Ischemia-Modified Albumin As A Marker For Acute Aortic Dissection: A Prospective Observational Study

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Research article

Keywords: aortic dissection, ischemia-modified albumin, pulmonary embolism, acute myocardial infarction, chest pain

Posted Date: July 21st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-588867/v2

Abstract

Background: Delayed or misdiagnosed aortic dissection can lead to death and morbidity. Ischemia-modified albumin (IMA) measures the cobalt binding capability and has been associated with mortality in patients with acute aortic dissection (AAD). However, it is unknown whether IMA levels can differentiate AAD in patients with chest pains.

Methods: A total of 100 suspected AAD patients were enrolled in this study. A cobalt-binding assay was used to determine the plasma IMA levels. In addition, the IMA levels of patients in different groups were compared based on the final diagnosis.

Results: IMA levels were significantly higher in the AAD group than in the AMI, PE, and other groups (63.98 ± 14.38, 52.57 ± 9.54, 49.26 ± 10.99, 37.99 ± 6.59, respectively) within 24 hours after the onset of symptoms. The area under the curve (AUC) based on the IMA level was 0.810 (95% CI, 0.708–0.897), and the best threshold of IMA was 59.35 u/ml (specificity, 85.7% and sensitivity, 66%). The decision and clinical impact curves indicated that the IMA had an excellent standardized net benefit and could be suitable for patient diagnosis.

Conclusion: IMA is elevated in AAD patients. The IMA levels have better performance for AAD than D-dimer and could be a potential biomarker with rapid and cost-effective diagnostic tests for early diagnosis of AAD. However, large-sample studies are needed to verify the findings.

Introduction

Acute aortic dissection (AAD) is a life-threatening vascular disease with a high death rate and morbidity [1, 2]. An untreated AAD can lead to increased mortality of 1–2% per hour after symptom onset. Besides, early diagnosis after patient symptom onset helps to prevent mortality [3, 4]. Currently, it is difficult to discriminate pulmonary embolism (PE) and acute myocardial infarction (AMI) from AAD in patients with chest pains [5]. Moreover, PE, AMI, and AAD have different treatment methods. It is difficult to differentiate AAD from other chest pain diseases due to the different clinical manifestations. Therefore, it is necessary to discover potential markers for CTA examination to prevent missed diagnosis and misdiagnosis.

Biochemical markers can also be used to diagnose AAD. Furthermore, some biomarkers related to the aortic medial layer (smooth muscle myosin) [6], elastic laminae of the aorta (soluble elastin fragments) [5], vascular interstitium (calponin) [7], and blood to vascular surfaces (D-dimer) [8] have been identified. To date, only D-dimer has achieved the highest diagnostic value during the first hour in emergency clinical practice. Although D-dimer has a high sensitivity, its specificity is relatively low at diagnosis in AAD [5]. Furthermore, D-dimer cannot discriminate between PE and AAD. Several disorders, such as stroke, acute limb ischemia, atrial fibrillation, and deep vein thrombosis are associated with increased plasma levels of D-dimer.

Previous studies have shown that IMA can be a myocardial ischemia marker [9] and can help to identify patients with acute coronary syndrome [9–11]. Recently, IMA and other cardiac markers (cTnT, CK-MB, NT-proBNP) have been investigated in various ischemia states [12]. Albumin cobalt binding tests are used to measure IMA levels. Transition metals can tightly bind to the exposed N-terminus of albumin [13]. Structural changes occur at the N-terminus of the protein in the presence of circular ischemia, reducing its binding capacity [9, 13]. Nevertheless, the role of IMA in clinical practice and AAD diagnosis is unknown.

This work aimed to explore the plasma concentrations of IMA in acute chest pain diseases, including AAD, PE, AMI, and non-cardiogenic chest pain, to evaluate its diagnostic performance in AAD.

Materials And Methods

Study patients

This was a single-center, prospective observational study. The research data can be obtained from corresponding authors upon reasonable request. Patients who had chest pains and suspected AAD in the emergency medicine department, Second Xiangya Hospital of Central South University, were enrolled in the study between November 2020 and February 2021. PE patients were enrolled from April 2019 to February 2021. PE patients were enrolled over a long duration because symptom onset took long, and few PE patients were available. All patients with chest pain who showed symptom onset within 24 h were enrolled to evaluate the diagnostic performance of IMA. The diagnosis criteria of AAD, PE, and AMI and exclusion criteria are described in Supplement materials (Table S1).

Peripheral blood was withdrawn from the brachial vein into a sodium citrate test tube within 24 hours of patients' visit and immediately treated with plasma and stored at -80°C. Blood samples were obtained using the same procedure described above for the different case-control groups. Baseline characteristics of patients were obtained from medical records and confirmed by the study physician. The Ethics Review Committee of the Second Xiangya Hospital approved the study. All patients provided written informed consents.

Measurements of IMA and D-dimer

The plasma stored at -80°C was centrifuged at 1500 g for 15 minutes to isolate the serum, then decanted. Serum IMA levels were measured using an albumin cobalt test kit (Yikang Science Technique Development Co., Changsha, China), following the manufacturer's instructions. D TOP700 automatic coagulation analyzer with D-dimer reagent was used to measure D-dimer.

Outcome

Computed tomography was used to confirm AAD in patients. Patients were diagnosed using AMI following the diagnosis criteria in Supplement materials (Table S1). A pulmonary artery computed tomography was used to confirm PE in patients.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (IQR), while categorical variables were expressed as frequencies. T-test or Mann–Whitney U-test (Skewed distribution) were used to compare continuous variables, while Fisher's exact test or Chi-square analysis were used to compare categorical variables.

The linear regression model was used to determine the time course of IMA levels. Mann–Whitney U-test (Skewed distribution) was used to compared the diagnostic performance of IMA and D-dimer in distinguishing AAD from all other diseases, AMI, and PE. ROC analyses were performed using only a continuous variable of IMA, D-dimer, or TnT without adjusting other risk factors.

A multivariate regression model was used to determine if IMA is associated with AAD. The area under the ROC, sensitivity, specificity, accuracy, positive and negative test results, positive predictive value, and negative predictive value were also calculated. Receiver operating characteristic curve (ROC) analysis was used to compared the diagnostic performance of IMA and D-dimer in distinguishing AAD from all non-AAD patients. The decision curve is used to evaluate the clinical application of a model, and estimates the standardized net benefit using the probability threshold, categorizing observations as 'high risk.' The clinical impact curve is an alternative plot for the decision curve. Decision and clinical impact curves were generated using the Decision Curve package in R (http://www.r-projec.org).

All tests were two-sided and statistical significance was set at $\alpha = 0.05$. The R Foundation was used for statistical analyses.

Results

Patient Demographics

A total of 100 patients were finally enrolled in the study. Eighty patients, including 30 AAD cases, 30 AMI cases, and 20 non-cardiogenic chest pain (NCCP), were enrolled from November 2020 to February 2021. Twenty PE patients were enrolled from April 2019 to February 2020. The baseline characteristics of AAD and non-AAD patients after 24 hours of symptom onset are shown in Table 1. The age, gender, onset time in hospital, and disease history were not significantly different between AAD and Non-AAD groups. However, D-dimer and IMA levels were significantly higher in AAD patients than in Non-AAD.

Table 1
Baseline characteristics of chest pain with AAD vs Non-AAD.

	Total	AAD	Non-AAD	*P*-value
No. of participates	100	30	70	
Gender, female	24 (24.00%)	5 (16.67%)	19 (27.14%)	0.261
Age, year	52.10 ± 13.35	49.30 ± 10.72	53.30 ± 14.23	0.106
Onset time to hospital, hours	5.00 (2.38, 9.25)	5.00 (3.00, 9.00)	4.50 (2.00, 10.50)	0.642
SBP, mmHg	134 ± 24	136 ± 24	133 ± 25	0.432
DBP, mmHg	77 ± 16	78 ± 15	77 ± 16	0.913
Hypertension	52 (52.00%)	18 (60.00%)	34 (48.57%)	0.295
Diabetes	19 (19.00%)	5 (16.67%)	14 (20.00%)	0.697
Stroke	5 (5.00%)	2 (6.67%)	3 (4.29%)	0.617
Chronic kidney disease	6 (6.00%)	3 (10.00%)	3 (4.29%)	0.270
Smoking	30 (30.00%)	12 (40.00%)	18 (25.71%)	0.153
Drinking	48 (48.00%)	16 (53.33%)	32 (45.71%)	0.485
TnT, ng/ml	9.60 (6.77, 20.21)	11.64 (9.13, 19.72)	8.98 (6.25, 22.18)	0.124
D-dimer, ug/ml	2.70 (1.77, 4.47)	4.05 (2.71, 6.26)	2.25 (1.56, 3.45)	0.001
IMA, u/ml	51.75 (41.05, 62.87)	65.15 (56.35, 74.65)	45.85 (39.42, 56.27)	< 0.001

IMA level (63.98 ± 14.38) was also higher in AAD patients than in AMI, PE, and NCCP groups. However, serum D-dimer levels were significantly higher in PE than in other groups (Fig. 1a and 1b; Table S2 and S3). IMA levels were positively associated with D-dimer levels (Pearson analysis) (Figure S1). Pearson's correlation coefficient was 0.12 in both AAD and AMI and was highest in PE (0.21). IMA level was positively associated with TnT in AMI but not in AAD patients. Pearson's correlation coefficients for AMI and AAD were 0.27 and−0.07, respectively (Figure S2).

IMA Distribution

Box plot analysis was used to determine IMA levels at various time points of symptom onset. For AAD patients, the IMA level peaked at 2–6 hours after symptoms onset. The IMA level was significantly higher at 2–4 h than after 12 h of symptom onset, where the levels reduced ($P < 0.05$) (Fig. 2). The number of patients with different chest pains at various time points of symptom onset is shown in Table S4. However, the number of patients at various time points of admission after symptom onset was not

significantly different (P = 0.244). IMA level was significantly high in AAD after adjustment of the confounders and covariates (Table 2).

Table 2
Relationship between IMA and AAD in different models.

Exposure	Non-adjusted	Adjust I	Adjust II
IMA	1.11 (1.06, 1.16) < 0.0001	1.12 (1.07, 1.17) < 0.0001	1.12 (1.06, 1.19) < 0.0001
IMA(per 5)	1.69 (1.35, 2.13) < 0.0001	1.75 (1.37, 2.22) < 0.0001	1.80 (1.37, 2.36) < 0.0001
IMA(per 10)	2.87 (1.81, 4.53) < 0.0001	3.05 (1.88, 4.94) < 0.0001	3.22 (1.87, 5.57) < 0.0001
Model I, adjusted for: None; Model II, adjusted for age; gender; Model III, adjusted for age, gender, hypertension, diabetes, stroke, chronic kidney disease, smoking, drinking, SBP; DBP.			

Diagnostic Performance evaluation

In the cohort study, the area under the ROC for 30 AAD patients versus all non-AAD control patients within 24 h symptom onset was 0.81 (0.708, 0.90) for IMA and 0.69 (0.59, 0.80) for D-dimer (Fig. 3a). IMA had the best threshold of 59.35 u/ml (specificity, 0.857 and sensitivity, 0.66) while that of D-dimer was 2.59 ug/ml (specificity, 0.857 and sensitivity, 0.66) (Fig. 3b) (Table 2). The decision and clinical impact curves indicated that the IMA had an excellent standardized net benefit and can be used for patient diagnosis (Fig. 4).

Discussion

Increased IMA indicates a reduced albumin-metal binding capacity associated with ischemia and the production of oxygen-free radical species [9, 14]. Albumin can act as a “sacrificial” antioxidant to reduce damage during reperfusion. IMA is caused by the damage to the N-terminus of albumin. Also, endothelial damage is caused by extracellular hypoxia, acidosis, Na-K pump malfunction, and free radical damage. The albumin-metal binding ability of copper, nickel, and cobalt decreases during acute ischemia, leading to metabolic protein variation (IMA) [15]. This study identified the significant increase in plasma IMA, a potential early novel biomarker for AAD diagnosis within 24 hours after symptom onset. Additionally, IMA was highly effective in distinguishing AAD from AMI, PE, and NCCP compared with D-dimer.

Similarly, previous reports have also shown that the IMA level is significantly high and could be a sensitive biochemical marker for the diagnosis of myocardial ischemia [10, 16]. Studies have shown that the IMA level in acute coronary syndromes increases within 10 minutes, then further increases for the next 6–12 hours, before decreasing to a normal level within 12–24 hours [17], consistent with this study [18, 19]. The FDA has approved IMA as a marker for myocardial infarction prognosis. However, the diagnostic accuracy of IMA for AMI diagnosis is unknown [20]. IMA, as a marker, has been investigated in the diagnosis of severe sepsis, bacterial infections and is associated with oxidative stress parameters [20]. However, no study has assessed the IMA value in cardiovascular disease diagnosis.

The study indicated that IMA could be a marker for AAD. The classical hypothesis shows that the albumin effect could be due to expansion of circulating plasma volume, which ensures adequate organ perfusion. This study indicated that the additional benefit could be due to the enhancement of the transport function of albumin, improving the outcome in AAD. Moreover, IMA can be generated in any regional ischemia. The disruption of aortic media changes aorta hemodynamics when aortic dissection occurs. Furthermore, intramural hemorrhage can cause diffusion, especially when the intimal layer is destroyed, thus the blood flow in the media. Endothelial damage is caused by blood flow and shear stress. Furthermore, aorta hemodynamics significantly changes in the large areas of the aorta. It can cause higher IMA circulation than in small or medium vessels of PE and acute coronary syndrome.

IMA is a nonspecific marker for tissue ischemia. It has been previously studied in patients with PE, acute mesenteric ischemia, cerebral hemorrhage, deep venous thrombosis, acute coronary syndrome, ischemic stroke, and stroke [21–25]. Herein, IMA levels were significantly high in AAD since aortic dissection can involve coronary artery, subclavian artery, and internal carotid artery. IMA also increases in patients with aortic cross-clamping, cross-clamping during arterial reconstruction, and chronic claudication [21].

This research suggests that IMA could be related to various circulation ischemia, such as AAD, PE, AMI, and NCCP. Although the IMA level was elevated in AMI and PE, it was lower than in AAD. In addition, the best threshold of IMA, specificity, and sensitivity were 59.35 u/L, 85.71%, and 66.67%, respectively. However, this best threshold excludes aortic dissection with a negative predictive value of 85.72%, similar to D-dimer (negative predictive value, 87.23%). Furthermore, a higher threshold of IMA was associated with higher positive predictive values. Therefore, IMA could be a promising biomarker for the early diagnosis of AAD.

This research could provide a novel biomarker for the early diagnosis of AAD. The diagnostic performance of IMA was also assessed. IMA showed a better diagnostic performance than D-dimer. However, this study has some limitations. This was a single-center study, and large-sample studies in multiple centers are required to validate the findings. Second, this study did not include all patients with nonspecific chest pains, thus selection bias. Finally, this study included only Chinese participants. Therefore, other participants from other regions should be used to validate the results. In summary, IMA can be used as a marker for AAD.

Conclusion

IMA has a better performance for AAD diagnosis than D-dimer and could be a potential biomarker for fast and cost-effective diagnostic testing. However, large samples- studies are needed to validate the findings.

Declarations

Ethics approval and consent to participate

This study was approved by the hospital institutional review board of the Second Xiangya Hospital Clinical Trial Registration Number: ChiCTR2000039546. The data were collected and reviewed in compliance with the ethical standards set out by the Ethics Committee of the institution and with the Declaration of Helsinki. All patients have signed consent information for review by the Ethics Committee of the institution. It was also assured that all data were used only for research purposes.

Consent for publication

Not applicable.

Availability of supporting data

All data generated or analyzed during this study are included in this published article.

Competing interests

All authors declared no conflicts of interest.

Founding

This work was supported by the Fundamental Research Funds for the Central Universities of Central South University (No.2020zzts291); the Key Research and Development Program of Hunan Province (No.2019SK2022).

Authors' contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; Yang Zhou, Xiangping Chai, and Cheng Tao took part in drafting, revising or critically reviewing the article; All authors gave final approval of the version to be published; All authors have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Acknowledgements

Not applicable.

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Figures

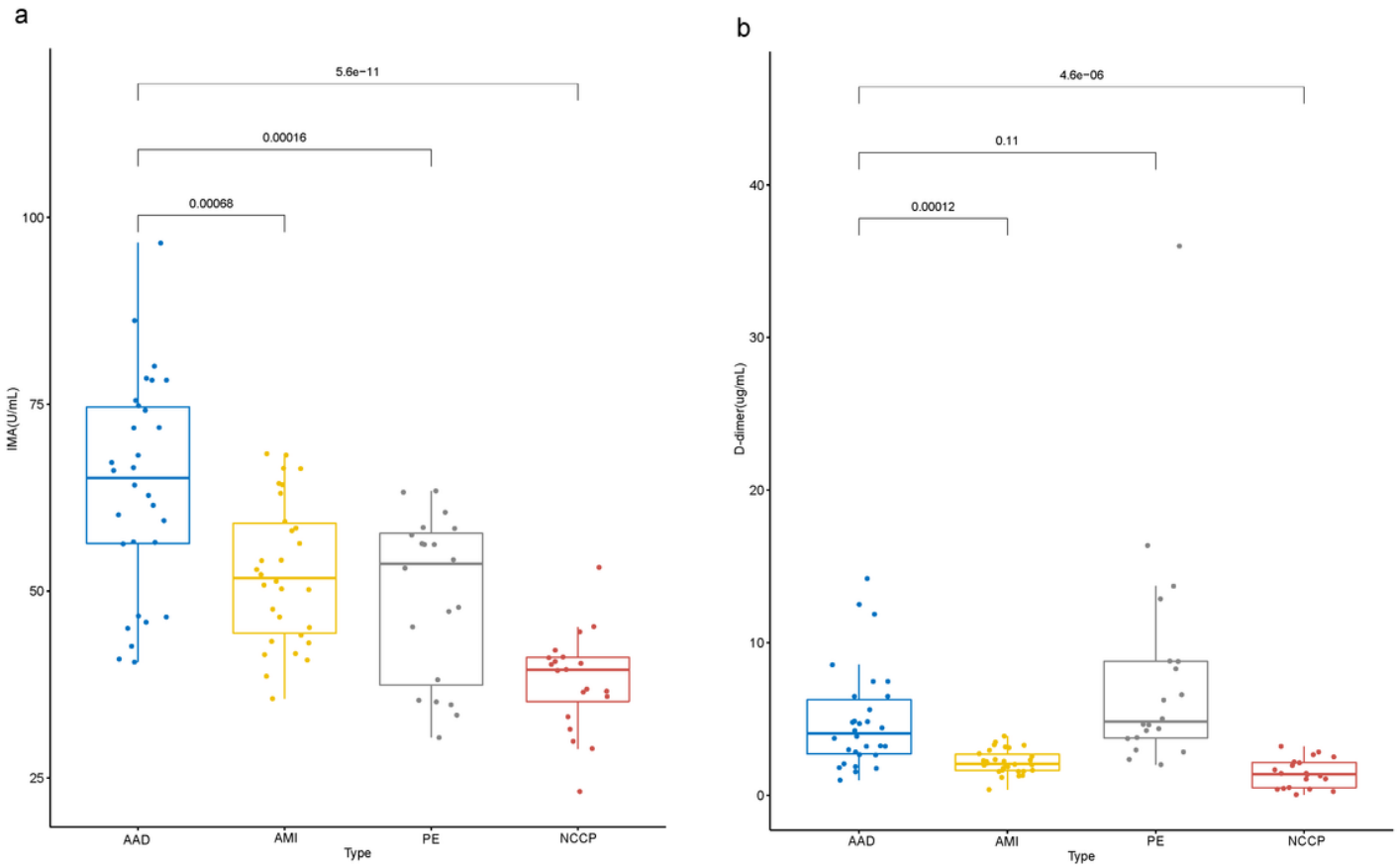

Figure 1

Boxplots of the analysis of IMA and D-dimer values in AAD, AMI, PE, and NP. (a) Distribution of IMA among AAD, AMI, PE, and NCCP. (b) Distribution of D-dimer among AAD, AMI, PE, and NCCP. IMA, ischemia modified albumin; AAD, acute aortic dissection; AMI, acute myocardial infarction; PE, pulmonary embolism; NCCP, non-cardiogenic chest pain.

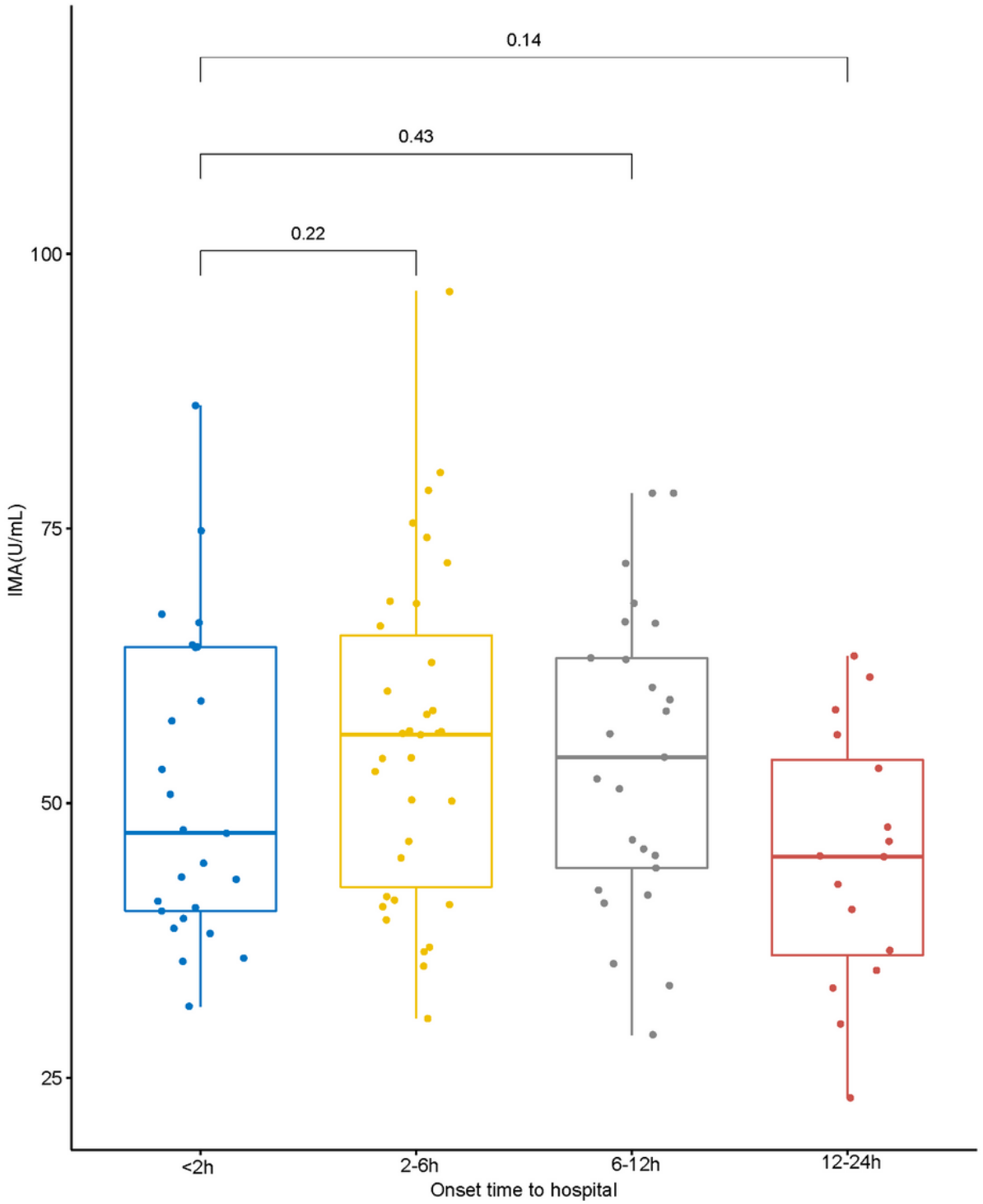

Figure 2

Levels of serum IMA according to time after symptoms onset in AAD patients. IMA, ischemia modified albumin; AAD, acute aortic dissection; *versus >12 hours group, P < 0.05;

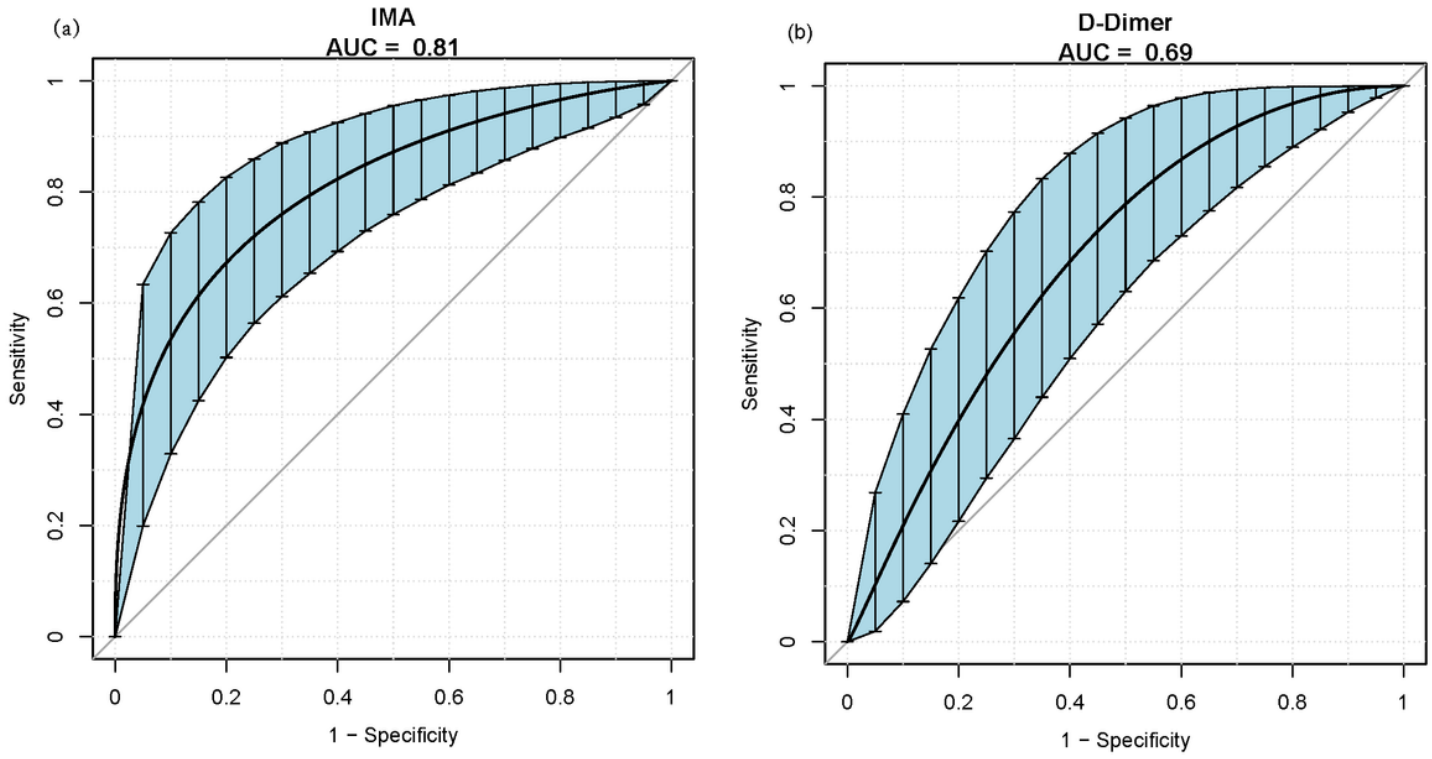

Figure 3

Receiver operating characteristic. (a) The AUC value of IMA for predicting AAD. (b) The AUC value of D-dimer for predicting AAD. Bule shading shows the bootstrap estimated 95% CI with AUC. IMA, ischemia modified albumin; AAD, acute aortic dissection; AUC, area under the curve;

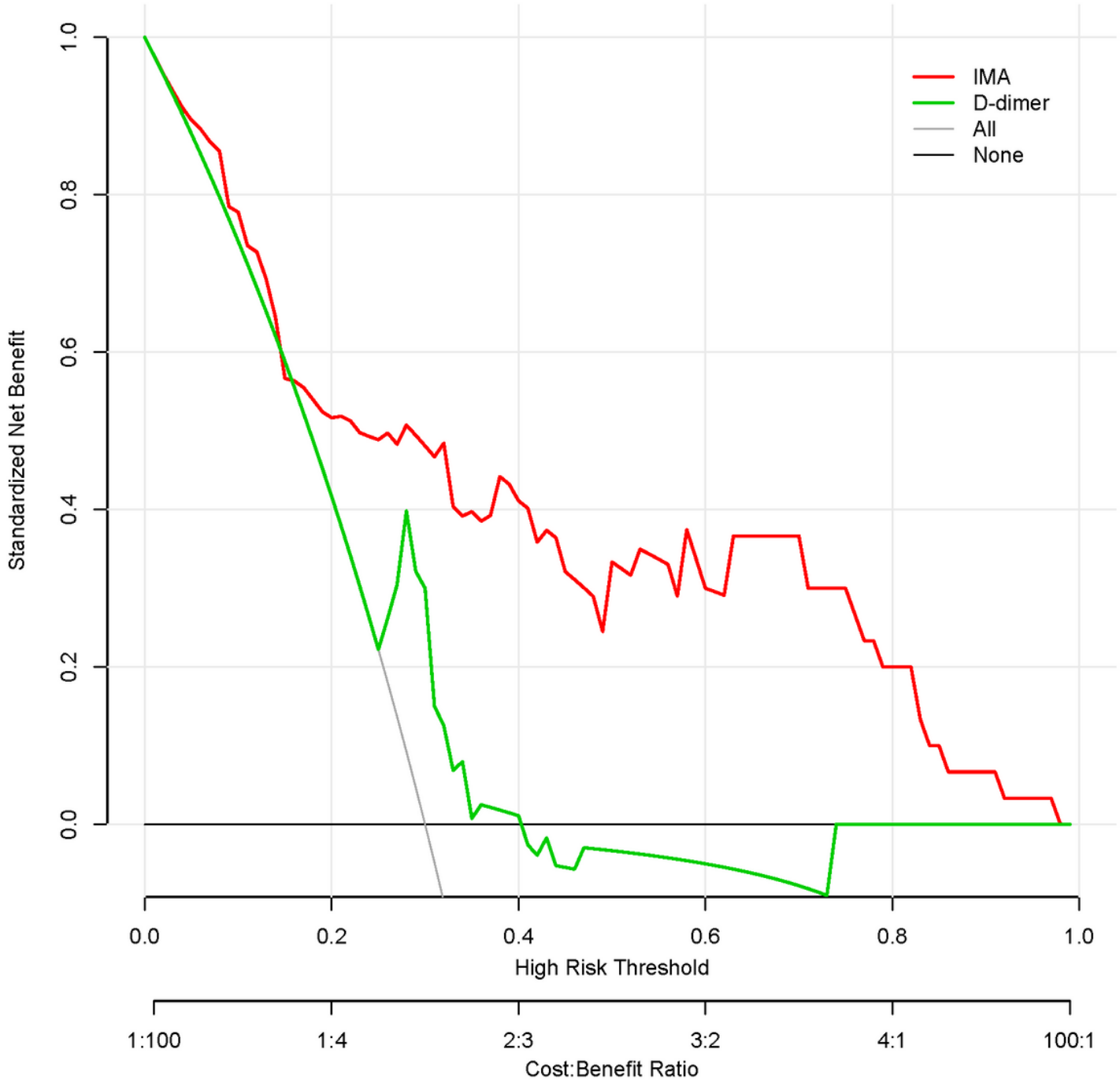

Figure 4

Clinical impact curve of the IMA and D-dimer for diagnosis of AAD, in which the levels of IMA predicted AAD had superior standardized net benefit.

Supplementary Files

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