Association of Triglycerides With Systemic Lupus Erythematosus-associated Kidney Injury

Haitao Yu (✉ yuhaitao7707@163.com )
The First Hospital of Lanzhou University  https://orcid.org/0000-0003-1087-4556

Danyang Li
The First Affiliated Hospital of Xi’an Jiaotong University

Jiajia Li
The First Hospital of Lanzhou University

Hengtong Han
The First Hospital of Lanzhou University

Lili Jiang
Lanzhou University of Technology

Research article

Keywords: Systemic lupus erythematosus, Kidney injury, Association rule mining, Apriori algorithm, Biomarker

DOI: https://doi.org/10.21203/rs.3.rs-299901/v1

License: ☺️ ☀️ This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
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 an autoimmune 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 injury could deteriorate the prognosis of patients with SLE, and the early diagnosis and active evaluation of patients with SLE-associated kidney 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-invasive and effective biomarkers to improve the diagnosis of SLE-associated kidney injury\cite{4, 9}.

Association rule analysis is a methodology that works on the selection of potential interactions among categorical variables from a large number of possibilities. The rule is defined as a connotation of the form \( A \Rightarrow B \). The sets of items A and B are 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 \( \text{support}(\%) = \frac{\text{number of diseases } A \cap B}{\text{total number of diseases}} \), and the confidence in an association rule is defined as \( \text{confidence}(\%) = \frac{\text{number of diseases } A \cap B}{\text{number of diseases } A} \), where \( A \cap B \) is the item set obtained by amalgamating A with B. 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 \( \text{lift} = \frac{(\text{number of diseases } A \cap B) \times (\text{total number of diseases})}{(\text{number of diseases } A) \times (\text{number of diseases } B)} \). In this paper, we employed well-defined metrics to identify the most important or optimal association rules from a transaction dataset without information loss\cite{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 mining approach 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 hematopoietic 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)\cite{14}, serum creatinine > 108\( \mu \)mol/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.LDYLL201731).

**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 18.0 was 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 of 574 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   | Control group | P     |
|--------------------------|-------------|---------------|-------|
|                          | (n = 158)   | (n = 158)     |       |
| **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/m²               | 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 > 108 µmol/L  | 14 (19.18)  | -             | -     |
| Urine protein > 0.5 g/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.
| Indicator                        | 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, 10⁹/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/1.73m²             | 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 characteristics 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/m²               | 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)              | 0.526   |
| LDH, U/L                 | 256.25 (187.95–350.48)            | 196.45 (167.40–240.00)        | 0.687   |
| 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, 10⁹/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

| 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/m²               | 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 with low-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.

Triglycerides may 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-five SLE 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 biomarkers to diagnose SLE-associated kidney injury from laboratory indicators by data mining and association rules.

Triglyceride, HDL, LDL, LDH, AST/ALT, $\alpha$-HBDH, total cholesterol, haemoglobin, PDW, hematocrit, 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 $\alpha$-HBDH were significantly higher, while haemoglobin and hematocrit 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 triglycerides 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.

Funding

This work was supported by the National Nature Science Foundations of China (grant number 81960388), the Longyuan Youth Innovation and Entrepreneurship Talents (grant number No. 9, 2020, Organization Department of Gansu Province), the Natural Science Foundation of Gansu Province (grant
number 20JR5RA367), and the Science and Technology Plan Project of Chengguan District Lanzhou City (grant number 2020-2-11-3).

Authors' contributions

HTY: study conception and design, review the data collection, manuscript and interpretation; YDL: data collection and data analysis, plotting, interpretation, and draft the manuscript; JYL: 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, and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Liu Z, Davidson A: Taming lupus-a new understanding of pathogenesis is leading to clinical advances. Nature medicine 2012, 18(6):871-882.
2. Kaplan MJ: Neutrophils in the pathogenesis and manifestations of SLE. Nature reviews Rheumatology 2011, 7(12):691-699.
3. Almaani S, Meara A, Rovin BH: Update on Lupus Nephritis. Clinical journal of the American Society of Nephrology: CJASN 2017, 12(5):825-835.
4. Aljaberi N, Bennett M, Brunner HI et al: Proteomic profiling of urine: implications for lupus nephritis. Expert review of proteomics 2019, 16(4):303-313.
5. Birmingham DJ, Rovin BH, Shidham G et al: Spot urine protein/creatinine ratios are unreliable estimates of 24 h proteinuria in most systemic lupus erythematosus nephritis flares. Kidney international 2007, 72(7):865-870.
6. Shidham G, Ayoub I, Birmingham D et al: Limited Reliability of the Spot Urine Protein/Creatinine Ratio in the Longitudinal Evaluation of Patients With Lupus Nephritis. Kidney international reports 2018, 3(5):1057-1063.
7. Smeenk RJ, Aarden LA, Swaak TJ: Laboratory tests as predictors of disease exacerbations in systemic lupus erythematosus: comment on the article by Esdaile et al. Arthritis and rheumatism 1996, 39(12):2083-2085.
8. Dumestre-Perard C, Clavarino G, Colliard S et al: Antibodies targeting circulating protective molecules in lupus nephritis: Interest as serological biomarkers. Autoimmunity reviews 2018, 17(9):890-899.
9. Pacheco-Lugo L, Saenz-Garcia J, Navarro Quiroz E et al: Plasma cytokines as potential biomarkers of kidney damage in patients with systemic lupus erythematosus. Lupus 2019, 28(1):34-43.
10. Zickert A, Sundelin B, Svenungsson E et al: Role of early repeated renal biopsies in lupus nephritis. Lupus science & medicine 2014, 1(1):e000018.
11. Qian G, Rao CR, Sun X et al: Boosting association rule mining in large datasets via Gibbs sampling. Proceedings of the National Academy of Sciences of the United States of America 2016, 113(18):4958-4963.
12. Zemedikun DT, Gray LJ, Khunti K et al: Patterns of Multimorbidity in Middle-Aged and Older Adults: An Analysis of the UK Biobank Data. Mayo Clinic proceedings 2018, 93(7):857-866.
13. Kim L, Myoung S: Comorbidity Study of Attention-deficit Hyperactivity Disorder (ADHD) in Children: Applying Association Rule Mining (ARM) to Korean National Health Insurance Data. Iranian journal of public health 2018, 47(4):481-488.
14. Furie R, Rovin BH, Houssiau F et al: Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. The New England journal of medicine 2020, 383(12):1117-1128.
15. Doesschate TT, van Haren E, Wijma RA et al: The effectiveness of nitrofurantoin, fosfomycin and trimethoprim for the treatment of cystitis in relation to renal function. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2020.
16. Stevens LA, Coresh J, Greene T et al: Assessing kidney function–measured and estimated glomerular filtration rate. The New England journal of medicine 2006, 354(23):2473-2483.
17. Marx V: Biology: The big challenges of big data. Nature 2013, 498(7453):255-260.
18. Navarro-Quiroz E, Pacheco-Lugo L, Lorenzi H et al: High-Throughput Sequencing Reveals Circulating miRNAs as Potential Biomarkers of Kidney Damage in Patients with Systemic Lupus Erythematosus. PloS one 2016, 11(11):e0166202.
19. Liu AC, Yang Y, Li MT et al: Macrophage activation syndrome in systemic lupus erythematosus: a multicenter, case-control study in China. Clinical rheumatology 2018, 37(1):93-100.
20. Chen SY, Du J, Lu XN et al: Platelet distribution width as a novel indicator of disease activity in systemic lupus erythematosus. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 2018, 23:48.
21. Jiang P, Bian M, Ma W et al: Eryptosis as an Underlying Mechanism in Systemic Lupus Erythematosus-Related Anemia. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology 2016, 40(6):1391-1400.
22. Zhou B, Xia Y, She J: Dysregulated serum lipid profile and its correlation to disease activity in young female adults diagnosed with systemic lupus erythematosus: a cross-sectional study. Lipids in health and disease 2020, 19(1):40.
23. Ludwig S, Mannherz HG, Schmitt S et al: Murine serum deoxyribonuclease 1 (Dnase1) activity partly originates from the liver. The international journal of biochemistry & cell biology 2009, 41(5):1079-1093.
24. Yang M, Ma N, Fu H et al: Hematocrit Level could Reflect Inflammatory Response and Disease Activity in Patients with Systemic Lupus Erythematosus. Clinical laboratory 2015, 61(7):801-807.
25. Vaya A, Alis R, Hernandez JL et al: RDW in patients with systemic lupus erythematosus. Influence of anaemia and inflammatory markers. Clinical hemorheology and microcirculation 2013, 54(3):333-
Yu HH, Wang LC, Lee JH et al: Lymphopenia is associated with neuropsychiatric manifestations and disease activity in paediatric systemic lupus erythematosus patients. Rheumatology (Oxford, England) 2007, 46(9):1492-1494.

Vaziri ND: HDL abnormalities in nephrotic syndrome and chronic kidney disease. Nature reviews Nephrology 2016, 12(1):37-47.

Vaziri ND: Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences. Kidney international 2016, 90(1):41-52.

Robciuc MR, Naukkarinen J, Ortega-Alonso A et al: Serum angiopoietin-like 4 protein levels and expression in adipose tissue are inversely correlated with obesity in monozygotic twins. Journal of lipid research 2011, 52(8):1575-1582.

Lv JQ, Zhang W, Wang S et al: The pentapeptide PLNPK inhibits systemic lupus erythematosus-associated renal damage. Inflammation research: official journal of the European Histamine Research Society [et al] 2010, 59(12):1081-1089.

Porrini E, Ruggenenti P, Luis-Lima S et al: Estimated GFR: time for a critical appraisal. Nature reviews Nephrology 2019, 15(3):177-190.