Apoptosis inhibitor of macrophage/CD5L is associated with disease activity in rheumatoid arthritis

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Abstract

Objective

To investigate the association between apoptosis inhibitor of macrophage (AIM) and disease activity in patients with rheumatoid arthritis (RA).

Methods

In this study, concentrations of serum AIM in 110 RA patients, 38 patients with osteoarthritis (OA) and 50 sex- and age-matched control subjects were determined by enzyme-linked immunosorbent assay (ELISA).

Results

Serum AIM concentrations in RA patients were dramatically higher than those from patients with OA or healthy controls. The levels of synovial fluid AIM displayed a significant increase as compared with OA patients. More importantly, AIM levels were significantly correlated with RA disease activity features such as ESR, CRP and DAS28. The predictive value of AIM on high disease activity was superior to those of CRP and ESR. A noteworthy correlation in our study was observed between the serum AIM levels and laboratory parameters, particularly serum lipids. Furthermore, serum AIM levels could be significantly down-regulated after effective integrative treatment.

Conclusion

AIM may serve as a novel sensitive biomarker to assist disease activity assessment and monitor therapeutic effects in active RA patients.

Key words

rheumatoid arthritis, apoptosis inhibitor of macrophage, disease activity

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Introduction

Rheumatoid arthritis (RA) is polyarticular, symmetric autoimmune disease with an estimate of nearly 0.5%~1% of the adult population worldwide (1, 2). It primarily involves persistent synovitis and extra- articular comorbidities, which could be the main cause of the increase in severity and mortality. If insufficiently treated, RA can lead to joint deformity and irreversible disability (3). Current treatment strategies is to suppress progression of inflammation, prevent of severe damage and improve quality of life (4). Indeed, the important management of rheumatoid arthritis is early identification, promptly DMARD therapy, as well as regularly assessment of disease activity until remission or low disease status. Especially for active patients, the recognition of severe patients can help clinicians modify treatment regimens and increase the likelihood of a better prognosis (3-5). Thus, a correct assessment of RA disease activity is important for rapid and specific treatment administration.

The detection of laboratory indicators, such as ESR and CRP, has been used to evaluate clinical disease activity, while these indicators are not sensitive and effective enough for RA patients at the active phase (6). Recently, several studies have found that calprotectin levels and MBDA score are associated with severity of RA (7, 8). Therefore, it is of great importance in finding a sensitive and objective biomarker for that will assess the disease activity in RA patients.

Apoptosis inhibitor of macrophage (AIM, also called CD5L), in accordance with its antiapoptotic effects *in vivo* and *in vitro*, was named AIM initially, which is mainly secreted by tissue-resident macrophages and epithelial cells in the lung (9). Earlier evidence indicated that AIM was implicated in protecting the survival of macrophages against various pathogens, such as *Bacillus anthracis*, *Listeria monocytogenes*, and *Mycobacterium tuberculosis* (10, 11). It was shown to bind to different types of immune cells including dendritic cell, leukocyte as well as epithilial cell, suggesting its regulatory role in the immune system (12).

Recent accumulating evidence has revealed that this protein performs many additional functions, ranging from the control of leukocyte recruitment and inflammatory responses to the regulation of lipid homeostasis (13, 14). Several reports have pointed to the contribution of AIM in many human pathologic conditions, mostly of inflammatory origin, including atherosclerosis, acute kidney injury, pulmonary involvement and cancer (15-18). Moreover, AIM can inhibit the production of TNF and IL-1β, while enhancing IL-10 secretion in peripheral blood monocytes (12, 19, 20). TNF, IL-1β and IL-10 participate in the pathogenic process of RA (21). In view of the above findings, AIM might be implicated in the modulation of autoimmunity and host immune homeostasis.

However, the circulating level of AIM in RA patients remains unclear. Therefore, the aim of the present study was to perform the correlation between AIM levels and RA clinical activity and to evaluate whether AIM could be used as a potential biomarker for the identifying of high activity and monitoring of therapeutic efficacy in RA.

Materials and methods

Study population and samples

A total of 110 RA patients including 24 patients with metabolic syndrome (MS) and 21 patients with interstitial lung diseases (ILD), 38 patients with osteoarthritis (OA) and 50 sex-&age-matched healthy volunteers were evaluated in this study. The diagnostic of RA fulfilled the 2010 revised ACR/EULAR criteria for RA (22), while OA patients were established by the 1986 ACR criteria (23). RA disease activity was assessed according to the 28-joint count Disease Activity Score combined with ESR value (DAS28-ESR) as described (24). From this score the patients were classified as follows: low activity, 2.6 ≤ DAS28-ESR ≤3.2, moderate activity 3.2 < DAS28-ESR ≤5.1, high activity DAS28-ESR >5.1. RA patients with <18 years, other autoimmune and infectious diseases, malignancy were excluded from this study.

Each RA patients received a standardised medical history collection from Clinical Electronic Medical Record. All serum samples were collected on ad-

mission from inpatient or outpatient of the First Affiliated Hospital of Chongqing Medical University from August 2018 to May 2019. Synovial fluid (SF) was obtained from active patients whenever possible. Response to treatment was interpreted based on EULAR criteria (25). Specifically, clinical features of 24 responders RA patients with moderate-high activity were reevaluated after effective treatment at 8 weeks of follow-up.

This study was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital of Chongqing Medical University, and informed consent was obtained from all participants. The experiments were carried out on basis of the regional Ethics Committee guidelines and Regulations.

Defnition of the metabolic syndrome and interstitial lung diseases

Criteria for clinical diagnosis of metabolic syndrome (MS) are adopted on the basis of 2005 American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) update statement (26). MS were defned as presence of three or more of the following five medical conditions: 1) waist circumference >102 cm in men and >88 cm in women; 2) triglycerides (TG) ≥1.7 mmol/L; 3) high density lipoprotein cholesterol (HDL-c) <1.03 mmol/L in men and <1.3 mmol/L) in women; 4) systolic blood pressure (SBC) ≥130 mmHg, or diastolic blood pressure (DBP) 85 mmHg; 5) fasting blood-glucose (FPG) ≥5.6 mmol/L, or previously diagnosed .

High-resolution computed tomography (HRCT) or other comparable radiological examination and pulmonary function tests (PFTs) were performed to assess the absence/presence of ILD in RA patients according to previously outlined protocols (27).

Measurement of laboratory markers

The erythrocyte sedimentation (ESR) was measured by the Westergren method. The levels of serum C3, C4, C-reactive protein (CRP) and rheumatoid factor (RF) were determined via turbidimetric immunoassay in line with the manufacturer's instructions. Anti-cyclic citrullinated peptide (anti-CCP) and anti-RA33 levels were determined by using enzyme-linked immunosorbent assay (ELISA). Anti-keratin antibodies (AKA) were assessed by fluorescence-enzyme immunoassay.

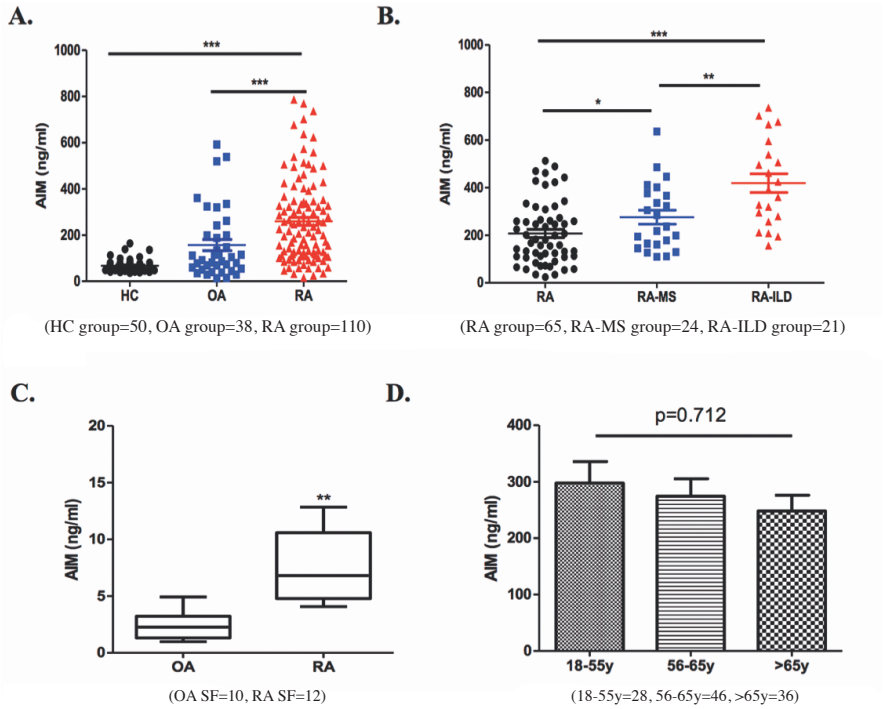

Fig. 1. Serum AIM concentrations were elevated in RA patients.
A: Determination of AIM concentrations in patients with rheumatoid arthritis (RA) and the controls. Serum was collected from 110 RA patients, 38 patients with osteoarthritis (OA) and 50 healthy controls (HC).
B: Scatter-plots of serum AIM levels in RA patiens with different comorbidities. RA-MS group (n=24), RA-ILD group (n=21) and RA group without severe comorbidities (n=65).
C: Synovial fluid of AIM levels in 12 patients with rheumatoid arthritis (RA) and 10 patients with osteoarthritis (OA).
D: Concentrations of serum AIM in different age groups. The Mann-Whitney test was used to compare differences in groups, and the Kruskal-Wallis test was used to test for differences in three group comparisons. $p<0.05$ as statistically significant (*$p<0.05$; **, $p<0.01$; ***$p<0.001$)

Quantification of apoptosis inhibitor of macrophage AIM/CD5L

The concentrations of AIM were determined by human AIM ELISA kit (My Biosource Inc., San Diego, CA) in accordance with the supplied instructions.

Statistical analysis

All data analyses were performed using IBM Statistics SPSS v. 22.0 or GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). Differences between groups were evaluated using the Mann-Whitney U test or Kruskal-Wallis test. The correlations of serum AIM concentrations with clinical characteristics were analysed by using Spearman's rank correlation. The AIM levels and DAS28 score before or after treatment were assessed by using a paired t-test. Differences in categorical variables was analysed using chi-square test. In addition, the diagnostic accuracy of biomarkers was determined by analysing the receiver operator characteristic (ROC) curves. *p*-values <0.05 were considered statistically significant.

Results

AIM levels is elevated in RA

To investigate a first insight into AIM release in RA, we measured AIM levels in the sera from 110 RA patients and in the synovial fluid (SF) from 12 RA patients by ELISA. The serum concentrations of AIM in RA patients were significantly elevated than those from patients with OA or healthy controls [median (interquartile range): AIM in RA patients 219.7 (111.2–346.1) ng/ml, OA patients 98.1 (53.1–209.4) ng/ml, healthy controls 59.6 (49.36–97.58) ng/ml, Fig. 1A]. The SF AIM levels of RA

patients displayed a significant increase as compared with OA patients (p=0.009, Fig.1C). AIM levels showed a slight reduction with age in RA patients, while no significant changes (Fig. 1D).

Additionally, in order to further explored the production of AIM in RA patients, we classified it as the following three groups according to the presence of comorbidities: RA-MS group (n=24), RA-ILD group (n=21) and RA group without severe comorbidities (n=65). Their clinical characteristics are shown in Supplementary Table S1. Compared with the RA group, the levels of ESR, CRP, RF, anti-CCP and DAS28 score in the RA-ILD group were significantly different. Importantly, We found serum AIM levels were significantly higher in RA-ILD group than in RA-MS and RA groups (p=0.008 and 0.0001, Fig. 1B). Moreover, AIM levels were also higher in serum from RA-MS group (median=236.5 ng/ml) than RA group (median=180.6 ng/ml, p=0.041)

Serum AIM levels and RA clinical disease activity

We next assessed the circulating levels of AIM in RA patients with different disease activity. Their clinical features as reflected by Table I. The significant differences in ESR, CRP, PLT, Neutrophil %, C3, RF and anti-CCP levels were observed among the different severity, while this differences did not exist in WBC, Hb and C4.

As illustrated in Fig. 2, the median of AIM were 106.9 ng/ml, 208.5 ng/ml and 311.8 ng/ml respectively, which were increasing from the low to high activity group. Serum AIM levels were markedly (p=0.025 and 0.0006) up-regulated in the high activity group as compared with other activity groups. Furthermore, up-regulation of AIM indicated a significant positive correlation with DAS28 (r=0.448, p=0.002), ESR (r=0.491, p<0.0001) and CRP (r=0.621, p<0.0001). Therefore, AIM levels could be correlated with the RA disease activity.

Correlation between AIM level with laboratory parameters in RA patients

The serum AIM level was significantly correlated with RF and anti- CCP antibody production in RA patients (r=0.333, p=0.001; r=0.251, p=0.031; Fig. 3A-B). Notably, AIM might be associated with antibody production in RA pathogenesis.

Lipid and lipoprotein metabolism have been implicated in the pathogenesis of autoimmune diseases. Therefore, we evaluated the possible correlation between serum lipids and AIM levels. A

Table I. Clinical features of the different disease severity in RA patients.

Clinical features	low activity (n=24)	Moderate activity (n=36)	High activity (n=50)	Kruskal-Wallis test p-value*
General demographics				
Female,n (%)	18 (75.0%)	25 (69.4%)	42 (84.0%)	0.182
Age, years	51.5±13.6	56.7±12.2	61.4±10.6	0.057
Disease duration, years	7.4 ±1.6	8.0±1.5	9.0±1.8	**0.038**
Laboratory measures, median (IQR)				
WBC (10^9/L)	6.9	7.0	6.8	0.635
Neutrophil %	76.3	67.2	62.0	**0.035**
Hb (g/L)	126.0	118.5	115.0	0.158
PLT (10^9/L)	282.0	246.5	232.0	**0.044**
C3 (g/L)	1.22	0.92	0.89	**0.024**
C4 (g/L)	0.28	0.25	0.22	0.351
TC (mmol/L)	4.2	4.4	4.5	0.244
TG (mmol/L)	1.1	1.1	1.3	**0.043**
HDL-c (mmol/L)	1.5	1.4	1.1	**0.021**
LDL-c (mmol/L)	2.5	2.7	2.8	0.160
APOA (g/L)	1.5	1.4	1.2	**0.014**
APOB (g/L)	0.8	0.9	1.0	**0.039**
RA disease characteristics, median				
TJC28	2	5	14	**0.000**
SJC28	1	3	10	**0.000**
ESR (mm/h)	19.0	50.0	70.0	**0.000**
CRP (mg/L)	5.9	17.1	19	**0.000**
RF (IU/mL)	37.2	59.9	184	**0.039**
AKA (+),n (%)	4 (16.7%)	8 (22.2%)	11 (22.0%)	0.316
Anti-CCP (U/mL)	12.4	56.9	54.9	**0.002**

IQR: interquartile range; WBC: white blood cells; Hb: hemoglobin; TC: total cholesterol; TG: triglycerides; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; APOA: apolipoprotein A; APOB: apolipoprotein B; TJC28: Tender joint count in 28 joints; SJC28: swollen joint count in 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factors; AKA: anti-keratin antibodies;Anti-CCP: anti- cyclic cirullinated peptide antibodies. *Bold values indicate statistical significance, p-value <0.05.

Table II. The correlation of apoptosis inhibitor of macrophage (AIM) and clinical indicators after eight-week integrative medicine treatment

Clinical indicators, median (IQR)	Pre-treatment	Post-treatment	p-value	Correlation	
				r	p
TJC28	16.0	10.0	**0.046**	0.413	**0.023**
SJC28	9.0	5.0	0.172	0.398	**0.029**
ESR (mm/h)	61.0	37.5	**0.008**	0.644	**0.000**
WBC (10^9/L)	6.8	6.0	0.055	0.413	**0.019**
Neutrophil %	71.7	61.5	**0.015**	0.369	**0.034**
HB (g/L)	113.0	115.0	0.326	0.272	0.146
PLT (10^9/L)	267.0	273.0	0.478	0.446	**0.014**
CRP (mg/L)	32.9	19.2	**0.025**	0.664	**<0.001**
RF (IU/mL)	104.0	64.9	0.275	0.364	0.057
Anti-CCP (U/mL)	239.4	60.3	**0.034**	0.263	0.204
RA33 (U/mL)	4.3	3.7	0.604	0.218	0.285
C3 (g/L)	1.28	0.86	**0.044**	0.236	0.104
C4 (g/L)	0.29	0.22	0.284	0.151	0.246
DAS28	6.2	5.4	**0.032**	0.597	**0.000**

*Bold values indicate statistical significance, p-value <0.05.

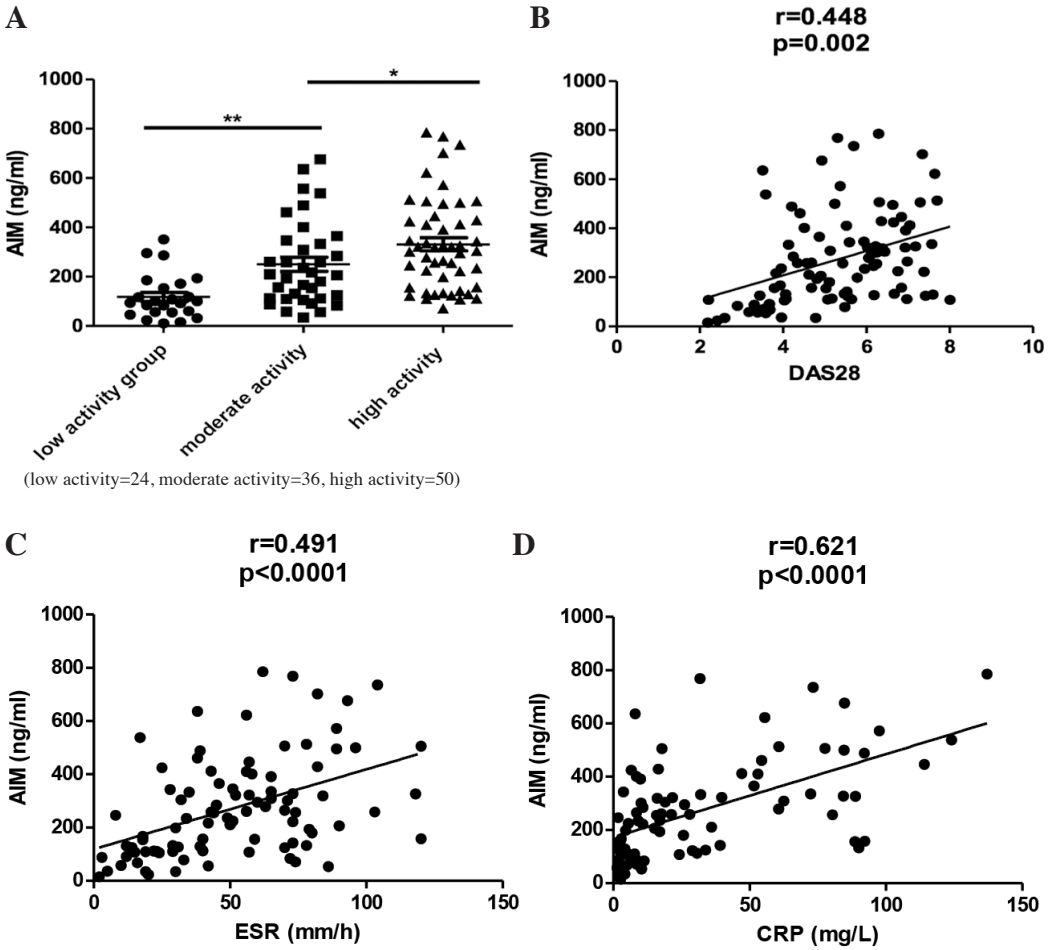

Fig. 2. The role of AIM in reflecting disease activity in RA.
A: AIM levels of RA patients at different disease activity status based on DAS28-ESR score. Each symbol represents an individual subject, and horizontal bars represent median values. The difference between groups was determined by non-parametric Mann-Whitney rank sum test (*p<0.05; **, p<0.01)
B-D: Correlation of serum AIM concentration with RA disease activity parameters including DAS28, ESR and CRP.

significant (r=0.282, p=0.016; r=0.272, p=0.021, respectively) positive correlation was observed between the AIM levels and TG (Fig. 3D), LDL-c (Fig. 3F), APOB (Fig. 3H) but not with TC (Fig. 3C) and LPa (Fig. 3I) . In contrast, a significant (r= -0.350, p=0.002; r= -0.429, p=0.0001) negative correlation was noted between AIM and HDL-c (Fig. 3E), APOA (Fig. 3G) in the RA patients.

Diagnosis of RA high disease activity
We determined the diagnostic value of AIM, ESR, CRP, anti-CCP and RF in active RA patients with high disease activity (Fig. 4, the data are shown in Suppl. Table S2). ROC-AUC analyses indicated that the area under curve of AIM yielded a markedly increased of 0.855 compared with those of CRP (0.635), ESR (0.794), RF (0.694) as well as anti-CCP (0.728) in predicting high disease activity. The optimal cut-off point of AIM was 219.6 ng/ml by calculating sensitivity (82.0%) and specificity (76.6%) of the ROC curve. Subsequently, combined detection of the levels of serum AIM, ESR and CRP showed that the area under the curve was 0.905. Its sensitivity and specificity was 86.8% and 82.4%. In consequence, diagnostic efficiency of combination biomarker was superior to those of the single detection for predicting high disease activity in active RA patients.

Intervention of integrative treatment on the production of AIM in RA patients
To detect the effect of AIM levels in RA patients after 8 weeks of integrative medicine therapy, finally 24 RA patients with moderate- high disease activity were eligible to enroll in our study for efficacy evaluation. The clinical features and treatment regimen of the integrative treatment group are shown in Suppl. Table S3. We found that AIM levels and DAS28 score were dramatically decreased after eight-week integrative treatment (p<0.0001, Fig. 5). Furthermore, disease activity parameters of CRP, anti-CCP as well as ESR were significantly decreased after treatment (p<0.05, Table II).

Correlation of serum AIM to clinical indicators before and after treatment
As shown in Table II, circulating AIM levels significantly correlated with WBC, PLT, levels of serum ESR and CRP, and scores of TJC28, SJC28 and DAS28. However, significant correlation failed to show between serum AIM and anti-CCP, RF and RA33 in RA patients.

Discussion

Rheumatoid arthritis (RA) is a typical systemic autoimmune disorder characterised by persistent synovitis caused by a failure of spontaneous regression of inflammation. In recent years, Some research has focused on new mechanisms of the innate and adaptive immune system that can affect the different stages of RA (28). Several investi-

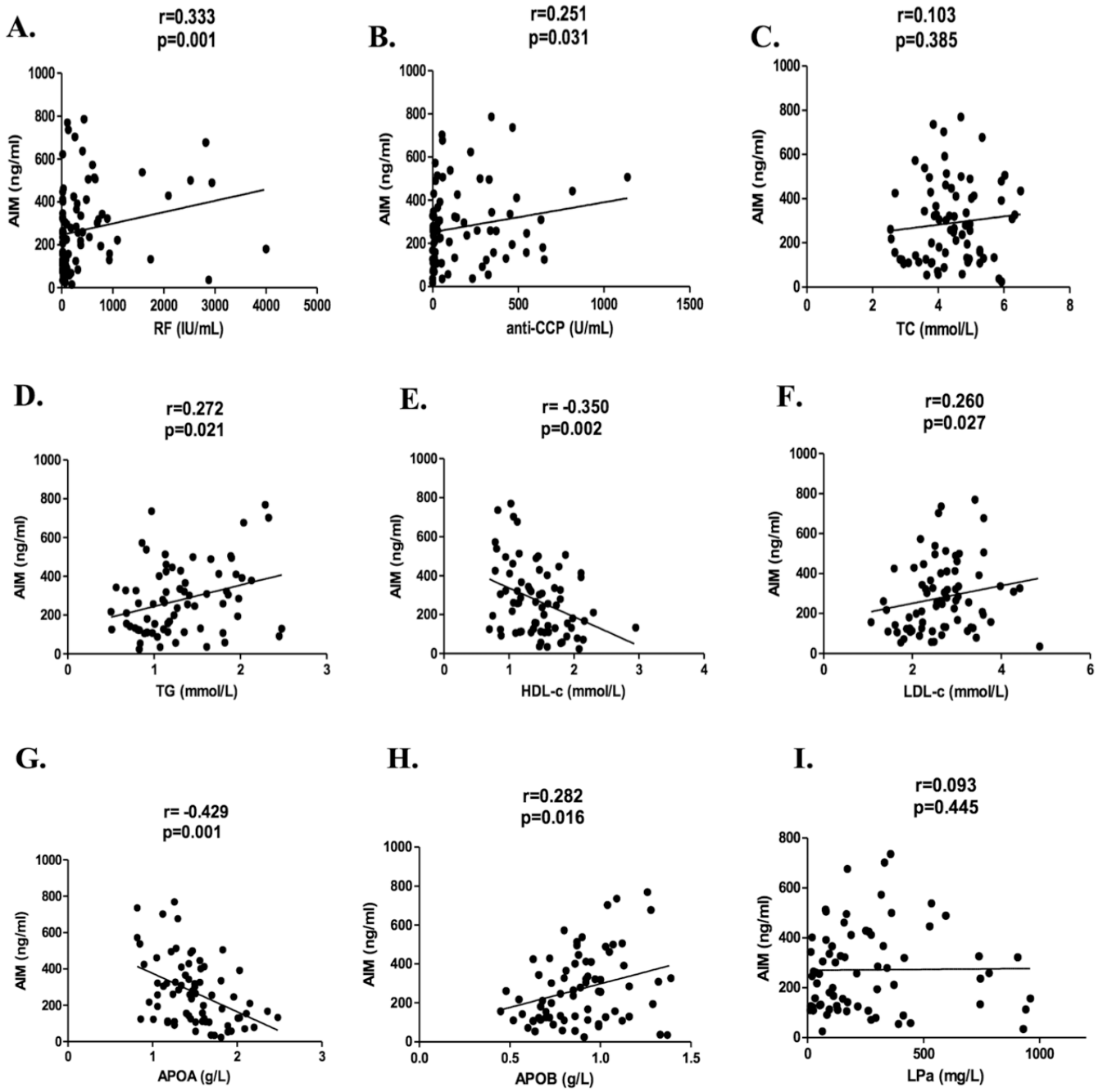

Fig. 3. Correlation between serum AIM and laboratory features of patients with RA.
Serum AIM was implicated in RF (**A**); anti-CCP (**B**); TC (**C**); TG (**D**); HDL-c (**E**); LDL-c (**F**); APOA (**G**); APOB (**H**); LPa (**I**). The non-parametric Spearman rank correlation test was used to determine correlations between two parameters.

gations have also shown that cytokine-mediated processes are involved in the inflammatory regulation pathogenesis and the recognition of autoimmune disease severity (3, 29). Apoptosis inhibitor of macrophage (AIM) is a soluble molecular in innate immunity, which can enhance the phagocytic activity against dead cells and facilitate to improvement of inflammatory diseases (30, 31). Further analysis showed that circulating AIM is stabilised in blood as a result of its interaction with IgM, a process that protects AIM from renal excretion (32). However, as far as we know, there have been no reports in RA. Here we provide the first evidence that AIM may serve as a biomarker for predicting RA disease activity and monitoring treatment.

In this study, we demonstrated that AIM levels in serum and synovial fluid (SF) from RA patients were elevated significantly in comparison with OA patients. These data shown that AIM may participate in the pathological process of RA host immune response and provide a new perspective for the discrimination of rheumatoid arthritis (RA) and osteoarthritis (OA).

More importantly, our findings suggested that AIM levels of RA patients with moderate-high activity was signif-

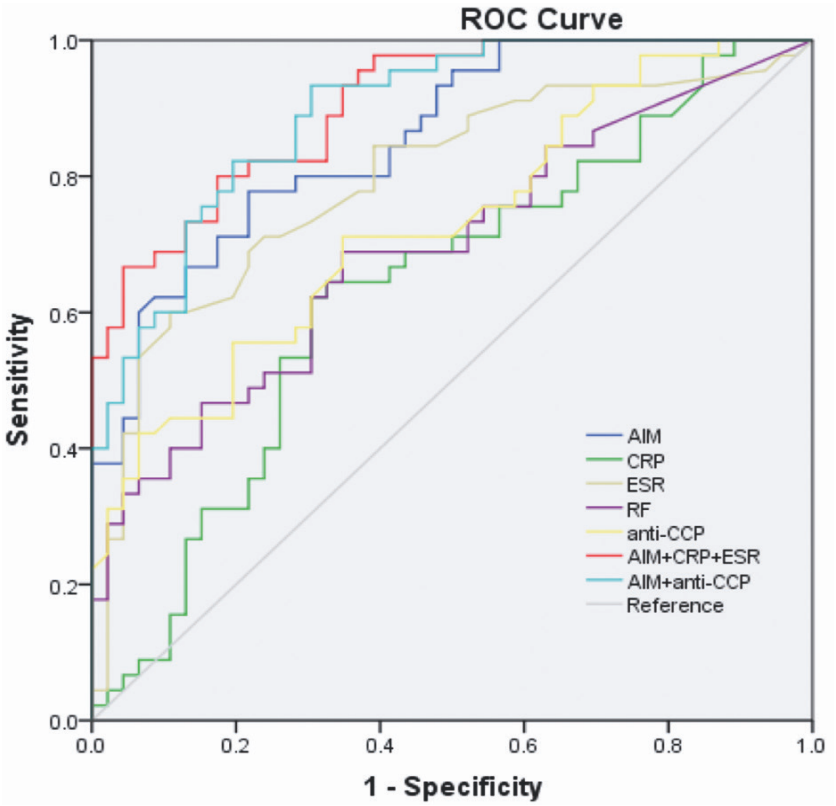

Fig. 4. Diagnosis of RA high disease activity.
ROC curve of serum anti-CCP, AIM, CRP, ESR and RF for identifcation of the high disease activity in RA. The AUC of serum AIM, CRP, ESR, RF and anti-CCP were 0.855 (95%CI, 0.781–0.929), 0.635 (95%CI, 0.520–0.792), 0.794 (95%CI, 0.699–0.888), 0.694 (95%CI, 0.585–0.802) and 0.728 (95%CI, 0.626–0.830), respectively.

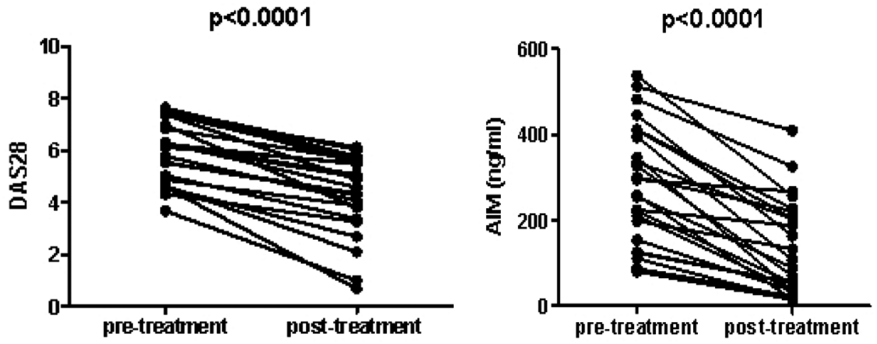

Fig. 5. Effect of treatment with integrative medicine on the production of AIM.
24 RA patients with moderate-high disease activity were eligible to enroll in our study for efficacy evaluation. Serum AIM concentrations and DAS28 score were measured before and after 8 weeks of effective integrative treatment. The data were analysed by using a paired t-test.

icantly higher than those of low activity as assessed by DAS28 score. Subsequently, we evaluated the diagnostic efficacy of AIM and other markers by analysing ROC curves. As expected, AIM was superior to those markers and its combined detection had a high sensitivity and specificity for predicting the higher activity of RA. Thus, AIM may be acted as a novel and sensitive biomarker for high disease activity in RA. Meaningfully, metabolic syndrome (MS) and interstitial lung disease (ILD) are common comorbidities in RA patients, while patients with high cumulative disease activity have an increased risk of comorbidity (33, 34). In our study, we found that circulating levels of AIM was statistically increased in the RA-MS group and the RA-ILD group as compared with the RA without comorbidities. This means that high AIM levels may be associated with disease severity to predict a poor outcome of active RA.

Interestingly, a significant correlation in our study was noted between AIM concentrations and laboratory parameters, particularly in serum lipids. AIM levels were positively correlated with TG, LDL-c and APOB, but negatively correlated with HDL-c and APOA. Previous studies have underlined that AIM may regulate lipid biosynthesis in pathogenic state and the effect of serum lipids could be considered in the determination of RA severity (13,35). These results indicated that AIM might be involved in lipid metabolic disturbance in RA patients, which strengthen AIM compatibility as a biomarker for disease activity.

In contrast to diagnosis, prognostic value of biomarkers in guiding treatment appear to be much stronger. Several biomarkers such as TNF-α, IL-6, IL-33 and MMP-3 were used to assess the effects of clinical treatment (36-38). In line with previous findings, our present results suggested that circulating levels of AIM could be significantly down- regulated after effective integrative treatment. Moreover, we also focused on the alteration of clinical characteristics and correlation with AIM levels before and after treatment in RA patients with moderate-high disease activity. Thus, AIM may be a potential marker for monitoring responses to therapy.

However, several limitations in our study should be considered. For one thing, synovial fluid samples of joints are relatively small and should be further verified in an enlarged samples; for another, the number of cases was too small to analyse AMI expression levels in the remission group. Most patients in our study were longstanding RA, the disease activity was assessed at admission and may not represent total chronic inflammation throughout their disease course. Future studies are still in need to evaluate the patients' status at the time of onset based on multicentre studies with long-term follow-up.

In summary, our findings indicate that AIM may be considered as a novel sensitive biomarker for predicting disease activity and monitoring therapeutic effects of RA patients, which could facilitate the recognition of patients with higher activity and the adjustment of medical treatment. Therefore, this study might have revealed a new insight for the study of RA disease activity, while the potential immunopathological role of AIM in RA autoimmunity remains to be further investigated.

Key messages

- AIM levels in serum and synovial fluid (SF) were up-regulated in RA patients.
- Elevated AIM concentration correlated with RA disease activity features.
- AIM might act as a novel sensitive biomarker for high disease activity for RA patients

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