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Correlations of serum beta 2-microglobulin level with disease activity and renal involvement in patients with systemic lupus erythematosus

Abstract

Objectives: To determine correlations of serum beta 2-microglobulin (β2-MG) level with disease activity and renal involvement in patients with systemic lupus erythematosus (SLE).

Methods: Two hundred eligible SLE patients were assigned into remission and active stage groups according to SLE disease activity index (SLEDAI) scores. They were also assigned into kidney damage and no kidney damage groups. Serum β2-MG, Scr, ALB, BUN, anti-dsDNA, complements C3, C4 and 24-h urinary total protein (UTP) were detected. Estimated glomerular filtration rate (eGFR) was calculated. Correlations of β2-MG level with SLEDAI score and eGFR were subjected to Spearman analysis. Affecting factors were explored by logistic multivariate regression analysis, and predictive values of β2-MG level for SLE, disease activity and renal damage were assessed by ROC curves.

Results: β2-MG, Scr, ALB, C3, C4, anti-dsDNA and UTP levels, eGFR and SLEDAI score were different between patients with different disease activities, and, except for eGFR, also between patients with different renal damage degrees (p<0.05). Serum β2-MG, Scr, ALB, C3, C4, anti-dsDNA, UTP, eGFR and SLEDAI score were independent factors for disease activity (p<0.05), and β2-MG, ALB, C3, UTP, eGFR and SLEDAI score were factors affecting renal damage (p<0.05). β2-MG level was correlated positively with SLEDAI score (r=0.877, p=0.000) and negatively with eGFR (r=−0.873, p=0.000). This level was highly valuable for predicting SLE, disease activity and renal damage.

Conclusions: Serum β2-MG levels in SLE patients are correlated positively with disease activity and negatively with renal involvement, being highly sensitive and specific for predicting SLE, disease activity and eGFR.

Keywords: beta 2-microglobulin; disease activity; renal involvement; systemic lupus erythematosus.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune-mediated chronic rheumatism involving multiple tissues and organs, and currently, with unclear etiology, it frequently occurs in young women [1]. The over-activation of immunocytes in the serum of SLE patients causes excessive production of autoantibodies, and the resulting immune complexes induce inflammatory stress in the body, thereby leading to involvement of many organs [2]. About 60–80% SLE experience different degrees of renal involvement, with the main manifestations of hematuria, proteinuria or renal insufficiency [3]. Therefore, individualized treatment should be performed clinically based on the renal involvement in patients. Consistent changes in the levels of numerous autoantibodies and complements result from the alternate occurrence of sable disease and active disease in SLE patients [4]. Hence, the evaluation of SLE disease activity is vital for the development of treatment schemes for SLE patients. The current commonly used standards for evaluating patients' disease activity such as SLE disease activity index (SLEDAI) involve complex evaluation contents and fail to simultaneously predict the renal involvement in patients [5], so identifying indexes for evaluating SLE disease activity and renal involvement has great implications in clinical practice. Beta 2-microglobulin (β2-MG) is a ubiquitous single-stranded polypeptide. As an important player in immune responses, β2-MG is often taken as a monitoring index for the diagnosis of kidney damage and the evaluation of renal disease prognosis [6]. Leffers et al. found that SLE patients had an obviously higher level of β2-MG than those in the normal physiological state [7]. However, there have been rare reports on the correlations of β2-MG with SLE disease activity and renal involvement. Therefore, the aim of this study was

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to explore the correlations of serum β2-MG levels with SLE disease activity and renal involvement as well as their clinical values in SLE diagnosis and prognosis evaluation.

Materials and methods

Baseline clinical data

A total of 200 SLE patients treated in our hospital from January 2016 to January 2020 were enrolled. Among them, there were 20 males and 180 females aged 17–72 years old with a mean of (36.34 ± 8.87) years old, and their duration of disease was 10 d–20 years, with a mean of (4.96 ± 9.32) years. Inclusion criteria [8]: Patients meeting four or more criteria in the 1997 revised American College of Rheumatology SLE classification criteria; those with no autoimmune diseases; those with no other connective tissue diseases. Exclusion criteria [9]: Patients with a history of viral or bacterial infections three months prior to enrollment; those with rheumatoid arthritis, hypertension or other cardiovascular diseases, diabetes, central system diseases, liver diseases or malignant tumors; those recently taking immunosuppressive drugs or such medicines that affect the levels of β2-MG or serum creatinine (Scr); those with kidney damage of other causes. Disease activity was scored based on SLEDAI, and patients were classified into remission stage (SLEDAI score <10 points, n=106) and active stage (SLEDAI score >10 points, n=94). Besides, the patients were divided into kidney damage group (n=120) and no kidney damage group (n=80) based on the qualitative analysis of urine protein (≥+++) or its quantification (24 h, ≥0.5 g) [10]. Another 100 healthy examinees were randomly selected as control group, including 15 males and 85 females, with the age of 17–63 years old and a mean of (35.45 ± 9.56) years old. This study was reviewed and approved by the Ethics Committee of our hospital. All the patients enrolled or their family members were informed of the purpose of this study and signed the informed consent.

Collection of basic data

The basic clinical data, including sex, age and body mass index (BMI), were collected. Moreover, 5 mL of fasting venous blood was drawn from all enrollees after 12 h of fasting, anti-coagulated by ethylenediaminetetraacetic acid, and centrifuged at 4 ℃ and 3,000 rpm for 15 min. The serum was then retained for detection. Subsequently, the serum was tested by professional testers using the modular P-800 automatic biochemical analyzer (Roche Diagnostics, Switzerland) to obtain the laboratory and immunological indices [11] serum β2-MG, Scr, albumin (ALB), blood urine nitrogen (BUN), anti-double-stranded DNA (dsDNA) antibody, and complements C3 and C4. In addition, the levels of 24-h urinary total protein (UTP) was measured. Additionally, estimated glomerular filtration rate (eGFR) was calculated based on the modification of diet in renal disease formula eGFR=186 × Scr − 1.154 × age − 2.03 × a (female: a=0.724, male: a=1) [12].

Statistical analysis

SPSS 20.0 software was employed for data analysis. The normally distributed quantitative data were expressed as (mean ± standard deviation) and compared among groups using the independent-samples t-test. The numerical data were represented as percentage, and intergroup comparisons were made using the χ^2-test. Spearman analysis was carried out to examine the correlations of β2-MG level with SLEDAI score and eGFR. The influencing factors for SLE disease activity and renal function were determined by logistic multivariate regression analysis, and receiver operating characteristic (ROC) curves were plotted to analyze the efficacy of β2-MG levels in predicting SLE, disease activity and renal damage. $p<0.05$ was considered statistically significant.

Results

Baseline clinical data of patients with different disease activities

No statistically significant differences were found between patients with different disease activities regarding sex, age, BMI, duration of disease and BUN levels (p>0.05). However, the differences in β2-MG, Scr, ALB, C3, C4, anti-dsDNA antibody and UTP levels, eGFR and SLEDAI scores were statistically significant (p<0.05) (Table 1).

Baseline clinical data of patients with different degrees of kidney damage

The patients with different degrees of kidney damage showed no statistically significant differences in sex, age, BMI, duration of disease and BUN levels (p>0.05), but statistically significant differences in serum β2-MG, Scr, ALB, C3, C4, anti-dsDNA antibody, UTP levels and SLEDAI scores (p<0.05) (Table 2).

Logistic multivariate regression analysis results

The dependent variables disease activity (assignment: active = 1, remission = 0) and kidney damage (assignment: damage = 1, no damage = 0) and independent variables serum β2-MG, Scr, ALB, C3, C4 and anti-dsDNA antibody levels (assignment: positive = 1, negative = 0) as well as SLEDAI scores were incorporated into the logistic multivariate regression model. It was found that serum β2-MG, Scr, ALB, C3, C4 and anti-dsDNA antibody levels and SLEDAI were independent factors affecting SLE disease activity (p<0.05), while β2-MG, ALB, C3, UTP, eGFR and SLEDAI scores served as independent influencing factors for kidney damage in SLE patients (Tables 3 and 4).

Table 1: Baseline clinical data of patients with different disease activities.

Index	Remission group (n=106)	Active group (n=94)	Control group (n=100)	F/χ^2	p-Value
Female, case (%)	96 (90.57)	84 (89.36)	85 (85.00)	1.687	0.430
Age, year	34.39 ± 10.19	38.53 ± 12.68	35.45 ± 9.56	1.052	0.673
BMI, kg/m^2	23.87 ± 3.54	23.74 ± 3.69	23.77 ± 3.58	0.168	2.866
Disease course	4.82 ± 4.18	5.11 ± 4.36		0.480	0.632
β2-MG, mg/L	3.22 ± 1.18	8.93 ± 2.24	1.89 ± 0.42	42.636	0.002
Scr, μmol/L	63.47 ± 11.06	152.73 ± 12.83	43.24 ± 8.31	5.739	0.000
ALB, g/L	33.93 ± 5.42	24.78 ± 6.72	45.37 ± 6.22	3.652	0.000
C3, g/L	0.68 ± 0.23	0.37 ± 0.11	1.13 ± 0.38	2.851	0.000
C4, g/L	0.34 ± 0.13	0.11 ± 0.06	0.52 ± 0.15	2.013	0.000
BUN, mmol/L	5.48 ± 2.53	10.21 ± 6.33	3.38 ± 1.66	0.521	0.072
Anti-dsDNA, IU/mL	91.34 ± 102.29	152.58 ± 108.16		4.113	0.000
UTP, mg/L	885.63 ± 593.62	4214.66 ± 2,569.98	136.73 ± 15.32	64.825	0.000
eGFR, mL/min	103.45 ± 32.47	68.22 ± 25.82	121.64 ± 30.77	7.839	0.000
SLEDAI	4.78 ± 2.55	15.78 ± 5.62		18.158	0.000

ALB, albumin; β2-MG, beta 2-microglobulin; BMI, body mass index; BUN, blood urine nitrogen; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; SLEDAI, SLE disease activity index; UTP, urinary total protein.

Table 2: Baseline clinical data of patients with different degrees of kidney damage.

Index	Kidney damage group (n=120)	No kidney damage group (n=80)	Control group (n=100)	F/χ^2	p-Value
Female, case (%)	108 (90.00)	72(90.00)	85(85.00)	1.617	0.445
Age, year	34.39 ± 10.19	38.53 ± 12.68	35.45 ± 9.56	1.052	5.673
BMI, kg/m^2	22.93 ± 3.72	23.89 ± 3.67	23.77 ± 3.58	0.168	2.866
Disease course	4.89 ± 4.11	5.05 ± 4.17		0.268	0.789
β2-MG, mg/L	3.44 ± 2.39	9.63 ± 2.15	1.89 ± 0.42	48.931	0.000
Scr, μmol/L	53.35 ± 14.37	184.13 ± 15.26	43.24 ± 8.31	15.453	0.000
ALB, g/L	34.17 ± 5.21	22.76 ± 8.29	45.37 ± 6.22	4.327	0.000
C3, g/L	0.61 ± 0.25	0.42 ± 0.09	1.13 ± 0.38	2.723	0.000
C4, g/L	0.28 ± 0.17	0.16 ± 0.04	0.52 ± 0.15	1.946	0.000
BUN, mmol/L	7.51 ± 8.36	8.03 ± 9.67	3.38 ± 1.66	0.549	0.458
Anti-dsDNA, IU/mL	182.42 ± 86.32	26.79 ± 234.73		6.628	0.000
UTP, mg/L	2,180.62 ± 472.78	2,877.45 ± 869.98	136.73 ± 15.32	17.843	0.000
eGFR, mL/min	8.21 ± 1.33	12.64 ± 6.45		7.303	0.000

ALB, albumin; β2-MG, beta 2-microglobulin; BMI, body mass index; BUN, blood urine nitrogen; dsDNA, double-stranded DNA; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; UTP, urinary total protein.

Table 3: Logistic multivariate regression analysis results of disease activity.

Index	β	SE	Wald	p-Value	Exp(β)	95% exp (β)
Constant	2.487	2.114	1.543	0.201		
β2-MG	0.141	0.075	5.081	0.023	10.34	5.79 ~ 13.21
ALB	−0.135	0.037	10.673	0.001	0.885	0.673 ~ 0.958
Scr	−0.127	0.003	4.326	0.032	1.073	0.993 ~ 1.214
C3	1.613	1.275	31.42	0.003	4.561	2.782 ~ 8.635
C4	0.862	2.97	6.765	0.01	3.128	1.198 ~ 4.613
Anti-dsDNA	4.56	0.02	0.001	0.04	4.35	2.53 ~ 8.69
SLEDAI	2.34	0.38	8.06	0.01	2.84	1.87 ~ 5.91

ALB, albumin; β2-MG, beta 2-microglobulin; dsDNA, double-stranded DNA; Scr, serum creatinine; SLEDAI, SLE disease activity index.

Table 4: Logistic multivariate regression analysis results of kidney damage.

Index	β	SE	Wald	p-Value	Exp(β)	95% exp (β)
Constant	−12.351	4.963	8.233	0.007		
β2-MG	0.346	0.291	1.383	0.027	2.262	1.73 ~ 3.49
ALB	−0.128	0.874	5.427	0.003	0.872	0.78 ~ 0.93
C3	−0.776	0.601	1.056	0.013	0.981	0.81 ~ 0.99
UTP	1.372	0.529	8.013	0.000	1.462	1.03 ~ 3.31
eGFR	−0.324	0.627	4.349	0.000	0.563	0.43 ~ 0.77
SLEDAI	1.567	0.384	5.673	0.010	1.485	1.02 ~ 3.36

ALB, albumin; β2-MG, beta 2-microglobulin; eGFR, estimated glomerular filtration rate; SLEDAI, SLE disease activity index; UTP, urinary total protein.

Correlation of β2-MG level with SLEDAI score and eGFR

The Spearman correlation analysis results showed that the level of β2-MG in SLE patients was positively correlated with SLEDAI scores (r=0.877, p=0.000) and negatively associated with renal function parameter eGFR (r=−0.873, p=0.000).

Predictive values of β2-MG level for SLE, disease activity and kidney damage

The predictive value of serum β2-MG levels for SLE was assessed using ROC curve analysis, and the results displayed that the area under the curve was 0.866, suggesting a high predictive value, and the cut-off value of β2-MG levels was 2.04 mg/L (Figure 1). ROC curve analysis was conducted to evaluate the value of serum β2-MG levels in predicting SLE disease activity. It was discovered that the area under the curve was 0.863, with a high predictive value, and the cut-off value of β2-MG levels was 6.69 mg/L (Figure 2). Additionally, the predictive value of serum β2-MG levels for kidney damage was analyzed using ROC curves. Based on the results, the area under the curve was 0.881, suggesting a high predictive value, and the cut-off value of β2-MG levels was 7.48 mg/L (Figure 3).

Discussion

Systemic lupus erythematosus (SLE) is a diffuse connective tissue disease involving multiple organs in the whole body due to the lack of immune tolerance. Its major pathological features include the generation of autoantibodies and the aggregation and deposition of immune complexes [13]. SLE mainly involves the kidneys, joint, skin, blood, nerves and other tissues and organs. This disease is prevalent in
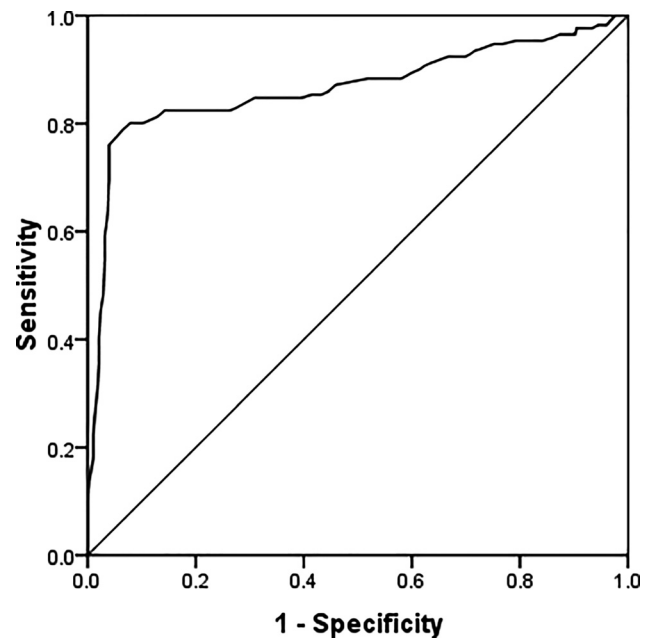

Figure 1: ROC curve of β2-MG level for SLE.
β2-MG, beta 2-microglobulin; ROC, receiver operating characteristic; SLE, systemic lupus erythematosus.

women at the childbearing age of 20–40 years old and affects few males, and it has relatively obvious heterogeneity. As a result, there has been no golden standard for the diagnosis of SLE clinically, greatly affecting the formulation of treatment regimens for patients [14]. Therefore, it is of great significance to seek biomarkers for SLE diagnosis, progression and organ involvement for the clinical diagnosis and treatment of SLE.

According to research, the kidneys are among the most frequently affected vital organs. SLE will ultimately progress into lupus nephritis in nearly 50% of SLE patients. Albuminuria is the most common clinical manifestation of SLE-induced kidney damage, and 24-h UTP is the gold standard for the diagnosis of albuminuria, but urine collection is completed in a relatively long period and
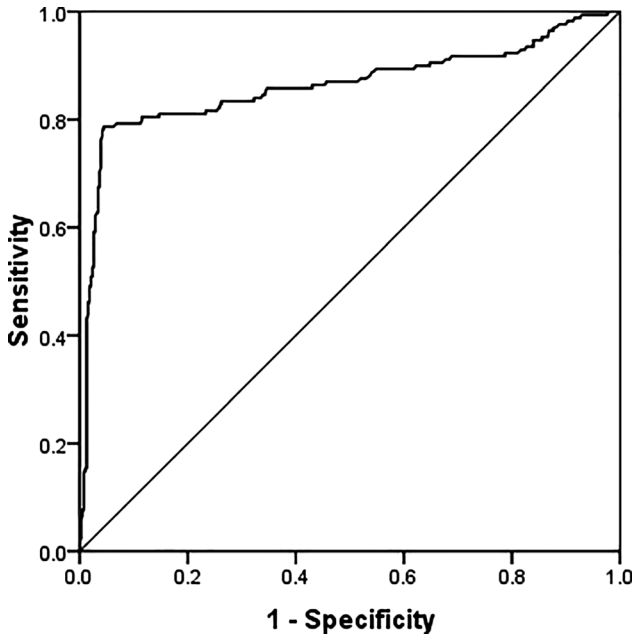
Figure 2: ROC curve of β2-MG level for SLE disease activity. β2-MG, beta 2-microglobulin; ROC, receiver operating characteristic; SLE, systemic lupus erythematosus.
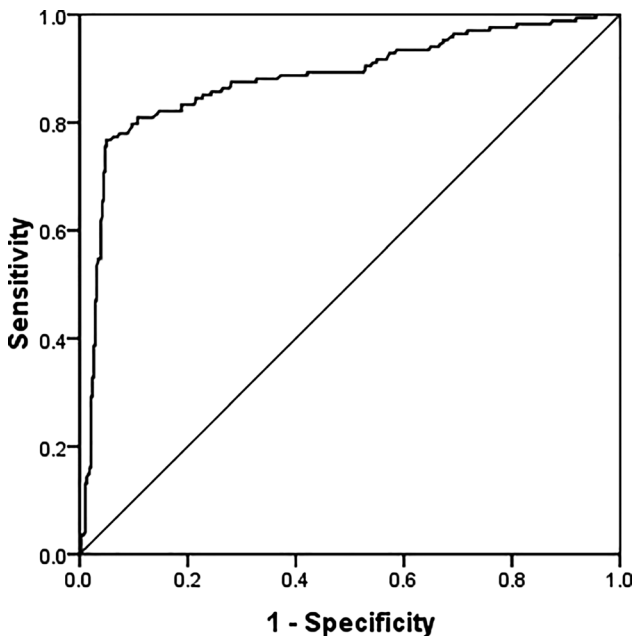

Figure 3: ROC curve of β2-MG level for kidney damage. β2-MG, beta 2-microglobulin; ROC, receiver operating characteristic.

requires good patient compliance, thereby bringing many uncertainties to clinical tests. Research into renal pathology revealed that the severity of glomerulus injury in patients is positively correlated with that of kidney damage caused by SLE [15]. As a gold indicator for the monitoring of patients' renal function, eGFR has such shortcomings as complex experimental operations and inaccurate test results, while renal function test parameters BUN and Scr tend to be affected by age, sex, inflammation and use of antibiotics, so they cannot accurately reflect the early changes in kidney damage in SLE patients [16]. SLE patients experience alternate periods of remission and relapse, so the corresponding treatment schemes need to be developed based on different symptoms of patients [17]. At present, disease activity is mainly assessed using the SLEDAI scoring system based on the clinical manifestations and laboratory test indicators of patients, but the SLEDAI scores cannot be used to evaluate the severity of kidney damage in patients [18]. β2-MG is a small-molecule protein released by lymphocytes. Wang et al. demonstrated that β2-MG was highly sensitive and specific in monitoring the early renal function in patients with secondary kidney damage [19]. According to the study of Abd-Elbaky et al. [20], β2-MG levels obviously rose in the serum of SLE patients, and the increase was evidently larger in the active stage of disease. However, the correlations of serum β2-MG levels in patients with SLE disease activity and renal involvement have been rarely reported. The present study, therefore, probed into such correlations by experiments. According to the results, the level of β2-MG was significantly raised in SLE patients ($p<0.05$), and patients in active stage had a significantly higher level of β2-MG than those in remission stage ($p<0.05$). In comparison with that in no kidney damage group, the level of β2-MG significantly rose in kidney damage group ($p<0.05$). The Spearman correlation analysis results showed that serum β2-MG levels had a positive correlation with SLEDAI scores ($r=0.877$, $p=0.000$) and a negative correlation with renal function parameter eGFR ($r=-0.873$, $p=0.000$). Besides, it was found through the logistic multivariate regression analysis that the level of serum β2-MG in patients was an independent affecting factor for SLE disease activity and kidney damage. Based on the ROC curve analysis results, β2-MG had high sensitivity and specificity in predicting SLE, SLE disease activity and kidney damage parameter eGFR. The shortcoming of this study was that the patients enrolled from the hospital were only retrospectively analyzed, but failed to be clinically observed for a long time. Therefore, more samples are needed to more deeply and systematically evaluate and verify whether β2-MG can serve as the monitoring indicator for SLE disease activity and renal involvement.

Conclusions

In summary, serum β2-MG levels in SLE patients are positively correlated with disease activity and negatively associated with renal involvement, and they are highly sensitive and specific in predicting SLE, SLE disease activity and kidney damage parameter eGFR. Moreover, they have high clinical value in the diagnosis of SLE and the prediction of disease progression.

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