Using AFR+PNI Model for Predicting Disease Activity in Patients With Systemic Lupus Erythematosus

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Abstract

Background: Systemic lupus erythematosus (SLE) is chronic autoimmune disease with multiple organ damage and is associated with poor prognosis and high mortality. Identification of universal biomarkers to predict SLE activity is challenging due to the heterogeneity of the disease. This study aimed to identify the indicators that are sensitive and specific to predict activity of SLE.

Methods: We retrospectively analyzed 108 patients with SLE. Patients were categorized into SLE with activity and without activity groups on the basis of SLE disease activity index. We analyzed the potential of routine and novel indicators in predicting the SLE activity using receiver operating characteristic curves and multivariate logistic regression. The Spearman method was used to understand the correlation between albumin to fibrinogen ratio (AFR), prognostic nutritional index (PNI), AFR+PNI model and disease activity.

Results: SLE with activity group had elevatory C3, ESR, CRP, D-dimer, fibrinogen, CRP to albumin ratio, positive rate of anti-dsDNA and ANUA, lower TBIL, TP, albumin, albumin/globulin, creatinine, HDL-C, hemoglobin, hematocrit, lymphocyte count, AFR, PNI. A further established model based on combination of AFR and PNI (AFR-PNI model) showed prominent value in distinguishing SLE with activity patients from SLE without activity patients. In addition, the sensitivity and specificity of AFR-PNI model +anti-dsDNA combination model were superior to AFR-PNI model. AFR and PNI were risk factors for SLE activity. Moreocer, AFR, PNI and AFR+PNI model correlated with disease activity. Furthermore, AFR, PNI, and AFR-PNI model were associated with fever, pleurisy, pericarditis, renal involvement.

Conclusion: These findings suggest that predictive model based on combination of AFR and PNI may be useful markers to identify active SLE in clinical practice.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with unknown pathogenesis, which affects several organ systems including renal, skin, joint and cardiovascular [1]. The chronic inflammatory state can lead to morbidity and mortality in SLE patients, e.g., the severe renal flares associated with end-stage renal disease and cardiovascular disease [2–3]. The treatment of patients who are prone to develop disease flare has become a major challenge for the prevention and control of SLE activity, which will improve the long-term outcome. Predicting changes in SLE disease activity could allow for closer monitoring and preemptive treatment, but existing clinical, and serologic markers have been only modestly predictive [4]. Novel, proactive serologic markers to predicting disease activity are thus critically needed.

Fibrinogen (Fbg) is a plasma protein produced in the liver that acts as an indicator of the state of thrombosis and plays a role in various concentrations of inflammation. It is an essential part of the blood coagulation cascade [5]. Increased Fbg have been found in SLE patients [6].Serum albumin is a well-known negative acute-phase protein whose levels decrease during inflammation and malnutrition [7]. Subnormal levels have commonly been reported in SLE patients and serum albumin has previously been

established as a potential surrogate marker of SLE disease activity [8]. Multiple studies have investigated the predictors of albumin to fibrinogen ratio (AFR) in cancer, sepsis and rheumatoid arthritis [9–11]. Although He et al. have showed AFR level was depressed in SLE patients [11], the value of AFR in determining disease activity remains to be understood.

On the other hand, lymphopaenia is one of the most frequent clinical manifestations in SLE, reported in up to 93% of patients [12]. previous studies have demonstrated that lymphopaenia has a significant clinical value because it can be associated with disease activity and damage accrual in SLE patients, proposing that lymphopaenia may be an expression of disease activity [13]. Prognostic nutritional index (PNI), which are calculated using serum albumin level and lymphocyte count, provide an effective estimation of SLE activity [14–16]. However, to the best of our knowledge, there have been no studies into the significance of combinations of AFR and PNI, in terms of predicting disease activity in SLE patients.

This study aimed to describe the routine laboratory features and new serological markers of patients who were SLE with activity and SLE without activity. We found new serological markers AFR, PNI and C-reactive protein to albumin ratio (CAR) had predictive value for SLE activity. A further established model based on combination of AFR and PNI produced a prominent effect on predicting the activity of SLE.

Materials And Methods

Study Population

The medical records of 108 patients who were admitted to Department of Rheumatology (outpatients and inpatients) across The First Affiliated Hospital of Nanchang University between November 2017 and December 2020 and were diagnosed with SLE were reviewed. All patients met the SLE revised diagnostic criteria of the ACR or Systemic Lupus International Collaborating Clinics (SLICC) classificatory criteria [17]. The exclusion criteria are SLE patients with overlapping syndrome, a history of cancer, or an active infection. Among them, 54 patients were new-onset SLE that first time diagnosis of SLE and no history of immunosuppressive drugs or corticosteroids use before recruitment. Other patients were re-visiting SLE receiving treatment with immunosuppressive drugs and corticosteroids. The SLE disease activity index (SLEDAI) was used to calculate disease activity [18]. SLE patients were classified into an SLE without active group (SLEDAI score < 7) or an SLE with active group (SLEDAI score ≥ 8) according to SLEDAI [19–20]. The collected data consisted of demographic information, laboratory tests and the patient characteristics of the two group are shown in Table 1. Of these 108 cases, 40 and 68 patients were SLE without active and with active cases, respectively. The present study was approved by the Ethics Committee of The First Affiliated Hospital of Nanchang University (approval on. 2014003) and complied with the Helsinki Declaration.

Table 1
Novel serological indicators and their formulas.

Indexes	Formulas
AAR	ALT (U/L)/AST (U/L)
THR	TG (mmol/L)/HDL-C (mmol/L)
AFR	ALB (g/L)/Fbg (g/L)
PNI	10*ALB (g/L) + 5*L counts (10^9)
MHR	M counts (10^9)/ HDL-C (mmol/L)
NLR	NEU counts (10^9)/L counts (10^9)
dNLR	NEU counts (10^9)/[WBC counts (10^9)-N counts (10^9)]
PLR	PLT counts (10^9)/L counts (10^9)
LMR	L counts (10^9)/M counts (10^9)
SII	PLT counts (10^9)*N counts (10^9)/L counts (10^9)
CAR	CRP (mg/L)/ALB (g/L)
ECR	ESR (mm/h)/CRP (mg/L)

AAR, alanine aminotransferase to aspartate aminotransferase ratio; THR, triglyceride to high density liptein cholesterol ratio; AFR, albumin to fibrinogen ratio; PNI, prognostic nutritional index; MHR, monocyte to high density liptein cholesterol ratio; NLR, neutrophil to lymphocyte ratio; dNLR, derived Neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; SII, systemic immune inflammation index; CAR, C-reactive protein to albumin ratio; ECR, erythrocyte sedimentation rate to C-reactive protein ratio.

Laboratory Measurements

We collected results of laboratory tests, such as autoantibody indexs, hematological and coagulation indicators, biochemical indices, and inflammatory markers. The autoantibody indexs include antinuclear antibody (ANA), anti-double-stranded DNA antibody (anti-dsDNA), and anti-extractable nuclear antigens (ENAs) antibodies. The ANA and anti-dsDNA were detected using the indirect immunofluorescence method with a commercially available diagnostic kit (EUROIMMUN, Germany) according to the manufacturer's instructions. Serum samples from SLE patients that were used to detedted ANA and anti-dsDNA were prepared at various dilution factors as follows: 1:100, 1:320, 1:640, 1:1000 and 1:10, 1:20, 1:40, 1:80, respectively. The sample was defined as ANA-positive or anti-dsDNA-positive when the signal could be detected with the serum diluted at 1:100 or 1:10. Anti-ENAs antibodies including antinuclear ribonucleoprotein/Smith antibody (anti-nRNP/Sm), anti-Smith antibody (anti-Sm), anti-ribosomal P antibody (anti-RIB-P), anti-nucleosome antibody (ANUA), anti-Sjögren'ssyndrome-related antigen A antibody (anti-SSA), anti-sjögren syndrome A antigen 52 antibody (anti-SS-A52), anti-Sjögren'ssyndrome-

related antigen B antibody (anti-SSB) were determined by immunoenzyme dot assay (EUROIMMUN, Germany) according to the manufacturer's instructions. The results of anti-ENA detection were determined as negative (–) or positive (+, ++, +++) by EUROBlotOne. The routine inflammatory examinations incorporate complement 3 (C3), complement 4 (C4), immunoglobulin G (IgG), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR). The levels of serum C3, C4, IgG, CRP were detected by nephelometry according to the manufacturer's protocol of IMMUNE800 (Beckman Coulter, USA) and ESR was determined according to the instructions described by the manufacturer of automatic measuring instrument for eSrXc-40B (Pu li Sheng, China). Serum routine biochemical examinations, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), total bilirubin (TBIL), direct bilirubin (DBIL), albumin (ALB), globulin (GLB), albumin/globulin (A/G), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), creatinine (CREA), urea, uric acid (UA), glucose (GLU), creatine kinase (CK), creatine kinase MB (CK-MB), lactate dehydrogenase (LDH), total cholesterol (CHOL), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high density liptein cholesterol (HDL-C), were assayed using HITACHI 7600 automatic biochemistry analyzer (HITACHI, Japan). The routine blood coagulation examinations including prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (Fbg), and D-dimer (D-D) were determined by CS-5100 automated blood coagulation analyzer (Sysmex, Kobe, Japan). The routine blood examinations including white blood cell counts (WBC), red blood cell counts (RBC), hemoglobin (HGB), hematocrit (HCT), platelet counts (PLT), neutrophil counts (N), neutrophil percentage (N%), lymphocyte counts (L), lymphocyte percentage (L%), monocyte counts (M) and monocyte percentage (M%) were detected on the SYSMEX XN-10 hematology analyzer (SYSMEX, Japan).

Novel serological indicators

SLE is a chronic autoimmune disease that affects several organ systems. Thus, the results of routine laboratory indicators are often abnormal. The new serological biomarkers listed in Table 1 were derived from a combination of two or more of the above routine laboratory indicators, including AAR, THR, AFR, PNI, NLR, dNLR, PLR, LMR, SII, CAR, and ECR. Table 1 lists the formulas used to calculate these novel serological indicators.

Statistical analysis

All analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, Illinois, USA) or GraphPad Prism version 5.0 (GraphPad Software Inc., San Diego, California, USA). Categorical variables have been represented as percentages and continuous variables have been denoted as mean ± standard deviation. Kolmogorov-Smirnov method was used to assess the normality of data. Student's t-test or Mann-Whitney U test were used to compare the data according to the normality. Categorical variables were compared using the χ^2 test. A receiver operating characteristic (ROC) curve was built to evaluate the predicted value of difference index between SLE with active group and without active group. Multivariate regression analysis (logistic regression) was used to analyze the risk factors. The nonparametric Spearman method was used for correlation analysis. $P < 0.05$ was considered to indicate statistically significant differences.

Results

Clinical and routine laboratory characteristics of patients with SLE

According to the SLEDAI, the 108 confirmed SLE patients were categorized into the without disease activity (SLEDAI score < 8) (40 cases) and with disease activity (SLEDAI score > 8) (68 cases) groups. Patient age [37.94 ± 13.56 vs 39.35 ± 12.97, P = 0.5973] and gender [57/11(83.82) vs 37/3(92.50), P = 0.1950] were similar between the two groups. As expected, SLEDAI score for SLE patients with activity group was higher than that for SLE patients without activity group (Table 2).

Table 2
Clinical and routine laboratory characteristics of patients with SLE

Categories	All patients (n = 108)	Without activity (n = 40)	With activity (n = 68)	Z or X^2value/p value
Females/males, n (%)	94/14 (87.04)	37/3 (92.50)	57/11 (83.82)	1.7/0.1950
Age, mean (S.D.), years	38.46 ± 13.30	39.35 ± 12.97	37.94 ± 13.56	0.5/0.5973
SLEDAI score, mean (S.D.)	9.94 ± 7.09	3.80 ± 2.00	13.54 ± 6.50*	0.0/<0.0001
New-onset SLE, n (%)	54 (50.00)	9 (22.50)	45 (66.18)*	19.22/<0.0001
Clinical symptoms				
Encephalosis, n (%)	1 (0.93)	0 (0.00)	1 (1.47)	0.6/0.4410
Paropsia, n (%)	2 (1.85)	0 (0.00)	2 (2.94)	1.2/0.2740
Lupus encephalopathy, n (%)	3 (2.78)	0 (0.00)	3 (4.41)	1.8/0.1780
Vasculitis, n (%)	6 (5.56)	0 (0.00)	6 (8.82)	3.7/0.0530
Arthritis, n (%)	46 (42.59)	4 (10.00)	42 (61.76)*	27.6/<0.0001
Myositis, n (%)	3 (2.78)	1 (2.50)	2 (2.94)	0.0/0.8930
Fever, n (%)	21 (19.44)	3 (7.50)	18 (26.47)*	5.8/0.0160
Rash, n (%)	36 (33.33)	6 (15.00)	30 (44.12)*	9.6/0.0020
Alopecia, n (%)	12 (11.11)	0 (0.00)	12 (17.65)*	7.9/0.005
Mucosal ulcer, n (%)	6 (5.56)	1 (2.50)	5 (7.35)	1.1/0.2880
Pleurisy, n (%)	20 (18.52)	2 (5.00)	18 (26.47)*	7.7/0.0060

SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; RI, Renal involvement; ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA antibody; anti-nRNP/Sm: antinuclear ribonucleoprotein/Smith antibody; anti-Sm, anti-Smith antibody; anti-RIB-P, anti-ribosomal P antibody; ANUA, Anti-nucleosome antibody; anti-SSA, anti-Sjögren'ssyndrome-related antigen A antibody; anti-SS-A52, Anti-sjögren syndrome A antigen 52 antibody; anti-SSB, anti-Sjögren'ssyndrome-related antigen B antibody; C3, complement 3; C4, complement 4; IgG, immunoglobulin G; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; TP, total protein; ALB, albumin; GLB, globulin; A/G, albumin/globulin; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; CREA, creatinine; UA, uric acid; GLU, glucose; CK, creatine kinase; LDH, lactate dehydrogenase; CHOL, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL- C, high density liptein cholesterol; D-D, D-dimer; PT, prothrombin time; INR, international normalized ratio; APTT, acivated partial thromboplastin time; TT, thrombin time; Fbg, fibrinogen; WBC, white blood cell counts; RBC, red blood cell counts; HGB, hemoglobin; HCT, hematocrit; PLT, platelet counts; L, lymphocyte count; L%, lymphocyte percentage; M, monocyte count; M%, monocyte percentage; N, neutrophil count; N%: neutrophil percentage. *$p < 0.05$ vs without active SLE patients.

Categories	All patients (n = 108)	Without activity (n = 40)	With activity (n = 68)	Z or X^2value/p value
Pericarditis, n (%)	18 (16.67)	2 (5.00)	16 (23.53)*	6.2/0.0130
RI, n (%)	41 (37.96)	3 (7.50)	38 (55.88)*	25.0/<0.0001
Autoantibody				
ANA, ≥ 1:320/ ≤1:100 (%)	62/11 (84.93)	17/3 (85.00)	45/8 (84.91)	0.0/0.992
Anti-dsDNA, P n/N n (%)	38/53(41.76)	4/22(15.38)	34/31(52.31)*	10.4/0.0010
Anti-nRNP/Sm, P n/N n (%)	45/36(55.56)	15/13(53.57)	30/23(56.60)	0.1/0.7940
Anti-Sm, P n/N n (%)	24/57(29.63)	7/21(25.00)	17/36(32.08)	0.4/0.5070
Anti-RIB-P, P n/N n (%)	24/57(29.63)	5/23(17.86)	19/34(35.85)	2.8/0.0920
ANUA, P n/N n (%)	34/47(41.98)	7/21(25.00)	27/26(50.94)*	5.1/0.0240
Anti-SSA, P n/N n (%)	48/33(59.26)	21/7(75.00)	27/26(50.94)*	4.4/0.0360
Anti-SS-A52, P n/N n (%)	41/40(50.62)	10/18(35.71)	31/22(58.49)	3.8/0.0510
Anti-SSB, P n/N n (%)	19/62(23.46)	8/20(28.57)	11/42(20.75)	0.6/0.4300
Routine inflammatory examination				
C3, mean (S.D.)	0.62 ± 0.26	0.67 ± 0.15	0.59 ± 0.31*	905.0/0.0316
C4, mean (S.D.)	0.14 ± 0.08	0.14 ± 0.06	0.14 ± 0.09	1052.0/0.2556
IgG, mean (S.D.)	18.20 ± 10.55	19.54 ± 14.27	17.38 ± 7.43	1093.0/0.5484

SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; RI, Renal involvement; ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA antibody; anti-nRNP/Sm: antinuclear ribonucleoprotein/Smith antibody; anti-Sm, anti-Smith antibody; anti-RIB-P, anti-ribosomal P antibody; ANUA, Anti-nucleosome antibody; anti-SSA, anti-Sjögren'ssyndrome-related antigen A antibody; anti-SS-A52, Anti-sjögren syndrome A antigen 52 antibody; anti-SSB, anti-Sjögren'ssyndrome-related antigen B antibody; C3, complement 3; C4, complement 4; IgG, immunoglobulin G; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; TP, total protein; ALB, albumin; GLB, globulin; A/G, albumin/globulin; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; CREA, creatinine; UA, uric acid; GLU, glucose; CK, creatine kinase; LDH, lactate dehydrogenase; CHOL, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL- C, high density liptein cholesterol; D-D, D-dimer; PT, prothrombin time; INR, international normalized ratio; APTT, acivated partial thromboplastin time; TT, thrombin time; Fbg, fibrinogen; WBC, white blood cell counts; RBC, red blood cell counts; HGB, hemoglobin; HCT, hematocrit; PLT, platelet counts; L, lymphocyte count; L%, lymphocyte percentage; M, monocyte count; M%, monocyte percentage; N, neutrophil count; N%: neutrophil percentage. *$p < 0.05$ vs without active SLE patients.

Categories	All patients (n = 108)	Without activity (n = 40)	With activity (n = 68)	Z or X^2value/p value
ESR, mean (S.D.)	50.62 ± 37.77	36.21 ± 34.16	59.17 ± 37.45 *	3.1/0.0026
CRP, mean (S.D.)	16.19 ± 34.01	5.34 ± 6.89	20.83 ± 39.96 *	700.0/0.0068
Routine biochemical examination				
ALT, mean (S.D.)	35.49 ± 65.43	39.39 ± 87.65	33.19 ± 48.47	1321.0/0.8064
AST, mean (S.D.)	42.07 ± 67.09	33.79 ± 33.02	46.94 ± 80.55	1178.0/0.2466
TBIL, mean (S.D.)	8.55 ± 11.69	11.82 ± 17.62	6.63 ± 5.24 *	1003.0/0.0231
DBIL, mean (S.D.)	2.88 ± 5.11	4.31 ± 8.08	2.04 ± 1.36	1193.0/0.2891
TP, mean (S.D.)	66.58 ± 13.98	72.37 ± 12.75	63.7 ± 13.62 *	3.5/0.0008
ALB, mean (S.D.)	35.14 ± 7.53	38.85 ± 5.92	32.97 ± 7.56 *	4.2/<0.0001
GLB, mean (S.D.)	32.51 ± 10.12	33.53 ± 12.74	31.92 ± 8.25	1348.0/0.9417
A/G, mean (S.D.)	1.15 ± 0.36	1.28 ± 0.44	1.08 ± 0.29 *	933.0/0.0067
GGT, mean (S.D.)	43.89 ± 61.86	48.25 ± 69.09	41.33 ± 57.57	0.6/0.5770
ALP, mean (S.D.)	76.25 ± 39.29	77.40 ± 29.67	75.57 ± 44.18	1141.0/0.1644
CREA, mean (S.D.)	71.25 ± 70.92	54.07 ± 16.00	81.36 ± 87.20 *	1035.0/0.039
Urea, mean (S.D.)	8.27 ± 15.24	5.34 ± 1.75	10.00 ± 19.00	1327.0/0.8337

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Categories	All patients (n = 108)	Without activity (n = 40)	With activity (n = 68)	Z or X^2value/p value
UA, mean (S.D.)	324.29 ± 14.90	324.55 ± 126.26	324.13 ± 108.64	0.0/0.9857
GLU, mean (S.D.)	5.2 ± 1.37	5.15 ± 1.21	5.33 ± 1.45	0.6/0.5217
CK, mean (S.D.)	86.25 ± 271.97	53.13 ± 47.55	105.33 ± 338.99	1247/0.9623
CK-MB, mean (S.D.)	18.15 ± 20.00	17.20 ± 6.66	18.70 ± 24.65	1046/0.1596
LDH, mean (S.D.)	313.44 ± 237.56	273.98 ± 113.05	336.52 ± 284.76	1020.0/0.1417
CHOL, mean (S.D.)	4.64 ± 3.77	5.05 ± 5.91	4.40 ± 1.49	1301.0/0.7098
TG, mean (S.D.)	1.96 ± 1.07	1.87 ± 0.96	2.02 ± 1.14	0.7/0.4905
LDL-C, mean (S.D.)	2.51 ± 1.05	2.29 ± 0.68	2.64 ± 1.20	1169.0/0.2243
HDL-C, mean (S.D.)	1.12 ± 0.39	1.25 ± 0.42	1.04 ± 0.36 *	2.8/0.0058
Routine blood coagulation examination				
D-D, mean (S.D.)	2.70 ± 8.02	0.84 ± 1.15	3.82 ± 9.99 *	767.5/0.0003
PT, mean (S.D.)	11.54 ± 2.94	11.43 ± 1.29	11.61 ± 3.59	1272.0/0.6636
INR, mean (S.D.)	1.00 ± 0.27	1.01 ± 0.13	0.99 ± 0.33	1154.0/0.2318
APTT, mean (S.D.)	30.54 ± 23.29	33.09 ± 37.31	29.02 ± 6.48	1137.0/0.1911
Fbg, mean (S.D.)	3.13 ± 1.17	2.70 ± 0.71	3.40 ± 1.32 *	876.5/0.0029
TT, mean (S.D.)	18.52 ± 2.84	18.05 ± 1.82	18.81 ± 3.29	1190.0/0.3355

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Categories	All patients (n = 108)	Without activity (n = 40)	With activity (n = 68)	Z or X^2value/p value
Routine blood examination				
WBC, mean (S.D.)	5.64 ± 3.15	6.20 ± 2.73	5.30 ± 3.35	1.44/0.1538
RBC, mean (S.D.)	3.73 ± 0.86	3.94 ± 0.88	3.61 ± 0.83	2.0/0.0501
HGB, mean (S.D.)	106.58 ± 26.60	115.15 ± 25.71	101.54 ± 25.98 *	2.6/0.0096
HCT, mean (S.D.)	0.33 ± 0.07	0.35 ± 0.07	0.32 ± 0.07*	831.0/0.0008
PLT, mean (S.D.)	193.41 ± 97.97	204.00 ± 91.23	187.18 ± 101.87	0.9/0.3913
L, mean (S.D.)	1.20 ± 0.75	1.44 ± 0.87	1.05 ± 0.64*	865.0/0.0017
L%, mean (S.D.)	22.62 ± 10.48	24.01 ± 10.46	21.81 ± 10.48	1.1/0.2942
M, mean (S.D.)	0.45 ± 0.30	0.52 ± 0.33	0.40 ± 0.28	1.8/0.0685
M%, mean (S.D.)	8.31 ± 4.10	8.64 ± 4.89	8.12 ± 3.57	1352.0/0.9594
N, mean (S.D.)	3.95 ± 2.67	4.16 ± 2.21	3.84 ± 2.92	0.6/0.5480
N%, mean (S.D.)	67.41 ± 13.17	65.85 ± 12.76	68.33 ± 13.40	0.9/0.3460

SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; RI, Renal involvement; ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA antibody; anti-nRNP/Sm: antinuclear ribonucleoprotein/Smith antibody; anti-Sm, anti-Smith antibody; anti-RIB-P, anti-ribosomal P antibody; ANUA, Anti-nucleosome antibody; anti-SSA, anti-Sjögren'ssyndrome-related antigen A antibody; anti-SS-A52, Anti-sjögren syndrome A antigen 52 antibody; anti-SSB, anti-Sjögren'ssyndrome-related antigen B antibody; C3, complement 3; C4, complement 4; IgG, immunoglobulin G; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; TP, total protein; ALB, albumin; GLB, globulin; A/G, albumin/globulin; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; CREA, creatinine; UA, uric acid; GLU, glucose; CK, creatine kinase; LDH, lactate dehydrogenase; CHOL, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL- C, high density liptein cholesterol; D-D, D-dimer; PT, prothrombin time; INR, international normalized ratio; APTT, acivated partial thromboplastin time; TT, thrombin time; Fbg, fibrinogen; WBC, white blood cell counts; RBC, red blood cell counts; HGB, hemoglobin; HCT, hematocrit; PLT, platelet counts; L, lymphocyte count; L%, lymphocyte percentage; M, monocyte count; M%, monocyte percentage; N, neutrophil count; N%: neutrophil percentage. *p < 0.05 vs without active SLE patients.

Clinical symptoms of SLE patients that were recruited in this study were shown in Table 2, the percentage of arthritis, fever, rash, alopecia, pleurisy, pericarditis and renal involvement (RI) in SLE with activity group were significantly higher than that in SLE without activity group, whereas the percentage of encephalosis, paropsia, lupus encephalopathy, vasculitis, myositis, mucosal ulcer did not show any significant differences between the two groups.

We observed that SLE with activity group and SLE without activity group showed no statistical difference in the positive rate of anti-nRNP/Sm, anti-Sm, anti-RIB-P, anti-Ro52 and anti-SSB count. However, the positive rate of anti-dsDNA and ANUA were significantly higher in SLE with activity group than in SLE without activity group, whereas the positive rate of anti-SSA was significantly lower (Table 2). And, many inflammatory indicators, including C3, ESR, and CRP, were also significantly higher in SLE with activity group than in SLE without activity group (Table 2).

Moreover, many biochemical indicators, including TBIL, TP, ALB, A/G, CREA and HDL-C were also significantly lower in SLE with activity group than in SLE without activity group. Conversely, many blood coagulation indicators, D-D and Fbg in SLE with activity group was significantly higher than in SLE without activity group (Table 2). However, the level of HGB, HCT and L counts decreased in SLE with activity group, while there were no differences in the WBC, RBC, PLT, L%, M, M%, L and L% between the two groups (Table 2).

Novel serological indicators for the severity of disease

The levels of new serological biomarkers, including AFR and PNI were decreased in SLE with activity group ($p < 0.0001$; Fig. 1C, D), while the level of CAR was elevated in SLE with activity group ($p = 0.0016$; Fig. 1K), compared to those in SLE without activity group. There was no significant difference in the levels of AAR, THR, MHR, NLR, dNLR, PLR, LMR, SII, ECR between SLE with activity group and SLE without activity group (Fig. 1A, B, E, F, G, H, I, J, L).

Development of the predictive model for discriminating between SLE with activity group and without activity group

The effect of these indicators with statistical significance on discriminating between SLE with activity group and SLE without activity group was further analyzed. To determine the potential of the novel serological indicators in predicting the activity of SLE, we generated ROC curves for each of the 3 serological indicators. Two indicators, including AFR (AUC: 0.741, 95% CI: 0.647–0.835, $P < 0.0001$, sensitivity: 56.72%, specificity: 87.50%, Cut-off: <11.14) and PNI (AUC: 0.727, 95% CI: 0.632–0.822, $P < 0.0001$, sensitivity: 58.82%, specificity: 85.00%, Cut-off: <346.1) had potential value in distinguishing SLE without activity group and SLE with activity group, which superior to CAR (AUC: 0.696, 95% CI: 0.586–0.806, $P = 0.0016$, sensitivity: 84.38%, specificity: 54.55%, Cut-off: >0.0597) (Fig. 2).

To develop the predictive models based on the combination of various indicators for distinguishing SLE with activity group from SLE without activity group, also considering the limited number of patients, we selected all indicators with AUC higher than 0.7 for further multivariate logistic regression analysis. The “enter method” of logistic regression model showed the equations as belown, $Y = -0.102*$ AFR$-0.008*$ PNI $+ 4.890$ (Table 3). The results demonstrated that the decreased AFR and PNI were risk factors for SLE activity ($P < 0.0500$) (Table 3).

Table 3
AFR and PNI in the equations

Variables	B	S.E.	Wald	df	P	Exp (B)
AFR	-0.102	0.051	3.954	1	0.047	0.903
PNI	-0.008	0.004	4.702	1	0.030	0.992
Constant	4.890	1.269	14.861	1	0.000	133.018
AFR, albumin to fibrinogen ratio; PNI, prognostic nutritional index.						

Comparing the performance of AFR + PNI model and single indicator

The predictive model based on combination of AFR and PNI performed best value in distinguishing SLE with activity group from SLE without activity group, with AUC of 0.765 (95% CI, 0.674–0.857) (Fig. 3), which superior to single AFR and single PNI (Table 4 and Fig. 2). When 0.7824 was used as the cutoff value, the sensitivity and specificity of AFR-PNI model were 67.16% and 82.50% respectively (Fig. 3). ALB presented an AUC of 0.724 (95% CI, 0.629–0.820), with a sensitivity of 57.35% and a specificity of 85.00% when 33.85 was used as the cutoff value. ESR presented an AUC of 0.710 (95% CI, 0.604–0.816), with a sensitivity of 57.81% and a specificity of 76.32% when 45.50 was used as the cutoff value. D-D presented an AUC of 0.709 (95% CI, 0.607–0.812), with a sensitivity of 71.21% and a specificity of 65.00% when 0.560 was used as the cutoff value (Table 4).

Table 4
ROC curves for the potential of serum biomarkers in predicting activity of SLE

Variables	AUC	*p*-value	95% C.I.	Sensitivity	Specificity	Cut-off
C3	0.628	0.0314	0.521–0.735	42.19	94.74	< 0.455
ESR	0.710	0.0004	0.604–0.816	57.81	76.32	> 45.50
CRP	0.659	0.0114	0.545–0.773	68.75	62.50	> 3.000
TBIL	0.631	0.0230	0.522–0.741	33.82	90.00	< 4.450
TP	0.680	0.0018	0.578–0.782	58.82	77.50	< 66.15
ALB	0.724	0.0001	0.629–0.820	57.35	85.00	< 33.85
A/G	0.657	0.0066	0.545–0.769	82.35	45.00	< 1.335
CREA	0.620	0.0387	0.512–0.727	72.06	50.00	> 51.40
HDL-C	0.642	0.0142	0.533–0.751	76.47	50.00	< 1.255
D-D	0.709	0.0003	0.607–0.812	71.21	65.00	> 0.560
Fbg	0.673	0.0029	0.572–0.774	31.34	97.50	> 4.035
HGB	0.662	0.0051	0.552–0.772	75.00	57.50	< 119.5
HCT	0.670	0.0033	0.561–0.779	80.88	52.50	< 0.3745
L	0.682	0.0016	0.581–0.783	60.29	75.00	< 1.000
AFR	0.741	< 0.0001	0.647–0.835	56.72	87.50	< 11.14
PNI	0.727	< 0.0001	0.632–0.822	58.82	85.00	< 346.1
CAR	0.696	0.0016	0.586–0.806	84.38	54.55	> 0.0597

C3, complement 3; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TBIL, total bilirubin; TP, total protein; ALB, albumin; A/G, albumin/globulin; CREA, creatinine; HDL- C, high density liptein cholesterol; D-D, D-dimer; Fbg, fibrinogen; HGB, hemoglobin; HCT, hematocrit; L, lymphocyte count; AFR, albumin to fibrinogen ratio; PNI, prognostic nutritional index; CAR, C-reactive protein to albumin ratio.

Anti-dsDNA is the most commonly used diagnostic marker and assessing activity marker for SLE. The aforementioned results demonstrate that AFR-PNI model may be used as a novel biomarker in the predicting activity of SLE. Thus, we evaluated the value of AFR-PNI model and anti-dsDNA combination model in SLE diagnosis by four-fold table. According to the optimal cut-off value of AFR-PNI model yielded in aforementioned results (> 0.7824), the AFR-PNI model + anti-dsDNA combination model could effectively discriminated the SLE with activity and SLE without activity, with a sensitivity of 82.81% (53/64), a specificity of 88.46% (23/26). The sensitivity and specificity of AFR-PNI model + anti-dsDNA combination model were superior to AFR-PNI model [sensitivity: 67.16%, specificity: 82.50%] and anti-dsDNA [sensitivity: 52.31% (34/65), specificity: 84.61% (24/26)].

Correlation of AFR, PNI, AFR-PNI model and other indicators

The aforementioned results demonstrated that SLE with activity group and SLE without activity group showed statistical difference in AFR, PNI. Subsequently, we determined the correlation between AFR, PNI, AFR-PNI model and other indicators including SLEDAI, new serological markers, routine laboratory indicators using Spearman's rank correlation coefficient. As shown in Table 5, we found that AFR strongly correlated with ALB, Fbg, ESR, CRP, CAR, PNI in SLE patients (r_s>0.5, P < 0.0500), AFR moderately correlated with SLEDAI, TP, A/G, LDH, D-D, ANUA in SLE patients (0.5 > r_s>0.3, P < 0.0500), and AFR weekly correlated with TBIL, DBIL, HDL-C, RBC, HGB, HCT, L, L%, N%, NLR, dNLR, PLR, LMR, THR, ECR, anti-SSA, anti-nRNP/Sm in SLE patients (0.3 > r_s>0.1, P < 0.0500). Whereas PNI strongly correlated with ALB, TP, A/G, D-D, RBC, HGB, HCT, CAR, AFR in SLE patients (r_s>0.5, P < 0.0500), PNI moderately correlated with SLEDAI, TBIL, LDH, HDL-C, ESR, L, CRP, THR, ANUA in SLE patients (0.5 > r_s>0.3, P < 0.0500), and PNI weekly correlated with DBIL, CREA, Urea, UA, TG, Fbg, PLT, L%, N%, NLR, dNLR, LMR, AAR in SLE patients (0.3 > r_s>0.1, P < 0.0500) (Table 5). Moreover, AFR-PNI model was found to strongly correlated with TP, ALB, A/G, D-D, Fbg, ESR, CRP, HCT, CAR, AFR, PNI in SLE patients (r_s>0.5, P < 0.0500), moderately correlated with SLEDAI, TBIL, LDH, HDL-C, RBC, HGB, L, ANUA, THR in SLE patients (0.5 > r_s>0.3, P < 0.0500), and weekly correlated with DBIL, CREA, UA, L%, N%, NLR, dNLR, PLR, LMR, ECR, anti-SSA in SLE patients (0.3 > r_s>0.1, P < 0.0500).

Table 5
Correlation of AFR, PNI, AFR-PNI model and other indicators

AFR			PNI			AFR-PNI model		
Categories	r_s	p value	Categories	r_s	p value	Categories	r_s	p value
SLEDAI	-0.3718	< 0.0001	SLEDAI	-0.4527	< 0.0001	SLEDAI	0.4665	< 0.0001
Anti-nRNP/Sm	-0.2416	0.0298	ANUA	-0.3062	0.0054	Anti-SSA	-0.2242	0.0442
Anti-SSA	0.2411	0.0302	TBIL	0.4555	< 0.0001	ANUA	0.3905	0.0003
ANUA	-0.3062	0.0054	DBIL	0.2422	0.0115	TBIL	-0.4007	< 0.0001
TBIL	0.2601	0.0068	TP	0.6439	< 0.0001	DBIL	-0.2464	0.0105
DBIL	0.1972	0.0417	ALB	0.9987	< 0.0001	TP	-0.6032	< 0.0001
TP	0.4117	< 0.0001	A/G	0.6008	< 0.0001	ALB	-0.8967	< 0.0001
ALB	0.5986	< 0.0001	CREA	-0.2123	0.0274	A/G	-0.5314	< 0.0001
A/G	0.3781	< 0.0001	Urea	-0.2184	0.0232	CREA	0.2102	0.0297
LDH	-0.3161	0.0012	UA	-0.2467	0.0101	UA	0.2097	0.0301
HDL-C	0.2974	0.0019	LDH	-0.3795	< 0.0001	LDH	0.4070	< 0.0001
D-D	-0.4750	< 0.0001	TG	-0.2185	0.0231	HDL-C	-0.3475	0.0002
Fbg	-0.8820	< 0.0001	HDL-C	0.3159	0.0009	D-D	0.6699	< 0.0001

SLEDAI, systemic lupus erythematosus disease activity index; anti-nRNP/Sm: antinuclear ribonucleoprotein/Smith antibody; ANUA, Anti-nucleosome antibody; anti-SSA, anti-Sjögren'ssyndrome-related antigen A antibody; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TBIL, total bilirubin; DBIL, direct bilirubin; TP, total protein; ALB, albumin; A/G, albumin/globulin; CREA, creatinine; UA, uric acid; LDH, lactate dehydrogenase; TG, triglyceride; HDL-C, high density liptein cholesterol; D-D, D-dimer; Fbg, fibrinogen; RBC, red blood cell counts; HGB, hemoglobin; HCT, hematocrit; L, lymphocyte count; L%, lymphocyte percentage; N%, neutrophil percentage; AFR, albumin to fibrinogen ratio; PNI, prognostic nutritional index; NLR, neutrophil to lymphocyte ratio; dNLR, derived Neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; CAR, C-reactive protein to albumin ratio; ECR, erythrocyte sedimentation rate to C-reactive protein ratio; THR, triglyceride to high density liptein cholesterol ratio; AAR, alanine aminotransferase to aspartate aminotransferase ratio.

AFR			PNI			AFR-PNI model		
ESR	-0.5287	< 0.0001	D-D	-0.6902	< 0.0001	Fbg	0.5778	< 0.0001
CRP	-0.5595	< 0.0001	Fbg	-0.2035	0.0355	ESR	0.5309	< 0.0001
RBC	0.2814	0.0033	ESR	-0.4517	< 0.0001	CRP	0.5529	< 0.0001
HGB	0.1924	0.0416	CRP	-0.4295	< 0.0001	RBC	-0.4762	< 0.0001
HCT	0.2898	0.0025	RBC	0.5699	< 0.0001	HGB	-0.4133	< 0.0001
L	0.2332	0.0156	HGB	0.5109	< 0.0001	HCT	-0.5028	< 0.0001
L%	0.2074	0.0321	HCT	0.5982	< 0.0001	L	-0.3322	0.0005
N%	-0.2046	0.0346	PLT	0.2124	0.0273	L%	-0.2839	0.0030
PNI	0.6034	< 0.0001	L	0.3615	0.0001	N%	0.2655	0.0057
NLR	-0.1992	0.0397	L%	0.2917	0.0022	AFR	-0.8808	< 0.0001
dNLR	-0.2081	0.0315	N%	-0.2574	0.0071	PNI	-0.8997	< 0.0001
PLR	-0.2195	0.0231	AFR	0.6034	< 0.0001	NLR	0.2520	0.0088
LMR	0.2371	0.0139	NLR	-0.2414	0.0119	dNLR	0.2688	0.0051
CAR	-0.6169	< 0.0001	dNLR	-0.2595	0.0067	PLR	0.1972	0.0417
THR	-0.2115	0.0288	LMR	0.2147	0.0255	LMR	-0.2460	0.0106

SLEDAI, systemic lupus erythematosus disease activity index; anti-nRNP/Sm: antinuclear ribonucleoprotein/Smith antibody; ANUA, Anti-nucleosome antibody; anti-SSA, anti-Sjögren'ssyndrome-related antigen A antibody; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TBIL, total bilirubin; DBIL, direct bilirubin; TP, total protein; ALB, albumin; A/G, albumin/globulin; CREA, creatinine; UA, uric acid; LDH, lactate dehydrogenase; TG, triglyceride; HDL-C, high density liptein cholesterol; D-D, D-dimer; Fbg, fibrinogen; RBC, red blood cell counts; HGB, hemoglobin; HCT, hematocrit; L, lymphocyte count; L%, lymphocyte percentage; N%, neutrophil percentage; AFR, albumin to fibrinogen ratio; PNI, prognostic nutritional index; NLR, neutrophil to lymphocyte ratio; dNLR, derived Neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; CAR, C-reactive protein to albumin ratio; ECR, erythrocyte sedimentation rate to C-reactive protein ratio; THR, triglyceride to high density liptein cholesterol ratio; AAR, alanine aminotransferase to aspartate aminotransferase ratio.

AFR			PNI			AFR-PNI model		
ECR	0.2222	0.0386	CAR	-0.5828	< 0.0001	CAR	0.6775	< 0.0001
			AAR	0.1995	0.0385	ECR	-0.2321	0.0269
			THR	-0.3304	0.0005	THR	0.3041	0.0014

SLEDAI, systemic lupus erythematosus disease activity index; anti-nRNP/Sm: antinuclear ribonucleoprotein/Smith antibody; ANUA, Anti-nucleosome antibody; anti-SSA, anti-Sjögren'ssyndrome-related antigen A antibody; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TBIL, total bilirubin; DBIL, direct bilirubin; TP, total protein; ALB, albumin; A/G, albumin/globulin; CREA, creatinine; UA, uric acid; LDH, lactate dehydrogenase; TG, triglyceride; HDL-C, high density liptein cholesterol; D-D, D-dimer; Fbg, fibrinogen; RBC, red blood cell counts; HGB, hemoglobin; HCT, hematocrit; L, lymphocyte count; L%, lymphocyte percentage; N%, neutrophil percentage; AFR, albumin to fibrinogen ratio; PNI, prognostic nutritional index; NLR, neutrophil to lymphocyte ratio; dNLR, derived Neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; CAR, C-reactive protein to albumin ratio; ECR, erythrocyte sedimentation rate to C-reactive protein ratio; THR, triglyceride to high density liptein cholesterol ratio; AAR, alanine aminotransferase to aspartate aminotransferase ratio.

Moreover, we investigated the relationship between AFR, PNI, AFR + PNI model and treatment. As shown in Fig. 4B, there was a trend towards reduced the level of PNI in new-onset SLE patients than in re-visiting SLE patients, but the difference was not statistically significant (P = 0.0805). And, the expression levels of AFR and AFR + PNI model did not show any remarkable differences between new-onset and re-visiting SLE patients (Fig. 4).

Relationship of AFR, PNI, AFR-PNI model and clinical symptoms

Our previous data suggested that AFR, PNI, AFR-PNI model could be used to predicte disease activity in patients with systemic lupus erythematosus. Thus, we explored the relationship between AFR, PNI, AFR-PNI model and clinical symptoms including arthritis, fever, rash, alopecia, pleurisy, pericarditis, RI, encephalosis, paropsia, lupus encephalopathy, vasculitis, myositis and mucosal ulcer. As shown in Fig. 5, we found PNI, AFR-PNI model were associated with fever, pleurisy, pericarditis, RI, and AFR was associated with pleurisy, pericarditis, RI. However, no relationship was found between AFR, PNI, AFR-PNI model and other clinical symptoms. Moreover, our results showed that many other laboratory indicators were associated with clinical symptoms of SLE (supplement Table 1).

Discussion

Predicting active SLE using reliablemarkers is of particular importance when it comes to implementing useful preventive strategies in clinical practice[21]. As we known, SLEDAI is the most commonly used to calculate disease activity. However, the numeration of SLEDAI need to synthesize many clinical symptoms

and abnormal laboratory tests. Thus, If there are some indexs that can be obtained from laboratory data using blood samples, clinicians would be able to objectively, simply and continuously evaluate the activity of SLE patients. Studies have confirmed the presence of hematological abnormalities, such as the content of anti-dsDNA, L, Fbg, CRP, ESR, HDL-C, LDH, ALB, et al, in SLE patients [6, 8, 12, 22–24]. The present study systematically explored the levels of routine laboratory indicators between SLE with active group and SLE without active group and showed that many laboratory indicators including anti-dsDNA, ANUA, Anti-SSA, C3, ESR, CRP, TBIL, TP, ALB, A/G, CREA, HDL-C, D-D, Fbg, HGB, HCT, L were differential expression in SLE with active group than that in SLE without active group. These factors are important indicators of inflammation and immune response. Thus, we analyzed the potential of these novel serological indicators calculated by conventional indexs in predicting the activity in SLE patients.

Among the 12 novel serological indicators including AAR, THR, AFR, PNI, NLR, dNLR, PLR, LMR, SII, CAR and ECR, the levels of AFR, PNI were significantly lower in SLE with active group, only CAR was significantly higher in SLE with active group than that in SLE without active group. Only one study has investigated the level of AFR and CAR in SLE [11]. Our findings agreed with those reported by He et al., where AFR was decreased and CAR was increased in SLE patients. However, the relationship between AFR, CAR, and clinical disease activity have not been investigated previously in SLE in previous study. Spearman method showed that AFR, CAR and PNI were all associated with disease activity measured by SLEDAI, autoantibodies, ESR, CRP, et al. As far as we are aware, there were three study has investigated the association of PNI with disease activity in SLE [14–16]. Our findings agreed with the results from those reports and suggest that PNI may be a useful index for the evaluation of disease activity. In addition, ROC curve showed that lower AFR and PNI could provide better predictive vaule in SLE activity (AUC > 0.7), but the AUC of CAR was inferior to 0.7. More importantly, logistic regression indicated lower AFR and PNI were risk factors for SLE activity. Thus, the present study considered together with previous work suggested that AFR and PNI could be a useful index for the evaluation of disease activity in SLE patients.

To the best of the authors knowledge, the present study is the first to constructe a prediction model of AFR and PNI and evaluate the value of prediction model in SLE activity. Our study demonstrated that the predictive model based on combination of AFR and PNI performed best value in distinguishing SLE with activity group from SLE without activity group, with AUC of 0.765, which superior to single AFR and single PNI. These results suggested that AFR and PNI have synergic effect on predicting activity occurrence in SLE. The predictive value based on combination of AFR and PNI = -0.102* AFR-0.008* PNI + 4.890. Moreover, our results indicated that the predictive value were correlated with commonly used indicators for SLE activity[6, 8, 21, 25, 26, 27, 28] including TP, ALB, A/G, D-D, Fbg, ESR, CRP, HCT, CAR, AFR, PNI, SLEDAI, TBIL, LDH, HDL-C, RBC, HGB, L, THR, C3, DBIL, CREA, UA, L%, N%, NLR, dNLR, PLR, LMR, ECR, anti-SSA, anti-dsDNA, ANUA, which suggested that the predictive model based on combination of AFR and PNI could be a useful novel index for the evaluation of disease activity in SLE patients.

As we known, anti-dsDNA is the traditional and most commonly used assessing activity marker for SLE [29, 30]. Furthermore, our study revealed that the AFR-PNI model + anti-dsDNA combination model could effectively discriminated the SLE with activity and SLE without activity, with a sensitivity of 82.81%

(53/64), a specificity of 88.46% (23/26), which were superior to AFR-PNI model and anti-dsDNA. These results indicated that the combination of AFR-PNI model and traditional autoantibody could further improve the predictive value.

The research from Ahn. et al showed that PNI was associated with lupus nephritis [15]. In this study, our data indicated PNI was associated with RI in agreement with the previous research, which suggesting PNI correlated with clinical symptoms of SLE. In addition, we found PNI was associated with fever, pleurisy and pericarditis. Moreover, the results demonstrated AFR was associated with pleurisy, pericarditis and AFR-PNI model was associated with fever, pleurisy, pericarditis.

There were potential limitations to this study. First, the assessment of clinical and laboratory datawas performed by reviewing medical records of patients. Second, the number of patients with inactive SLE patients included was relatively small. Third, serial changes in AFR, PNI, prediction model were not assessable and the adjustment for treatment was not possible owing to the retrospective study design. Fourth, we only included Chinese patients, these findings cannot be generalised to other ethnicities. Additional studies are required to validate our findings and reveal the association between prediction model and the active in SLE patient.

Conclusions

In conclusion, the authors have demonstrated that AFR, PNI in SLE with active group were significantly decreased than that in SLE without active group and AFR, PNI were better correlated with disease activity. The model generated by combining AFR and PNI may accurately and easily predict activity of SLE. Moreover, AFR, PNI, AFR-PNI model were associated with clinical symptoms. We are aware that the results reported are preliminary and further multicenter studies based on larger cohorts are required.

Abbreviations

AAR, alanine aminotransferase to aspartate aminotransferase ratio; A/G, albumin/globulin; AFR, albumin to fibrinogen ratio; ALP, alkaline phosphatase; ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA antibody; anti-nRNP/Sm: antinuclear ribonucleoprotein/Smith antibody; anti-RIB-P, anti-ribosomal P antibody; anti-Sm, anti-Smith antibody; anti-SSA, anti-Sjögren'ssyndrome-related antigen A antibody; anti-SS-A52, Anti-sjögren syndrome A antigen 52 antibody; anti-SSB, anti-Sjögren'ssyndrome-related antigen B antibody; ALB, albumin; ALT, alanine aminotransferase; ANUA, Anti-nucleosome antibody; APTT, acivated partial thromboplastin time; AST, aspartate aminotransferase; C3, complement 3; C4, complement 4; CAR, C-reactive protein to albumin ratio; CHOL, total cholesterol; CK, creatine kinase; CREA, creatinine; CRP, C-reactive protein; DBIL, direct bilirubin; D-D, D-dimer; dNLR, derived Neutrophil to lymphocyte ratio; ECR, erythrocyte sedimentation rate to C-reactive protein ratio; ESR, erythrocyte sedimentation rate; Fbg, fibrinogen; GGT, γ-glutamyltransferase; GLB, globulin; GLU, glucose; HCT, hematocrit; HDL- C, high density liptein cholesterol; HGB, hemoglobin; IgG, immunoglobulin G; INR, international normalized ratio; L, lymphocyte count; L%, lymphocyte percentage; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; LMR, lymphocyte to monocyte ratio; M, monocyte count; M%, monocyte percentage; MHR,

monocyte to high density liptein cholesterol ratio; N, neutrophil count; N%, neutrophil percentage; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PLT, platelet counts; PNI, prognostic nutritional index; PT, prothrombin time; RBC, red blood cell counts; RI, Renal involvement; SII, systemic immune inflammation index; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; TBIL, total bilirubin; TG, triglyceride; THR, triglyceride to high density liptein cholesterol ratio; TP, total protein; TT, thrombin time; UA, uric acid; WBC, white blood cell counts.

Declarations

Authors' contributions

QL, HSZ participated in designing the study, performed statistical analyses and drafted the manuscript. PF carried out flow cytometry analysis and drafted the manuscript. QYX carried out data acquisition of marker of inflammation, performed statistical analyses and drafted the manuscript. BQF carried out data acquisition of urine protein, performed statistical analyses and drafted the manuscript. YG performed data acquisition of disease activity and severity, performed statistical analyses and drafted the manuscript. QSH performed data acquisition of disease activity and severity, performed statistical analyses and drafted the manuscript. ZKH participated in designing the study, carried out data acquisition of marker of autoimmune response, performed statistical analyses and drafted the manuscript. JML conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The dataset supporting the conclusions of this article will be available to the Editors and Reviewers upon request.

Consent for publication

The authors declare that they agreed to publish.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (2014003) and was carried out in compliance with the Helsinki Declaration. Informed consent was obtained from all participants before they entered the study.

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Figures

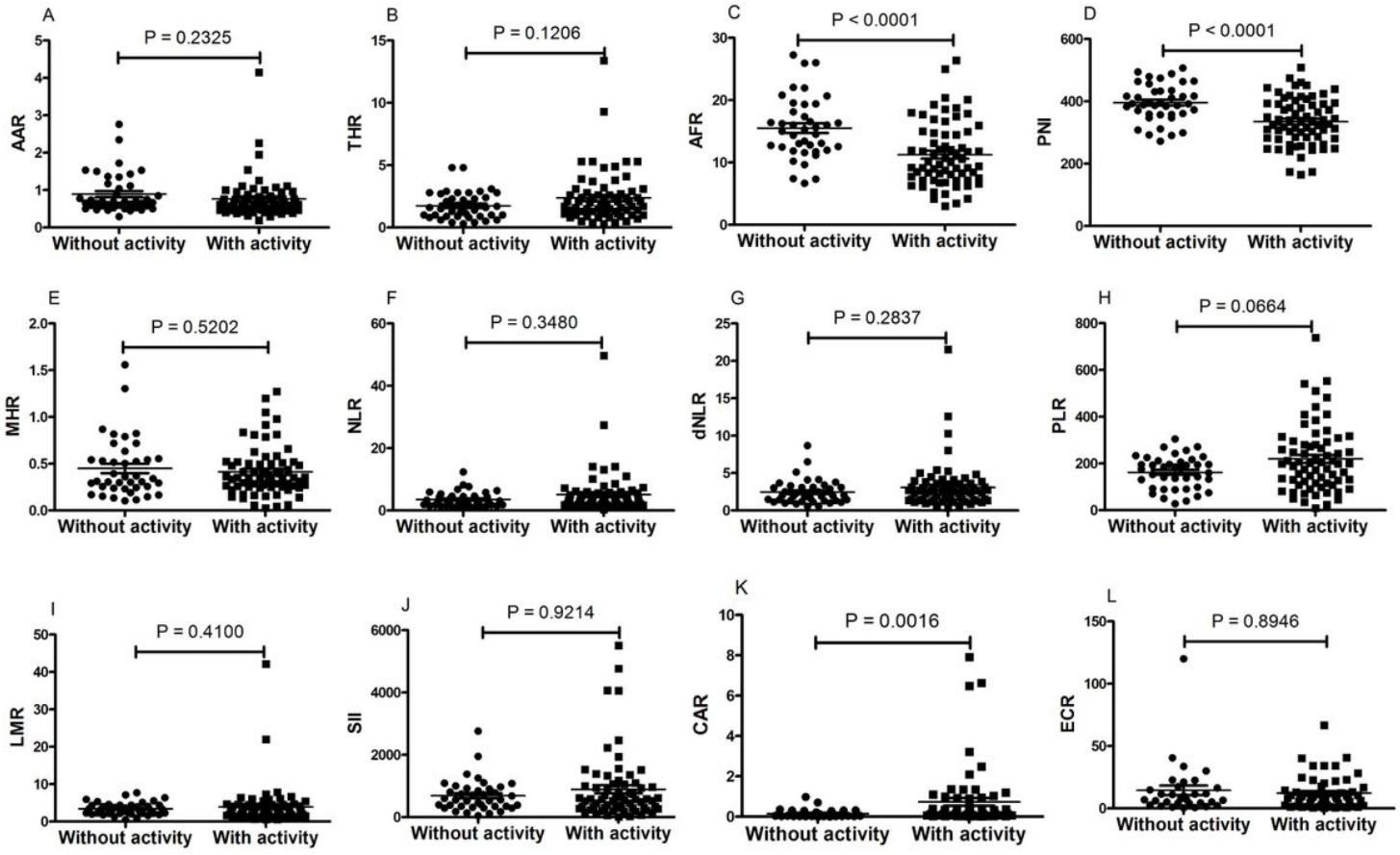
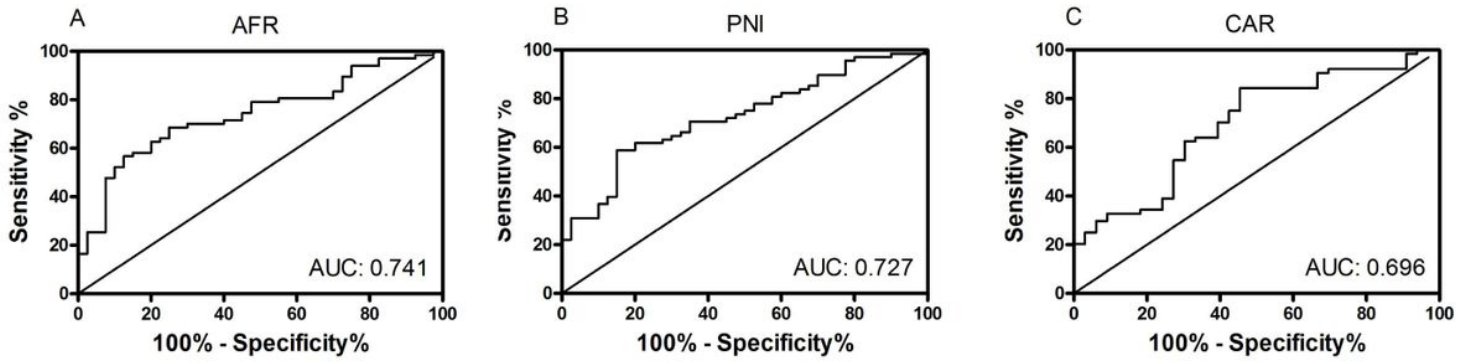


Figure 1

The comparison of different novel serological indicators according to systemic lupus erythematosus (SLE) activity. (A) There was no significant difference in the level of alanine aminotransferase to aspartate aminotransferase ratio (AAR) between SLE with activity group and SLE without activity group. (B) There was no significant difference in the level of triglyceride to high density liptein cholesterol ratio (THR) between SLE with activity group and SLE without activity group. (C)The level of albumin to fibrinogen ratio

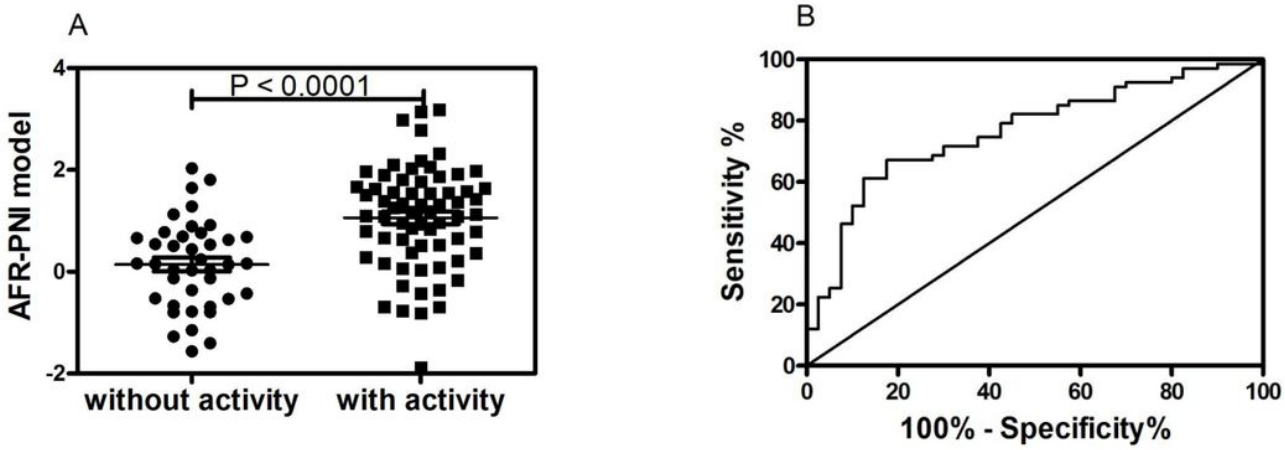
(AFR) was decreased in SLE with activity group compared to that in SLE without activity group. (D) The level of prognostic nutritional index (PNI) was decreased in SLE with activity group compared to that in SLE without activity group. (E) There was no significant difference in the level of monocyte to high density liptein cholesterol ratio (MHR) between SLE with activity group and SLE without activity group. (F) There was no significant difference in the level of neutrophil to lymphocyte ratio (NLR) between SLE with activity group and SLE without activity group. (G) There was no significant difference in the level of derived Neutrophil to lymphocyte ratio (dNLR) between SLE with activity group and SLE without activity group. (H) There was no significant difference in the level of platelet to lymphocyte ratio (PLR) between SLE with activity group and SLE without activity group. (I) There was no significant difference in the level of lymphocyte to monocyte ratio (LMR) between SLE with activity group and SLE without activity group. (J) There was no significant difference in the level of systemic immune inflammation index (SII) between SLE with activity group and SLE without activity group. (K) the level of C-reactive protein to albumin ratio (CAR) was elevated in SLE with activity group compared to that in SLE without activity group. (L) There was no significant difference in the level of erythrocyte sedimentation rate to C-reactive protein ratio (ECR) between SLE with activity group and SLE without activity group.



Variables	AUC	*p*-value	95% C.I.	Sensitivity	Specificity	Cut-off
AFP	0.741	<0.0001	0.647-0.835	56.72	87.50	<11.14
PNI	0.727	<0.0001	0.632-0.822	58.82	85.00	<346.1
CAR	0.696	0.0016	0.586-0.806	84.38	54.55	>0.0597

Figure 2

Receiver operator characteristic curve (ROC) of albumin to fibrinogen ratio (AFR), prognostic nutritional index (PNI) and C-reactive protein to albumin ratio (CAR) in predicting disease activity. (A) ROC of AFR in predicting disease activity. (B) ROC of PNI in predicting disease activity. (C) ROC of CAR in predicting disease activity.



Variables	AUC	P-value	95% C.I.	Sensitivity	Specificity	Cut-off
2-Maker Model	0.765	<0.0001	0.674-0.857	67.16	82.50	>0.7824

Figure 3

The effect of AFR+PNI model on discriminating between systemic lupus erythematosus (SLE) with activity group and SLE without activity group. (A) The predictive value of AFR+PNI model in SLE with activity group was increased than that in SLE without activity group. (B) ROC of AFR+PNI in predicting disease activity.

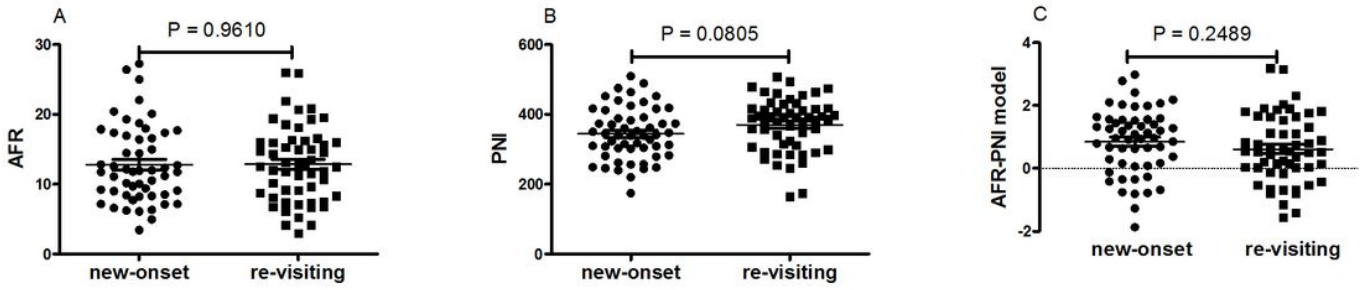


Figure 4

The comparison of albumin to fibrinogen ratio (AFR), prognostic nutritional index (PNI) and AFR+PNI model according to new-onset and re-visiting systemic lupus erythematosus (SLE) patients. (A) The expression level of AFR did not show any remarkable differences between new-onset and re-visiting SLE patients. (B) There was a trend towards reduced the level of PNI in new-onset SLE patients than in re-visiting SLE patients, but the difference was not statistically significant. (C) The expression level of AFR+PNI model did not show any remarkable differences between new-onset and re-visiting SLE patients.

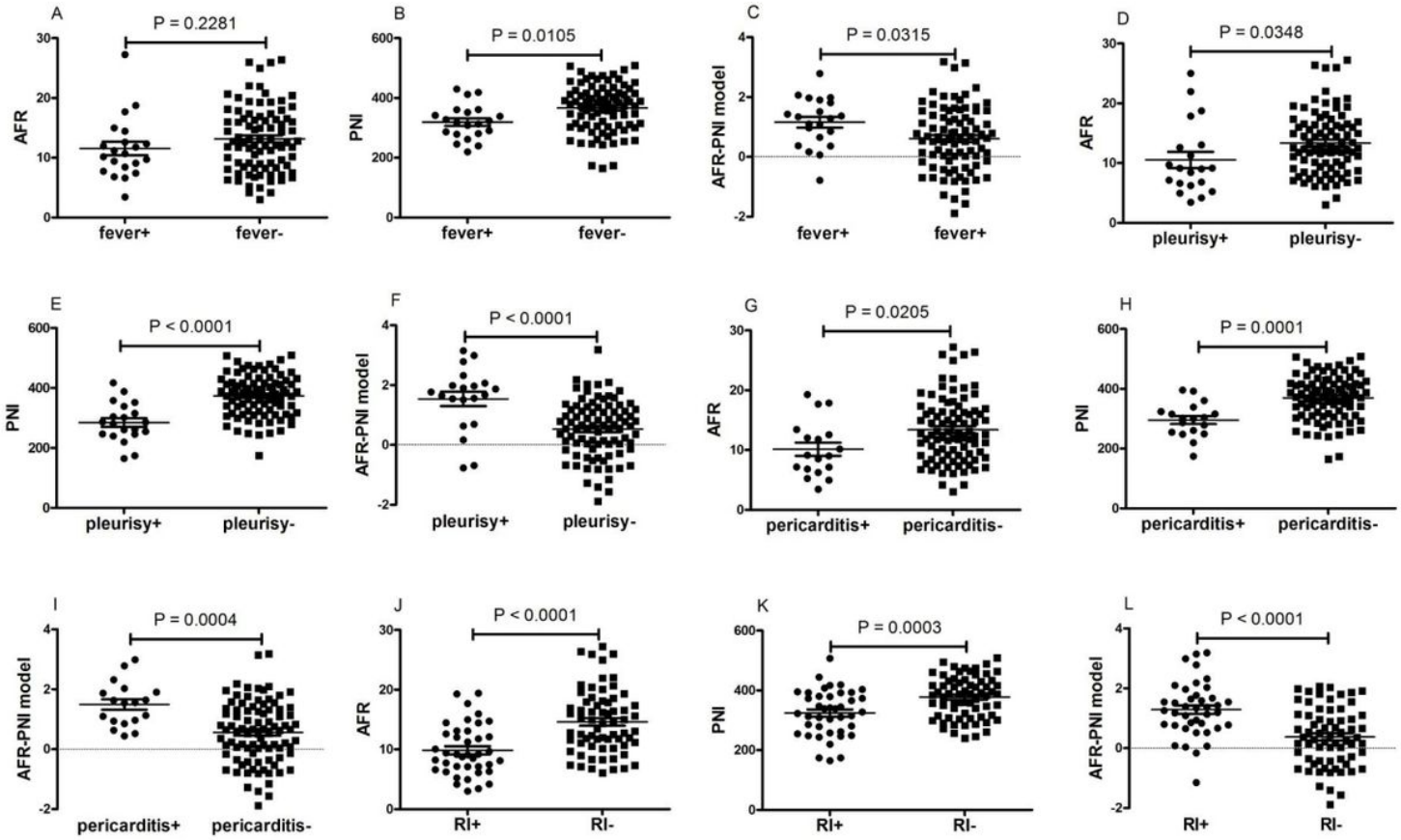


Figure 5

Relationship of albumin to fibrinogen ratio (AFR), prognostic nutritional index (PNI) and AFR-PNI model and clinical symptoms. (A) The expression level of AFR did not show any remarkable differences between SLE patients with fever and SLE patients without fever. (B) The level of PNI was decreased in SLE patients with fever compared to that in SLE patients without fever. (C) The level of AFR-PNI model was increased in SLE patients with fever compared to that in SLE patients without fever. (D) The level of AFR was decreased in SLE patients with pleurisy compared to that in SLE patients without pleurisy. (E) The level of PNI was decreased in SLE patients with pleurisy compared to that in SLE patients without pleurisy. (F) The level of AFR-PNI model was increased in SLE patients with pleurisy compared to that in SLE patients without pleurisy. (G) The level of AFR was decreased in SLE patients with pericarditis compared to that in SLE patients without pericarditis. (H) The level of PNI was decreased in SLE patients with pericarditis compared to that in SLE patients without pericarditis. (I) The level of AFR-PNI model was increased in SLE patients with pericarditis compared to that in SLE patients without pericarditis. (J) The level of AFR was decreased in SLE patients with renal involvement (RI) compared to that in SLE patients without RI. (K) The level of PNI was decreased in SLE patients with RI compared to that in SLE patients without RI. (L) The level of AFR-PNI model was increased in SLE patients with RI compared to that in SLE patients without RI.

Supplementary Files

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- supplementTable.docx