



## Potential biomarkers for early diagnosis of acute aortic dissection



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### ABSTRACT

**Objective:** The purpose of this study was to identify biological markers for early diagnosis of acute aortic dissection (AAD).

**Methods:** 76 patients presented to the emergency room with acute chest pain within 6 h of occurrence were recruited for this study, and AAD diagnosed by aortic CTA. Biomarkers were measured by ELISA. ROC curve and Pearson correlation analysis were used to evaluate the sensitivity and specificity to diagnosis of AAD.

**Results:** The serum levels of  $\alpha$ -SMA, smMHC, sELAF, PC1 and D-dimer were significantly higher in AAD patients than in other groups ( $P < 0.05$ ). Significant correlations between smMHC, sELAF, PC1, and D-dimer level were observed in AAD. Any combination of two markers showed good sensitivity (94.29%) and specificity (85.37%).

**Conclusion:** smMHC, sELAF, PC1, or D-dimer alone is a biomarker for early diagnosis of AAD, but the combination of these markers has significantly higher diagnostic value.

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### Introduction

Acute aortic dissection (AAD) is an aortic emergency with increasing incidence worldwide. The reported mortality rate has risen to 38% and the early misdiagnosis rate is 31.8%.<sup>1–3</sup> The chest X-rays and transthoracic echocardiography have shown some limitations on the clinical diagnosis of AAD. Although transesophageal echocardiography can be used to distinguish false lumen from true lumen, the risks associated with this procedure should not be overlooked. Also, transesophageal echocardiography is unable to visualize distal aortic dissections. Computed tomography and magnetic resonance imaging are valuable for AAD diagnosis, but computed tomography is unable to locate site of tear and needs iodinated contrast and magnetic resonance imaging is time consuming, may only be available in larger centers, and also is contraindicated in patients with metallic implants.<sup>2,4</sup> Biomarker analysis is an accurate, fast, and convenient method for the diagnosis of various diseases. However, specific biomarkers for early identification of AAD are not yet available.

Myosin heavy chain (MHC) is an “electric motor” protein, which can interact with actin filaments, and is detected primarily in blood vessel walls and smooth muscle cells.<sup>5</sup>  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) is a cytoskeletal protein of VSMCs that plays an important role in maintaining systolic and diastolic function in VSMCs.<sup>6</sup> Elastin is a key structural component of the extracellular matrix and is degraded by proteolytic enzymes into soluble elastin fragments (sELAF).<sup>7</sup> Previous studies demonstrated that the levels of serum  $\alpha$ -SMA, smooth muscle myosin heavy chain (smMHC), and human sELAF were significantly higher in patients with AAD than in healthy people and acute myocardial infarction patients.<sup>8–10</sup> However, the use of these biomarkers for early diagnosis of AAD has not been fully established. D-dimer level has been used to rule out AAD, but its diagnostic sensitivity decreases if the threshold value is inappropriate.<sup>11</sup> Polycystin 1 (PC1), encoded by the Pkd1 gene, is a 500 kD protein, which is mainly expressed in smooth muscle cells and intima cells of the vascular wall. PC1 plays a crucial role in maintaining the structural integrity and stability of the vessel wall.<sup>12</sup> Our previous studies also found that PC1 level is closely related to the pathogenesis of AAD.<sup>13</sup> However, the value of a combination of these biomarkers for early diagnosis of AAD has not been evaluated.

In this study, the diagnostic value of serum  $\alpha$ -SMA, smMHC (smooth muscle myosin heavy chain), sELAF, PC1, or D-dimer level as well as combinations of these biomarkers were

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investigated by comparing their levels in AAD patients with their levels in patients with AMI, other chest pain patients, and healthy subjects.

## Subjects and methods

### Study design

This was a single-center prospective observational study.

### Study population

All patients presented to the emergency room with chest pain between December 2012 and March 2014 who had not been diagnosed with AAD previously were recruited for this study. The exclusion criteria were: 1) patients with a confirmed diagnosis before presenting to the emergency room; 2) pregnant patients; 3) patients under 18 years of age, and 4) patients with tumor, traumatic aortic dissections, infectious disease, and known coagulation and bleeding disorders. All patients underwent computed tomographic angiography (CTA) examination. The study subjects were then classified as AAD (patients with AAD), STEMI (patients with acute ST elevation myocardial infarction), NSTEMI (patients with acute non-ST elevation myocardial infarction), APE (patients with acute pulmonary embolism), and other-chest-pain (OCP, chest pain patients without AAD, STEMI, NSTEMI or APE) group. Ten age and gender matched healthy subjects were recruited as control from people presenting to the hospital for their annual physical examination.

### Study methods

All patients were sent into the rescue room immediately after they signed the “informed consent form”. Information on the clinical characteristics of patients was collected. The serum levels of  $\alpha$ -SMA, MHC, sELAF, PC1, and D-dimer were examined by ELISA kits.

### Statistical analysis

Statistical analysis was performed using SPSS17.0 and Med-Cale software. Data were presented as mean  $\pm$  standard deviation (SD). Differences in measurement data were compared using single factor analysis of variance among groups and SKN- $q$  test between each 2 groups. Tamhane's T2 test and Student's  $t$ -test were used for comparison of data without homogenous variances. The receiver-operating characteristic (ROC) curves were used to analyze diagnostic accuracy. Binary score was computed by Med-Cale Software. Cut point is a mark point corresponding to criterion values with the biggest AUC. Pearson correlation analysis was used to assess the correlation between

each set of 2 biomarkers. A  $P < 0.05$  was considered statistically significant.

## Results

### Baseline characteristics

Of the 35 AAD patients diagnosed by CTA imaging, 19 had Stanford type A dissection and 16 had type B. The number of cases of STEMI, NSTEMI, and APE were 15, 7, and 8, respectively. Of the 11 patients with other chest pain, 3 had pleurisy, 7 had unstable angina, and 1 had reflux esophagitis. There were no significant differences in age, sex, height, and body mass index between groups.

### Serum levels of $\alpha$ -SMA, smMHC, sELAF, PC1 and D-dimer

ELISA showed that the mean serum level of  $\alpha$ -SMA, smMHC, sELAF, PC1 and D-dimer was significantly higher in AAD patients than in 5 other groups of patients ( $P < 0.05$ ). No significant differences in the levels of  $\alpha$ -SMA and smMHC were observed between patients with STEMI, NSTEMI, APE, OCP, and healthy control ( $P > 0.05$ ). The sELAF and PC1 levels were significantly higher in patients with STEMI, NSTEMI, APE, and OCP than in healthy controls ( $P < 0.05$ ), but no differences were observed between patients with STEMI, NSTEMI, APE, and OCP ( $P > 0.05$ ). The D-dimer levels were significantly higher in patients with APE than in patients with STEMI, NSTEMI, OCP, and healthy controls ( $P < 0.05$ ). No differences in D-dimer levels were observed between patients with STEMI, NSTEMI and OCP ( $P > 0.05$ ) (Table 1).

### ROC curve analysis of the diagnostic value of a single biomarker in AAD

ROC curve analysis showed that D-dimer had a sensitivity of 80% and a specificity of 90.21% at the cutoff level of 2.11  $\mu$ g/ml in patients with AAD. PC1 had a sensitivity of 85.71% and specificity of 75.61% at the cutoff level of 357.33 pg/ml smMHC only had an advantage in diagnostic specificity (90.24% at the cutoff level of 2.11 ng/ml). sELAF had a sensitivity of 82.86% at the cutoff level of 97.07 ng/ml. The diagnostic value of  $\alpha$ -SMA was lower than that of the other 4 biomarkers because  $\alpha$ -SMA had a sensitivity of 54.29% (Table 2, Fig. 1). The cutoff values showing favorable sensitivity and specificity in ROC curve analysis were designated as diagnostic thresholds.

### The diagnostic value of combined biomarkers in AAD

There were significant correlations between serum smMHC, sELAF, PC1, and D-dimer levels. Therefore, the actual measurements of these 4 biomarkers were converted into binary quantitative

**Table 1**  
Mean serum levels of biomarkers in each group.

Biomarkers	AAAD (n = 35)	STEMI (n = 15)	NSTEMI (n = 7)	APE (n = 8)	OCP (n = 11)	HC (n = 10)
$\alpha$ -SMA (ng/ml)	71.63 $\pm$ 37.44	49.62 $\pm$ 19.75 <sup>a</sup>	46.38 $\pm$ 21.10 <sup>a</sup>	51.86 $\pm$ 16.37 <sup>a</sup>	41.64 $\pm$ 21.62 <sup>a</sup>	50.62 $\pm$ 11.58 <sup>a</sup>
smMHC (ng/ml)	2.36 $\pm$ 0.53	1.88 $\pm$ 0.22 <sup>a</sup>	1.71 $\pm$ 0.18 <sup>a</sup>	1.93 $\pm$ 0.31 <sup>a</sup>	1.87 $\pm$ 0.26 <sup>a</sup>	1.70 $\pm$ 0.17 <sup>a</sup>
sELAF (ng/ml)	111.68 $\pm$ 16.58	86.79 $\pm$ 20.77 <sup>ab</sup>	83.02 $\pm$ 21.40 <sup>ab</sup>	92.12 $\pm$ 16.84 <sup>ab</sup>	90.47 $\pm$ 17.32 <sup>ab</sup>	63.06 $\pm$ 8.17 <sup>a</sup>
PC1 (pg/ml)	464.87 $\pm$ 95.03	309.83 $\pm$ 70.64 <sup>ab</sup>	293.10 $\pm$ 65.99 <sup>ab</sup>	336.59 $\pm$ 67.97 <sup>ab</sup>	320.09 $\pm$ 58.57 <sup>ab</sup>	230.17 $\pm$ 74.28 <sup>a</sup>
D-dimer ( $\mu$ g/ml)	7.05 $\pm$ 6.15	1.06 $\pm$ 0.83 <sup>abc</sup>	0.69 $\pm$ 0.54 <sup>abc</sup>	1.98 $\pm$ 1.53 <sup>ab</sup>	0.66 $\pm$ 0.80 <sup>abc</sup>	0.18 $\pm$ 0.02 <sup>bc</sup>

a:  $P < 0.05$  when compared with Group AAD; b:  $P < 0.05$  when compared with the Control; c:  $P < 0.05$  when compared with Group APE; The rest pairs did not reach to statistical significance ( $P > 0.05$ ).

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