

# Activities of Serum Adenosine Deaminase and its Isoenzymes in Patients with Systemic Lupus Erythematosus, Rheumatoid Arthritis, Ankylosing Spondylitis and Myasthenia Gravis

## Die Aktivitäten der Adenosin-Desaminase im Serum sowie deren Isoenzyme bei Patienten mit systemischem Lupus erythematoses, rheumatoider Arthritis, Spondylitis ankylosans und Myasthenia gravis

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### Schlüsselwörter

ADA-Aktivität, Isoenzym, Autoimmunerkrankung, Diagnose

### Key words

ADA activity, isoenzyme, autoimmune disease, diagnosis

### Bibliography

DOI <https://doi.org/10.1055/a-1024-3495>

Online-Publikation: 21.11.2019

Akt Rheumatol 2020; 45: 348–355

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ISSN 0341-051X

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### ABSTRACT

**Objective** The aim of this study was to evaluate the changes and diagnostic value of serum ADA activity in autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), and myasthenia gravis (MG).

**Methods** Serum ADA activity, including total ADA (tADA) and its isoenzymes (ADA1 and ADA2), was determined in patients with different autoimmune diseases (144 RA, 114 SLE, 55 AS, 68 MG). The changes in serum ADA activity in patients were analysed. A receiver operating characteristic (ROC) curve ana-

lysis was applied to evaluate the diagnostic performance of serum ADA activity.

**Results** Compared with healthy controls, the serum tADA activity in SLE patients was significantly increased ( $p < 0.001$ ), while the serum tADA activity in patients with RA, AS and MG did not change ( $p > 0.05$ ). The ROC analysis showed that the optimal cut-off value of serum tADA activity for SLE diagnosis was 10.5 U/L (79.8 % specificity and 74.6 % sensitivity; likelihood ratio (LR): 3.693;  $p < 0.001$ ). Moreover, our results showed that there were no significant changes of ADA1 and ADA2 activity in RA, AS and MG patients, while the serum ADA2 activity was significantly increased in SLE patients. The ROC analysis showed that ADA2 activity could be used in diagnosing SLE with 75.4 % specificity and 78.1 % sensitivity (LR: 3.175). Based on the ROC curve analysis, serum tADA activity (79.8 % specificity and 74.6 % sensitivity; likelihood ratio (LR): 3.693) and ADA2 activity (75.4 % specificity and 78.1 % sensitivity; LR: 3.175) are unlikely to be used in diagnosing SLE. Furthermore, there was a positive correlation between tADA activity and SLE disease activity ( $r = 0.303$ ,  $p = 0.010$ ). Notably, serum tADA activity in SLE patients with arthritis was higher than in patients without arthritis ( $p = 0.005$ ), which suggests that tADA activity might be related to lupus arthritis.

**Conclusion** These findings suggest that serum tADA and ADA2 activity might play an important role in SLE progression.

### ZUSAMMENFASSUNG

**Ziel** Ziel dieser Studie war es, die Veränderungen sowie den diagnostischen Wert der ADA-Aktivität im Serum bei Autoimmunerkrankungen, einschließlich des systemischen Lupus erythematoses (SLE), der rheumatoiden Arthritis (RA), der Spondylitis ankylosans (AS) sowie der Myasthenia gravis (MG) zu beurteilen.

**Methoden** Die ADA-Aktivitäten im Serum, einschließlich Gesamt-ADA (tADA) sowie ihrer Isoenzyme (ADA1 und ADA2) wurden bei Patienten mit verschiedenen Autoimmunerkrankungen (144 RA, 114 SLE, 55 AS, 68 MG) bestimmt. Die Verän-

derungen der ADA-Aktivität im Serum bei den Patienten wurden analysiert. Die Grenzwertoptimierungskurve (ROC) wurde verwendet, um die Diagnostikleistung der ADA-Aktivitäten im Serum zu beurteilen.

**Ergebnisse** Im Vergleich zu den gesunden Kontrollen war die tADA-Aktivität im Serum bei den SLE-Patienten deutlich erhöht ( $P < 0,001$ ), während die tADA-Aktivität im Serum bei den Patienten mit RA, AS und MG unverändert blieb ( $P > 0,05$ ). Darüber hinaus wurden in unseren Ergebnissen gezeigt, dass es keine signifikanten Veränderungen bei den ADA1- und ADA2-Aktivitäten der RA-, AS- und MG-Patienten gaben, während die ADA2-Aktivität im Serum bei den SLE-Patienten deutlich erhöht

wurde. Die ROC-Analyse zeigte, tADA-Aktivität (mit 79,8 % iger Spezifität und 74,6 % iger Sensitivität; LR: 3.693) und ADA2-Aktivität (mit 75,4 % iger Spezifität und 78,1 % iger Sensitivität; LR: 3.175) sind unwahrscheinlich bei der diagnose SLE. Außerdem gab es eine positive Korrelation zwischen tADA-Aktivität sowie SLE-Krankheitsaktivität ( $r = 0,303$ ,  $P = 0,108$ ). die Serum-tADA-Aktivität bei SLE-Patienten mit Arthritis höher war als bei Patienten ohne Arthritis ( $P = 0.005$ )

**Konklusion** Diese Ergebnisse deuten darauf hin, dass die tADA- sowie ADA2-Aktivität im Serum eine wichtige Rolle bei der SLE-Progression spielen könnte

## Introduction

Adenosine deaminase (ADA, EC 3.5.4.4) is a ubiquitously expressed metabolic enzyme, and catalyzes the irreversible deamination of adenosine and deoxyadenosine [1]. Several lines of evidence have identified that high concentration of adenosine in microenvironment acts as a natural brake on immune cell functions, and limits hyperergic inflammatory responses [2, 3]. Thus, as the adenosine degrading enzyme, ADA plays an important role in human immune system. Accumulating evidence have revealed its critical role in development, maturation and function of the immune system [4]. ADA activity can partly reflect the immunocompetence in human. Firstly, ADA deficiency results in the severe combined immunodeficiency disease in human [5, 6]. Patients with ADA deficiency are showing marked lymphopenia. The T, B and NK cells are all dysplastic in patients with ADA deficiency [7, 8]. On the other hand, hyperactivity of ADA also could be linked with immune imbalance. Several evidence have shown that serum ADA activity changed in autoimmune diseases, such as systemic lupus erythematosus (SLE) and Rheumatoid arthritis (RA) [9–15]. However, the most of studies were based on small numbers of patients. Thus, more studies using larger cohorts of patients with autoimmune diseases are needed.

RA, SLE, Ankylosing spondylitis (AS) and Myasthenia gravis (MG) are the common autoimmune diseases. In the present study, we investigated the activity of ADA and its isoenzymes (ADA1 and ADA2) in serum of patients with these 4 types of autoimmune diseases. The main objective of this study is to evaluate the change of serum ADA activity in patients with different autoimmune diseases.

## Method

### Patients and serum

Four types of autoimmune diseases were included in this study: 144 RA patients and 144 sex & age matched healthy controls; 114 patients with SLE and 114 sex & age matched healthy controls; 55 patients with AS and 55 sex & age matched healthy controls; 68 patients with MG and 68 sex & age matched healthy controls. Patients with RA, SLE, AS were recruited from the department of rheumatism and immunology, MG patients were recruited from the de-

partment of internal neurology. The corresponding sex & age matched healthy controls were recruited at the same time. Peripheral blood was collected and subjected to 4000 rpm centrifuge for 5min at 4 °C to obtain serum. Serum was stored at 4 °C and the serum ADA activity was measured within 7 days. Ethical approval was obtained from the ethics committee of Tangdu Hospital, The Fourth Military Medical University.

### Serum ADA activity detection assay

Serum total ADA (tADA) activity was measured with enzymatic method kit (Sichuan Maccura Biotechnology, China), adapted to the automated biochemistry analyzer (Hitachi 7600, Japan). The serum ADA2 activity was measured in the presence of 0.1mM erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA). The serum ADA1 activity was calculated by subtracting the ADA2 activity from tADA activity. The results were expressed as Unit per Liter (U/L). ADA enzyme remain stable for at least 7days at 4 °C. In this study, ADA activity was measured within 7 days.

### Receiver operating characteristic curve analysis

Receiver operating characteristic (ROC) curve analysis was applied by plotting sensitivity against (1-specificity) for various levels of serum ADA activity. The optimal cutoff value that best distinguished patients with disease from healthy individuals was determined at maximum value for Youdens' index, which was defined as the difference between the true positive rate and the false positive rate [sensitivity – (1-specificity)]. The overall diagnostic accuracy was estimated based on area under the ROC curve (AUC).

### Statistical analysis

Serum tADA, ADA1 and ADA2 activity were expressed in median and interquartile range (IQR). Wilcoxon's test was used to analyze the variation of serum ADA activity in patients with autoimmune diseases. Spearman rank correlation analysis was used to estimate the correlation between ADA activity and SLE disease activity. The  $\chi^2$  test was used to compare sex difference between RA, SLE, AS and MG patients. A P-value < 0.05 was used to define statistical significance. All analyses were performed by using R version 3.4.2.

## Results

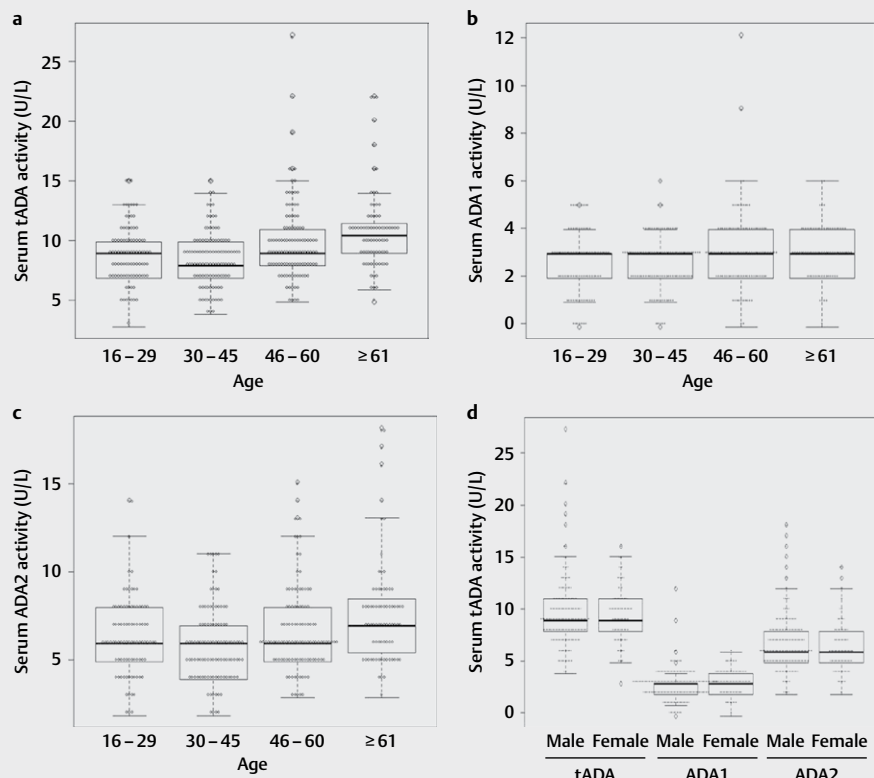
### There are significant differences in age and sex characteristics between patients with different autoimmune diseases

Firstly, we analyzed the age and sex characteristics of RA, SLE, AS and MG patients. RA patients are mostly middle-aged and elderly females (Age: 55.5 (IQR: 47–66); Male/Female: 34/110); SLE pa-

tients are mostly young and middle-aged females (Age: 35 (IQR: 27–48.75); Male/Female: 13/101); AS patients are mostly young and middle-aged males (Age: 29 (IQR: 22–40.5); Male/Female: 45/10); MG patients are mostly middle-aged persons (Age: 50 (IQR: 30–60.5); Male/Female: 32/36). These results showed that the age and sex characteristics are significantly different between patients with different autoimmune diseases (► **Table 1**).

► **Table 1** The age and sex characteristics of RA, SLE, AS and MG patients.

Patients	Male / Female	P value				Age	P value			
		vs RA	vs SLE	vs AS	vs MG	Median (IQR)	vs RA	vs SLE	vs AS	vs MG
RA	34 / 110	–	0.012	0.000	0.001	55.5 (47–66)	–	0.000	0.000	0.001
SLE	13 / 101	0.012	–	0.000	0.000	35 (27–48.75)	0.000	–	0.013	0.001
AS	45 / 10	0.000	0.000	–	0.000	29 (22–40.5)	0.000	0.013	–	0.000
MG	32 / 36	0.000	0.000	0.000	–	50 (30–60.5)	0.001	0.001	0.000	–



► **Fig. 1** Box plots showing the serum ADA activity in persons with different age and sex. **a, c** The serum tADA and ADA2 activity were increased in persons with age older than 60, **b** There was no significant difference of serum ADA1 activity between persons with different age, **d** There were no significant differences of serum tADA, ADA1 and ADA2 activity between females and males.

# Serum tADA and ADA2 activity were increased in people older than 60

To investigate whether the serum ADA activity was different in people with different age, we divided all of healthy subjects ( $n = 381$ ) in this study into 4 groups according to their age: ▶ **Fig. 1a–c**. The results showed that there was no significant difference of ADA activity between people with age  $\leq 45$  ( $P > 0.01$ ), while the serum tADA and ADA2 activity were both significantly increased in people with age  $> 60$  ( $P < 0.01$ ). Furthermore, the difference of serum ADA activity between males and females was also analyzed (▶ **Fig. 1d**). The median value of serum tADA activity in males ( $n = 124$ ) and females ( $n = 257$ ) are both 9 (IQR: 8–11) U/L, there was no significant difference of serum tADA activity between males and females ( $P = 0.344$ ), and moreover, there were also no significant differences of serum ADA1 and ADA2 activity between males and females ( $P > 0.01$ ). Taken together, serum ADA activity was independent of sex, while the serum tADA and ADA2 activity were increased in people with age  $> 60$ .

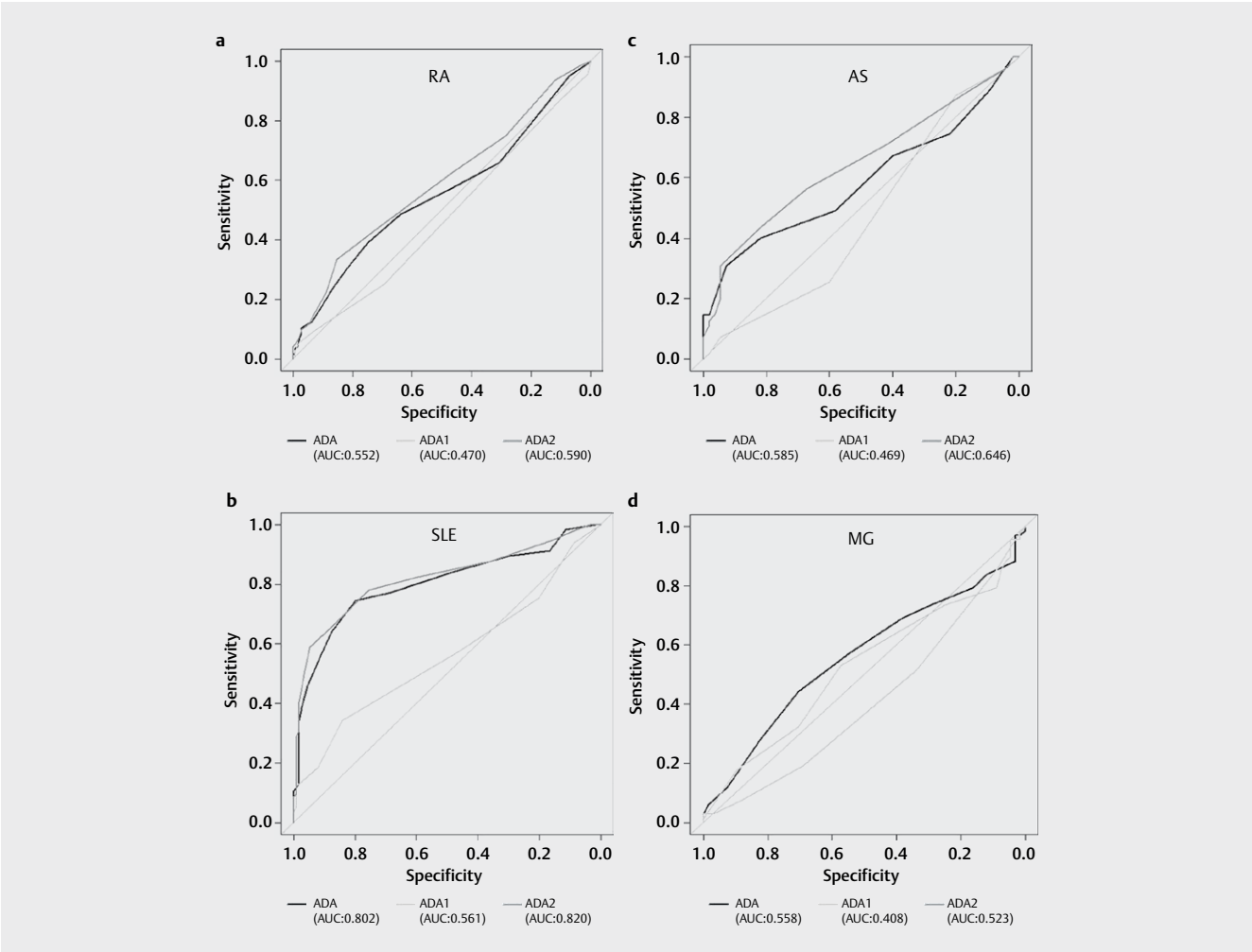
# Serum ADA activity pattern in patients with different autoimmune diseases

## Serum ADA activity pattern in RA patients

The median (IQR) serum tADA, ADA1 and ADA2 activity in 144 RA patients were 10 (IQR: 8–13), 3 (IQR: 2–3.25) and 8 (IQR: 5.75–10) U/L, respectively. As the results showed in ▶ **Table 2**, compared

▶ **Table 2** Serum ADA activity in RA patients and corresponding healthy controls.

	Control	RA	P value
Male / Female	34 / 110	34 / 110	–
Age (median (IQR))	57 (46.75–64)	55.5 (47–66)	0.899
tADA (median (IQR))	10 (8–11.25)	10 (8–13)	0.125
ADA1 (median (IQR))	3 (2–4)	3 (2–3.25)	0.356
ADA2 (median (IQR))	7 (5–9)	8 (5.75–10)	0.008



▶ **Fig. 2** ROC curves analysis of serum tADA, ADA1 and ADA2 activity for diagnosing patients with RA, SLE, AS or MG. The results showed that serum ADA activity could not be used to diagnose RA, SLE, AS and MG **a, b, c, d**. Serum tADA activity with a cut-off value of 10.5 U/L yielded the optimal diagnostic performance for SLE patients (79.8 % specificity and 74.6 % sensitivity; LR: 3.693), and serum ADA2 activity with a cut-off value of 7.5 U/L yielded the optimal diagnostic performance for SLE patients (75.4 % specificity and 78.1 % sensitivity; LR: 3.175).

with that in sex- and age- matched healthy controls, the serum tADA and ADA1 activity were not changed in RA patients ( $P=0.125$ ;  $P=0.356$ ), while serum ADA2 activity were increased slightly ( $P=0.008$ ). These results showed that serum ADA activity detection could not be used in diagnosing of RA patients (► Fig. 2a).

### Serum ADA activity pattern in SLE patients

The median serum tADA, ADA1 and ADA2 activity in 114 patients with SLE were 13 (IQR: 10.25–17.75), 3 (IQR: 2–4) and 11 (IQR: 8–14) U/L, respectively (► Table 3). Compared with that in sex- and age- matched healthy controls, the serum tADA and ADA2 activity were significantly increased in SLE patients ( $P<0.001$ ;  $P<0.001$ ), while there was no significant difference of the serum ADA1 activity between SLE patients and healthy controls ( $P=0.104$ ). Based on the ROC curve analysis, the optimal cut-off value for tADA and ADA2 activity were 10.5 U/L and 7.5 U/L (► Fig. 2b). At this level, the specificity and sensitivity of tADA activity were 79.8 % and 74.6 % (LR: 3.693), the specificity and sensitivity of ADA2 were 75.4 and 78.1 % (LR: 3.175), respectively. In regard of the low LR, the serum ADA activity was unlikely to be used in SLE diagnosing.

### Serum ADA activity pattern in AS patients

The median serum tADA, ADA1 and ADA2 activity in 55 patients with AS were 9 (IQR: 7.5–12), 3 (IQR: 2–3.5) and 7 (IQR: 5–9) U/L, respectively. As the results shown in ► Table 4, there were no significant differences of serum tADA and ADA1 activity between AS patients and healthy controls ( $P=0.123$ ;  $P=0.571$ ), while ADA2 activity in AS patients' serum were increased slightly ( $P=0.008$ ). Taken together, there data indicated that the serum ADA activity detection would not be helpful in diagnosing of AS patients (► Fig. 2c).

► Table 3 Serum ADA activity in SLE patients and corresponding healthy controls.

	Control	SLE	P value
Male / Female	13 / 101	13 / 101	–
Age (median (IQR))	35 (26.25–46.75)	35 (27–48.75)	0.928
tADA (median (IQR))	9 (7–10)	13 (10.25–17.75)	<0.001
ADA1 (median (IQR))	3 (2–3)	3 (2–4)	0.104
ADA2 (median (IQR))	6 (5–7)	11 (8–14)	<0.001

► Table 4 Serum ADA activity in AS patients and corresponding healthy controls.

	Control	AS	P value
Male / Female	45/10	45/10	–
Age (median (IQR))	30 (23.5–41)	29 (22–40.5)	0.711
tADA (median(IQR))	9 (8–10)	9 (7.5–12)	0.123
ADA1 (median (IQR))	3 (2–4)	3 (2–3.5)	0.571
ADA2 (median (IQR))	6 (5–7)	7 (5–9)	0.008

### Serum ADA activity pattern in MG patients

The median serum tADA, ADA1 and ADA2 activity in 68 patients with MG were 8 (IQR: 6–11), 3 (IQR: 2–3) and 5 (IQR: 4–8) U/L, respectively. As the results shown in ► Table 5, there were no significant differences of serum tADA, ADA1 and ADA2 activity between MG patients and corresponding healthy controls ( $P=0.243$ ;  $P=0.056$ ;  $P=0.64$ ). Therefore, serum ADA activity could not be a diagnostic marker for MG patients (► Fig. 2d).

### The association between serum ADA activity and manifestation of SLE patients

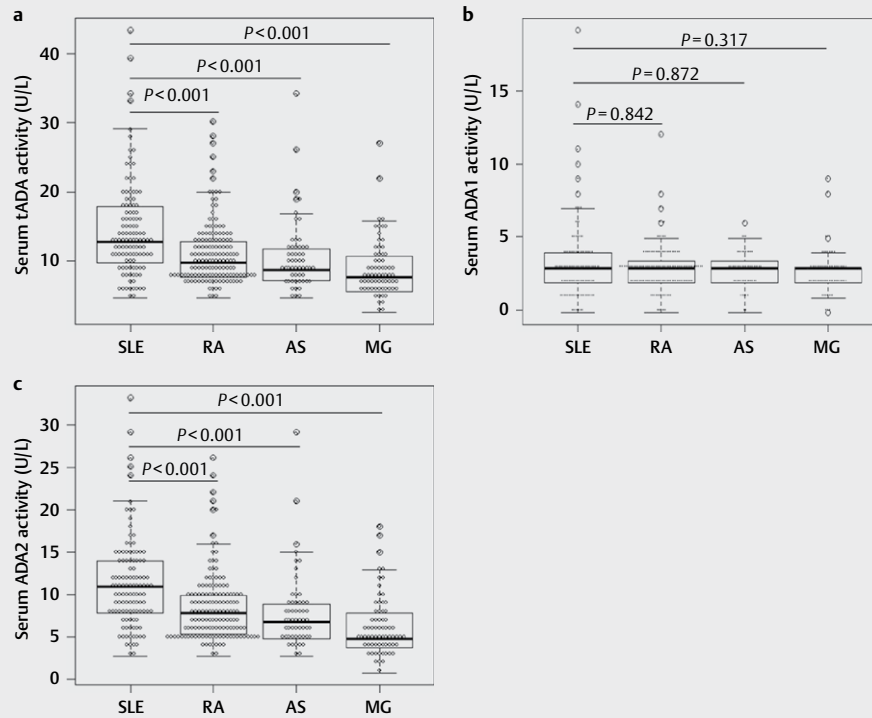
Compared with that in healthy controls and patients with the other autoimmune diseases (RA, AS and MG), the serum tADA and ADA2 activity were significantly increased in SLE patients (► Fig. 3a–c). We further analyzed the correlation between serum ADA activity and SLE disease activity by using spearman's correlation analysis. SLE disease activity was assessed by using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI). The result showed that there was a positive correlation between tADA activity and SLEDAI ( $r=0.303$ ,  $P=0.010$ ). Furthermore, we analyzed the association between serum ADA activity and manifestation of SLE patients (► Table 6). The results showed that the positive rate of multiple manifestations such as low complement (73.91 %), rash (56.52 %), anti-dsDNA antibodies (53.62 %), arthritis (39.13 %) and proteinuria (31.88 %) were lower than the positive rate of increased serum tADA (74.6 %) in SLE patients. Notably, the serum tADA activity in SLE patients with arthritis were higher than that in patients without arthritis (► Table 6,  $P=0.005$ ), which suggested that tADA activity might be related to subtype of SLE with arthritis.

## Discussion

ADA plays an important role in growth and differentiation of lymphocytes and macrophages. ADA activity is elevated during T cell response, and is considered as a non-specific marker of T lymphocyte mediated immunoresponse [16]. Thus ADA activity may change in patients with abnormal immunity. In the present study, we aimed to evaluate the change of ADA and its isoenzymes (ADA1 and ADA2) activity in patients with different autoimmune diseases. To the end, we investigated the serum ADA activity in four types of

► Table 5 Serum ADA activity in MG patients and corresponding healthy controls.

	Control	MG	P value
Male / Female	32/36	32/36	–
Age (median (IQR))	47.5 (33.75–58.25)	50 (30–60.5)	0.850
tADA (median (IQR))	9 (7–11)	8 (6–11)	0.243
ADA1 (median (IQR))	3 (2–4)	3 (2–3)	0.056
ADA2 (median (IQR))	6 (4–7.25)	5 (4–8)	0.64



► **Fig. 3** The difference of serum ADA activity between SLE and other autoimmune diseases: RA, AS and MG patients. **a, c** Serum tADA and ADA2 activity in SLE patients were higher than that in RA, AS and MG patients. **b** There was no difference of serum ADA1 activity between RA, AS, MG and SLE patients.

► **Table 6** The association between serum tADA activity and manifestations of SLE patients.

Manifestations	Positive rate (%)	tADA activity in positive patients (U/L)	tADA activity in negative patients (U/L)	P
Low complement	73.91	15 (12–20)	13.5 (10.25–16.75)	0.137
Rash	56.52	15 (13–22)	13.5 (9–17.75)	0.091
Anti-dsDNA antibodies	53.62	16 (13–20)	14 (11–17.25)	0.223
Arthritis	39.13	17 (14–22)	13 (10.25–16)	0.005
Proteinuria	31.88	14.5 (13–17.75)	15 (12–20)	0.791
Fever	26.08	19 (12–22)	15 (11.5–18)	0.247
Leukopenia	26.08	15 (12–20)	15 (11.5–19)	0.758
Alopecia	24.63	14 (12–22)	15 (12–19)	0.660
Thrombocytopenia	21.74	16 (13–21)	14.5 (12–18)	0.250
Hematuria	17.39	14 (12–21)	15 (12–19)	0.943
Myositis	10.14	16 (11.5–21.5)	15 (12–19.5)	0.765
Pyuria	10.14	16 (12.5–22)	15 (12–19.75)	0.661
Mucosal ulcers	10.14	15 (13.5–21)	14.5 (12–19.75)	0.505
Pleurisy	8.70	14 (12.25–18)	15 (12–20)	0.654

autoimmune diseases (RA, SLE, AS and MG). The findings are summarized as follows: 1) Serum tADA and ADA2 activity were significantly increased in SLE patients as compared with that in healthy

controls, while there were no differences of ADA activity between patients with RA, AS, MG and healthy controls. 2) Base on ROC curve analysis, serum tADA activity (79.8% specificity and 74.6%



sensitivity; LR: 3.693) and ADA2 activity (75.4% specificity and 78.1% sensitivity; LR: 3.175) are unlikely to be used in diagnosing SLE.3) Serum tADA activity was positive correlated with SLE disease activity ( $r=0.303$ ,  $P=0.011$ ). The serum tADA activity might be related to lupus arthritis.

In this study, four common autoimmune diseases and the corresponding sex- and age- matched healthy controls were recruited. The sex and age characteristics of RA, SLE, AS and MG patients are different. RA and SLE patients are mostly females, AS patients are mostly males, while the morbidity of MG in female and males is about the same. The median age of RA patients is significantly older than SLE, AS and MG patients. By dividing healthy subjects into different groups according to their sex or age, our results showed that the serum ADA activity were independent of sex, while were increased in people older than 60.

Our results showed that there were no significant differences of serum ADA activity between patients with RA, AS, MG and healthy controls. However, several studies previously reported that serum ADA activity was increased in RA and MG patients. Sari RA et al. and Vinapamula KS et al., have shown the increased serum ADA activity in 37 and 46 RA patients, respectively [9, 17]. Chiba S et al., have reported higher serum ADA activity in 31 MG patients than that in controls [18, 19]. These conflict results indicated that the change of serum ADA activity between ethnicities might be different. Notably, the small number of samples included in above studies may cause inaccuracy. Therefore, further studies in larger cohorts are needed.

The serum tADA and ADA2 activity in SLE patients were significantly increased compared with that in healthy controls. This finding about serum tADA activity in SLE is consistent with our previous reports [20]. And moreover, serum tADA and ADA2 activity in SLE patients were significantly higher than that in patients with the other autoimmune diseases, which means that serum tADA and ADA2 activity detection could be helpful in distinguish SLE patients from other autoimmune diseases. Notably, there was a positive correlation between tADA activity and SLE disease activity, which suggested that tADA activity might be helpful in monitoring the disease activity. Several studies have reported that interferon level (such as IFN-1 $\alpha$ , IFN- $\alpha$  and IFN- $\lambda$ 3) were increased in SLE patients [21–23], which suggested the change of interferon signature were involved in SLE development. We will investigate the potential association between ADA activity and interferon in SLE patients in further study. In conclusion, our data suggested that increased ADA activity might play an important role in SLE progression, especially in lupus arthritis.

## Acknowledgment

This study is supported by the National Natural Science Foundation of China (no. 81702732). All authors have read and approved the final version for submission.

## Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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