Association of Triglycerides With Systemic Lupus Erythematosus-associated Kidney Injury

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Abstract

Background: Kidney injury of systemic lupus erythematosus (SLE) contributes to major mortality of SLE. To explore biomarkers is necessary for diagnosing and supervising SLE-associated kidney injury. However, few effective biomarkers can be used for it.

Methods: Apriori algorithm of association rules was employed to identify laboratory biomarkers related to SLE-associated kidney injury. Logistic regression analysis was conducted to identify its risk factors, and spearman correlation analysis was used to evaluate the correlation between biomarkers and disease activity of SLE-associated kidney injury.

Results: Ten biomarkers were mined by association rule mining. Among them, triglycerides, lactate dehydrogenase and α-hydroxybutyrate dehydrogenase were significantly higher, and haemoglobin and haematocrit were significantly lower in patients with SLE-associated kidney injury than in those without kidney injury. Furthermore, triglycerides were an independent risk factor for SLE-associated kidney injury. There were more patients with SLE-associated kidney injury, SLE disease activity index 2000, blood urea nitrogen, creatinine, proteinuria and urine pathology cast (P-CAST) in the high-triglyceride group. Triglycerides were positively correlated with proteinuria and P-CAST, and they were negatively correlated with albumin and immunoglobulin G. The area under the receiver operating characteristic curve for triglycerides was 0.72,and the optimal cut-off level was 1.84 mmol/l, which provided 64.4% sensitivity and 75.9% specificity in predicting SLE-associated kidney dysfunction. 50% SLE-associated kidney injuries patients with negative proteinuria could be identified by high triglyceride levels. In addition, higher levels of triglycerides were found at the time of onset of kidney injury. With the change in SLE-associated kidney injury, the variation in triglyceride levels is opposite to the evaluated glomerular filtration rate.

Conclusion: triglycerides are associated with SLE-associated kidney injury and may be a potential biomarker for auxiliary diagnosis of SLE-associated kidney injury.

Introduction

Systemic lupus erythematosus(SLE) is anautoimmune disease that impairs multiple organ functions. Kidney injury is a common and severe organ-specific manifestation of SLE, occurring up to 50% of adults and 70% of children with the disease[1, 2].Kidney injurycould deteriorate the prognosis of patients with SLE, and the early diagnosis and active evaluation of patients with SLE-associatedkidney injury play a pivotal role in promoting its therapeutic effect[3]. Conventional laboratory markers, such as proteinuria, urinary protein-to-creatinine ratio, serum complement 3 and complement 4 and anti-dsDNA antibodies, are non-invasive biomarkers for evaluating kidney damage in patients with SLE. However, they play a limited role in diagnosing ongoing or relapsing SLE-associated kidney injury because of restrictive sensitivity and specificity[4−8].Renal biopsy is a gold standard method of diagnosing SLE-associated kidney injury,and it is a useful tool for evaluating clinical efficacy[9, 10].However, renal biopsy is an invasive procedure with a high risk of complications, which limits its widespread application. Therefore, it

is necessary to find non-invasiveand effective biomarkers to improve the diagnosis of SLE-associatedkidney injury[4, 9].

Association rule analysisis a methodology that works on the selection of potential interactions among categorical variables from a large number of possibilities. The ruleis defined as a connotation of the form A ⇒ B. The sets of items A and Bare called the "antecedent" and "consequent", respectively. As a result of the association rule analysis, association rules are evaluated on the values of support and confidence. The support of the association rule is defined as support(%)=[number of diseases A ∩ B]/[total number of diseases], and the confidence in an association rule is defined as confidence(%) = [number of diseases A ∩ B]/[number of diseases A], where A ∩B is the item set obtained by amalgamating AwithB. The support of an item set measures its commonness, and the confidence of an association rule measures its association strength. By the essential meaning of lift, we can also define the lift for a rule, which is lift = [(number of diseases A∩ B)×(total number of diseases)]/[(number of diseases A) × (number of diseases B)].In this paper, we employed well-defined metrics to identify the most important or optimal association rules from a transaction dataset without information loss[11−13].

To our knowledge, few studies have linked association rule analysis to traditional data processing in diagnosing SLE with kidney injury.Here, we proposed an association rule miningapproach to identify an optimal logistic model of biomarkers for diagnosing SLE-associated kidney injury.

Material And Methods

Study population

This retrospective study examined the records of 158 consecutive hospitalized cases with a diagnosis of SLE, fulfilling the diagnostic criteria of the American College of Rheumatology in 1997, between July 2011 and January 2018 at the First Hospital of Lanzhou University. The age of these patients ranged from 18 to 60 years old, 103 of whom had never received immunosuppressive therapy, and 55 patients with SLE had stopped receiving immunosuppressive therapy for more than 12 weeks. All patients who underwent blood transfusion or were diagnosed with malignancy, other autoimmune diseases, lymphoproliferative disorders, infections, and haematopoietic diseases were excluded. Additionally, 158 age- and sex-matched healthy controls were enrolled. All patients with SLE were divided into two subgroups: SLE-associated kidney injury group and non-SLE-associated kidney injury group. The diagnostic criteria of SLE-associated kidney injury was patients with SLE who met one of the following criteria: biopsy-proven lupus nephritis(class III, IV, V, III + V, and IV + V)[14],serum creatinine > 108μmol/L,proteinuria > 0.5 g/24h, red blood cells > 5/HP or urine pathology cast (P-CAST). The study protocol was approved by the Research Ethics Committee of the First Hospital of Lanzhou University (No.LDYYLL201731).

Laboratory values and clinical assessment

Demographic data, clinical characteristics and laboratory test results of enrolled subjects, including sex, age, body mass index (BMI), systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) score, SLE damage index, blood cell common tests, urine common tests, lactate dehydrogenase (LDH), blood urea nitrogen, serum creatinine, uric acid, the ratio of aspartate aminotransferase to alanine aminotransferase (AST/ALT), total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), albumin, total protein, α-hydroxybutyrate dehydrogenase (α-HBDH), proteinuria, complement 3, complement 4, immunoglobulin G (IgG), immunoglobulin A and immunoglobulin M, were extracted from the medical records. The estimated glomerular filtration rate (eGFR) was calculated with the indexes of serum creatinine, age and weight. A SLEDAI-2K score greater than 4 was defined as active SLE disease.

Association rule mining (ARM)

ARM is a data mining technique that finds the association between an item and variables from various kinds of databases. The process of ARM can be 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 for 70 elements consisted of 54 laboratory indicators, 15 patient demographics, and 1 disease status variable. The indicators associated with SLE-associated kidney injury were identified by using the Apriori algorithm module in SPSS Modeler 18.0, the disease state variable was considered an antecedent, and laboratory indicators were the consequents.

Statistical analysis

The quantitative demographic data are presented as the mean ± standard deviation for normally distributed variables, and the chi-square test was used to analyse categorical variables. SPSS Modeler 18.0was performed for data mining. Student's t-test was used for normally distributed variables, and the Mann-Whitney U-test was employed for others. Logistic regression analysis was conducted to identify the independent risk factors for SLE-associated kidney injury. In addition, Spearman correlation analysis was used to evaluate the correlation between biomarkers and the disease activity of SLE-associated kidney injury. Furthermore, a receiver operating characteristic (ROC) curve was constructed to determine the value of biomarkers for predicting SLE with kidney injury. All data were analysed by SPSS 22.0 statistical software (SPSS Inc., Chicago, USA). $P < 0.05$ was considered statistically significant.

Results

Characteristics of participants

A total of574 patients with SLE were collected, among whom 269 patients were excluded because they either had received immunosuppressive therapy or had not stopped immunosuppressive therapy for more than 12 weeks, 57 patients were excluded because their age were either less than 18 years or over 60 years, and 90 patients were excluded because they met our exclusion criteria (Supplementary Fig. 1). Thus, a total of 158 patients with SLE were enrolled in this study, and 73 (46.20%) of them had kidney injury(Supplementary Fig. 1). Laboratory indicators, such as triglycerides, AST/ALT and red cell distribution width (RDW), were significantly higher in patients with SLE than in healthy controls ($P < 0.05$). However, total cholesterol, haemoglobin, platelet distribution width (PDW), haematocrit, absolute lymphocyte count (LYM), albumin and total protein were significantly lower in patients with SLE than in healthy controls (Table 1).

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

	SLE group (n = 158)	Control group (n = 158)	P
Patient demographics			
Age, years	37.05 (24.74−49.36)	36.72 (25.59−47.85)	0.953
Gender, n (%)			1.000
Male	11 (6.96)	11 (6.96)	
Female	147 (93.04)	147 (93.04)	
SLE damage index, score	0.00 (0.00−1.00)	-	-
SLEDAI-2K, score	7.00 (4.00−11.00)	-	-
BMI, kg/m^2	21.09 (19.14−23.05)	-	-
Kidney injury, n (%)	73 (46.20)	-	-
Renal biopsy class	26 (35.62)	-	-
III/III + V	4 (15.4)	-	-
IV/IV + V	18 (69.2)	-	-
V only	4 (15.4)	-	-
Creatinine > 108μmol/L	14 (19.18)	-	-
Urine protein > 0.5g/d	55 (75.34)	-	-
Red blood cell > 5/HP	50 (68.49)	-	-
P-CAST	30 (41.09)	-	-
Laboratory indicators			
Triglyceride, mmol/L	1.68 (1.20−2.44)	1.08 (0.81−1.45)	< 0.000[***]
HDL, mmol/L	0.86 (0.65−1.11)	1.31 (1.16−1.51)	< 0.000[***]
LDL, mmol/L	2.01 (1.58−2.75)	2.40 (1.69−3.11)	0.005[**]

SLE: systemic lupus erythematosus; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PDW: platelet distribution width; RDW-SD: red cell distribution width; LYM: absolute value of lymphocyte; BUN: blood urea nitrogen; LDH: lactic dehydrogenase; α-HBDH: α-hydroxybutyrate dehydrogenase; P-CAST: urine pathology cast; GFR: glomerular filtration rate. [**]P< 0.01, [***]P< 0.001.

	SLE group (n = 158)	Control group (n = 158)	P
Total cholesterol, mmol/L	3.52 (2.88–4.66)	4.58 (0.82–8.34)	< 0.000***
AST/ALT	1.53 (1.12–2.09)	1.33 (1.14–1.65)	0.003**
Hemoglobin, g/L	108.50 (88.00-121.25)	139.19 (125.68–142.7)	< 0.000***
PDW, fl	13.70 (12.20–16.20)	16.75 (15.93–17.57)	< 0.000***
Hematocrit, %	32.03 (24.48–39.58)	42.85 (39.09–46.61)	< 0.000***
RDW-SD, fl	47.50 (43.90–52.90)	42.55 (39.96–45.14)	< 0.000***
LYM, 10^9/L	1.01 (0.68–1.46)	1.93 (1.44–2.42)	< 0.000***
BUN, mmol/L	4.71 (3.51–6.83)	4.54 (3.56–5.52)	0.087
Creatinine, μmol/L	61.25 (51.00-77.28)	57.20 (52.50-65.75)	0.068
Uric acid, μmol/L	294.00 (236.00-381.25)	304.75 (227.71-381.79)	0.827
LDH, U/L	213.00 (173.00-314.75)	-	-
α-HBDH, U/L	192.00 (150.00-273.00)	-	-
Proteinuria, g/24h	0.43 (0.14–1.81)	-	-
Albumin, g/L	34.21 (26.71–41.71)	46.40 (44.2–48.6)	< 0.000***
P-CAST/μL	0.39 (0.00-1.13)	-	-
Total protein, g/L	67.14 (55.38–78.90)	77.31 (72.58–82.04)	< 0.000***
GFR, ml/min/1.73m^2	128.80 (76.23-181.37)	138.45 (113.3-163.6)	0.040*

SLE: systemic lupus erythematosus; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PDW: platelet distribution width; RDW-SD: red cell distribution width; LYM: absolute value of lymphocyte; BUN: blood urea nitrogen; LDH: lactic dehydrogenase; α-HBDH: α-hydroxybutyrate dehydrogenase; P-CAST: urine pathology cast; GFR: glomerular filtration rate. **P< 0.01, ***P< 0.001.

Data mining

To identify laboratory indicators for diagnosing kidney injury in patients with SLE, common laboratory indicators were collected, and their correlations with SLE-associated kidney injury were analysed by data mining. According to the association rule, SLE-associated kidney injury was defined as the antecedent,

and laboratory indicators, including routine blood examination items, blood biochemical examination items, and routine urine examination items, were defined as the consequents of the association rule. The Apriori algorithm identified ten biomarkers with strong association rules of support > 1%, confidence thresholds > 60% and lift > 1. The results showed that triglyceride, LDH, AST/ALT, α-HBDH, total cholesterol, haemoglobin, PDW, haematocrit, RDW and LYM were strongly associated with kidney injury in SLE (Supplementary table 1).

Triglycerides may be an independent risk factor for SLE-associated kidney injury

Patients with SLE were divided into two groups: SLE-associated kidney injury group (46.2%) and SLE-no kidney injury group (53.8%) (Table 2). Compared with patients with SLE-no kidney injury, triglyceride, LDH and α-HBDH were significantly higher, and age, haemoglobin and haematocrit were significantly lower in patients with SLE-related kidney injury (Table 2).

Table 2
Univariate analysis of demographics and clinical characteristic associated with SLE-related kidney injury patients.

	SLE-related kidney injury (n = 73)	SLE-no kidney injury (n = 85)	P value
Patient demographics			
Age, years	34.00 (25.00-41.50)	39.00 (28.50−46.00)	0.019*
Gender (M/F)	5/68	6/79	0.959
Disease duration, months	12.00 (1.40−36.00)	7.00 (2.00−30.00)	0.789
BMI, kg/m^2	21.09 (18.83−23.44)	21.00 (19.36−22.88)	0.936
Indicators mined by association rules			
Triglyceride, mmol/L	2.07 (1.58−3.19)	1.42 (1.07−1.82)	< 0.001***
HDL, mmol/L	0.85 (0.60−1.11)	0.88 (0.72−1.11)	0.526
LDL, mmol/L	2.07 (1.45−2.89)	2.12 (1.33−2.91)	0.687
LDH, U/L	256.25 (187.95-350.48)	196.45 (167.40−240.00)	0.001***
AST/ALT	1.71 (1.10−2.58)	1.45 (1.13−1.85)	0.093
α-HBDH, U/L	231.50 (156.00-316.75)	183.00 (149.00-213.00)	0.003**
Total cholesterol, mmol/L	3.47 (2.82−5.26)	3.53 (2.88−4.32)	0.272
Hemoglobin, g/L	100.30 (74.09-126.51)	110.06 (76.75-124.45)	0.015*
PDW, fl	13.70 (11.60-16.05)	13.65 (12.48−16.25)	0.424
Hematocrit, %	29.95 (21.78−38.12)	34.30 (29.45−37.25)	0.001***
RDW-SD, fl	47.50 (44.00-52.50)	47.65 (43.83−53.45)	0.938
LYM, 10^9/L	0.99 (0.61−1.44)	1.05 (0.70−1.48)	0.438

BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; LDH: lactic dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; α-HBDH: α-hydroxybutyrate dehydrogenase; PDW: platelet distribution width; RDW-SD: red cell distribution width-standard deviation; LYM: absolute value of lymphocyte; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 3 shows the OR of SLE-related kidney injury and triglycerides according to multiple logistic regression analysis. After adjusting for potential risk factors, such as age, sex, body mass index,

haematocrit, haemoglobin, α-HBDH, and LDH, the OR (95% CI) of SLE-associated kidney injury and high triglycerides was 2.44 (1.48–4.03) compared to that of SLE-associated kidney injury and low triglycerides.

Table 3
Binary logistic regression analysis of risk factors associated with SLE-kidney injury.

Index	ORs (95%CIs)	P value
Triglyceride, mmol/L	2.44 (1.48–4.03)	0.001**
LDH, U/L	1.01 (0.10–1.03)	0.179
α-HBDH, U/L	0.99 (0.98–1.01)	0.371
Hemoglobin, g/L	1.08 (0.99–1.18)	0.074
Hematocrit, %	0.73 (0.54-1.00)	0.050
Age, years	0.99 (0.95–1.02)	0.410
Gender	0.48 (0.09–2.54)	0.388
BMI, kg/m^2	1.02 (0.89–1.16)	0.828
LDH: lactic dehydrogenase; α-HBDH: α-hydroxybutyrate dehydrogenase; SLEDAI-2K: systemic lupus erythematosus disease activity Index 2000; BMI: body mass index; **$P< 0.01$.		

Baseline characteristics in low- and high-triglyceride patients with SLE

Two SLE patients without triglyceride tests were excluded, and 156 patients with SLE were divided into two groups according to the normal upper limit of serum triglycerides (0.8–1.8 mmol/L)(Supplementary Fig. 1). A triglyceride level above the normal upper limit was classified as the high-triglyceride group, while a triglyceride level equal or below the normal upper limit was classified as the low-triglyceride group(Supplementary Fig. 1). The demographic and clinical features and laboratory indexes were analysed between the two groups. There were more SLE patients with kidney injury in the high-triglyceride group than in the low-triglyceride group (69.12% vs. 29.55%; $p< 0.001$). The increased levels of blood urea nitrogen, creatinine, proteinuria and urine pathology cast (P-CAST) and decreased levels of immunoglobulin G (IgG), albumin and total protein could reflect kidney injury. Strikingly, SLEDAI-2K, blood urea nitrogen, creatinine, proteinuria and P-CAST levels were significantly higher, while age, IgG, albumin and total protein levels were significantly lower in SLE patients with high-triglyceride than that withlow-triglyceride (Table 4).

Table 4
Baseline characteristics of SLE patients with low- and high-triglyceride.

	Low-triglyceride (n = 88)	High-triglyceride (n = 68)	P value
Patient demographics			
Age, years	39.10 (27.4−50.8)	32.50 (24−45)	0.028*
Gender (M/F)	6/82	5/63	1.000
SLEDAI-2K, score	5.00 (3.25-9.00)	9.00 (4.00−14.00)	< 0.001***
Disease duration, months	10.50 (2.00−36.00)	7.75 (2.25−24.88)	0.857
BMI	20.75 (19.23−23.18)	21.31 (18.38−24.24)	0.781
Kidney injury, n (%)	26 (29.55)	47 (69.12)	< 0.001***
Gallbladder disorders, n (%)	19 (21.59)	13 (19.12)	0.704
Cardiovascular diseases,n (%)	16 (18.18)	20 (29.41)	0.099
Hematologic disorders, n (%)	15 (17.05)	11 (16.18)	0.885
Liver injury, n (%)	12 (13.64)	8 (11.76)	0.729
Thyroid disorders, n (%)	11 (12.50)	9 (13.24)	0.892
Splenic disorders, n (%)	7 (7.95)	4 (5.88)	0.852
Neurological symptoms, n (%)	3 (3.41)	4 (5.88)	0.726
Blood urea nitrogen, mmol/L	4.35 (3.36−5.49)	5.66 (3.79−9.29)	0.004**
Creatinine, μmol/L	58.90 (51.00-66.15)	65.35 (51.48−98.95)	0.024*
Anti-ds-DNA antibody (+), n (%)	17 (19.32%)	14 (20.59%)	0.888
Anti-sm antibody (+), n (%)	26 (29.55%)	23 (33.82%)	0.396
ESR, mm/h	52.00 (18.75-86.00)	43.00 (27.00−79.00)	0.644
Immunoglobulin G, g/L	17.85 (13.90-25.13)	14.90 (9.89−19.50)	0.002**
Immunoglobulin A, g/L	2.66 (2.01−3.70)	3.01 (2.21−3.52)	0.436
Immunoglobulin M, g/L	1.38 (0.96−2.03)	1.24 (0.90−1.81)	0.650
Complement 3, G/L	0.71 (0.40−0.96)	0.50 (0.32−0.77)	0.010*

M: male; F: female; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; P-CAST: urine pathology cast; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

	Low-triglyceride (n = 88)	High-triglyceride (n = 68)	P value
Complement 4, G/L	0.14 (0.06−0.23)	0.095 (0.06−0.17)	0.168
CRP, mg/L	3.89 (3.27−13.05)	3.34 (3.08−9.68)	0.267
Proteinuria, g/24h	0.25 (0.13−0.83)	0.95 (0.30−3.14)	< 0.001***
Albumin, g/L	37.55 (31.63−42.05)	31.37 (23.93−38.81)	< 0.001***
P-CAST/µL	0.25 (0.00-0.59)	0.52 (0.12−2.29)	0.001**
Total protein, g/L	70.67 (60.5-80.84)	62.21 (50.22−74.2)	< 0.001***

M: male; F: female; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; P-CAST: urine pathology cast; [*]P< 0.05, [**]P< 0.01, [***]P< 0.001.

Triglyceridesmay be correlated with SLE-associated kidney injury

Elevated proteinuria and P-CAST and decreased serum albumin and IgG are common markers of kidney damage. In patients with SLE-associated kidney injury, positive correlations were observed between triglycerides and proteinuria (Fig. 1A) and urine P-CAST (Fig. 1D) in SLE-associated kidney injury. Meanwhile, a negative correlation was shown between triglycerides and serum albumin (Fig. 1B) and serum IgG (Fig. 1C) in SLE-associated kidney injury.

The diagnostic value of triglycerides for SLE-associated kidney injury

Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value of triglycerides to distinguish SLE patients with and without kidney injury. The results showed that the area under the ROC curve for triglycerides was 0.72, and the optimal cut-off level was 1.84 mmol/l, which provided 64.4% sensitivity and 75.9% specificity in predicting SLE-associated kidney dysfunction (Fig. 2). Proteinuria is a key indicator for the clinical evaluation of kidney damage. Proteinuria > 0.5 g/24h was defined as positive proteinuria,while proteinuria ≤ 0.5 g/24h was defined as negative proteinuria. Interestingly, 50% (8/16) of SLE-associated kidney injuries with negative proteinuria could be identified by high triglyceride levels (Table 5).

Table 5
The relationship between triglyceride and proteinuria in SLE-associated kidney injury patients.

	Proteinuria (+), n	Proteinuria (-), n	Total
High triglyceride, n	37	8	45
Low triglyceride, n	17	8	25
Total	54	16	70

Triglycerides may reflect the process of SLE-associated kidney injury

Eighty-fiveSLE patients without kidney injury at baseline were enrolled, and eight of them progressed to kidney injury. Among these eight SLE patients, the level of triglycerides was significantly higher at the onset of SLE-associated kidney injury than at baseline for the SLE-no kidney injury group ($P < 0.05$) (Fig. 3A). Furthermore, one SLE patient had fluctuating levels of triglycerides, and the kidney injury progression was evaluated with the eGFR marker[14–16].Interestingly, the level of triglycerides increased, accompanied by a decline in eGFR (Fig. 3B).

Discussion

The growing amount of electronically available data has augmented data-sets[17]. ARM is one of the important data mining techniques. Kidney injury is a common complication of SLE, and non-invasive, easily accessible and accurate diagnostic markers for SLE are lacking[18]. The Apriori algorithm, as a classical ARM from transaction data, is mostly deterministic and can identify the relationships between diseases and biomarkers from a large amount of data. In this study, we identified non-invasive and easily accessible biomarkersto diagnose SLE-associated kidney injury from laboratory indicators by data mining and association rules.

Triglyceride, HDL, LDL, LDH, AST/ALT, α-HBDH, total cholesterol, haemoglobin, PDW, haematocrit, RDW and LYM were extracted from the laboratory indicators, and all of them were significantly different between patients with SLE and healthy controls. These results are consistent with previous studies[19–26].To our knowledge, we first found that triglyceride, LDH and α-HBDH were significantly higher, whilehaemoglobin and haematocrit were significantly lower in the group of patients with SLE with kidney injury. We demonstrated that elevated triglycerides may be an independent risk factor for SLE-related kidney injury by logistic regression analysis and SLE patients with SLE-related kidney injury occur mainly around at 34 years of age.

The elevated triglyceride level is caused by reduced clearance and increased synthesis of lipoproteins. Because HDL dysfunction in nephrotic syndrome could result in impaired LPL-mediated lipolysis of triglyceride-rich lipoproteins, this process plays a key role in dysregulating triglyceride-rich lipoprotein[27].These observations suggest that HDL abnormalities are associated with impairment of triglycerides clearance. Patients with renal disease often have reduced clearance of triglyceride-rich lipoproteins due to hepatic lipase deficiency, which impairs the function of the liver to metabolize triglycerides[28]. In contrast to inhibiting the clearance of circulating triglycerides, inhibition of LPL by high circulating ANGPTL4 can also improve the synthesis of triglycerides[28, 29].

We proved that many more patients with SLE had kidney injury in the high-triglyceride group than in the low-triglyceride group. This result indicates that triglycerides are correlated with SLE-associated kidney injury. Proteinuria, urea P-CAST, urea nitrogen, creatinine, IgG, albumin, total protein and SLEDAI-2K are associated with kidney damage. SLEDAI-2K, urea nitrogen, creatinine, proteinuria and P-CAST levels were significantly higher in the high-triglyceride group, while age, IgG, albumin and total protein levels were obviously lower in the high-triglyceride group. These results further suggest that a high level of triglycerides may be associated with SLE-related kidney injury. In addition, triglycerides were positively correlated with proteinuria and P-CAST and negatively correlated with serum albumin and IgG in patients with SLE-associated kidneys. These results illuminate that triglycerides are correlated with the disease activity of SLE-associated kidney injury.

SLE-associated kidney injury results in inflammatory cell infiltration, which leads to glomerular filtration barrier injury and tubular reabsorption damage in patients with SLE[30]. The reduced glomerular filtration rate causes increased serum urea nitrogen and creatinine concentrations. Albumin and total protein were significantly lower in the high-triglyceride group than in the low-triglyceride group, and albumin was negatively correlated with triglycerides. The reason may be that serum albumin and total protein are filtered out through urine discharge resulting from the damaged kidneys of patients with SLE with low triglycerides.

The area under the ROC curve analysis for triglycerides suggested that triglycerides could distinguish patients with SLE with kidney injury from patients with SLE without kidney injury. Importantly, our results showed that 50% of SLE-associated kidney injury patients with negative proteinuria could be identified by high triglyceride levels. These results suggested that triglycerides may be a biomarker for assessing SLE-associated kidney injury, and combined with proteinuria, they could provide a better prediction of SLE-associated kidney injury.

To the best of our knowledge, our study is the first to illustrate that triglycerides are significantly higher during the progression from SLE without kidney injury to SLE-associated kidney injury. A low eGFR often indicates severe kidney impairment[31]. As expected, we further found that as the level of triglycerides increased, the eGFR decreased. This result suggests that triglycerides may reflect the occurrence and progression of SLE-associated kidney injury.

Conclusion

Taken together, the findings of our study demonstrate that tiglycerides are related to SLE-associated kidney injury. Triglycerides may be potential biomarker for complementing the clinical assessment of SLE-associated kidney injury.

Abbreviations

SLE: systemic lupus erythematosus; P-CAST: urine pathology cast; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; LDH: lactic dehydrogenase; AST/ALT: the ratio of aspartate aminotransferase to alanine aminotransferase; HDL: high density lipoprotein; LDL: low density lipoprotein; α-HBDH: α-hydroxybutyrate dehydrogenase; IgG: immunoglobulin G; eGFR: estimated glomerular filtration rate; ARM: association rule mining; RDW: red cell distribution width; PDW: platelet distribution width; LYM: absolute value of lymphocyte; BMI: body mass index; ROC: receiver operating characteristic.

Declarations

Ethical Approval and Consent to participate

The study protocol was approved by the Research Ethics Committee of the First Hospital of Lanzhou University (No.LDYYLL201731). This is a retrospective study and the method had been approved by the Research Ethics Committee of the First Hospital of Lanzhou University, so the study can be exempted consent to participate.

Consent for publication

Not applicable.

Availability of supporting data

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

HTY: study conception and design, review the data collection, manuscript andinterpretation; YDL: data collection and data analysis, plotting, interpretation, and draft themanuscript; JJL: data collection and interpretation, plotting and interpretation; THH: data collection and interpretation, LLJ: study conception and design, review the manuscript, All authors made significant intellectual contributions and have read, reviewed, andapproved the final manuscript.

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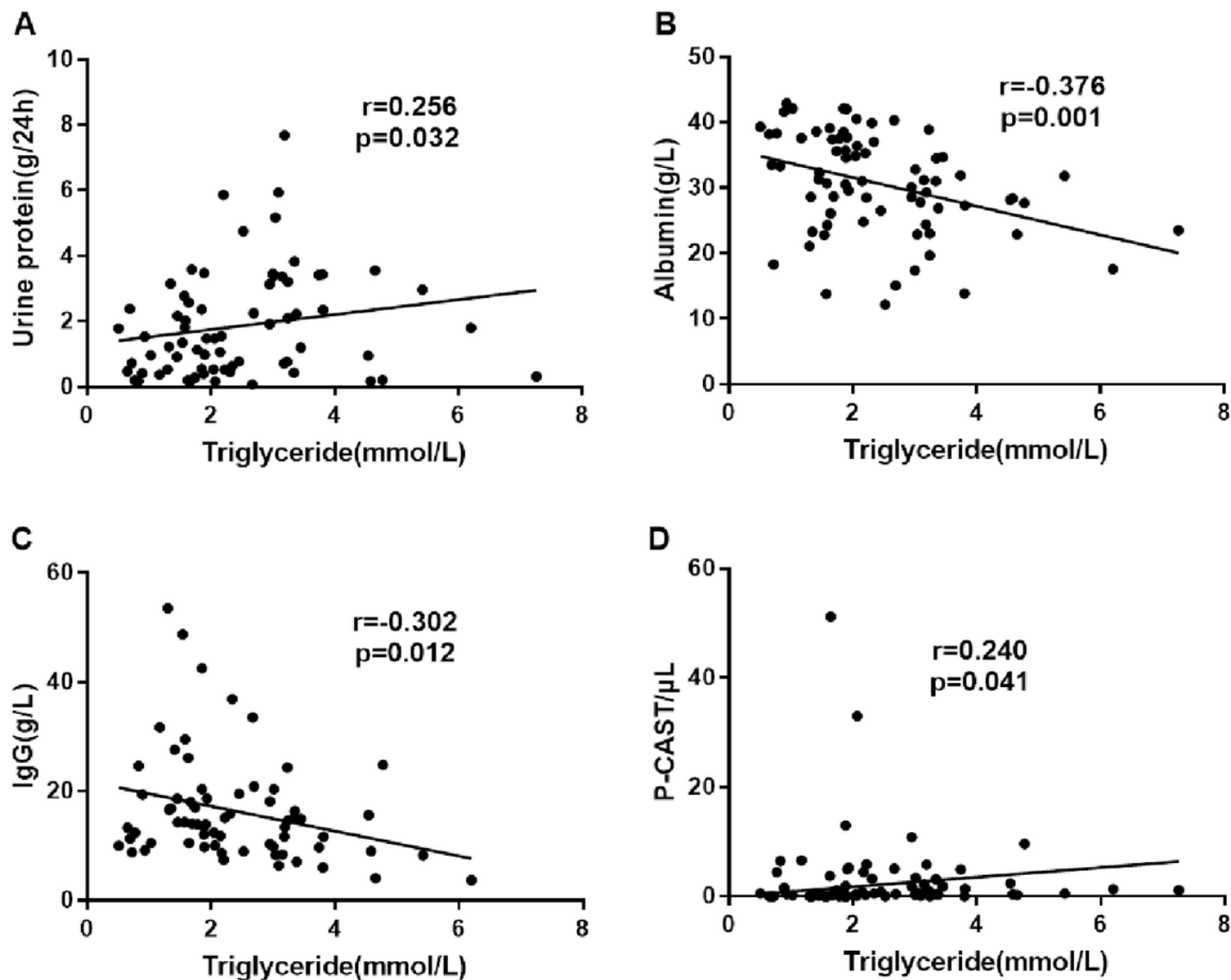
Figures

Figure 1

The correlations between triglycerides and indicators of SLE-associated kidney injury, including urine protein (A), IgG (C), and P-CAST (D), were determined by Spearman correlation analysis in patients with SLE-associated kidney injury. The correlation between triglycerides and albumin (B) was determined by Pearson correlation analysis. P <0.05 was considered statistically significant. IgG: immunoglobulin G; P-CAST: urine pathology cast.
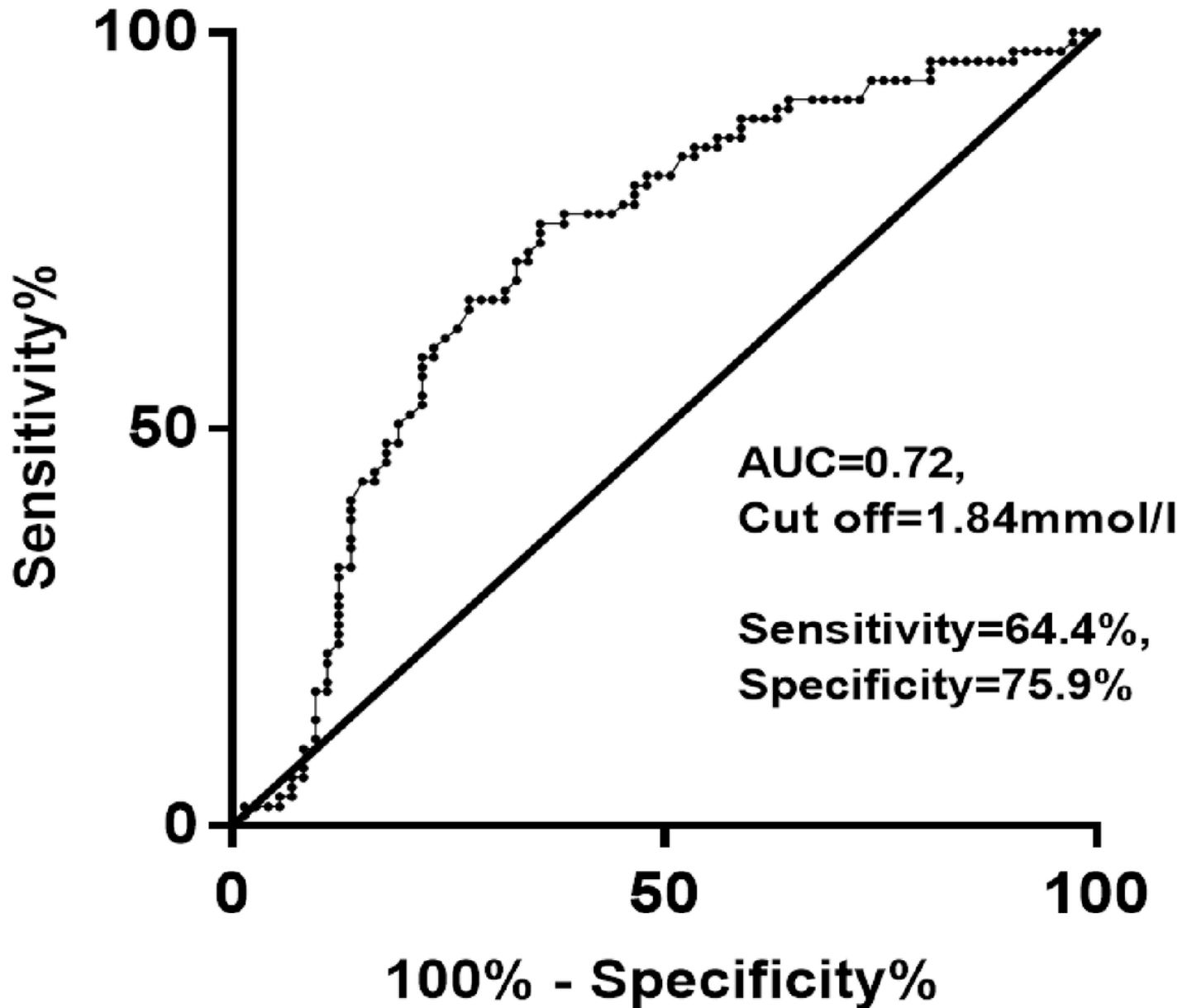
Figure 2

ROC curve analysis of triglycerides to distinguish SLE-associated kidney injury from non-SLE-associated kidney injury. ROC: receiver operating characteristic.
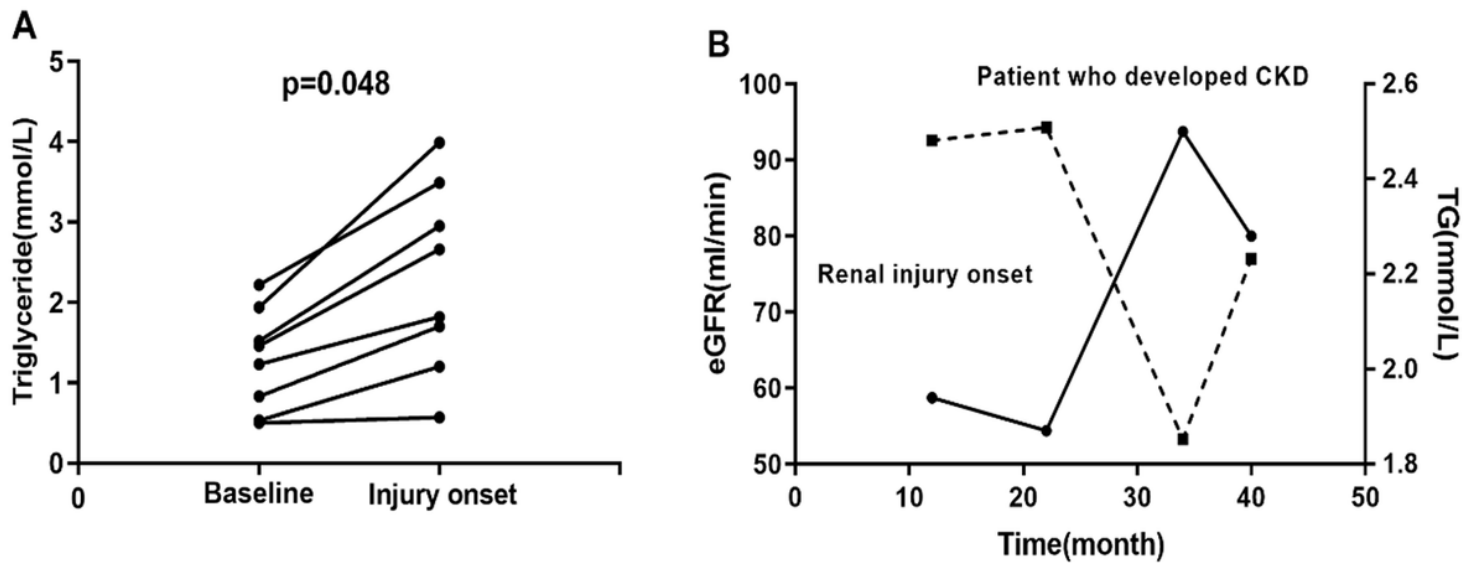
Figure 3

Patients with SLE with different levels of serum triglycerides experience different outcomes. Patients showed higher levels of triglycerides when they developed renal involvement (A). One patient with a persistent decreasing trend of triglyceride levels had sustained amelioration of kidney function (B). eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease.

Supplementary Files

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- Supplementaryfigure1.tif
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