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Alpha-hydroxybutyrate dehydrogenase as a biomarker for predicting systemic lupus erythematosus with liver injury

Haitao Yu[a,*,1], Hengtong Han[a,1], Jiajia Li[a], Danyang Li[a], Lili Jiang[b]

[a] Department of Clinical Laboratory, The First Hospital of Lanzhou University, Lanzhou University, Lanzhou, Gansu, PR China
[b] School of Material Science and Technology, Lanzhou University of Technology, Lanzhou, Gansu, PR China

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ABSTRACT

Purpose: To explore potential biomarkers for identifying systemic lupus erythematosus (SLE) with liver injury.
Methods: This retrospective study examined the records of 158 SLE cases. The Apriori algorithm of association rules was employed to identify laboratory indexes related to liver injury in SLE patients.
Results: The ratio of albumin to globulin; levels of alpha-hydroxybutyrate dehydrogenase (α-HBDH), calcium, hemoglobin, urine protein, total cholesterol; absolute value of lymphocytes; red cell distribution width and hematocrit were identified by the Apriori algorithm from SLE-related liver injury patients. α-HBDH was identified as an independent risk factor for SLE-related liver injury. There were more SLE patients with liver injury in high-α-HBDH group than in low-α-HBDH group (64.63% vs. 21.05%; $P < 0.001$). In high-α-HBDH group, levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and gamma-glutamyl transpeptidase (GGT), and the AST/ALT ratio were significantly higher, and albumin and complement 3 (C3) were markedly lower. Moreover, α-HBDH level was significantly higher in the SLE-related liver injury patients than in the non-SLE-related liver injury patients. In addition, α-HBDH was positively correlated with levels of AST and LDH, the AST/ALT ratio, and the SLE Disease Activity Index 2000, and it was negatively correlated with albumin and C3. The optimal cutoff value of α-HBDH for distinguishing SLE patients with and without liver injury was 258.50 U/L, which provided a 60.94% sensitivity and a 94.67% specificity.
Conclusion: α-HBDH could be used to evaluate the disease activity of SLE-related liver injury, and it may be a potential biomarker for diagnosing SLE-related liver injury.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that damages multiple organs, including the liver, kidney, and circulatory system [1–3]. Liver injury is a common finding in SLE patients [4,5]. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) can be used to detect liver injury. However, ALT is not a valid biomarker for predicting the severity of liver injury or dysfunction, and it is a nonspecific and unreliable indicator of minor liver injury [6]. The cause of elevated ALT cannot be explained in the majority (69.0%) of cases [7]. Unfortunately, few reports have focused on specific biomarkers for predicting liver injury in SLE.

Alpha-hydroxybutyrate dehydrogenase (α-HBDH) is a myocardial enzyme and is often used in the diagnosis of myocardial infarction [8]. Elevated α-HBDH can also be associated with liver damage [9]. However, the role of α-HBDH in SLE-related liver injury is still unclear.

An association rule is a kind of rule-based machine learning that can be used to mine and identify indicators associated with specified variables in a database [10,11]. These rules have been used in medical research, including research on Alzheimer's disease, outpatient prescription drugs, adverse drug reactions, risk factors for childhood caries and cancer [12–16].

In this study, we applied association rules, which are a type of big data mining technology, to evaluate possible biomarkers for predicting SLE-related liver injury. Our study demonstrated that α-HBDH was a relatively independent predictor of SLE-related liver injury. α-HBDH was increased in the serum of SLE patients, and it was positively correlated with the SLE disease activity index (SLEDAI-2000). Furthermore, α-HBDH was significantly higher in SLE patients with liver injury than in those without liver injury, and it was significantly correlated with the ratio of AST to ALT (AST/ALT) and levels of AST, albumin, and lactate dehydrogenase (LDH) in patients with SLE. Our

* Corresponding author.
E-mail address: yuhaitao7707@163.com (H. Yu).
[1] These authors contributed equally to this work.

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study indicates that α-HBDH may be a potential biomarker of liver injury in patients with SLE.

2. Patients and methods

2.1. Participants

This retrospective study examined the records of 158 consecutive patients with a diagnosis of SLE that fulfilled the 1997 diagnostic criteria of the American College of Rheumatology (ACR); the patients were treated between February 2010 and May 2018 at the First Hospital of Lanzhou University. All SLE patients who underwent blood transfusions or had malignancies, other autoimmune diseases, lymphoproliferative disorders, infections, or hematopoietic diseases were excluded. None of the patients had been previously treated with mammalian target of rapamycin (mTOR) inhibitors or other treatments for at least 6 months. In addition, 158 age- and sex-matched healthy subjects without any disease were enrolled in the control group. The study protocol was approved by the Research Ethics Committee of the First Hospital of Lanzhou University (No. LDYYLL201731). All SLE patients were classified into two subgroups: the non-SLE-related liver injury group and the SLE-related liver injury group. SLE-related liver injury was determined when two of the following diagnostic criteria were met: ALT > 40 U/L, AST > 40 U/L, total bilirubin > 25.6 μmol/L, inversion of the ratio of albumin to globulin (ALB/GLO), LDH > 300 U/L, alkaline phosphatase (ALP) > 120 U/L, or gamma-glutamyl transpeptidase (GGT) > 50 U/L [17].

2.2. Data extraction

Clinical characteristics, demographic data and laboratory test results of all enrolled subjects were extracted from their medical records. A total of 64 indicators, including the indexes of routine blood tests, routine biochemical tests, immunological tests and routine urine tests, from clinical detection projects were included for the association rule mining. The indexes of routine blood tests (e.g., hemoglobin, the absolute value of lymphocytes, red cell distribution width, and hematocrit) were tested by automatic blood analysis instruments (Sysmex, Kobe, Japan) with their supporting reagents (Sysmex, Kobe, Japan). The routine biochemical tests (e.g., ALB/GLO, α-HBDH, calcium, urine protein, total cholesterol, AST, ALT, AST/ALT, ALB, LDH, and GGT) and routine urine tests were analyzed by automatic biochemical analysis instruments (Beckman Coulter, Brea CA, USA) with their supporting reagents (Jiuqiang, Beijing, China). ACA-IgG and ACA-IgM were detected by enzyme-linked immunosorbent assays (EUROIMMUN Medical Laboratory Diagnostics, Lübeck, Germany), and CRP, complement 3 (C3), complement 4 (C4), immunoglobulin M (IgM) and immunoglobulin G (IgG) were detected by specific protein instruments (Siemens Healthineers, Erlangen, Germany) with their supporting reagents (Siemens Healthineers, Erlangen, Germany).

2.3. Association rule mining and the Apriori algorithm

Association rule mining (ARM) is a data mining technique that finds the association between an item and variables from various kinds of databases, such as relational databases, transactional databases, and other forms of data repositories. The process of mining association rules can be described as follows: given a database, let I = {i1, i2, …, im} be a set of items and D be a set of database transactions, and each transaction T contains the set of items such that $T \in I$. The form of association rules is defined as follows: $A \Rightarrow B$, where $A \in I$, $B \in I$ and $A \cap B \neq \varnothing$. A is the antecedent, and B is the consequent of the rule. Every association rule has support and confidence. The percentage of transactions in D containing both A and B is defined as support, which is equal to the probability, $P(A \cap B)$. A confidence measure is defined by the following: it is the percentage of transactions in D containing A that also contain B. This is equal to the conditional probability of having B given A, $P(B|A)$. That is,

$$\text{support } (A \Rightarrow B) = P(A \cap B)$$
$$\text{confidence } (A \Rightarrow B) = P(B|A) = P(A \cap B)/P(A)$$

The strength of association rules is described by support and confidence values. The aim of an association rule is to mine all association rules having support and confidence values not less than the given threshold value (minsupport and minconfidence values), which are specified by the user. Such association rules are also called strong association rules. In data mining, associations can be generated using this "support-confidence" framework, but not all of the rules satisfying the minimum support and minimum confidence thresholds can be applied. In our approach, we employed a lift value to assess rules, which is a correlation measure between the antecedent and the consequent. For rule $A \Rightarrow B$, the lift is defined as $P(B|A)/P(B)$. In general, the lift of strong association rules should be greater than 1, which lets us know the degree to which those two occurrences are dependent on one another, and it makes those rules potentially useful for predicting the consequent in future data sets.

Association rule mining can be roughly divided into two steps:

In the first step, all the frequent itemsets that have more than minimum support in the transaction database are found. In the second step, strong association rules that meet the minimum confidence level from frequent itemsets are generated. The Apriori algorithm is a classical ARM technique, and it computes the frequent itemsets in the database through several iterations. Then, the strong association rules that meet the criteria are found from the frequent itemsets.

In our study, the itemset of association rules with 65 elements consists of 64 laboratory indicators and 1 disease status variable. The indicators associated with SLE-related liver injury were identified by using the Apriori algorithm module in SPSS Modeler 18.0, the disease state variable was considered an antecedent, and the laboratory indicators were the consequents.

2.4. Statistical analysis

Statistical assays were performed using SPSS statistics 23.0 (SPSS, Inc., Chicago, IL, USA), SPSS Modeler 18.1 (SPSS, Inc., Chicago, IL, USA) and GraphPad Prism 5.0 software (GraphPad Software Inc., San Diego, CA, USA). Values are expressed as the mean ± standard

Table 1
Demographics and clinical characteristics of SLE patients and healthy subjects.

	SLE group		Control group		P-value
	N	Results	N	Results	
Patient demographics					
Age (years)	158	37.05 ± 12.31	158	36.72 ± 11.13	0.953
Gender (M/F)	158	11/147	158	11/147	1.000
Disease duration, months	158	8.25 (2.00–36.00)	–	–	–
SLEDAI-2000, score	158	7.00 (4.00–11.00)	–	–	–
< 5 score	58	58 (37.34%)	–	–	–
≥5 score	100	100 (62.66%)	–	–	–
Accompanying diseases/organ damage					
Anemia, n (%)	158	83 (52.53%)	–	–	–
Kidney damage, n (%)	158	73 (46.20%)	–	–	–
Liver injury, n (%)	158	72 (45.57%)	–	–	–
Gallbladder diseases, n (%)	158	34 (21.52%)	–	–	–
Hepatic diseases, n (%)	158	17 (10.76%)	—	–	–
Splenic diseases, n (%)	158	10 (6.33%)	–	–	–

Abbreviation: SLEDAI-2000: Systemic Lupus Erythematosus Disease Activity Index. Data are presented as the means ± standard deviation for age and as the interquartile range for sex. P values were determined by Student's *t*-test for continuous variables and the Mann-Whitney *U* test for others.

Table 2
The laboratory indicators of connecting to SLE-liver injury strongly.

Antecedent	Consequent	Lift	Support (%)	Confidence (%)
SLE-liver injury	ALB/GLO	1.46	30.38	66.67
SLE-liver injury	α-HBDH	1.40	33.54	73.61
SLE-liver injury	Calcium	1.25	31.65	69.44
SLE-liver injury	Hemoglobin	1.20	39.24	86.11
SLE-liver injury	LYM#	1.11	39.24	86.11
SLE-liver injury	RDW-SD	1.09	31.01	68.06
SLE-liver injury	UPRO	1.08	31.01	68.06
SLE-liver injury	Hematocrit	1.07	40.51	88.89
SLE-liver injury	TC	1.03	29.75	65.28

Abbreviation: ALB/GLO: the ratio of albumin to globulin; α-HBDH: hydroxybutyrate dehydrogenase; LYM#: the absolute value of lymphocyte; RDW-SD: red cell distribution width; UPRO: urine protein; TC: total cholesterol.

deviation according to SPSS statistics 23.0 software. Student's *t*-test was used for continuous variables, and the Mann-Whitney *U* test was employed for others. The Spearman correlation coefficient was determined in the analysis of correlations, and logistic regression analysis was conducted to find the independent risk factors for SLE-related liver injury using SPSS statistics 23.0 software. Receiver operating characteristic (ROCs) curves were used to assess the sensitivity and specificity of the indicators by GraphPad Prism 5.0 software. $P < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1. Characteristics of participants

The demographic and clinical features of the 158 SLE patients and the 158 sex- and age-matched healthy controls are shown in Table 1. Age and sex were not different between SLE patients and the healthy controls. Moreover, 45.57% of the SLE patients had liver injury, which is the SLE complication with the third highest incidence rate (Table 1).

3.2. Laboratory indicators associated with SLE-related liver injury

According to the association rule algorithm, SLE-related liver injury was the antecedent of the association rule, and the laboratory indicators, including routine blood examination items, blood biochemical examination items, and routine urine examination items, were the consequents of the association rule. The Apriori algorithm identified 9 strong association rules with support and confidence thresholds of 1% and 60%, with a lift > 1. The results showed that ALB/GLO, α-HBDH, calcium, hemoglobin, the absolute value of lymphocytes (LYM#), the red blood cell distribution width (RDW-SD), urine protein, hematocrit, and total cholesterol (TC) were strongly associated with liver injury in SLE (Table 2).

3.3. Laboratory data and patient demographics in SLE with and without liver injury

The SLE patients were divided into two groups: SLE patients with and without liver injury. Compared with those without SLE-related liver injury, the SLE patients with liver injury were significantly younger, had a shorter disease duration and had higher SLE Disease Activity Index (SLEDAI-2000) scores (Table 3). The levels of calcium, LYM#, hemoglobin, hematocrit, and TC were significantly decreased in SLE patients with liver injury, whereas α-HBDH was elevated compared to that seen in the SLE patients without liver injury (Table 3). The IgG anticardiolipin antibodies (ACA-IgG) and IgM anticardiolipin antibodies (ACA-IgM) were not significantly different between the SLE patients with and without liver injury ($P = 0.948$) (Table 3).

3.4. α-HBDH may be an independent risk factor for liver injury in SLE

Table 4 shows the OR of SLE-related liver injury and α-HBDH according to multiple logistic regression analysis. After adjustment for potential risk factors, such as age, calcium, hemoglobin, LYM#, hematocrit, and TC, the OR (95% CI) of SLE-related liver injury and high

Table 3
Univariate analysis of demographics and clinical characteristic associated with SLE-liver injury patients.

	SLE-liver injury N = 72 (45.57%)		Non-SLE-liver injury N = 86 (54.43%)		P-value
	N	Results	N	Results	
Patient demographics					
Age (years)	72	34.00 (24.25–40.75)	86	39.50 (28.00–46.00)	0.019*
Gender (M/F)	72	7/65	86	4/82	0.212
Disease duration, months	72	5.25 (1.00–24.00)	86	12.00 (2.88–48.00)	0.013*
SLEDAI-2000, score	72	8.50 (4.00–13.75)	86	6.00 (3.75–10.00)	0.006**
< 5 score	21	21 (29.17%)	37	37 (43.02%)	0.072
≥5 score	51	51 (70.83%)	49	49 (56.98%)	
Indicators mined by association rules					
ALB/GLO	72	1.08(0.3–9)	86	1.38 (0.35–14.4)	0.147
α-HBDH, U/L	64	326.18 ± 218.10	75	167.00 (138.00–194.00)	0.000***
Calcium, mmol/L	70	1.98 ± 0.19	86	2.09 ± 0.19	0.001***
Hemoglobin, g/L	72	100.04 ± 22.81	86	110.16 ± 26.57	0.012*
LYM#, 10^9/L	72	0.84 (0.60–1.23)	86	1.20 (0.78–1.58)	0.000***
RDW–SD, fl	71	48.20 (44.00–54.60)	84	46.70 (43.68–52.08)	0.128
UPRO (+)	49	49 (71.01%)	51	51 (61.45%)	0.216
UPRO (−)	20	20 (28.99%)	32	32 (38.55%)	
Hematocrit, %	72	30.08 ± 7.23	86	33.65 ± 7.46	0.000***
TC, mmol/L	70	3.30 (2.60–4.41)	85	3.68 (3.06–4.82)	0.038*
Anticardiolipin antibody					
ACA-IgG, GPL/ml	9	1.40 (0.65–4.18)	13	3.58 (0.45–6.10)	0.948
ACA-IgM, MPL/ml	9	1.80 (0.90–4.50)	13	2.00 (0.50–6.00)	0.948

Abbreviation: SLEDAI-2000: systemic lupus erythematosus disease activity Index; ALB/GLO: the ratio of albumin to globulin; α-HBDH: alpha-hydroxybutyric dehydrogenase; LYM#: absolute value of lymphocyte; RDW-SD: red cell distribution width; UPRO: urine protein; TC: total cholesterol. ACA-IgG: anticardiolipin antibody-IgG; ACA-IgM: anticardiolipin antibody-IgM; Data are presented as the means ± standard deviation or interquartile range.*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. P values were determined by Student's *t*-test for continuous variables and the Mann-Whitney *U* test for others.

Table 4
Binary logistic regression analysis of risk factors associated with SLE-liver injury.

Index	ORs (95%CIs)[2]	P-value
α-HBDH,U/L	1.01 (1.00–1.02)	0.001**
Calcium, mmol/L	0.95 (0.01–11.67)	0.970
Hemoglobin, g/L	1.02 (0.96–1.08)	0.535
LYM#, 109/L	0.52 (0.24–1.16)	0.109
Hematocrit, %	0.92 (0.75–1.14)	0.452
TC, mmol/L	0.96 (0.75–1.23)	0.738
Age(years)	1.00 (0.97–1.03)	0.848

Abbreviation: α-HBDH: alpha-hydroxybutyric dehydrogenase; LYM#: the absolute value of lymphocyte; TC: total cholesterol. **P < 0.01.

α-HBDH was 1.01 (1.00–1.02) compared with that of SLE-related liver injury and low α-HBDH.

3.5. Baseline characteristics in low- and high-α-HBDH patients with SLE

SLE patients were divided into two groups according to the normal upper limits of serum α-HBDH (72.00–182.00). An α-HBDH above the normal upper limit was classified into the high-α-HBDH group, while an α-HBDH below the normal upper limit was classified into the low-α-HBDH group.

The demographic and clinical features and laboratory indexes were analyzed between the two groups. Compared with the low-α-HBDH group, there were more SLE patients with liver injury in the high-α-HBDH group (64.63% vs. 21.05%; P = 0.000); the AST/ALT ratio and AST, ALT, LDH, and GGT levels were significantly higher in the high-α-HBDH group, while LDH and C3 levels were significantly lower in the high-α-HBDH group (Table 5).

3.6. α-HBDH was correlated with SLE-related liver injury and its activity

AST, ALT, albumin, and LDH were employed to assess liver function. The correlation between α-HBDH and SLE-related liver injury was analyzed in SLE patients with liver injury. The results showed that α-HBDH was significantly positively correlated with AST, the AST/ALT ratio, and LDH but negatively correlated with albumin (Fig. 1). No significant correlation was observed between α-HBDH and ALT (r = −0.104; P = 0.412) (Fig. 1). Next, correlation analysis was applied to the relationship between α-HBDH and the disease activity of SLE-related liver injury. A strong positive correlation was observed between α-HBDH and SLEDAI-2000 (r = 0.390; P < 0.001) (Fig. 2A). Furthermore, α-HBDH was negatively correlated with C3 levels (r = −0.286; P = 0.001) (Fig. 2B). No significant correlation was observed between α-HBDH and erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement 4 (C4), IgG, IgM, or IgA (data not shown).

3.7. α-HBDH may predict SLE-related liver injury

ROC curve analysis was performed to determine the cutoff value of α-HBDH for distinguishing SLE-related liver injury from non-SLE-related liver injury. The results revealed that the area under the ROC curve of α-HBDH was 0.82 and the optimal clinical cutoff level was 258.50 U/L, which provided a 60.94% sensitivity and a 94.67% specificity (Fig. 3).

Table 5
Baseline characteristics of SLE patients with Low- and High-α-HBDH.

	High-α-HBDH N = 82 (58.99%)		Low-α-HBDH N = 57 (41.01%)		P-value
	N	Results	N	Results	
Patient demographics					
Age, years	82	35.50 (25.00–45.00)	57	41.32 ± 13.36	0.014*
Gender (M/F)	82	7/75	57	3/54	0.688
SLEDAI-2000, score	82	9.00 (4.00–14.00)	57	5.00 (2.00–9.00)	0.001**
Disease duration, months	82	11.50 (1.30–27.38)	57	6.00(2.00–30.25)	0.840
Clinical manifestation					
Liver injury, n (%)	53	53 (64.63)	12	12 (21.05)	0.000***
Renal damage, n (%)	27	27 (32.93)	16	16 (28.07)	0.542
Gallbladder disorders, n (%)	19	19 (23.17)	13	13 (22.81)	0.960
Cardiovascular diseases, n (%)	17	17 (20.73)	11	11 (19.30)	0.836
Hematologic disorders, n (%)	17	17 (20.73)	8	8 (14.04)	0.312
Thyroid disorder, n (%)	14	14 (17.07)	8	8 (14.04)	0.629
Neurological symptoms, n (%)	5	5 (6.10)	0	0 (0)	0.151
Laboratory indexes					
AST, U/L	82	36.00 (26.00–61.00)	57	23.00 (18.00–33.50)	0.000***
ALT, U/L	82	22.50 (15.75–36.00)	57	17.00 (12.00–28.00)	0.016*
AST/ALT	82	1.81 (1.28–2.70)	57	1.42 (1.06–1.74)	0.001**
ALB, g/L	82	33.23 ± 6.79	57	38.30 (32.15–42.10)	0.001**
LDH, U/L	82	294.00 (226.88–362.88)	57	171.30 (143.35–193.50)	0.000***
GGT, U/L	82	33.40 (18.95–82.48)	57	26.00 (15.00–43.20)	0.006**
ESR, mm/h	71	49.00 (27.00–86.00)	49	53.00 (16.50–74.50)	0.280
CRP, mg/L	64	4.00 (3.08–21.68)	46	3.38 (3.28–7.24)	0.769
C3, G/L	75	0.54 (0.32–0.84)	50	0.80 (0.43–1.01)	0.008**
C4, G/L	75	0.10 (0.05–0.17)	50	0.15 (0.06–0.24)	0.053
IgM, G/L	73	1.23 (0.84–1.88)	50	1.30 (0.93–1.95)	0.678
IgG, G/L	74	16.60 (13.48–22.45)	50	15.70 (11.70–22.55)	0.351

Abbreviation: SLEDAI-2000: systemic lupus erythematosus disease activity Index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALB: albumin; LDH: lactate dehydrogenase; GGT: gamma-glutamyl transpeptidase; ESR: erythrocyte sedimentation rate; CRP: C-reaction protein; C3: complement 3; C4: complement 4; IgM: immunoglobulin M; IgG: immunoglobulin G; Data are presented as the means ± standard deviation or interquartile range. *P < 0.05, **P < 0.01, *P < 0.001. P values were determined by Student's *t*-test for continuous variables and the Mann-Whitney *U* test for others.

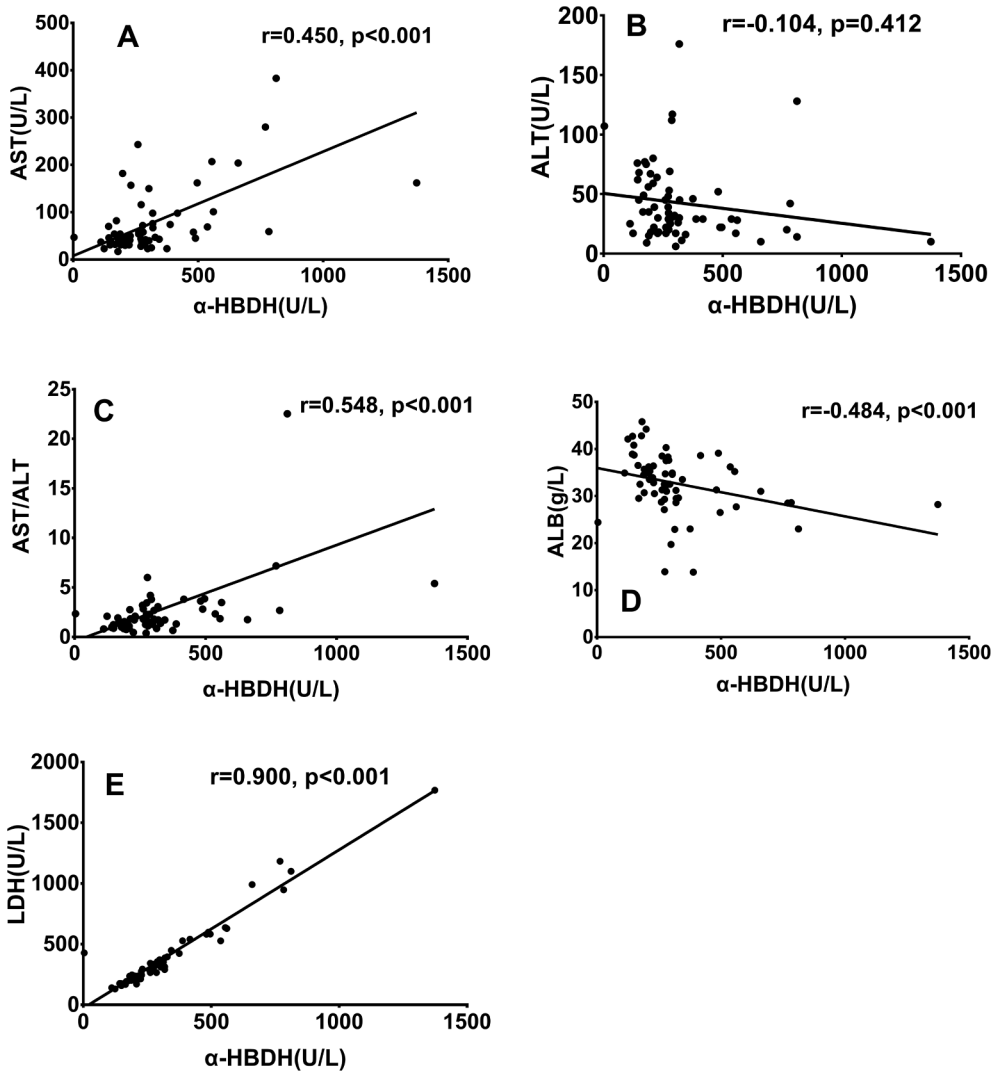

Fig. 1. The correlation between α-HBDH and indicators of SLE-live injury, including AST (A), ALT (B), the AST/ALT ratio (C), ALB (D) and LDH (E), was determined by Spearman correlation analysis in patients with SLE-related liver injury. The number of SLE-related liver injury patients was 72. α-HBDH: alpha-hydroxybutyric dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALB: albumin; LDH: lactate dehydrogenase. $P < 0.05$ was considered statistically significant.

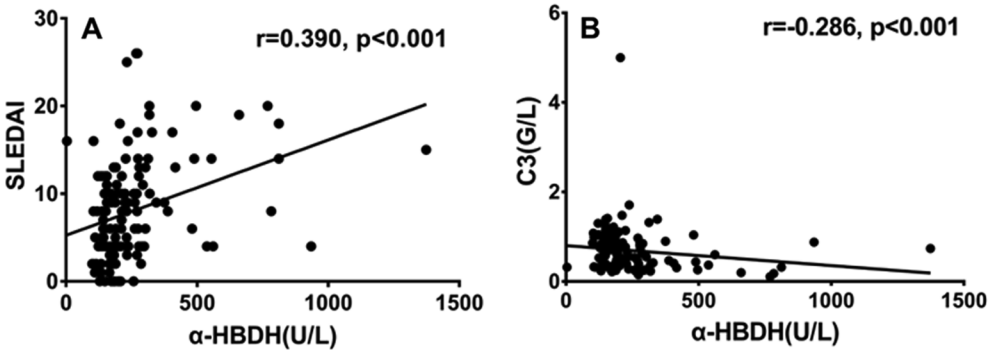

Fig. 2. The correlation between α-HBDH and indicators of SLE activity, including SLEDAI-2000 (A) and C3 (B), was determined by Spearman correlation analysis in patients with SLE-related liver injury. The number of SLE-related liver injury patients was 72. α-HBDH: alpha-hydroxybutyric dehydrogenase; SLEDAI-2000: Systemic Lupus Erythematosus Disease Activity Index; C3: complement 3. $P < 0.05$ was considered statistically significant.

4. Discussion

SLE can affect multiple tissues and organs throughout the body. The percentage of SLE patients in our study population with liver function injury was 45.57%, which is in accordance with the range of 25% to 50% of SLE patients who have abnormal liver enzymes [4]. ALT is a common indicator to assess liver function. However, it is a nonspecific and unreliable indicator of minor liver injury [6], and elevated ALT is unexplained in the majority (69.0%) of cases [7]. The specific biomarkers for predicting liver injury in SLE are still unclear.

A combination of data mining and logistic regression analysis can be used to determine the risk factors or influencing factors of diseases [18]. This strategy can quickly and accurately use data analysis and statistics to obtain valuable information. In this study, data mining and logistic regression analysis were employed to identify and evaluate markers that could reflect liver injury in SLE. ALB/GLO, α-HBDH,

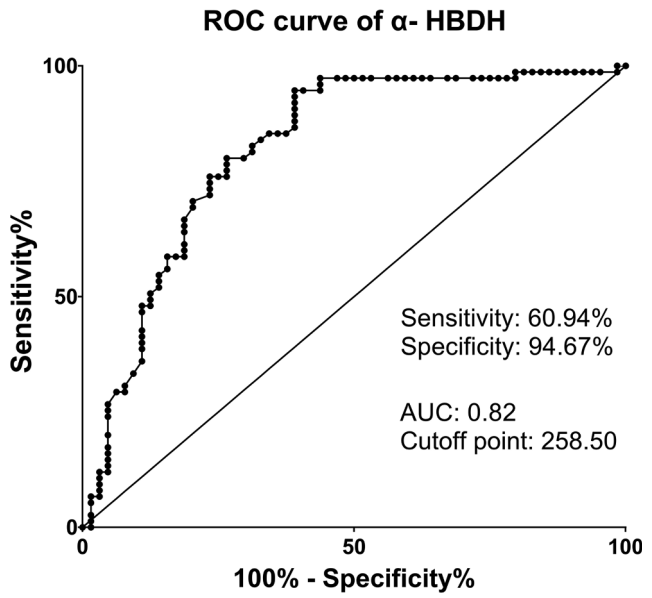

Fig. 3. Receiver operating characteristic (ROC) curve analysis of α-HBDH to distinguish SLE-related liver injury from non-SLE-related liver injury. The number of SLE patients was 139. AUC: area under the curve.

calcium, hemoglobin, LYM#, RDW-SD, urine protein, hematocrit, and TC were identified by using association rules. These results indicate that these parameters may be associated with SLE-related liver injury. Furthermore, α-HBDH, calcium, hemoglobin, LYM#, and TC were significantly different between the SLE-related liver injury group and the non-SLE-related liver injury group. α-HBDH was found by logistic regression to be an independent risk factor for SLE-related liver injury.

α-HBDH can convert α-ketobutyric acid to α-hydroxybutyric acid, which is considered to be an indirect reflection of lactate dehydrogenase isoenzyme 1 (LDH-1) and lactate dehydrogenase isoenzyme 2 (LDH-2) activity. It has low activity in the liver tissue and is mainly present in cardiomyocytes and red blood cells [8,19,20]. In our study, we found that α-HBDH was elevated in SLE patients with liver injury compared with those without liver injury. Furthermore, patients with SLE were divided into high-α-HBDH and low-α-HBDH groups. More SLE patients with liver injury were in the high-α-HBDH group than in the low-α-HBDH group. These results indicate that a high-α-HBDH value may reflect SLE with liver injury, and this idea is consistent with previous research showing that elevated α-HBDH can be associated with liver injury [9]. Moreover, the markers related to liver injury, including AST, ALT, the AST/ALT ratio, ALB, LDH, and GGT, were obviously different between the high-α-HBDH group and the low-α-HBDH group. These results further suggest that α-HBDH may be associated with liver injury in SLE.

Liver disease, which was defined as a $\geq$2-fold elevation in the levels of AST or ALT, was associated with the production of antiphospholipid antibody in the SLE [5]. Mammalian target of rapamycin compound 1 (mTORC1)-dependent mitochondrial dysfunction contributes to the production of antiphospholipid antibody [21]. mTOR is a central regulator in cell growth, activation, proliferation, and survival. Recent studies have shown that activation of mTOR occurs in both the immune system and liver [22,23], and it represents early manifestations of pathogenesis in SLE [21]. The liver is the only organ that may be a harbinger of SLE onset via presence of mitochondrial dysfunction, antiphospholipid antibody production, and mTOR activation [24]. Thus, mTOR activation plays an important role in liver injury by promoting antiphospholipid antibody production in SLE. Moreover, mTOR activation can act on downstream targets and upregulate the expression of LDH-1 and LDH-2 [25,26], which could result in an increase in serum α-HBDH levels. Therefore, we speculate that elevated α-HBDH in patients with SLE-related liver injury may be associated with the activation of mTOR. In the future, we will investigate the specific mechanism of α-HBDH elevation in patients with SLE-related liver injury and its role in the process of SLE liver injury.

In addition, correlations between α-HBDH and liver function indicators were investigated, and our results showed that α-HBDH was significantly positively correlated with AST, the AST/ALT ratio, and LDH and negatively correlated with ALB. These results confirm that α-HBDH could be used to detect liver injury in SLE, and the degree of α-HBDH elevation was correlated with the severity of liver injury. The reason for the lack of a significant correlation between α-HBDH and ALT may be that α-HBDH inhibits the autophagy of hepatic cells through mTOR and therefore limits increases in ALT.

Traditionally, SLEDAI-2000 and C3 are considered probable biomarkers for SLE disease activity evaluation [27]. Our results showed that α-HBDH was positively correlated with SLEDAI-2000 and negatively correlated with C3, suggesting that it could assess the activity of the disease in SLE patients. Furthermore, the ROC curve results suggested that α-HBDH could better distinguish SLE patients with liver injury from those without liver injury, and it could identify the presence of SLE-related liver injury.

In conclusion, α-HBDH may be a potential biomarker for diagnosing liver injury in SLE.

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