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Original Article

Diagnostic value of liver function enzymes for choledocholithiasis

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Abstract: The study aimed to investigate the diagnostic value of liver function enzymes in patients with choledocholithiasis. The retrospective study included 120 choledocholithiasis patients (experimental group), 110 cholecystolithiasis patients (control group) and 60 healthy subjects (healthy group) from January 2013 to December 2014. Blood sample was extracted from each participant, and biochemical tests were performed for alanine aminotransferase (ALT), aspartate aminotransferase (AST), acid phosphatase (ACP), gamma-glutamyltranspeptidase (GGT), direct Bilirubin (DBIL) and indirect Bilirubin (IBIL). Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic value of each biochemical parameter for choledocholithiasis. A binary logistic regression model was established to assess the combined predictive power of two parameters. The experimental group had markedly increased serum levels of ALT, AST, ACP, GGT, DBIL and IBIL than the control group and the healthy group. ROC analysis revealed that of the 6 biochemical parameters, ALT, AST and GGT had area under the curve (AUC)>0.8. ALT, AST and GGT had low sensitivity (74.20%; 67.50%; 56.70%) and high specificity (80.00%; 93.60%; 92.70) at the optimal cutoff value (31.5 U/L; 39.0 U/L; 93.60%). Logistic regression analysis revealed that ALT and AST were independent predictors of common bile duct (CBD) stones. The combination of ALT and AST (AUC=0.85) did not markedly improved the AUC compared with ALT or AST singly. ALT, AST and GGT might be recommended as diagnostic biomarkers for CBD stone. The liver function test could only serve as a subsidiary diagnostic method.

Keywords: Bile duct stones, liver function, enzymatic indexes, logistic regression analysis

Introduction

Choledocholithiasis refers to the gallstones formed in the common bile duct (CBD) [1]. Approximately, 7-20% of cholelithiasis cases are choledocholithiasis cases whose primary treatment choice is cholecystectomy [2]. Among its varied clinical syndromes and signs, common bile duct obstruction and concomitant acute suppurative cholangitis are two primary syndromes [2, 3]. The common bile duct obstruction might result in life-threatening conditions, such as cholangitis and acute pancreatitis. There are several available diagnostic imaging tests for choledocholithiasis, such as abdominal ultrasound [4], computed Tomography (CT) [5] and magnetic resonance cholangiopancreatography (MRCP) [6]. However, these tests are expensive and time-costing with unsatisfactory diagnostic accuracy. Although the sensitivity and specificity of intraoperative cholangiography (IOC) to detect CBD stone are reported to be 100% and 98%, respectively, IOC is an invasive procedure and might cause serious complications or even death [7]. An easy, cheap and non-invasive test for diagnosis of CBD stone will greatly benefits the patients.

Liver function test is a part of the safe and cheap routine blood biochemical tests and provides useful information for the diagnosis and management of liver dysfunction [8]. Several liver function-associated enzymes are assayed, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), acid phosphatase (ACP), gamma-glutamyltranspeptidase (GGT), direct Bilirubin (DBIL), indirect Bilirubin (IBIL). DBIL and IBIL have been established as useful surrogate biomarkers for diagnosis of CBD construction [9, 10]. However, the serum BIL level may not be closely associated with the seriousness of CBD construction, because the BIL might be metabolized by the liver compensation function [11]. There is evidence that the AST/ALT ratio is associated with the liver fibro-

sis degree [12]. Elevated AST/ALT ratio has been reported to be a diagnostic marker of alcoholic liver disease [13]. Although the serum levels of these liver enzymes have been assessed in patients with CBD stone [14], the diagnostic value of these biochemical biomarkers for CBD stone has not been fully elucidated.

To address the issue, the study studied the difference of ALT, AST, ACP, GGT, DBIL and IBIL between choledocholithiasis patients, cholecystolithiasis patients and healthy subjects. Receiver operating characteristic (ROC) analysis was performed to analyze the predictive strength of each parameter for choledocholithiasis. A binary logistic regression model and an ROC curve based on the model were used to assess the combined predictive power of two parameters.

Materials and method

Patients

The retrospective study included 120 patients with choledocholithiasis who underwent choledocholithotomy and choledochoscope exploration in our hospital from January 2013 to December 2014. The patients were diagnosed with choledocholithiasis based on results of MRCP, colour duplex ultrasonography and computerized tomography (CT). They had no history of stomach, duodenum or hepatobiliary system diseases. The exclusion criteria were: hypertension, heart disease, diabetes, pancreatitis, pancreatic cancer, acute inflammation of hepatobiliary system, purulent inflammation of biliary tract. The 120 patients were defined as the experimental group. We also selected 110 patients with cholecystolithiasis who received cholecystectomy in our hospital from January 2013 to December 2014 (control group). Moreover, 60 normal subjects who had body examination in our hospital from January 2013 to December 2014, were also included in the study (healthy group). They were free from liver disease or cholelithiasis based on the abdominal CT images. All participants of the study were diagnosed by the same experienced surgeons.

Biochemical analysis

Peripheral venous blood of 3-5 mL was collected from each member after overnight fasting. The blood sample was centrifuged for 10 min at 2000 r/min, and the supernatant was collected and stored in -80°C refrigerator. The serum samples underwent biochemical measurement of ALT, AST, ACP, GGT, DBIL and IBIL by using enzyme-linked immuno sorbent assay (ELISA) kits (K-X BIOTECHNOLOGY Company, Shanghai, China). The experiment was performed in accordance with the instructions. Finally, the optical density (OD) value of each sample was measured at 450 nm by a Absorbance Microplate Reader (ELx800, Bio-Tek).

According to the data collected by our hospital, the normal ranges of these parameters were defined as follows: ALT, 0-38 U/L; AST, 0-38 U/L; ACP, 32-140 U/L; GGT, 0-54 U/L; DBIL, 0-6.8 μmol/L; IBIL, 0-14 μmol/L. Values within the normal ranges were defined as normal values. Values above the normal ranges were defined as abnormal values.

Statistical analysis

Each experiment was repeated three times. SPSS software (19.0 software, SPSS, Chicago, Illinois) was utilized for statistical analysis. Quantitative data was expressed as means ± standard deviation. Comparison of quantitative data was performed using Student t test or one-way analysis of variance (ANOVA). Comparison of qualitative data was performed using Chi-square test. The non-parametric Kruskal-Wallis test was used for multiple comparisons of non-normally distributed data among three groups.

ROC curve analysis and logistic conditional regression model

In order to detect the optimal cutoff value, area under the curve (AUC), specificity and sensitivity of ALT, AST, ACP, GGT, DBIL and IBIL for choledocholithiasis, a ROC curve was constructed with the biochemical data. AUC value >0.8 suggested good predictive power of a biomarker for choledocholithiasis; AUC value 0.6-0.8, moderate predictive power; AUC value <0.6, poor predictive power [15]. The optimal cutoff value was determined when the sum of sensitivity and specificity reached the maximal. For the purpose of evaluating the combined predictive power of two biomarkers for choledocholithiasis, a binary logistic conditional regression model by a forward stepwise manner was fitted [16] and a ROC curve based on the logistic

Table 1. Baseline characteristics of members in different groups

	Experimental group (n=120)	Control group (n=110)	Healthy group (n=60)	*P*-value
Male/female (n, %)	53 (44.2%)	56 (50.9%)	30 (50.0%)	0.556
Age (mean ± SD, years)	46.86 ± 11.57	44.03 ± 10.86	45.21 ± 12.54	0.175
Disease course (mean ± SD, years)	5.23 ± 1.63	4.98 ± 1.92	/	0.287

SD, standard deviation.

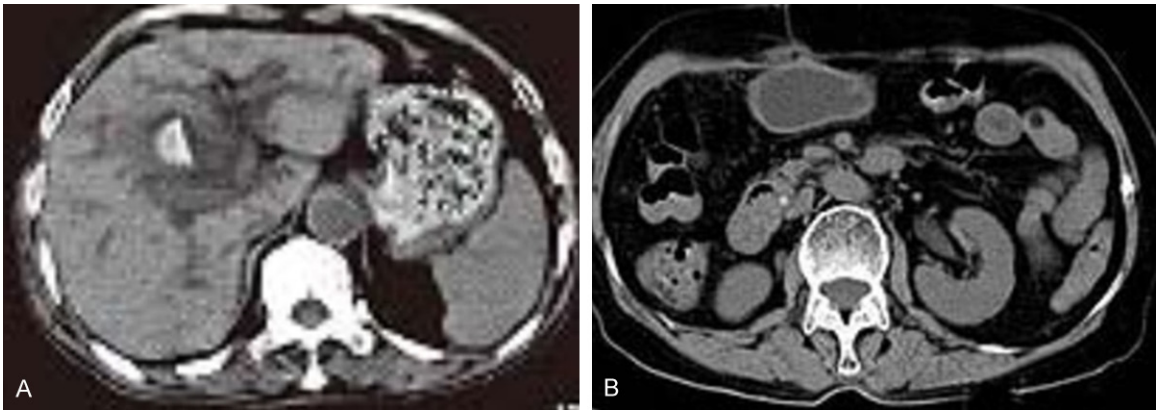

Figure 1. CT images. A. A representative CT image of a patient with choledocholithiasis in the experimental group; B. A representative CT image of a patient with cholecystolithiasis in the control group.

regression model was constructed [17]. The AUC of the ROC curve was then calculated.

Results

Demographic data of participants in different groups

Baseline characteristics of members in experimental group, control group and healthy group were summarized in **Table 1**. There was no significant difference in sex, age and disease course between the 3 groups ($P>0.05$). A presentative CT image of choledocholithiasis and cholecystolithiasis was displayed in **Figure 1A** and **1B**, respectively.

Analysis of ALT, AST, ACP, GGT, DBIL and IBIL

The biochemical analysis revealed data of ALT, AST, ACP, GGT, DBIL and IBIL for each group. The members in each group were categorized into 2 subgroups based on the data of each parameter: normal subgroup and abnormal subgroup (**Table 2**). Chi-square test revealed significant differences in percentages of abnormal patients between the three groups for ALT, AST, ACP, GGT, DBIL and IBIL, respectively ($P<0.001$).

In order to further analyze the differences of these biochemical parameters between the three groups, the mean serum levels of ALT, AST, ACP, GGT, DBIL and IBIL were compared between the three groups by the non-parametric Kruskal-Wallis test. As shown in **Table 3**, the differences were significant between the experimental group, control group and healthy group in the mean levels of ALT, AST, ACP, GGT, DBIL and IBIL, respectively ($P<0.001$). Specifically, the experimental group had markedly elevated levels of ALT, AST, ACP, GGT, DBIL and IBIL than the control group and the healthy group. The control group had significantly lower levels of ALT and AST ($P<0.05$), but higher levels of GGT, DBIL and IBIL ($P<0.001$) compared to the healthy group. Yet, the difference in the serum level of ACP did not achieve significance between the control and the healthy groups ($P>0.05$).

ROC curve analysis

For the purpose of analyzing the power of the 6 biochemical parameters to predict choledocholithiasis, the ROC curve analysis was performed with the data (**Figure 2**). As shown in **Table 4**, the AUC for ALT, AST, ACP, GGT, DBIL and IBIL

Table 2. The number of patients with abnormal or normal values of liver function enzyme in each group

Enzyme	Subgroup	Experimental group (n=120)	Control group (n=110)	Healthy group (n=60)	*P*-value
ALT	Abnormal (n)	72	9	3	<0.001
	Normal (n)	48	101	57	
AST	Abnormal (n)	81	7	2	<0.001
	Normal (n)	39	103	58	
ACP	Abnormal (n)	59	5	3	<0.001
	Normal (n)	61	105	57	
GGT	Abnormal (n)	68	8	3	<0.001
	Normal (n)	52	102	57	
DBIL	Abnormal (n)	52	7	1	<0.001
	Normal (n)	68	103	59	
IBIL	Abnormal (n)	43	4	2	<0.001
	Normal (n)	77	106	58	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ACP, acid phosphatase; GGT, gamma-glutamyltranspeptidase; DBIL, direct Bilirubin; IBIL, indirect Bilirubin.

Table 3. Comparison of serum levels of the liver function enzymes in different groups

Enzyme	Experimental group (n=120)	Control group (n=110)	Healthy group (n=60)	*P*-value
ALT (U/L)	182 (11-497)[a]	22 (9-344)[b]	25 (1-55)[c]	<0.001
AST (U/L)	80 (8-159)[a]	15 (2-156)[b]	20 (1-45)[c]	<0.001
ACP (U/L)	158 (33-257)[a]	90 (33-259)[b]	101 (33-156)[b]	<0.001
GGT (U/L)	92 (14-168)[a]	30 (5-160)[b]	28 (6-87)[c]	<0.001
DBIL (μmol/L)	11.0 (2.1-55.0)[a]	5.0 (2.0-45.2)[b]	4.0 (1.0-10.5)[c]	<0.001
IBIL (μmol/L)	17 (2-25)[a]	12 (3-29)[b]	10 (1-19)[c]	<0.001

With regard to superscripts a, b and c, values labeled by different letters are significantly different from each other ($P<0.05$); values labeled by the same letter (a or b or c) are not significantly different from each other ($P>0.05$). ALT, alanine aminotransferase; AST, aspartate aminotransferase; ACP, acid phosphatase; GGT, gamma-glutamyltranspeptidase; DBIL, direct Bilirubin; IBIL, indirect Bilirubin.

was 0.819, 0.841, 0.744, 0.817, 0.657 and 0.627, respectively ($P<0.001$). Among the 6 parameters, ALT, AST and GGT had AUC>0.8, indicating good predictive power for choledocholithiasis. They were further analyzed for the optimal cutoff value (**Table 4**). The optimal cutoff value of ALT was 31.5 U/L, where its sensitivity and specificity were 74.20% and 80.00%, respectively. The optimal cutoff value of AST was 39.0 U/L, where its sensitivity and specificity were 67.50% and 93.60%, respectively. GGT had the optimal cutoff value at 53.0 U/L with 56.70% sensitivity and 92.70% specificity.

Logistic regression analysis

In light of the low sensitivities of ALT, AST and GGT singly, we attempted to evaluate the combined diagnosis power of two parameters. Because the AUC of ALT or AST was greater, a binary logistic conditional regression model by a forward stepwise manner was fitted for ALT and AST (**Table 5**). It revealed that ALT and AST were independent predictors of choledocholithiasis (ALT, $P<0.01$, 95% CI: 1.002-1.010; AST, $P<0.001$, 95% CI: 1.011-1.035). The fitted formula: ln (P/1-P)=-1.427+0.006 × ALT+0.023 × AST (P, the incidence of choledocholithiasis). With the *P*-value, a ROC curve based on the logistic regression model was constructed. As a result, the AUC was 0.85 for the combination of ALT and AST ($P<0.001$). It suggests that the combined predictive power of ALT and AST is not remarkably improved in comparison with ALT (AUC=0.819) or AST (AUC=0.841) singly.

Discussion

Choledocholithiasis could cause the obstruction of CBD that might result in life-threating diseases, such as cholangitis and acute pancreatitis. These diseases have surprisingly high morbidities and mortalities. Liver functions test was a routine examination on the blood samples of patients. They delivered useful information for diagnosis and treatment of hepatic dysfunction. The purpose of the study was to investigate the diagnostic value of biochemical parameters ALT, AST, ACP, GGT, DBIL and IBIL for CBD stone and to screen valuable diagnostic biomarker.

Chi-square test revealed that the percentages of patients with abnormal values of ALT, AST, ACP, GGT, DBIL or IBIL were significantly different between experimental group, control group and healthy group. Moreover, the serum levels of the 6 biochemical parameters were remark-

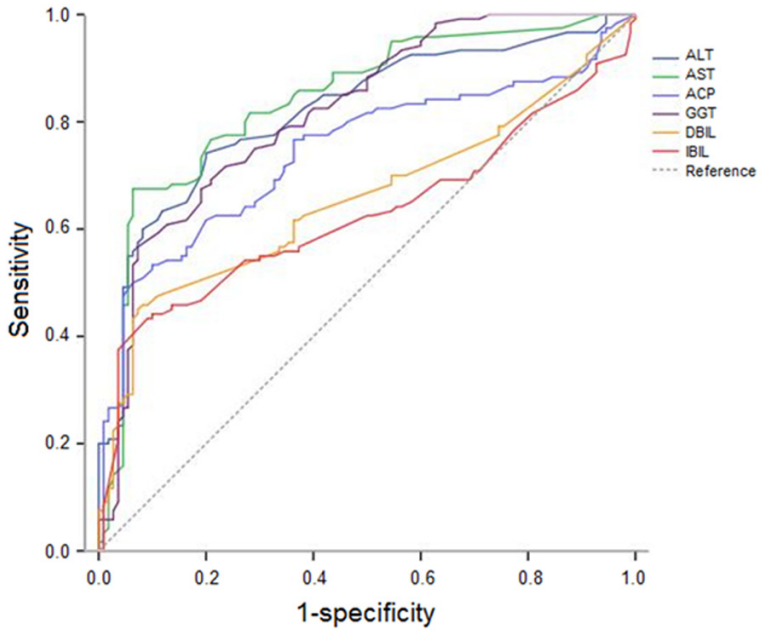

Figure 2. The ROC curves of ALT, AST, ACP, GGT, DBIL and IBIL in CBD stone.

Table 4. Results of ROC curve analysis

	AUC	95% CI	Cutoff point (U/L)	Sensitivity (%)	Specificity (%)	*P*-value
ALT	0.819	0.764-0.874	31.5	74.20	80.00	<0.001
AST	0.841	0.788-0.894	39.0	67.50	93.60	<0.001
ACP	0.744	0.679-0.809	53.0	56.7	92.7	<0.001
GGT	0.817	0.763-0.872	/	/	/	<0.001
DBIL	0.657	0.585-0.729	/	/	/	<0.001
IBIL	0.627	0.553-0.701	/	/	/	0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ACP, acid phosphatase; GGT, gamma-glutamyltranspeptidase; DBIL, direct Bilirubin; IBIL, indirect Bilirubin; ROC, receiver operating characteristic; AUC, area under the curve.

Table 5. The binary logistic conditional regression model for ALT and AST

	B	S.E,	Wals	df	*P*-value	Exp (B)	95% CI of EXP (B)
ALT	0.006	0.002	7.786	1	0.005	1.006	1.002-1.010
AST	0.023	0.006	14.463	1	0.000	1.023	1.011-1.035
Constant	-1.427	0.234	37.191	1	0.000	0.240	

B, partial regression coefficient; S.E, standard error; Wals, $(B/S.E)^2$; df, degree of freedom; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

ably higher in the experimental group than those in the control group and the healthy group. In line with the result, substantial elevations of AST, ALT and BIL have been reported in patients with choledocholithiasis by a previous study [18]. These results suggest that measurement of ALT, AST, ACP, GGT, DBIL or IBIL could provide valuable information to discriminate choledocholithiasis patients from cholecystolithiasis patients and healthy subjects. Nevertheless, it has been reported that GGT serum level is not significantly different between the patients with cholelithiasis and the patients with choledocholithiasis [19]. Therefore, further studies with large sample size are necessary to validate these findings.

ALT and AST are liver parenchymal cells-associated enzymes [21]. They are not only elevated in liver damage, but also detected in cardiac and skeletal muscle and red blood cells [14, 22]. GGT enzyme is responsible for transferring the gamma-glutamyl moiety of the glutathione in the glutathione cycle. It is present in several tissues, such as bile duct, kidney and gallbladder, and has been considered a useful biomarker for multiple liver diseases [20, 21]. In the present study, the ROC analysis showed that only ALT, AST and GGT have AUC>0.8, suggesting good diagnostic strength for CBD stone. They might be recommended as diagnostic biomarkers for CBD stone. Furthermore, GGT is reported to be significantly different between the patients with CBD stone and the patients with CBD stone-induced obstruction, and subsequently is recommended as a diagnostic marker for CBD obstruction [21].

The study revealed that atoptimal cutoff point value, ALT, AST and GGT had low sensitivity and high specificity for diagnosis of CDB stone. It indicates that patients of CBD stone are very likely to be detected, but a moderate proportion of patients with CBD stone and normal serum levels of ALT, AST and GGT might be

overlooked. Similarly, AST level is found to be changed only in 50.8% of the patients [22]. These findings reveal that diagnostic imaging tests should be performed for patients with normal serum levels of ALT, AST and GGT to rule out the possibility of CBT stone.

Furthermore, the study also evaluated the combined diagnostic power of ALT and AST by performing a binary logistic conditional regression analysis. ALT and AST were independent predictors of CBD stone. Disappointingly, their combined predictive power (AUC=0.85) was not remarkably improved compared with that of ALT or AST singly. These results suggest that liver function tests could not be used as a primary reliable diagnostic method, but only serve as a complimentary method. Similarly, there is evidence that increased liver enzymes do not play primary roles in diagnosis of CBD stone in biliary colic patients [23]. However, liver functions test is a preferable option in less-developed places where imaging test equipment is not available. This is a preliminary study. Further studies are necessary to be conducted in a large number of patients and to detect the combined predictive power of ALT, AST and GGT.

Collectively, ALT, AST and GGT were suggested to be good diagnostic biomarkers for CBD stone. Liver functions test is an auxiliary diagnostic method. Diagnostic imaging tests are necessary for patients who have normal serum levels of ALT, AST and GGT to exclude the possibility of CBD stone. The findings contribute to a better understanding of the diagnostic value of the liver function enzymes for CBD stone.

Disclosure of conflict of interest

None.

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