutamyl transpeptidase was the most reliable variable for predicting the presence of CBD stones, with a sensitivity of 80.6 % and a specificity of 75.3 % at the cut-off level of 224 IU/L. The elevated LFT values decreased significantly from the start of the follow-up assessment to before cholecystectomy in the AC – CBD group, but were unchanged before stone removal in the AC + CBD group.

Conclusion The LFT values on initial admission and the changes in LFT values over time are reliable predictors of CBD stones in patients with AC.

Introduction

Approximately 10–15 % of patients with gallbladder (GB) stones are known to have common bile duct (CBD) stones at the time the GB stones are detected [1, 2]. The presence

of CBD stones introduces a therapeutic dilemma for choosing between endoscopic and surgical removal of the CBD stones, as well as the method and timing of cholecystectomy. This situation is particularly challenging in patients with acute cholecystitis (AC) who need a prompt decision regarding early cholecystectomy. Therefore, accurate prediction of the presence of CBD stones is essential to allow surgeons to select the optimal surgical strategy for AC. However, radiologic imaging modalities that are commonly used in clinical practice, such as ultrasonography (US) and computed tomography (CT), display low sensitivities and specificities for predicting the presence of CBD stones [3, 4]. Although magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) are

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good diagnostic modalities for detecting possible CBD stones, they cannot be routinely used because of their high cost and invasiveness, respectively [5–7]. Moreover, they may not be available in small-volume hospitals or in emergent settings. Therefore, there is a need for simple and noninvasive first-line diagnostic tools that can identify patients at high risk of having CBD stones, and prompt the use of more definitive diagnostic tools such as MRCP or ERCP in AC patients.

Most patients with CBD stones have abnormal liver function test (LFT) values, such as aspartate aminotransferase (AST), alkaline phosphatase (ALT), alkaline phosphatase (ALP), total bilirubin (TB), and γ -glutamyl transpeptidase (GGT). In previous studies, preoperative LFT could predict the presence of CBD stones in patients with GB stones, and several scoring systems based on LFT were proposed [2, 8–15]. However, the role of LFT in the prediction of CBD stones has been limited to patients with chronic cholecystitis (CC) and has been rarely reported in AC patients [16, 17]. Although CBD stones are not always present in AC patients, AC is often associated with elevated LFT values for various reasons, including reactive hepatitis, portal tract inflammation, and occasionally direct pressure on the biliary tract from the distended GB [18–21]. Moreover, the clinical manifestation is similar between AC with and without CBD stones [17, 22]. Therefore, it is unclear whether the LFT scoring systems for predicting CBD stones that were established in CC patients can also be applied to AC patients.

In this study, we compared LFT values between patients with and without CBD stones to evaluate the role of LFT in predicting the presence of CBD stones in AC patients.

Materials and methods

Study population

Between March 2004 and December 2009, 1059 patients presented with gallbladder-related symptoms to the emergency room at the Seoul National University Bundang Hospital, Korea. Of these, 654 AC patients without biliary pancreatitis or other diseases that may cause LFT abnormalities, such as viral or drug-related hepatitis, malignancy, and Mirizzi syndrome, were retrospectively analyzed in this study. We excluded patients with biliary pancreatitis because it is usually caused by tiny stones, which may cause transient LFT abnormalities, and are spontaneously passed out [17, 22]. The 654 AC patients were divided into two groups: AC patients without CBD stones (AC – CBD group; $n = 556$) and AC patients with CBD stones (AC + CBD group; $n = 98$). We also identified a group of 200 CC patients without CBD stones (CC – CBD group), with the cohort of

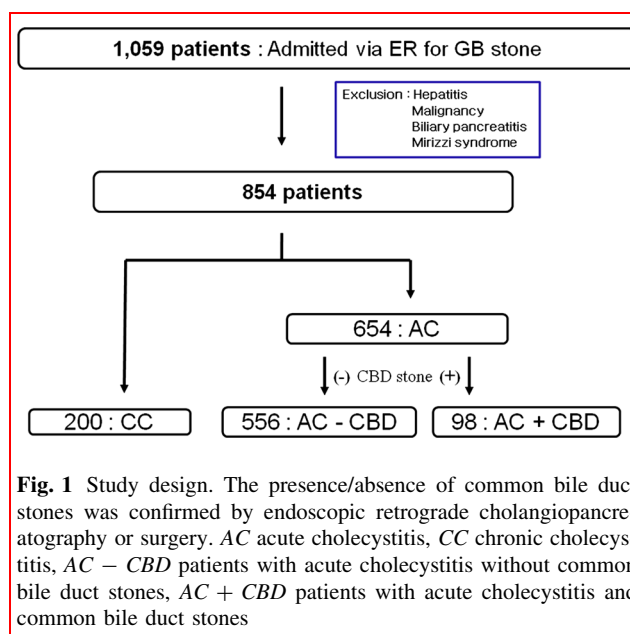


Fig. 1 Study design. The presence/absence of common bile duct stones was confirmed by endoscopic retrograde cholangiopancreatography or surgery. AC acute cholecystitis, CC chronic cholecystitis, AC – CBD patients with acute cholecystitis without common bile duct stones, AC + CBD patients with acute cholecystitis and common bile duct stones

1059 patients, and compared their LFT values with those in the AC – CBD group to confirm that the changes in LFT values were related to AC (Fig. 1).

According to the 2013 Tokyo Guidelines, AC was defined as local signs of inflammation (Murphy’s sign or right upper abdominal tenderness), a systemic sign of inflammation (fever, elevated C-reactive protein, or elevated white blood cell count), and imaging findings characteristic of AC [23, 24]. The AC + CBD group only included patients with CBD stones, which were detected by ERCP or surgery.

ERCP was indicated for patients with either (1) increased serum bilirubin and ALP or GGT concentrations with a dilated bile duct, or (2) visible bile duct stones detected by ultrasonography (US) or computed tomography (CT). If indicated, ERCP was performed as soon as possible. Patients with increased bilirubin and ALP or GGT concentrations and a nondilated bile duct underwent LFT and received short-term conservative management. ERCP was performed if the LFT values did not improve during the follow-up period. Percutaneous cholecystostomy was performed in patients with high surgical risk owing to the presence of severe comorbidities. Intraoperative cholangiography was not carried out to detect possible CBD stones.

Laboratory data

The clinical data, including the LFT values, were obtained from the patients’ medical records. The LFT, including TB, AST, ALT, ALP, and GGT, were measured on the first day of acute admission in all AC patients. Follow-up LFT data obtained during the index admission were available for 186 (28.4 %) patients: 123 patients in the AC – CBD group

and 63 patients in the AC + CBD group. The follow-up LFT were performed before/after cholecystectomy in the AC – CBD group and before/after removing the CBD stones in the AC + CBD group. The LFT values recorded upon ER admission and at the follow-up during the index admission were analyzed in this study.

Study design

This retrospective study was designed as follows. First, the LFT values recorded at ER admission were compared between the AC – CBD group and the CC – CBD group to confirm the LFT abnormalities were related to AC. We also compared the LFT values between the AC – CBD and AC + CBD groups to determine the impact of the presence of CBD stones in AC patients. Second, the predictability and the cut-off value for each LFT for predicting the presence of CBD stones in AC patients were calculated using receiver operating characteristic (ROC) curve analysis. Third, the changes in LFT values from ER admission to the follow-up tests during the index admission were compared between the AC – CBD and AC + CBD groups to evaluate the impact of CBD stones on the changes in LFT values over time in AC patients. Written informed consent was obtained from all patients before each procedure. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital.

Statistics

Continuous variables are presented as the mean and range. The χ^2 test was used to compare categorical variables. Continuous variables were compared using independent-samples *t* tests, one-way analysis of variance (ANOVA), and repeated-measures analysis of variance (RANOVA), as appropriate. The sensitivity and specificity of our predictive model were estimated by ROC curve analysis, and the overall diagnostic performance of each LFT was compared using the area under the ROC curve. All of the analyses were performed using SPSS 17.0 for Windows (release 17.0 SPSS Inc., Chicago, IL, USA), MedCalc for Windows (version 11.2, MedCalc Software, Mariakerke, Belgium), and SAS statistical software (version 9.1; SAS institute, Cary, NC, USA). Differences were considered significant at *P* values of <0.05.

Results

Characteristics of AC patients

The AC patients (i.e., AC – CBD and AC + CBD groups) comprised a total of 378 men (57.8 %) and 276 women

(42.4 %), with a mean age of 58.2 years (17–95 years). The mean age (58.0 vs. 59.4 years) and percentage of males (57.3 vs. 57.1 %) were not significantly different between the AC – CBD and AC + CBD groups. However, the AC patients included more males (57.8 vs. 47.5 %, *P* = 0.008) and older patients (58.0 vs. 53.8 years, *P* = 0.003) than the CC – CBD group.

Percutaneous cholecystostomy was performed before cholecystectomy in 101 (15.4 %) AC patients, including 92 (16.6 %) in the AC – CBD group and 9 (9.2 %) in the AC + CBD group (*P* = 0.401). In the AC – CBD group, cholecystectomy was performed during initial admission in 433 (77.9 %) patients and in the next admission in the remaining 123 patients. In the AC + CBD group, the CBD stones were removed by endoscopic sphincterotomy in 92 (93.9 %), percutaneous transhepatic biliary drainage in 2 (2.0 %) patients, and CBD exploration during cholecystectomy in 4 (4.1 %) patients. Seventy-nine (80.6 %) patients underwent cholecystectomy after removal of the CBD stones during their initial admission.

LFT values on ER admission in the CC – CBD, AC – CBD, and AC + CBD groups

The mean LFT values on ER admission were significantly greater in the AC – CBD group than in the CC – CBD group (all, *P* < 0.001) (Table 1). The mean LFT values were significantly greater in the AC + CBD group than in the AC – CBD group (all, *P* < 0.001). The value for at least one LFT was more than 2 times higher than the normal value in 220 (39.6 %) patients in the AC – CBD group and in 92 (93.9 %) patients in the AC + CBD group.

Predictability of each LFT for the presence of CBD stones in AC patients

ROC curve analyses were performed to evaluate the predictability of each LFT for the presence of CBD stones in AC patients. The areas under the ROC curves (95 % confidence interval) were as follows: TB, 0.757 (0.695–0.819); AST, 0.768 (0.709–0.827); ALT, 0.769 (0.710–0.828); ALP, 0.749 (0.687–0.811); and GGT, 0.816 (0.762–0.870) (all, *P* < 0.001) (Fig. 2). The pairwise comparisons of the ROC curves revealed that GGT was the most reliable variable for predicting the presence of CBD stones (*P* < 0.001). The optimal GGT cut-off value was 224.0 IU/L with a sensitivity of 80.6 % and specificity of 75.3 % (Table 2).

Change in LFT values over time in AC patients

According to the results of RANOVA, the LFT values in the AC – CBD group decreased significantly during a mean follow-up of 4.0 days (1–11 days) before

Table 1 Liver function test results on initial admission to the emergency room

	CC (<i>n</i> = 200)	AC – CBD (<i>n</i> = 556)	AC + CBD (<i>n</i> = 98)	<i>P</i> *
TB (mg/dL)	0.72 ± 0.33 (0.1–2.7)	1.72 ± 1.48 (0.2–8.6)	4.08 ± 3.3.04 (0.6–23.0)	<0.001
AST (IU/L)	26.0 ± 26.3 (2–278)	89.9 ± 152.9 (4–618)	275.3 ± 209.4 (15–1086)	<0.001
ALT (IU/L)	28.6 ± 26.0 (2–224)	96.2 ± 159.7 (6–653)	317.4 ± 239.6 (9–919)	<0.001
ALP (IU/L)	74.1 ± 28.9 (22–346)	114.3 ± 78.0 (26–631)	213.9 ± 118.2 (48–554)	<0.001
GGT (IU/L)	36.5 ± 40.2 (8–229)	186.5 ± 215.7 (10–1180)	488.4 ± 316.4 (35–1652)	<0.001

Values are presented as the mean ± SD (range)

CC chronic cholecystitis, AC – CBD patients with acute cholecystitis without common bile duct stones; patients with acute cholecystitis with common bile duct stones, TB total bilirubin, AST aspartate aminotransferase, ALT alanine aminotransferase, ALP alkaline phosphatase, GGT γ -glutamyl transpeptidase

* *P*-values were determined by one-way analysis of variance. According to the post hoc analysis with Tukey's multiple comparison test, all of the variables were significantly different among the three groups (CC < AC – CBD < AC + CBD; *P* < 0.001)

cholecystectomy, and decreased even further after a mean follow-up of 3.9 days (2–7 days) after cholecystectomy (Fig. 3). By contrast, in the AC + CBD group, there were no improvements in any LFT variable, except for ALP, during a mean follow-up of 4.3 days (1–12 days) before removing the CBD stones, but all LFT values improved significantly after a mean follow-up of 4.3 days (2–14 days) after removing the CBD stones (Fig. 3).

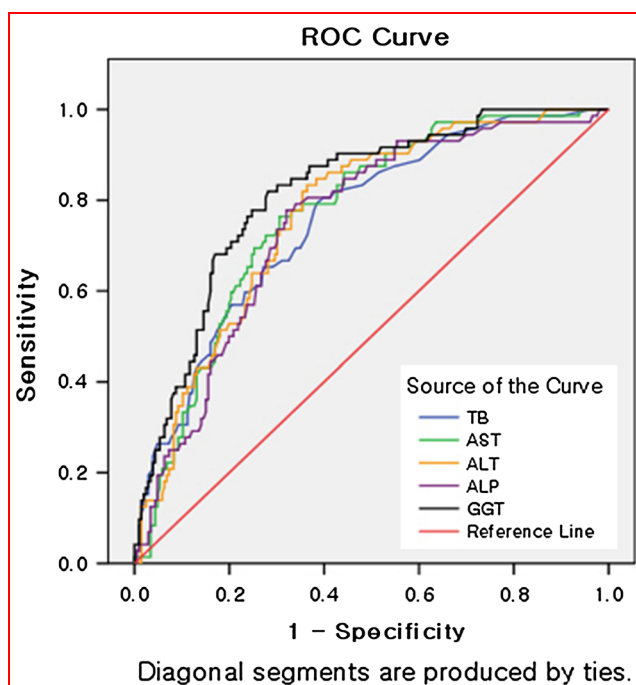


Fig. 2 Receiver operating characteristic curves for individual liver function tests as predictors of common bile duct stones. The sensitivity (true-positive fraction) and 1-specificity (false-positive fraction) with the area under the curve were computed for each possible value of the predicted model. ALP alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, GGT γ -glutamyl transpeptidase, TB total bilirubin

Discussion

This study confirmed the usefulness of initial LFT for the prediction of CBD stones in AC patients based on the analysis of the largest dataset to have been reported to date. Although AC-related inflammation was associated with LFT abnormalities, even in the absence of CBD stones, the levels of all LFT variables were significantly greater in the AC + CBD group than in the AC – CBD group. Of the LFT assessed in this study, GGT was the most powerful predictor for CBD stones. The sensitivity and specificity of GGT for predicting the presence of CBD stones at the cut-off level of 224.0 IU/L were over 75 %, which were similar to or better than the values reported in other studies [9, 16]. In addition, unlike previous studies that only analyzed the initial LFT values as possible predictors of CBD stones [16, 17, 25], the present study showed the usefulness of monitoring the changes in LFT variables over time. Although the LFT values improved during a short period of treatment in the AC – CBD group, they did not improve until the removal of the CBD stones in the AC + CBD group. These findings imply that the inflammation-related LFT abnormalities in AC patients are transient and resolved over time, but cannot recover without removing the CBD stones. However, improvements in LFT values during the follow-up period may suggest that the CBD stones were spontaneously passed, avoiding unnecessary ERCP. Therefore, follow-up LFT, if the clinical situation permits, are likely to be helpful in predicting the presence of CBD stones if the initial LFT results are moderately elevated. Finally, our analysis of the LFT profiles, including the LFT values recorded on ER admission and the changes in LFT values over time, highlight the utility of using LFT to identify AC patients likely to have CBD stones.

LFT as first-line diagnostic tests offer potential clinical benefits in terms of the diagnosis and treatment of CBD

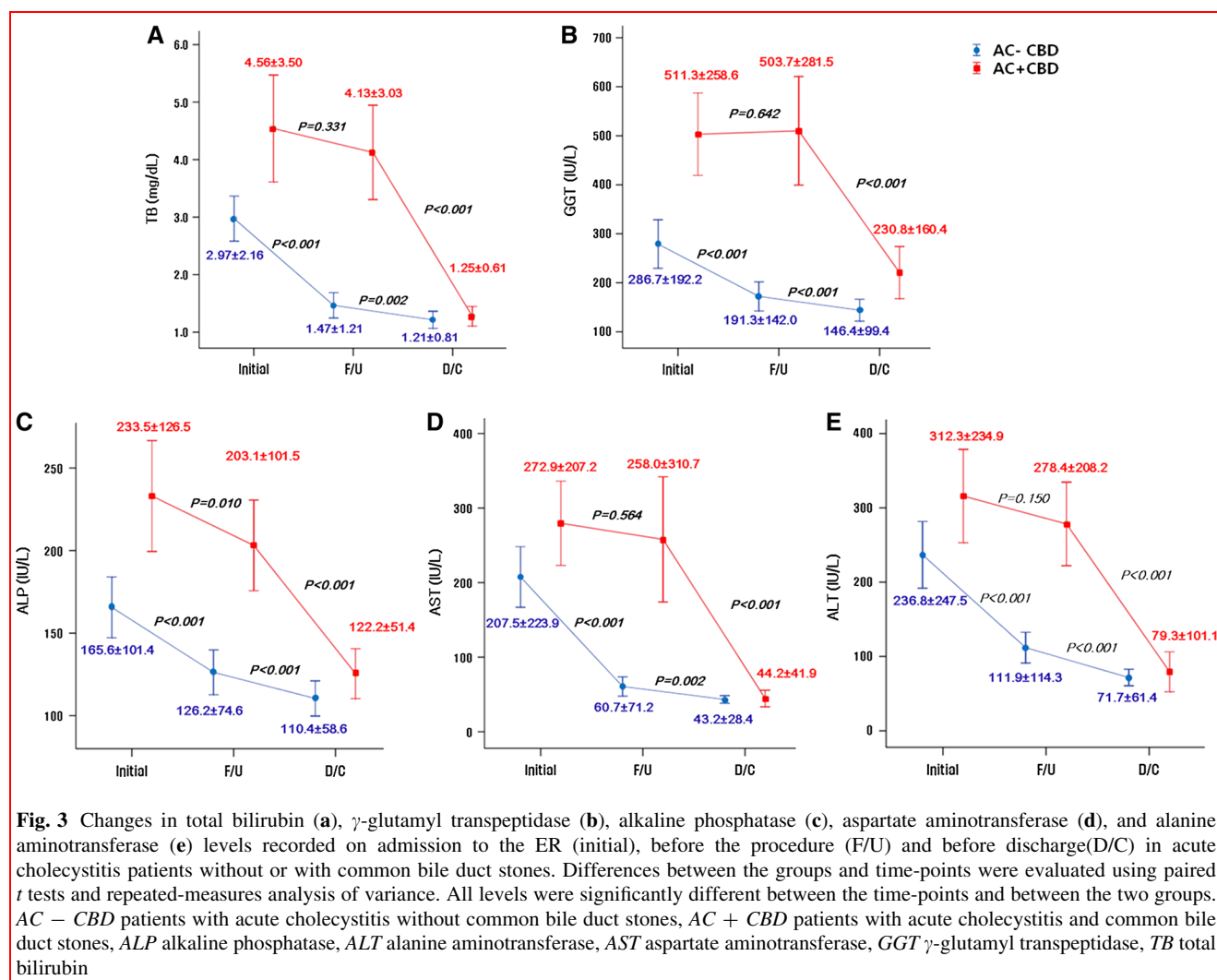
Table 2 Sensitivity and specificity of predicting common bile duct stones for individual liver function tests

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
TB	2.10 mg/dL	74.5	77.7	35.9	94.1	76.1
AST	106.0 IU/L	74.5	80.9	40.3	93.7	79.0
ALT	102.0 IU/L	79.6	78.9	40.4	93.6	79.4
ALP	138.0 IU/L	71.4	78.0	36.4	92.9	77.0
GGT	224.0 IU/L	80.6	75.3	50.0	91.4	74.1

PPV positive predictive value, NPV negative predictive value, TB total bilirubin, AST aspartate aminotransferase, ALT alanine aminotransferase, ALP alkaline phosphatase, GGT γ -glutamyl transpeptidase

stones, not only in CC patients, but also in AC patients. First, these tests can avoid the risk of potential complications and the medical cost associated with ERCP and MRCP in patients without CBD stones. The negative predictive value of elevated LFT values were >90 %. Second, they make it possible to perform cholecystectomy

promptly, by avoiding the delay associated with performing ERCP and MRCP and obtaining negative findings in AC patients without CBD stones. This is particularly valuable now that there is strong evidence supporting early laparoscopic cholecystectomy for AC in terms of reducing morbidity, length of hospital stay, and costs. Third,



although trans-abdominal US and conventional CT are commonly performed in AC patients, these modalities have limitations for the diagnosis of CBD stones. The secondary finding of bile duct dilatation was reported to be a reliable predictor of CBD stones, with relatively high sensitivity and specificity [26]. However, US and conventional CT are less accurate than ERCP or MRCP for the detection of CBD stones. Intervening bowel gas makes it difficult to interpret the distal part of the CBD and noncalcified stones by US, because they appear dark against the background of the bile, and they are not readily detected by CT. Although these data were not reported, elevated LFT values occurring together with relevant radiologic finding improved the diagnostic power for detecting CBD stones in the present study. Moreover, the diagnostic value of LFT is magnified in primary care settings and in developing countries where US or CT are unavailable. The sensitivity and specificity of LFT in this study were similar to or better than US or CT radiologic findings.

There are some limitations to the present study. First, this study was conducted retrospectively. The patients were not managed according to a standardized protocol. Patients with acute cholecystitis were not evaluated or treated according to standardized procedures or a clinical algorithm. The time from initial admission to the treatment of CBD stone was not consistent. Follow-up LFT were only performed in patients who received conservative treatments for some time before definitive treatment of their CBD stones. There may be limited benefits to follow-up LFT in some AC patients who require prompt treatment. Second, the presence of CBD stones was confirmed surgically or by ERCP. It is possible that small CBD stones could spontaneously pass out before removal of the CBD stones, and thus only affect the LFT values recorded on admission. Conversely, small CBD stones may not cause elevated LFT values and might be missed. Third, the LFT values in AC patients may differ according to the stage of the disease at the time the patient was admitted. These factors might be responsible for the wide ranges of LFT values in AC patients that were reported in prior studies and in the present study [16, 17, 22]. Therefore, a well-designed prospective study is necessary to evaluate the diagnostic performance of LFT for CBD stones in AC patients.

In conclusion, this study revealed that the LFT values recorded on initial admission and the changes in LFT values over time reflect CBD stones in patients who do not pass their stones spontaneously. Our findings suggest that LFT can be adopted as first-line diagnostic tests for predicting the presence of CBD stones in AC patients to avoid unnecessary time, risk, and medical cost associated with ERCP and MRCP by identifying patients at high risk of

CBD stones who would benefit from further diagnostic tests and treatments.

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Compliance with ethical standards

Conflicts of interest Nothing to declare.

References

1. Mitchell SA, Jacyna MR, Chadwick S (1993) Common bile duct stones: a controversy revisited. *Br J Surg* 80:759–760
2. Ko CW, Lee SP (2002) Epidemiology and natural history of common bile duct stones and prediction of disease. *Gastrointest Endosc* 56:S165–S169
3. Baron RL (1987) Common bile duct stones: reassessment of criteria for CT diagnosis. *Radiology* 162:419–424
4. Prat F, Meduri B, Ducot B et al (1999) Prediction of common bile duct stones by noninvasive tests. *Ann Surg* 229:362–368
5. Rijna H, Borgstein PJ, Meuwissen SG et al (1995) Selective preoperative endoscopic retrograde cholangiopancreatography in laparoscopic biliary surgery. *Br J Surg* 82:1130–1133
6. Folsch UR, Nitsche R, Ludtke R et al (1997) Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. *N Engl J Med* 336:237–242
7. Tham TC, Lichtenstein DR, Vandervoort J et al (1998) Role of endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis in patients undergoing laparoscopic cholecystectomy. *Gastrointest Endosc* 47:50–56
8. Collins C, Maguire D, Ireland A et al (2004) A prospective study of common bile duct calculi in patients undergoing laparoscopic cholecystectomy: natural history of choledocholithiasis revisited. *Ann Surg* 239:28–33
9. Yang MH, Chen TH, Wang SE et al (2008) Biochemical predictors for absence of common bile duct stones in patients undergoing laparoscopic cholecystectomy. *Surg Endosc* 22:1620–1624
10. Menezes N, Marson LP, Debeaux AC et al (2000) Prospective analysis of a scoring system to predict choledocholithiasis. *Br J Surg* 87:1176–1181
11. Shiozawa S, Tsuchiya A, Kim DH et al (2005) Useful predictive factors of common bile duct stones prior to laparoscopic cholecystectomy for gallstones. *Hepatogastroenterology* 52:1662–1665
12. Topal B, Van de Moortel M, Fieus S et al (2003) The value of magnetic resonance cholangiopancreatography in predicting common bile duct stones in patients with gallstone disease. *Br J Surg* 90:42–47
13. Stain SC, Marsri LS, Froes ET et al (1994) Laparoscopic cholecystectomy: laboratory predictors of choledocholithiasis. *Am Surg* 60:767–771
14. Koo KP, Traverso LW (1996) Do preoperative indicators predict the presence of common bile duct stones during laparoscopic cholecystectomy? *Am J Surg* 171:495–499
15. Liu TH, Consorti ET, Kawashima A et al (2001) Patient evaluation and management with selective use of magnetic resonance cholangiography and endoscopic retrograde cholangiopancreatography before laparoscopic cholecystectomy. *Ann Surg* 234:33–40

16. Peng WK, Sheikh Z, Paterson-Brown S et al (2005) Role of liver function tests in predicting common bile duct stones in acute calculous cholecystitis. *Br J Surg* 92:1241–1247
17. Padda MS, Singh S, Tang SJ et al (2009) Liver test patterns in patients with acute calculous cholecystitis and/or choledocholithiasis. *Aliment Pharmacol Ther* 29:1011–1018
18. Indar AA, Beckingham IJ (2002) Acute cholecystitis. *BMJ* 325:639–643
19. Geraghty JM, Goldin RD (1994) Liver changes associated with cholecystitis. *J Clin Pathol* 47:457–460
20. Triger DR, MacIver AG, Gamlen TR et al (1976) Liver abnormalities and gallstones: a prospective combined clinical, histological and surgical study. *Br J Surg* 63:272–277
21. Trowbridge RL, Rutkowski NK, Shojania KG (2003) Does this patient have acute cholecystitis? *JAMA* 289:80–86
22. Chang CW, Chang WH, Lin CC et al (2009) Acute transient hepatocellular injury in cholelithiasis and cholecystitis without evidence of choledocholithiasis. *World J Gastroenterol* 15:3788–3792
23. Yokoe M, Takada T, Strasberg SM et al (2013) TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). *J Hepato Biliary Pancreat Sci* 20:35–46
24. Kiriya S, Takada T, Strasberg SM et al (2013) TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos). *J Hepato Biliary Pancreat Sci* 20:24–34
25. Hammarstrom L, Ranstam J (1998) Factors predictive of bile duct stones in patients with acute calculous cholecystitis. *Dig Surg* 15:323–327
26. Neitlich JD, Topazian M, Smith RC et al (1997) Detection of choledocholithiasis: comparison of unenhanced helical CT and endoscopic retrograde cholangiopancreatography. *Radiology* 203:753–757