Relationship between Clinical Systemic Lupus Erythematosus Symptoms and Indexes of Blood, Renal Function, Liver Function and Immunology

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ABSTRACT

Objective: This paper aimed to study the relationships between clinical systemic lupus erythematosus (SLE) symptoms and indexes of blood, renal function, liver function and immunology.

Methods: Total 117 SLE patients were collected, and clinical symptoms and biochemical indexes of blood, renal function, liver function and immunology were determined. Then, adaptive lasso analysis was used to analyse the potential relationship between the clinical symptoms of SLE and biochemical indexes.

Results: The present results indicated that pleurisy is closely related to the red blood cells (RBC), haemoglobin (Hb) and urea nitrogen (BUN) with the $|\beta_j|$ values of 0.0045, 0.0168 and 0.0064, respectively; oedema is closely related to the albuminuria and cylindruria with $|\beta_j|$ values of 0.0198 and 0.1170; alopecia has closely correlations with liver damage and aspartate aminotransferase (AST), ($|\beta_j|$ values were 0.0033 and 0.0104); fever is correlated to liver damage ($|\beta_j|$ values were 0.0011); raynaud phenomenon is closely correlated to the triglycerides (TG) and Anti-U1 Ribonucleoprotein (u1RNP) with $|\beta_j|$ value of 0.0012 and 0.0012; facial redness and arthralgia have close correlations with SSA ($|\beta_j|$ value were 0.3580 and 0.0047; arthritis and pericarditis are closely related to anti-nucleosome antivodies (AnuA) with $|\beta_j|$ values of 0.0038 and 0.0026.

Conclusion: The present study indicated that some biochemical, including RBC, Hb, BUN, albuminuria and cylindruria, liver damage, AST, TG, SSA, AnuA and u1RNP, are closely to the prognosis of SLE and it's important to control these biochemical indexes during the treatment period.

Keywords: Adaptive lasso analysis, biochemical indexes, clinical symptoms, systemic lupus erythematosus

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INTRODUCTION

It is well known that systemic lupus erythematosus (SLE) is a typical chronic life threatening inflammatory autoimmune disease (1, 2). Systemic lupus erythematosus is characterized by excessed release of autoantibodies which might result in end organ damage (3, 4). It is estimated that the SLE incidence is approximately 50-100 per 100 000 people with a ratio of 9:1 in female to male (5, 6). Currently, a large number of investigations have devoted into SLE, and great improvements have been achieved in the diagnosis and treatment of SLE (7). Currently, diagnostic criteria for definite diagnosis of SLE mainly include clinical symptoms, biochemical indexes (blood parameters, renal & liver functions indexes and immunological indexes).

The clinical symptoms are commonly the first manifestations of SLE, such as facial redness, rush in trunk and limbs, thirst, arthralgia, arthritis, photaesthesia, oral ulcer, oedema, dryness of eye, alopecia, fever, raynaud phenomenon, pericarditis, pleurisy and multiple serositis (8). In addition, the biochemical indexes, including blood indexes, renal and liver functions indexes and immunological indexes, are very important evidences for finding early stage SLE (8, 9). There are might be some potential relationship between the clinical symptoms of SLE and biochemical indexes. However, there is no report about the relationship between clinical SLE symptoms and indexes of blood, renal function, liver function and immunology. Thereby, in this present study, 117 SLE patients were enrolled and the adaptive lasso analysis was used to analyse the potential relationship between the clinical symptoms of SLE and biochemical indexes. This research has significant reference value for the early diagnosis and prognosis of SLE clinically.

METHODS AND MATERIALS

Subjects and experimental protocol

Total 117 patients admitted to the People's Hospital of Xinjiang Uygur Autonomous Region with a definite diagnosis of SLE according to clinical symptoms and biochemical examinations. The basic characteristics and clinical symptoms of SLE patients are described in Table 1. All the patients collected were required to read and sign an informed consent forms voluntarily before enrollment and all our experimental protocols were approved by the ethical committee of the People's Hospital of Xinjiang Uygur Autonomous Region (No. 201306-s007).

Furthermore, vein blood samples of the SLE patients were collected. The blood parameters were analysed by automated haematology analyser including white blood cells (WBC), red blood cells (RBC), platelet (PLT) and haemoglobin (Hb) [Table 2]. The renal and liver functions indexes were determined by automatic biochemical analyser, including creatinine, albuminuria, cylindruria, urea nitrogen (BUN), hematuria, pyuria (Table 3), total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), albumin (ALB), globulin (GLO), Triglyceride, gamma-glutamyl transpeptidase (GGT), glutamic oxalacetic transaminase (AST), glutamic-pyruvic transaminase (ALT) and alkaline phosphatase (ALP) (Table 4).

Immunological indexes including complement (C) 3, C4, C1q, immunoglobulin (Ig) G, anti-cardiolipin antibody (ACL), IgM, IgA and anti-unc leosom e antibody (AnuA), anti-Sjogren's syndrome (SS) A antibody, SSB, anti-RO52 antibody, anti-Jo-1 antibody, anti-u1 RNP antibody, anti-centromere protein B (CENP-B), anti-Sm antibody, anti-Scl70 antibody, anti-histone antibody and perinuclear anti-neutrophil cytoplasmic antibody (pANCA) were determined by enzyme linked immunosorbent assays (ELISA), and anti-nuclear antibody (ANA) titer and anti-double-stranded DNA antibodiy (ds DNA) were determined by indirect immunofluorescence assays. Systemic lupus erythematosus disease activity index (SLEDAI)

scores were evaluated according to reported methods [10] (Table 5).

Data analysis

The data of clinical symptoms and biochemical indexes of SLE were regressed by using adaptive lasso and the adaptive lasso estimator was expressed as previous report (11):

$$\hat{\beta} = \arg\min_{\beta} \| y - X\beta \|_2^2 + \lambda \sum_{j=1}^{p} \omega_j \mid \beta_j \mid,$$

Where $\omega_j (j = 1, ..., p)$ are the adaptive data-driven weights, p is the number of predictor variables, λ is the tuning parameter.

Due to the disease status is a binary response which follows a binomial distribution, we used LQA algorithm to obtain the sparse shrinkage estimate based on generalized linear models (12). The tuning parameter λ can be selected a grid of values, with values of λ selected from [0.1, 1.5], using bayesian information criterion (BIC). The weights allow the adaptive lasso to apply different amounts of shrinkage to different coefficients and hence to more severely penalize coefficients with small values. To adjust effect of nation, gender and age, weight of three factors were set to zero, accept the defaults for the remainder. $|\beta_j| > 0.001$ was used as the critical value, this measure can select the significant variables while filtering the weak ones.

RESULTS

Relationship between SLE symptoms and blood parameters

As can be seen from the Table 6, $|\beta_j|$ values of the relationship between SLE symptoms and blood parameters were shown. The results indicated that pleurisy is closely related to the RBC and Hb with the $|\beta_j|$ values of 0.0045 and 0.0168, respectively.

Relationship between SLE symptoms and renal functions

Relationships between SLE symptoms and renal functions were described in Table 6. From the present results, pleurisy has a close correlation to BUN with the $|\beta_j|$ value of 0.0064. In addition, the present results also showed that oedema is closely related to the albuminuria and cylindruria and the $|\beta_j|$ values were 0.0198 and 0.1170, respectively.

Relationship between SLE symptoms and liver functions indexes

As can be seen from the Table 7, relationships between SLE symptoms and liver functions indexes were described. The present research indicated that alopecia has closely correlations with liver damage and AST ($|\beta_j|$ values were 0.0033 and 0.0104, respectively). Furthermore, fever is correlated to the liver damage ($|\beta_j|$ values were 0.0011). Besides, raynaud phenomenon is closely correlated to the TG with the $|\beta_j|$ value of 0.0012.

Relationship between SLE symptoms and immunological indexes

Table 8 described the $|\beta_j|$ values of the relationships between SLE symptoms and immunological indexes. From the results, facial redness and arthralgia have close correlations with SSA ($|\beta_j|$ value were 0.3580 and 0.0047, respectively). Furthermore, arthritis and pericarditis are closely related to the AnuA with the $|\beta_j|$ values of 0.0038 and 0.0026, respectively. In addition, raynaud phenomenon has close correlation with u1RNP ($|\beta_j|$ value was 0.0012). Besides, pleurisy and oedema are closely related to SLEDAI scores ($|\beta_j|$ value were 0.0413 and 0.0518, respectively).

DISCUSSION

This paper investigated the relationships between clinical SLE symptoms and indexes of blood, renal function, liver function and immunology for the first time, and found that clinical SLE symptoms are closely correlated to some biochemical indexes including RBC, Hb, BUN, albuminuria and cylindruria, liver damage, AST, TG, SSA, AnuA, u1RNP, *etc*. Thereby, the present research indicated that these biochemical indexes might be closely to the prognosis of SLE and it is important to control these biochemical indexes during the treatment period.

Because the disease status is commonly affected by a small number of factors, penalized regression would shrink some factors of coefficient vector to zero, which indicate that the corresponding factors are not associated with the disease status (11, 12). Lasso is a useful technique for simultaneous estimation and variable selection. Furthermore, adaptive lasso is a novel version of lasso whose weights is used for penalizing different coefficients, and it have been demonstrated that adaptive lasso could be used to select the significant variables while filtering the weak ones (13, 14). In this study, adaptive lasso was used to penalty function which can adjust effect of some factors by different weights and $|\beta_j| > 0.001$ was used as the critical value.

It's well-known that SLE would result in multi-organs' disorders or damages, such as heart, liver, skin, digestive tract and kidney (15, 16). Therefore, SLE leads to various biomarkers of the function of multi-organs. Finding the significant biomarkers of a disease is essential for the controlling and treatment of this disease (17). In this present research, based on adaptive lasso analysis, some significant biochemical indexes have been found to have close relationships with the clinical symptoms of SLE, and these indexes including RBC, Hb, BUN, albuminuria and cylindruria, liver damage, AST, TG, SSA, AnuA, u1RNP, *etc*. Importantly, these biochemical indexes might be closely to the prognosis of SLE and therefore controlling these biochemical indexes during the treatment period might be beneficial for treating SLE.

CONCLUSION

In conclusion, the present study indicated that some biochemical, including RBC, Hb, BUN, albuminuria and cylindruria, liver damage, AST, TG, SSA, AnuA and u1RNP, are closely to the prognosis of SLE and it's important to control these biochemical indexes during the treatment period.

AUTHORS' NOTE

The authors declare that there is no conflict of interests.

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Table 1: Baseline demographics and clinical symptoms of the collected patients

Baseline demographics and clinical symptoms (n = 117)				
Age			**Oedema**		
	<20	11		Yes	20
	20-50	91		No	97
	>50	15			
Gender			**Dryness of eye**		
	Male	9		Yes	6
	Female	108		No	111
Thirst			**Alopecia**		
	Yes	12		Yes	44
	No	105		No	73
Facial redness			**Fever**		
	Yes	55		Yes	55
	No	62		No	62
Rush in trunk and limbs			**Raynaud phenomenon**		
	Yes	22		Yes	19
	No	95		No	98
Arthralgia			**Pericarditis**		
	Yes	72		Yes	15
	No	42		No	102
Arthritis			**Pleurisy**		
	Yes	64		Yes	18
	No	53		No	99
Photaesthesia			**Multiple serositis**		
	Yes	14		Yes	7
	No	103		No	110
Oral ulcer					
	Yes	28			
	No	89			

Table 2: Results of blood examinations of the collected patients

Blood indices (n=117)							
WBC		**RBC**		**PLT**		**Hb**	
$< 3 \times 10^9$/L	18	$< 3.5 \times 10^{12}$/L	22	$< 100 \times 10^9$/L	19	< 110 g/L	43
$3-4 \times 10^9$/L	24	3.5-4.0	36	$100-200 \times 10^9$/L	57	110-120 g/L	25
$4-6 \times 10^9$/L	31	4.0-4.5	36	$200-300 \times 10^9$/L	27	120-130 g/L	31
6-10	33	4.5-5.0	22	$> 3\,00 \times 10^9$/L	14	130-160 g/L	16
$> 10 \times 10^9$/L	11	$> 5.0 \times 10^{12}$/L	1			> 160 g/L	2

Table 3: Results of renal function examinations of the collected patients

Renal function index (n = 117)					
Creatinine value			**BUN**		
	< 44 μmol/L	30		< 2.9 mmol/L	9
	44-100 μmol/L	73		2.9-5.0 mmol/L	47
	100-150 μmol/L	1		5.0-7.5 mmol/L	34
	> 150 μmol/L	13		7.5-10.0 mmol/L	7
				> 10.0 mmol/L	21
Albuminuria			**Hematuria**		
	Yes	37		Yes	19
	No	80		No	98
Cylindruria			**Pyuria**		
	Yes	19		Yes	16
	No	98		No	101

Table 4: Results of liver function examinations of the collected patients

Liver function indices (n = 117)			
TC		**Triglyceride**	
< 2.8 mmol/L	17	< 1.0 mmol/L	12
2.8 - 4.0 mmol/L	34	1.0-1.8 mmol/L	44
4.0 - 6.0 mmol/L	38	1.8-3.0 mmol/L	24
> 6.0 mmol/L	26	> 3.0 mmol/L	37
HDL		**GGT**	
< 1.0 mmol/L	35	< 20 g U/L	41
1.0-1.1 mmol/L	11	20-40 U/L	30
1.1-1.5 mmol/L	26	40-60 U/L	12
1.5-2.0 mmol/L	9	60-100 U/L	10
> 2.0 mmol/L	36	> 100 U/L	24
LDL		**AST**	
< 1.5 mmol/L	28	< 20 g U/L	34
1.5-2.0 mmol/L	16	20-40 U/L	42
2.0-3.0 mmol/L	30	40-60 U/L	20
3.0-3.5 mmol/L	4	60-100 U/L	11
> 3.5 mmol/L	39	> 100 U/L	10
ALB		**ALT**	
< 20 g/L	11	< 20 g U/L	44
20-30 g/L	21	20-40 U/L	36
30-35 g/L	27	40-60 U/L	15
35-40 g/L	37	60-100 U/L	9
> 40 g/L	20	> 100 U/L	13
GLO		**ALP**	
< 20 g/L	1	< 30 g U/L	3
20-30 g/L	37	30-50 U/L	29
30-35 g/L	27	50-90 U/L	56
35-40 g/L	23	90-150 U/L	14
> 40 g/L	29	> 150 U/L	15
Liver function damage			
Yes	23		
No	94		

Table 5: Results of immunological examinations and SLEDAI scores of the collected patients

Immunological indices (n = 117)					
Complement C3		**C1q**		**ACL**	
< 0.2 g/L	11	< 1 RU/mL	28	< 1 RU/mL	39
0.2 - 0.5 g/L	26	1 - 10 RU/mL	25	1 - 5 RU/mL	29
0.5 - 0.8 g/L	35	10 - 20 RU/mL	10	5 - 12 RU/mL	8
0.8-1.2 g/L	37	20-100 RU/mL	6	12-40 RU/mL	2
> 1.2 g/L	8	> 100 RU/mL	48	> 40 RU/mL	39
Complement C4		**AnuA**		**SLEDAI score**	
< 0.02 g/L	14	<1 RU/mL	51	<4	15
0.02 - 0.1 g/L	22	1-20 RU/mL	39	5-9	47
0.1 - 0.2 g/L	52	10-100 RU/mL	6	10-14	29
0.2-0.3 g/L	23	100-200 RU/mL	3	15-25	22
> 0.3 g/L	5	> 200 RU/mL	18	>25	3
IgG		**IgA**		**IgM**	
< 6 g/L	3	< 1.0 g/L	5	< 0.5 g/L	9
6- 10 g/L	15	1.0- 2.0 g/L	24	0.5-1.5 g/L	64
10 - 16g/L	33	2.0 - 4.0 g/L	48	1.5-2.5g/L	16
16-30 g/L	38	4.0 – 6.0 g/L	14	2.5-3.5 g/L	4
> 30 g/L	28	> 6.0 g/L	26	> 3.5 g/L	24
ANA titer		**ANA**		**Sm**	
<100	6	Yes	115	Yes	36
100-400	42	No	2	No	81
400-1000	26	**pANCA**		**cANCA**	
1000-4000	14	Yes	56	Yes	17
> 4000	29	No	61	No	100
SSA		**SSB**		**ds DNA**	
Yes	81	Yes	36	Yes	77
No	36	No	81	No	60
RO52		**u1 RNP**		**Scl70**	
Yes	77	Yes	52	Yes	14
No	40	No	65	No	103
JO-1		**CENP-B**		**Anti-histone antibody**	
Yes	12	Yes	21	Yes	46
No	105	No	96	No	71

Table 6: Relationship between SLE symptoms and indexes of renal functions and blood

	Creatinine	BUN	Albuminuria	Cylindruria	Hematuria	Pyuria	WBC	PLT	RBC	Hb
					$\lvert\beta_j\rvert$ value					
Facial redness	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Rush in trunk and limbs	0.0000	0.0000	0.0001	0.0002	0.0000	0.0000	0.000	0.0000	0.0000	0.0000
Arthralgia	0.0000	0.0000	0.0000	0.0000	0.0002	0.0001	0.0000	0.0000	0.0000	0.0000
Arthritis	0.0000	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000
Photaesthesia	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Oral ulcer	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Thirst	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Dryness of eye	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Alopecia	0.0000	0.0000	0.0000	0.0000	0.0000	0.0003	0.0000	0.0000	0.0000	0.0000
Fever	0.0000	0.0000	0.0000	0.0001	0.0000	0.0002	0.0000	0.0000	0.0007	0.0000
Raynaud phenomenon	0.0000	0.0000	0.0000	0.0000	0.0002	0.0000	0.0000	0.0000	0.0002	0.0000
Pericarditis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Pleurisy	0.0000	**0.0064**	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**0.0045**	**0.0168**
Multiple serositis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Oedema	0.0000	0.0000	**0.0198**	**0.1170**	0.0000	0.0000	0.0000	0.000	0.0000	0.0000

Data was analysed by adaptive lasso analysis, and $\lvert\beta_j\rvert$ value > 0.001 was considered as significant.

Table 7: Relationship between lupus symptoms and liver functions indexes

					$|\beta_j|$ value						
	TC	TG	HDL	LDL	Liver damage	ALB	GLO	ALT	AST	GGT	ALP
Facial redness	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Rush in trunk and limbs	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Arthralgia	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Arthritis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Photaesthesia	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Oral ulcer	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Thirst	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Dryness of eye	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Alopecia	0.0001	0.0000	0.0002	0.0000	**0.0033**	0.0000	0.0000	0.0000	**0.0104**	0.0000	0.0000
Fever	0.0000	0.0003	0.0000	0.0000	**0.0011**	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000
Raynaud phenomenon	0.0003	**0.0012**	0.0000	0.0000	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Pericarditis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Pleurisy	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Multiple serositis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Oedema	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Data was analysed by adaptive lasso analysis, and $|\beta_j|$ value > 0.001 was considered as significant.

Table 8: Relationship between lupus symptoms and immunological indexes & SLEDAI scores

| | $|\beta_j|$ value | | | | | | | | | | | | | | | |
	C3	C4	IgG	IgA	IgM	ANA	dsDNA	Sm	AnuA	u1RNP	SSA	SSB	RO52	CENP	Anti-histone antibody	SLEDAI
Facial redness	0.0000	0.0001	0.0000	0.0000	0.0000	0.0002	0.0000	0.0000	0.0000	0.0000	**0.3580**	0.0000	0.0000	0.0000	0.0000	0.0000
Rush in trunk and limbs	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Arthralgia	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	**0.0047**	0.0000	0.0003	0.0001	0.0000	0.0000
Arthritis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**0.0038**	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Photaesthesia	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0000	0.0003	0.0000	0.0000
Oral ulcer	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Thirst	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Dryness of eye	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Alopecia	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0000	0.0001	0.0000	0.0000
Fever	0.0000	0.0005	0.0000	0.0001	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	0.0004	0.0000	0.0000	0.0000	0.0000	0.0000
Raynaud phenomenon	0.0002	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**0.0012**	0.0000	0.0005	0.0000	0.0000	0.0000	0.0000
Pericarditis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**0.0026**	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Pleurisy	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**0.0413**
Multiple serositis	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0048	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Oedema	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**0.0518**

Data was analysed by adaptive lasso analysis, and $|\beta_j|$ value > 0.001 was considered as significant.