

# A novel association of adenosine deaminase with paroxysmal atrial fibrillation: a propensity score analysis from a case-control study

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**Background:** Prior work has identified age, body mass index, underlying heart disease, and other comorbidities as risk factors for atrial fibrillation. To date, studies have examined single baseline measures of traditional risk factors, and data on biomarker associations are lacking.

**Objective:** We sought to explore novel biochemical measures possibly associated with incident PAF after balancing the traditional risk factors.

**Methods:** Men or women aged  $\geq 18$  years that were hospitalized between 1<sup>st</sup> Jan. 2010 and 31<sup>st</sup> Dec. 2013 for paroxysmal atrial fibrillation (PAF) and for health checkup (non-PAF) were included. We used propensity score methods to mitigate the influence of the nonrandom selection of PAF and non-PAF patients. Logistic regression was applied for analysis of risk factors for PAF.

**Results:** A total of 1,802 eligible patients were identified, in whom, 895 patients had at least one exclusion criterion. After excluding these patients, the total analytic cohort numbered 907 patients. Of these, 779 patients were for control group and 128 patients were for PAF group. Propensity score matching was used to obtain a balanced cohort of 124 patients per group. The PAF and non-PAF groups were well matched on demographic and clinical characteristics after propensity matching. Risk factors for PAF on multivariate stepwise logistic regression model included adenosine deaminase (ADA) [odds ratio (OR) =0.9160, P=0.015, 95% confidence interval (CI): 0.8536-0.9829], mitral valvular regurgitation (OR =3.4611, P=0.001, 95% CI: 1.7000-7.0467) and left atrial diameter (OR =1.0913, P=0.001, 95% CI: 1.0387-1.1465). Only the ADA was a protective factor for the occurrence of PAF.

**Conclusions:** The ADA seems to be associated with PAF. The current study provides new insights into the prevention and treatment of PAF.

**Keywords:** Risk factors; adenosine deaminase (ADA); paroxysmal atrial fibrillation (PAF); propensity score

Submitted Jan 14, 2015. Accepted for publication Mar 10, 2015.

doi: 10.3978/j.issn.2072-1439.2015.04.10

View this article at: <http://dx.doi.org/10.3978/j.issn.2072-1439.2015.04.10>

## Introduction

With the advent of catheter ablation (1) and new oral anticoagulants for atrial fibrillation (2-4), the treatment of atrial fibrillation has made much progress recently. However, atrial fibrillation is still a common cardiac rhythm disturbance in clinical practice and an important indicator of morbidity and mortality, and increases in prevalence with advancing age. Atrial fibrillation is usually classified into three forms of paroxysmal, persistent and permanent (5).

In several studies, patients who develop sustained forms of atrial fibrillation (persistent/permanent) have higher rates of cardiovascular disease (CVD) morbidity and mortality than those who develop paroxysmal atrial fibrillation (PAF). PAF is a common form at the early onset stage, particularly within the 1<sup>st</sup> year of diagnosis, which will progress to sustained forms of atrial fibrillation if not timely or properly approached (6). Therefore, identification of factors that predispose to PAF may play an important role in lowering atrial fibrillation-related morbidity and improving response

to traditional therapies.

Prior work has indentified age (6-8), body mass index (9,10), underlying heart disease (11,12), and other comorbidities such as chronic obstructive pulmonary disease and hypertension as risk factors for atrial fibrillation (8,11). To date, studies have examined single baseline measures of traditional risk factors, and data on biomarker associations are lacking. We sought to explore novel biochemical measures possibly associated with PAF after balancing the traditional risk factors.

## Methods

### *Ethics statement*

All patient records were anonymized and de-identified prior to analysis, and the Institutional Review Board waived the need for informed consent due to the retrospective nature of this study. This study protocol has been approved by the Institutional Review Board of Soochow University and conforms to the principals outlined in the Declaration of Helsinki.

### *Patients*

Consecutive patients aged  $\geq 18$  years that were hospitalized in the department of cardiology, the First Affiliated Hospital of Soochow University from 1<sup>st</sup> Jan. 2010 through 31<sup>st</sup> Dec. 2013 for PAF and for health checkup were included. Clinical and lab data for initial medical contacts were collected for those with multiple hospitalizations or checkups. Patients with PAF usually had more than two diagnoses and were in bad condition as compared with those hospitalized for health check-ups. Therefore, patients' selection in PAF group was limited to those with at most two diagnoses so as to increase the success rate of matching. Exclusion criteria included thyroid dysfunction, severe liver function abnormalities, chronic renal failure, acute coronary syndrome within 1 month, acute stroke within 1 month, congenital heart diseases, rheumatic or prosthetic valvular heart diseases, pulmonary stenosis, acute or chronic respiratory failure and coexistence of atrial fibrillation and paroxysmal supraventricular tachycardia.

### *Definition of PAF*

A patient has had two or more episodes, and atrial fibrillation is considered as recurrent. If recurrent atrial

fibrillation terminates by itself, it is designated paroxysmal. Termination by pharmacological therapy or electrical cardioversion before expected spontaneous termination less than 7 days does not change the designation paroxysmal (5). The atrial fibrillation diagnosis was based on electrocardiogram during the hospitalization period.

### *Diagnoses and definitions*

Primary hypertension is diagnosed based on the systolic and/or diastolic blood pressure  $\geq 140/90$  mmHg or on confirmatory past history now on antihypertensive treatments (13); type 2 diabetes mellitus is diagnosed based on a plasma glucose  $\geq 7.0$  mmol/L after fasting for at least 8 hours or on 2-hour plasma glucose  $\geq 11.1$  mmol/L during OGTT or on a random plasma glucose  $\geq 11.1$  mmol/L in patients with classic symptoms of hyperglycemia or on hyperglycemic crisis or on a confirmatory past history now on anti-hyperglycemic treatments (14); dyslipidemias are diagnosed based on the total cholesterol level  $\geq 6.22$  mmol/L or on the low density cholesterol level  $\geq 4.14$  mmol/L or on the high density cholesterol level  $\geq 1.55$  mmol/L or  $\leq 1.04$  mmol/L, or on the triglyceride  $\geq 2.26$  mmol/L (15); coronary artery diseases are diagnosed based on the confirmatory myocardial infarction history or on diameter stenosis of one of major coronary arteries  $\geq 50\%$  on angiography; pulmonary diseases include acute pulmonary infection, pulmonary malignancies, chronic obstructive airway diseases and pneumothorax; other CVDs include sick sinus disease, sinus bradycardia, mitral stenosis, hypertrophic cardiomyopathy, congenital heart diseases, paroxysmal atrial tachycardia, ventricular tachycardia and coronary artery atherosclerosis; the miscellaneous include acute tonsillitis, chronic gastritis, syphilis, depression, urinary tract infection, acute upper respiratory tract infection and rheumatoid arthritis. The presence of the above mentioned diseases is considered as positive and calculated as percentages.

### *Transthoracic echocardiography*

Transthoracic echocardiography was performed by experienced echocardiologists on all patients for obtaining echo parameters, such as ejection fraction, tricuspid pressure gradient in systole, root aortic diameter, right ventricular diameter, right atrial diameter, left atrial diameter, ventricular septal thickness, left ventricular posterior wall thickness, left ventricular end-systolic

diameter and left ventricular end-diastolic diameter; for obtaining ranked parameters, such as aortic regurgitation, tricuspid regurgitation and mitral regurgitation. Slight, mild, moderate and severe regurgitation judged by echocardiologists was recorded as 0.5, 1, 2 or 3, respectively and no regurgitation judged by echocardiologists was recorded as 0. Mild to moderate regurgitation judged by echocardiologists was recorded as  $(1+2)/2=1.5$ . Moderate to severe regurgitation would be addressed in the same manner.

### ***Biochemical marker examination***

Venous blood sample taking was done in the morning after 8-hour fasting to examine the serum lipid profile, biochemical markers and blood glucose levels using those routine methods according to the products specifications.

### ***Statistical analysis***

Categorical or ordered variables are presented as frequencies or percentages, and unadjusted comparisons were performed using  $\chi^2$  or Fisher exact or Cochran-Mantel-Haenszel (CMH) tests where appropriate. Continuous variables are presented as mean  $\pm$  SD or median [IQR (interquartile range)], and unadjusted comparisons were made using independent-sample *t*-tests or Wilcoxon rank-sum test.

We used the propensity score method to mitigate the influence of the nonrandom selection of PAF and non-PAF patients. The propensity score for an individual is defined as the conditional probability of the presence of PAF given the individual's covariates. To estimate these scores, we created a logistic regression model on the following covariates: (I) demographic variables, such as age, sex, body weight, height, systolic and diastolic blood pressure at admission; (II) clinical variables, such as primary hypertension, type 2 diabetes mellitus, dyslipidemia, coronary artery disease, other CVDs, pulmonary diseases, and the miscellaneous.

We performed a one-to-one nearest neighbor match on the logit of the propensity score without a caliper. Percent bias calculations and *t*-tests were applied for balancing check of covariates both before and after matching. For good balancing, *t*-tests for equality of means should be no significant after matching, and the standardized bias should be less than 5% after matching. Paired *t*-test or sign-rank test or  $\chi^2$  test or Fisher exact test were used where

appropriate for propensity-score matched data. Univariate logistic regression and multivariate stepwise logistic regression were performed on those significant variables found by paired *t*-test or sign-rank test. Significance level for removal from and addition to the model were preset at 0.1 and 0.05, respectively. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Statistical significance was defined as  $P < 0.05$ . All statistical analyses were performed using Stata 12.0.

## **Results**

A total of 1,802 eligible patients were identified between 1<sup>st</sup> Jan. 2010 and 31<sup>st</sup> Dec. 2013. A total of 895 patients had at least 1 exclusion criterion. After excluding these patients, the total analytic cohort numbered 907 patients. Of these, 779 patients were for health checkup, and 128 patients were diagnosed as PAF. Propensity score matching was used to obtain a balanced cohort of 124 patients per group.

### ***After-matching balancing check for covariates based on which propensity scores were estimated***

The *t*-test is not significant for all means of covariates after matching. The absolute values of %bias for most covariates were around 5% with the only two exceptions of sex and diastolic pressure, showing a small unbalance of 9.8% and 9.7%, respectively. The overall mean %bias is 4% after matching. See *Table 1*.

### ***Baseline demographic and clinical variables before and after propensity score matching***

Patient characteristics for the unadjusted and propensity score-matched patients are given in *Table 2*. As many as eight covariates were significantly different ( $P < 0.05$ ) between the both groups before matching. However, all covariates were comparable and well balanced ( $P > 0.05$ ) between the both groups after propensity score matching.

### ***Echocardiography parameters before and after propensity score matching***

Before propensity score matching of demographic and clinical variables, most echocardiography parameters were significantly different ( $P < 0.05$ ) between the PAF group and the non-PAF group except those of ejection fraction, septal thickness and left ventricle (LV) end-systolic,

**Table 1** Balancing check of covariates before and after propensity score matching based on logit model

Variable	Unmatched or matched	Mean		%bias	t-test	
		Treated	Control		t	P
Sex (male)	U	0.50394	0.43132	14.6	1.53	0.127
	M	0.50000	0.45161	9.7	0.76	0.448
Marriage (married)	U	0.99213	0.91784	36.4	3.02	0.003
	M	0.99194	0.99194	0.0	0.00	1.000
Age (yr)	U	61.74700	47.42200	112.5	10.60	0.000
	M	61.33000	61.84200	-4.0	-0.37	0.708
Height (cm)	U	163.36000	163.61000	-3.2	-0.34	0.734
	M	163.35000	162.87000	6.2	0.49	0.628
Weight (cm)	U	64.72400	62.17100	23.1	2.41	0.016
	M	64.63700	64.82300	-1.7	-0.13	0.895
Systolic pressure (mmHg)	U	128.32000	123.46000	30.2	3.23	0.001
	M	128.23000	129.10000	-5.4	-0.41	0.686
Diastolic pressure (mmHg)	U	77.96100	78.06300	-1.0	-0.11	0.916
	M	78.35500	79.33900	-9.8	-0.79	0.430
Hypertension	U	0.40945	0.15661	58.3	6.87	0.000
	M	0.41935	0.41935	0.0	0.00	1.000
Type 2 diabetes mellitus	U	0.03150	0.01155	13.7	1.75	0.080
	M	0.03226	0.02419	5.6	0.38	0.703
Dyslipidemia	U	0.00787	0.04878	-24.8	-2.11	0.035
	M	0.00806	0.00806	0.0	0.00	1.000
Coronary artery disease	U	0.00000	0.00000			
	M	0.00000	0.00000			
Other CVDs	U	0.11024	0.01669	39.0	5.85	0.000
	M	0.08871	0.06452	10.1	0.71	0.476
Pulmonary diseases	U	0.03937	0.01027	18.7	2.56	0.011
	M	0.04032	0.04032	0.0	0.00	1.000
The miscellaneous	U	0.10236	0.07445	9.8	1.08	0.278
	M	0.10484	0.10484	0.0	0.00	1.000

Dichotomous variables were taken as 1 for "yes", otherwise as 0. U, unmatched; M, matched; CVD, cardiovascular disease.

end-diastolic diameter. After propensity score matching, most echocardiography parameters were well-balanced and showed no significant differences ( $P>0.05$ ) between the both groups while only five parameters of tricuspid pressure gradient, right atrial diameter, left atrial diameter, mitral valvular regurgitation and tricuspid regurgitation were significantly different ( $P<0.05$ ). See *Table 3*.

#### ***Lipid profile and biochemical markers before and after propensity score matching***

Before propensity score matching of demographic and clinical variables, up to 13 biochemical markers of  $\gamma$ -glutamyl transferase, blood urea nitrogen, uric acid, total bilirubin, total protein, albumin, direct bilirubin, phosphorus, creatinine, high sensitive C-reactive protein,

**Table 2** Demographic and clinical variables by group among unadjusted and propensity-matched cohorts

Variables	Unadjusted data			Propensity score matched data		
	Control group (n=779)	PAF group (n=128)	P value	Control group (n=124)	PAF group (n=124)	P value
Age (yr)	48.10 (19.60)	61.55 (12.98)	<0.0001	61.62 (12.03)	61.48 (12.54)	0.6007
Height (cm)	163.00 (12.00)	163.00 (11.00)	0.4293	163.00 (12.00)	163.00 (11.00)	0.6322
Body weight (kg)	61.00 (15.00)	65.00 (15.00)	0.0090	64.82±10.99	64.64±11.22	0.8933
Systolic pressure (mmHg)	120.00 (20.00)	129.50 (21.00)	0.0026	130.00 (20.00)	130.00 (20.00)	0.6996
Diastolic pressure (mmHg)	80.00 (14.00)	80.00 (15.00)	0.9357	80.00 (15.00)	80.00 (15.00)	0.4509
Sex (male)	336 (43.13)	65 (50.78)	0.1060	56 (45.16)	62 (50.00)	0.4460
Marriage (married %)	715 (91.78)	127 (99.22)	0.0030	123 (99.19)	123 (99.19)	1.0000
Primary hypertension (%)	122 (15.66)	52 (40.63)	<0.0001	52 (41.94)	52 (41.94)	1.0000
Type 2 diabetes mellitus (%)	9 (1.16)	4 (3.13)	0.0980	3 (2.42)	4 (3.23)	1.0000
Dyslipidemia (%)	38 (4.88)	1 (0.78)	0.0340	1 (0.81)	1 (0.81)	1.0000
Coronary artery diseases (%)	0 (0.00)	1 (0.78)	0.1410	0 (0.00)	0 (0.00)	1.0000
Other CVDs (%)	13 (1.67)	14 (10.94)	<0.0001	8 (6.45)	11 (8.87)	0.4740
Pulmonary diseases (%)	8 (1.03)	5 (3.91)	0.0260	5 (4.03)	5 (4.03)	1.0000
The miscellaneous (%)	58 (7.45)	13 (10.16)	0.2900	13 (10.48)	13 (10.48)	1.0000

Values are mean ± SD or n (%) or median (IQR) where appropriate. PAF, paroxysmal atrial fibrillation; CVD, cardiovascular disease; IQR, interquartile range.

calcium, sodium and indirect bilirubin were significantly different ( $P<0.05$ ) between the PAF group and the non-PAF group. After propensity score matching, most biochemical markers were well balanced and only four markers of prealbumin, aspartic aminotransferase, creatinine and adenosine deaminase (ADA) were significantly different ( $P=0.0440$ ,  $P=0.0371$ ,  $P=0.0149$  and  $P=0.0091$ , respectively) between the both groups. See *Table 4*.

#### ORs for PAF using logistic regression analysis

Univariate logistic regression analysis was performed on tricuspid pressure gradient, right atrial diameter, left atrial diameter, creatinine, ADA, prealbumin, aspartic aminotransferase, mitral valvular regurgitation and tricuspid regurgitation that were significantly different by univariate analysis between the both groups. Risk factors with significant differences for PAF included tricuspid pressure gradient (OR =1.0409,  $P=0.002$ , 95% CI: 1.0152-1.0674), right atrial diameter (OR =1.0763,  $P=0.010$ , 95% CI: 1.0176-1.1384), left atrial diameter (OR =1.09,  $P=0.001$ , 95% CI: 1.04-1.15), mitral valvular regurgitation (OR =3.4611,  $P=0.001$ , 95% CI: 1.7000-7.0467), tricuspid regurgitation (OR =1.0409,  $P=0.002$ , 95% CI: 1.0152-1.0674)

and ADA (OR =0.9160,  $P=0.015$ , 95% CI: 0.8536-0.9829). See *Table 5*.

Risk factors, which remained to be kept in multivariate stepwise logistic regression model, included ADA (OR =0.9160,  $P=0.015$ , 95% CI: 0.8536-0.9829), mitral valvular regurgitation (OR =3.4611,  $P=0.001$ , 95% CI: 1.7000-7.0467) and left atrial diameter (OR =1.0913,  $P=0.001$ , 95% CI: 1.0387-1.1465). See *Table 5*.

#### Discussion

We have demonstrated that the ADA was associated with PAF. To the best of our knowledge, this is the first study to report a novel association of ADA with PAF. Every 1 U/L increase of ADA corresponded to reduction of the PAF by about 8% in the current study. The well-established demographic and clinical risk factors for atrial fibrillation included age (6-8), body mass index (9,10), underlying heart disease (16), hypertension and chronic obstructive pulmonary disease (8,11); the biochemical marker risk factors for atrial fibrillation included hemoglobin A1c (17), glomerular filtration rate (18), C-reactive protein (19), and serum albumin levels (20), etc. We used the propensity score method to mitigate the impacts of traditional demographic

**Table 3** Echocardiography parameters by group among unadjusted and propensity-matched cohorts

Variables	Unadjusted data			Propensity score matched data		
	Control group (n=779)	PAF group (n=128)	P value	Control group (n=124)	PAF group (n=124)	P value
Ejection fraction	0.69 (0.08)	0.68 (0.09)	0.2352	0.69 (0.07)	0.68 (0.09)	0.2776
Tricuspid pressure gradient (mmHg)	17.00 (21.00)	21.00 (9.00)	<0.0001	19.00 (22.00)	21.00 (8.50)	0.0030
Root aortic diameter (mm)	30.00 (5.00)	31.00 (5.50)	0.0023	32.00 (5.00)	31.00 (5.00)	0.2147
Right ventricular diameter (mm)	30.00 (5.00)	31.00 (5.00)	0.0005	30.00 (6.50)	31.00 (5.00)	0.2645
Right atrial diameter (mm)	34.00 (6.00)	37.00 (5.00)	<0.0001	35.05±4.44	36.59±4.76	0.0091
Septal thickness (mm)	9.00 (2.00)	9.00 (2.00)	0.0002	9.00 (2.00)	9.00 (2.00)	0.6244
LV posterior wall thickness (mm)	8.00 (1.00)	9.00 (2.00)	<0.0001	8.94±1.15	8.95±1.10	0.9051
LV end-systolic diameter (mm)	29.00 (5.00)	31.00 (5.00)	0.0030	29.00 (5.00)	31.00 (5.00)	0.1667
LV end-diastolic diameter (mm)	48.00 (5.00)	49.00 (5.50)	0.0005	49.00 (7.00)	49.00 (5.50)	0.3013
Left atrium diameter (mm)	35.00 (7.00)	39.00 (8.00)	<0.0001	37.10±4.97	39.57±5.69	0.0003
<b>AV regurgitation</b>						
0	613 (79.69)	72 (56.25)	<0.0001	74 (59.68)	70 (56.45)	0.8725
0.5	125 (16.05)	42 (32.81)		34 (27.42)	40 (32.26)	
1	32 (4.11)	11 (8.59)		12 (9.68)	11 (8.87)	
1.5	9 (1.16)	2 (1.56)		4 (3.23)	2 (1.61)	
2	0 (0.00)	1 (0.78)		0 (0.00)	1 (0.81)	
<b>MV regurgitation</b>						
0	380 (48.78)	41 (32.03)	<0.0001	61 (49.19)	40 (32.26)	0.0003
0.5	370 (47.50)	63 (49.22)		54 (43.55)	62 (50.00)	
1	28 (3.59)	17 (13.28)		9 (7.26)	15 (12.10)	
1.5	1 (0.13)	2 (1.56)		0 (0.00)	2 (1.61)	
2	0 (0.00)	4 (3.13)		0 (0.00)	4 (3.23)	
2.5	0 (0.00)	1 (0.78)		0 (0.00)	1 (0.81)	
<b>PV regurgitation</b>						
0	779 (100.00)	128 (100.00)	1.0000	0 (0.00)	0 (0.00)	1.0000
<b>TV regurgitation</b>						
0	237 (30.42)	17 (13.28)	<0.0001	33 (26.61)	17 (13.71)	0.0068
0.5	446 (57.25)	71 (55.47)		69 (55.65)	70 (56.45)	
1	75 (9.63)	26 (20.31)		16 (12.90)	26 (20.97)	
1.5	17 (2.18)	6 (4.69)		4 (3.23)	4 (3.23)	
2	2 (0.26)	6 (4.69)		1 (0.81)	5 (4.03)	
2.5	1 (0.13)	2 (1.56)		0 (0.00)	2 (1.61)	
3	1 (0.13)	0 (0.00)		1 (0.81)	0 (0.00)	

Values are mean ± SD or n (%) or median (IQR) depending on the data distribution. PAF, paroxysmal atrial fibrillation; LV, left ventricle; AV, aortic valve; MV, mitral valve; PV, pulmonary valve; TV, tricuspid valve; IQR, interquartile range.

**Table 4** Biochemical markers by group among unadjusted and propensity-matched cohorts

Variables	Unadjusted data			Propensity score matched data		
	Control group (n=779)	PAF group (n=128)	P value	Control group (n=124)	PAF group (n=124)	P value
$\alpha$ -Hydroxybutyrate dehydrogenase (U/L)	124.00 (34.00)	128.50 (34.00)	0.1385	132.00 (32.00)	129.00 (33.50)	0.4842
$\gamma$ -Glutamyl transferase (U/L)	20.00 (18.20)	23.90 (20.00)	0.0011	24.00 (20.00)	23.00 (20.05)	0.7120
Lactate dehydrogenase (U/L)	162.00 (42.00)	169.00 (39.50)	0.0617	172.00 (45.45)	169.00 (40.50)	0.9186
Prealbumin (mg/L)	204.90 (62.00)	210.85 (66.85)	0.6472	197.30±43.42	208.28±49.99	0.0440
Blood urea nitrogen (mmol/L)	4.90 (1.70)	5.30 (2.10)	0.0031	5.20 (1.75)	5.30 (2.05)	0.4394
Uric acid (mmol/L)	281.00 (115.00)	302.00 (123.05)	0.0026	307.00 (102.50)	301.00 (122.80)	0.8002
Total cholesterol (mmol/L)	4.37 (1.16)	4.41 (1.19)	0.3804	4.45±0.77	4.34±0.88	0.2251
Total bilirubin (mmol/L)	13.10 (7.40)	15.05 (8.55)	0.0029	13.50 (8.40)	14.95 (8.55)	0.3203
Total protein (mg/L)	69.70 (8.10)	66.95 (8.95)	0.0004	68.50 (7.80)	67.00 (9.30)	0.2725
Chloride (mmol/L)	102.80 (2.70)	102.80 (2.65)	0.3554	102.65 (2.80)	102.80 (2.75)	0.4650
Globulin (mg/L)	25.80 (5.40)	25.15 (6.35)	0.1688	26.40 (5.95)	25.20 (6.35)	0.0978
Triglyceride (mmol/L)	1.08 (0.89)	1.18 (0.91)	0.3203	1.15 (0.84)	1.18 (0.94)	0.8292
Albumin (mg/L)	43.80 (5.40)	42.10 (5.20)	0.0002	42.57±4.08	42.51±4.23	0.8998
Ratio of albumin to globulin	1.70 (0.40)	1.70 (0.30)	0.6707	1.63±0.28	1.68±0.25	0.0755
Direct bilirubin (mmol/L)	6.50 (2.90)	7.10 (3.35)	0.0069	6.45 (3.70)	7.10 (3.45)	0.1119
Alkaline phosphatase (U/L)	74.00 (29.00)	74.50 (33.60)	0.9583	79.60 (30.00)	75.50 (34.10)	0.0995
Phosphorus (mmol/L)	1.15 (0.26)	1.09 (0.26)	0.0010	1.10±0.17	1.08±0.18	0.3916
Creatinine (mmol/L)	66.00 (22.00)	74.00 (24.50)	<0.0001	68.50 (21.50)	74.00 (24.50)	0.0149
Creatine kinase (U/L)	78.00 (40.00)	80.00 (35.20)	0.9263	79.00 (45.00)	79.50 (35.00)	0.6197
Adenosine deaminase (U/L)	10.80 (3.90)	10.70 (4.15)	0.8710	11.80(4.20)	10.70 (4.20)	0.0091
Glucose (mmol/L)	5.08 (0.77)	5.12 (0.87)	0.7426	5.17 (0.74)	5.15 (0.89)	0.8477
Alanine aminotransferase (U/L)	18.00 (13.00)	19.00 (13.45)	0.2692	18.00 (16.00)	19.00 (13.00)	0.5094
Aspartic aminotransferase (U/L)	21.00 (8.00)	21.00 (7.00)	0.2256	23.00(8.00)	21.00 (7.00)	0.0371
Hs C-reactive protein (mg/L)	0.71 (1.32)	2.28 (0.20)	<0.0001	1.12 (1.67)	1.15 (2.12)	0.3440
Calcium (mmol/L)	2.28±0.15	2.25±0.15	0.0259	2.28±0.15	2.25±0.15	0.1599
Sodium (mmol//L)	140.70 (2.70)	141.30 (2.90)	0.0024	141.00 (2.90)	141.25 (2.85)	0.4241
Potassium (mmol/L)	3.96±0.32	3.92±0.36	0.2935	3.94±0.35	3.92±0.37	0.3990
Indirect bilirubin (mmol/L)	6.40 (4.80)	10.70 (4.15)	0.0035	7.20 (5.10)	7.70 (5.00)	0.6197

Values are mean ± SD or median (IQR). PAF, paroxysmal atrial fibrillation; ADA, adenosine deaminase; IQR, interquartile range.

and clinical covariates in order to ensure the reliability of biochemical marker results in the current study. The demographic and clinical covariates were well balanced, and a relative part of biochemical markers and echocardiography parameters was also balanced after propensity matching. As well as the ADA, the traditional risk factors, such as tricuspid

pressure gradient, right atrial diameter, left atrial diameter, mitral valvular regurgitation, tricuspid regurgitation and creatinine were also identified as risk factors for atrial fibrillation in the current study, which was consistent with previous studies (18,21,22). That the traditional risk factors have been retained in the current study has in turn confirmed

**Table 5** Logistic regression analysis

Variables	Crude OR	95% CI	P value	Adjusted OR	95% CI	P value
Adenosine deaminase	0.9160	0.8536-0.9829	0.015	0.9148	0.8496-0.9849	0.018
MV regurgitation	3.4611	1.7000-7.0467	0.001	2.6742	1.2704-5.6291	0.010
Left atrial diameter	1.0913	1.0387-1.1465	0.001	1.0733	1.0188-1.1307	0.008
Prealbumin	1.0051	0.9996-1.0105	0.067	–		
Aspartic aminotransferase	0.9730	0.9446-1.0024	0.071	–		
Creatinine	1.0141	0.9999-1.0284	0.050	–		
TV regurgitation	2.1642	1.2154-3.8536	0.009	–		
Tricuspid pressure gradient	1.0409	1.0152-1.0674	0.002	–		
Right atrial diameter	1.0763	1.0176-1.1384	0.010	–		

Adjusted OR denotes adjustment for adenosine deaminase, MV regurgitation and left atrial diameter each other. –, denotes the data unavailable because of removal of these variables from multivariable stepwise logistic regression model. OR, odds ratio; CI, confidence interval; ADA, adenosine deaminase; MV, mitral valve; TV, tricuspid valve.

the reliability of the current study.

Stepwise multivariate logistic regression analysis revealed that ADA, mitral valvular regurgitation and left atrial diameter remained to be independent risk factors for the occurrence of PAF, among which the adenosine was the only protective factor for the occurrence of PAF.

The ADA is an important enzyme with three family members of ADA 1, 2 and L (23), of which, the ADA 2 is the most abundant in human plasma (24). The ADA levels reflect cellular immune functionality (25) and are also closely associated with CVDs (26-28). Adenosine, a degradation product of ATP, has been attributed to exert different effects on heart: a protective agent for reperfusion heart on one hand (29-31) and a harmful agent for induction of some heart diseases such as atrial fibrillation and atrial flutter on the other hand (32-34). The induction of atrial fibrillation by adenosine has been well recognized and the possible underlying mechanisms include sympathoexcitatory effects, direct stimulatory effects on pulmonary vein tissue and the shortening of atrial action potential duration (32). This at least means that the adenosine has a property of double-edged sword and that the maintenance of the adenosine at an appropriate level is important. The ADA can regulate intra- and extracellular levels of adenosine through hydrolytic deaminase to inosine. That the lower adenosine concentrations resulting from the relatively higher ADA prolong the atrial action potential duration and decrease the sympathetic nerve activity may explain, at least in part, the higher ADA concentration as a protective factor for PAF revealed in the current study.

### Limitations

A case-control study design is potentially subjected to confounding factors if there is differential ascertainment of risk factors between cases and controls. We minimized this factor by using standardized methods for data collection in both cases and controls. A selection bias of controls is also an issue in a case-control study that has to be addressed. We minimized these factors using propensity score matching. Some of the risk factors were ascertained or measured based on history or self-report and therefore ascertained with some error. The actual blood pressure value is potentially confounded because it might have fallen in some patients as a result of the drug used. Similarly, glucose concentrations rise and fall as a result of diet and drug used and are therefore not indication of earlier levels. In our study, the patients' past histories, blood pressure values and glucose concentrations were all recorded as clinical variables for statistical analysis so as to minimize this possible confounding factor.

In conclusion, our study has shown that the ADA, as a protective factor, seems to be associated with PAF. The current study provides new insights into the prevention and treatment of PAF. A prospective, randomized controlled study should be designed for further confirming this association. The remaining six traditional risk factors are also identified in the current study, which suggest that modification of traditional risk factors should not be ignored.

### Acknowledgements

*Disclosure:* The authors declare no conflict of interest.



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**Cite this article as:** Liu L, He YM, Hu CF, Zhao X, Xu HF, Yang XJ. A novel association of adenosine deaminase with paroxysmal atrial fibrillation: a propensity score analysis from a case-control study. *J Thorac Dis* 2015;7(4):662-671. doi: 10.3978/j.issn.2072-1439.2015.04.10