



Lysophosphatidic Acid May Be a Novel Biomarker for Early Acute Aortic Dissection

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Background: Misdiagnosis and delayed diagnosis of acute aortic dissection (AAD) significantly increase mortality. Lysophosphatidic acid (LPA) is a biomarker related to coagulation cascade and cardiovascular-injury. The extent of LPA elevation in AAD and whether it can discriminate sudden-onset of acute chest pain are currently unclear.

Methods: We measured the plasma concentration of LPA in a cohort of 174 patients with suspected AAD chest pain and 30 healthy participants. Measures to discriminate AAD from other acute-onset thoracalgia were compared and calculated.

Results: LPA was significantly higher in AAD than in the AMI, PE, and the healthy (344.69 ± 59.99 vs. 286.79 ± 43.01 vs. 286.61 ± 43.32 vs. 96.08 ± 11.93 , $P < 0.01$) within 48 h of symptom onset. LPA level peaked at 12 h after symptom onset, then gradually decreased from 12 to 48 h in AAD. LPA had an AUC of 0.85 (0.80–0.90), diagnosis threshold of 298.98 mg/dl, a sensitivity of 0.81, specificity of 0.77, and the negative predictive value of 0.85. The ROC curve of LPA is better than D-dimer ($P = 0.041$, Delong test). The decision curve showed that LPA had excellent standardized net benefits.

Conclusion: LPA showed superior overall diagnostic performance to D-dimer in early AAD diagnosis may be a potential biomarker, but additional studies are needed to determine the rapid and cost-effective diagnostic tests in the emergency department.

Keywords: aortic dissection, biomarker, lysophosphatidic acid, diagnosis, chest pain

INTRODUCTION

Aortic dissection is a life-threatening cardiovascular disease that causes ~10,000 deaths in the United States each year (21% before admission and 32% in-hospital) (1, 2). Recently, Sweden indicated that the incidence has increased about 7.2/100,000 (3). However, the early identification and diagnosis of high-risk chest pain as acute aortic dissection (AAD) is the major challenge. Treatment measures include coronary angiography and thrombolytic drugs, which may cause poor prognosis in 24.8% of AAD, who are misdiagnosed as acute myocardial infarction (AMI) or acute pulmonary embolism (PE) (4–6). Not only that, chest CT or MRI is time-money-consuming and limited by emergency room conditions compared to biomarkers for the diagnosis of AAD (7, 8).

Several researches have investigated AAD potential biomarkers for faster and more accurate clinical treatment, such as smooth muscle myosin (9), calcium binding protein (10), soluble elastin fragments (11), soluble ST2 (5), and D-dimer (12). While increased values for D-dimers raise suspicion for AAD (4), it is difficult to use it to discriminate AAD from PE in daily practice, and there are nine (2.43%) exhibited negative D-dimer results in 370 AAD patients according to our previous studies (13). Moreover, the younger and smaller thrombosis groups have low specificity. A valuable diagnostic marker should provide information for early identification or elimination to improve the clinical treatment of AAD (12).

Lysophosphatidic acid (LPA) is a small and simple glycerophospholipid (1-acyl-2-hydroxy-3-phosphoglycerol structure) (14), which is an early molecular marker of coagulation cascade activation and cardiovascular-injury (15, 16). Previous researches have shown that lysophosphatidylcholine (LPC) was also involved in aortic aneurysm formation and decreased substantially in AAD, which is hydrolyzed to produce LPA (17, 18). The LPA may be produced earlier than D-dimer, or have a better diagnostic performance than D-dimer and AAD risk scoring system (19, 20), but the relationship between LPA and AAD is unclear. The plasma LPA levels of patients with acute chest pain (AAD, AMI, PE) and healthy participants were measured and compared to evaluate the diagnostic performance in distinguishing AAD from other chest pains.

METHODS

Research Sample

This is a single-center retrospective cohort including patients with suspected AAD within 48 h of onset and healthy participants, who came from the emergency department and medical examination center of the Second Xiangya Hospital of

Central South University (Changsha, China) between May 2020 and January 2021. All suspected AAD patients were examined for medical imaging and D-dimer for the final diagnosis (19, 21). The exclusion criteria are shown in **Supplementary Table 1**.

About 3–5 ml of whole blood was taken from the brachial vein and placed in a sodium citrate anticoagulant tube immediately after hospital admission. The samples were centrifuged at 1000 r/min for 15 min to process into plasma, and stored at -80°C . All sample processing methods are similar.

The Ethics Committee of the Second Xiangya Hospital of Central South University approved this study. Informed consent was obtained from all patients. However, consent was obtained from a family member in a case of sudden death after admission or during autopsy.

Outcome

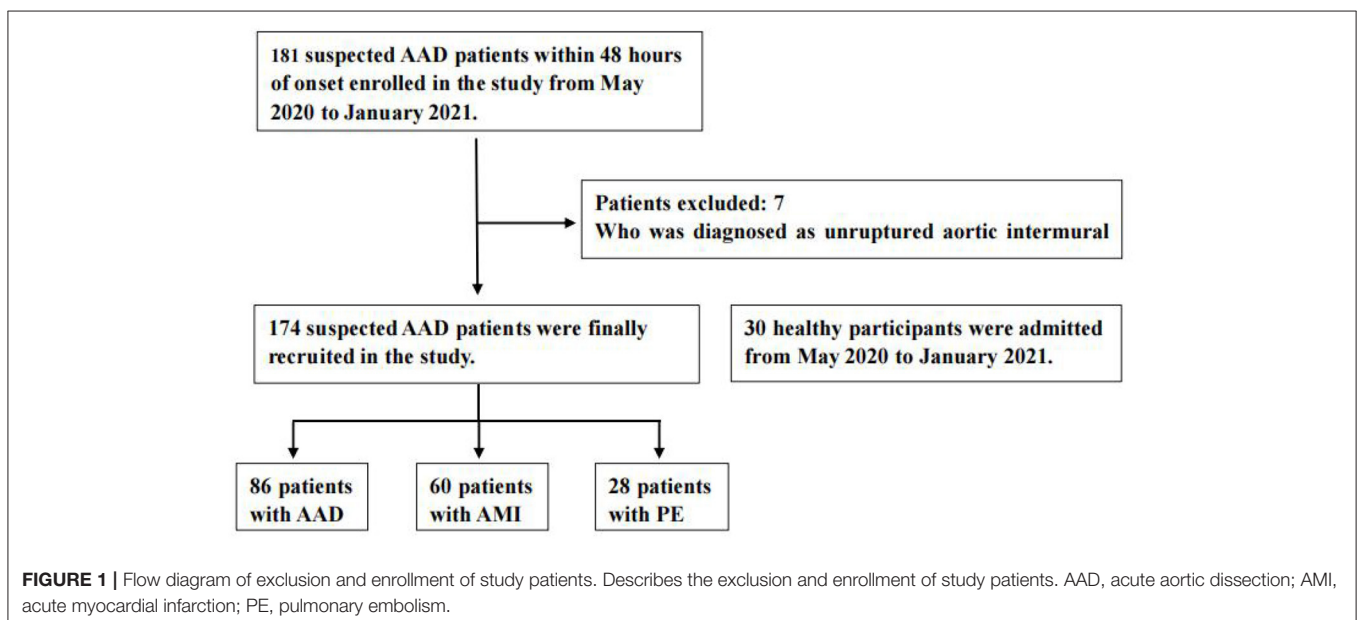
All patients with AAD, characterized by symptoms onset-time within 48 h, had image information from aortic computed tomography to confirm the final diagnosis. AMI diagnosis criteria were: (1) chest pain lasting >20 min, (2) Serial ECG changes with new pathological Q waves or ST-segment and T-wave changes, and (3) a plasma creatine kinase-myocardial band elevation (more than twice the normal level or cardiac troponin I (cTnI) level > 0.1 ng/ml). A positive pulmonary artery computed tomography scan was for PE diagnosis.

Measurement of LPA

The processed serum was measured by the human lysophosphatidic acid kit (Wuhan Huamei Bioengineering Co., Ltd.), and D-dimer was detected by the TOP700 automatic coagulation analyzer.

Statistical Analysis

Continuous variables were expressed as mean \pm standard deviation or median (IQR). ANOVA and Kruskal-Wallis test



were used for parametric and non-parametric data in multiple groups, *T*-test and Mann-Whitney *U*-test were used as a *post-hoc* analysis. Categorical variables were expressed as frequencies and compared using Fisher's precision probability test or Chi-square analysis. Logistic regression analysis was also used. *P* = 0.05 was considered statistically significant. Pearson correlation and delong test (22) were used to compare the relationship and ROC curve between LPA and D-dimer. The decision curve for a theoretical distribution was given to describe expected net benefit (23, 24).

The R (<https://www.r-project.org/>), The R Foundation, and EmpowerStats (<http://www.empowerstats.com>), X&Y Solutions Inc, Boston, MA were used for all statistical analyses.

RESULTS

A total of 204 patients, including 86 AAD patients, 60 AMI patients, 28 PE patients, and 30 healthy participants (Normal), were selected (Figure 1). The patient characteristics after 48 h of onset are shown in Table 1 and Supplementary Table 2. AAD patients were mostly younger males with no significant difference in symptom onset time in all groups than non-AAD patients (Supplementary Table 3). The D-dimer and LPA levels were significantly higher in AAD patients than in non-AAD patients on the whole (Supplementary Table 2). LPA level (344.69 ± 59.99) was significantly different from AMI, PE, and Normal. However, AMI and PE were not statistically different (Figure 2A). D-dimer levels in AAD and PE were

TABLE 1 | Baseline characteristics of chest pain patients with AAD vs. other groups.

	AAD	AMI	PE	Normal	P-value
No. of participates	86	60	28	30	
Gender, male	58 (67.44) [#]	32 (53.33)	12 (42.86) [†]	16 (53.33)	0.087
Age, year	53.60 ± 11.46 ^{**}	57.30 ± 5.34 [†]	55.36 ± 5.15	54.67 ± 4.33	0.077
Onset time to hospital, hours	11.45 ± 5.12	10.00 ± 4.43	11.32 ± 3.84	-	0.168
HR,/min	81.33 ± 18.22	79.57 ± 10.57	81.57 ± 10.82	78.37 ± 11.38	0.722
SBP, mmHg					
Left-S	141.21 ± 38.62	136.25 ± 15.99	136.32 ± 12.58	135.07 ± 15.03	0.608
Right-S	135.58 ± 36.93	135.40 ± 15.71	136.32 ± 13.21	135.50 ± 14.39	0.998
Difference-S	18.00 (7.00–31.00) ^{**#}	3.00 (2.00–5.00) [†]	2.00 (2.00–4.00) [†]	3.00 (2.00–4.00) [†]	<0.001
DBP, mmHg					
Left-D	79.90 ± 22.31	83.42 ± 11.87	84.25 ± 9.60	79.83 ± 13.53	0.473
Right-D	76.94 ± 20.02 ^{**}	83.83 ± 12.06 [†]	84.96 ± 11.35	81.63 ± 13.25	0.030
Difference-D	10.00 (4.00–13.75) ^{**#}	3.00 (2.00–4.25) [†]	3.00 (1.75–6.00) [†]	3.00 (2.00–5.00) [†]	<0.001
History of					
Hypertension, %	72 (83.72) ^{**#}	25 (41.67) ^{†#}	7 (25.00) ^{†*}	5 (16.67) ^{†**#}	<0.001
Diabetes, %	5 (5.81) ^{**#}	17 (28.33) ^{†#}	5 (17.86) [†]	3 (10.00) ^{**}	0.002
Stroke, %	6 (6.98)	4 (6.67)	2 (7.14)	0 (0)	0.530
Chronic kidney disease, %	12 (13.95)	12 (20.00) [#]	3 (10.71) [*]	0 (0)	0.067
OSAS, %	26 (30.23) ^{**}	0 (0) ^{†#}	7 (25.00) ^{**}	0 (0) ^{†#}	<0.001
COPD, %	5 (5.81)	2 (3.33)	3 (10.71)	0 (0)	0.257
Marfan, %	2 (2.33)	0 (0)	0 (0)	0 (0)	0.428
CAD, %	10 (11.63) ^{**}	26 (43.33) ^{†#}	5 (17.86) ^{**}	0 (0) ^{†**#}	<0.001
Valvular heart disease, %	2 (2.33) ^{**#}	8 (13.33) [†]	3 (10.71) [†]	0 (0) ^{**#}	0.017
Smoking, %	49 (56.98) [#]	27 (45.00) [#]	4 (14.29) ^{†*}	7 (23.33) ^{†*}	<0.001
Drinking, %	21 (24.42) [#]	11 (18.33)	3 (10.71) [†]	6 (20.00) [#]	0.056
Medication history					
Aspirin, %	12 (13.95) [*]	11 (18.33)	5 (17.86)	0 (0)	0.100
Clopidogrel, %	7 (8.14) [*]	9 (15.00)	3 (10.71)	0 (0)	0.134
Statin, %	16 (18.60) [*]	10 (16.67)	3 (10.71)	0 (0)	0.075
Hormone, %	3 (3.49) [*]	2 (3.33)	1 (3.57)	0 (0)	0.784
D-dimer, ug/ml	7.58 ± 4.80 ^{**}	3.14 ± 2.11 ^{†#}	8.49 ± 5.22 ^{**}	0.59 ± 0.43 ^{†**#}	<0.001
LPA, mg/dl	344.69 ± 59.99 ^{**#}	286.79 ± 43.01 [†]	286.61 ± 43.32 [†]	96.08 ± 11.93 ^{†**#}	<0.001

AAD, acute aortic dissection; AMI, acute myocardial infarction; PE, pulmonary embolism; SBP, systolic blood pressure; DBP, diastolic blood pressure; OSAS, obstructive sleep apnea syndrome; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; LPA, lysophosphatidic acid. *P* < 0.05, statistically different. [†]Significance vs. "AAD," ^{**}Significance vs. "AMI," [#]Significance vs. "PE," ^{*}Significance vs. "Normal."

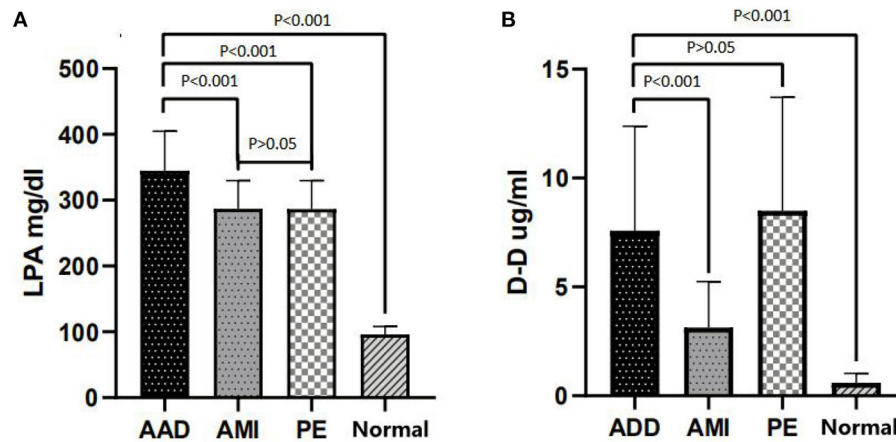


FIGURE 2 | LPA and D-dimer levels in chest pain patients with AAD vs. other groups. **(A)** LPA distribution (Mean \pm standard deviation) in AAD, AMI, PE, and Normal. **(B)** D-dimer distribution (Mean \pm standard deviation) in AAD, AMI, PE, and Normal. LPA, lysophosphatidic acid; AAD, acute aortic dissection; AMI, acute myocardial infarction; PE, pulmonary embolism; Normal, healthy participants.

TABLE 2 | Multivariate regression analysis for AAD diagnosis.

Exposure	Univariate analysis			Multi-factor analysis		
	OR	95% CI	P	OR	95% CI	P
Difference-S, mmHg	1.56	1.33, 1.84	<0.001	1.42	1.13, 1.78	0.003
Difference-D, mmHg	1.41	1.26, 1.57	<0.001	1.20	0.87, 1.67	0.272
Right-D, mmHg	0.97	0.96, 0.99	0.005	0.93	0.87, 1.00	0.047
Hypertension, %	11.26	5.64, 22.49	<0.001	9.67	1.93, 48.32	0.006
Diabetes, %	0.23	0.08, 0.63	0.004	0.04	0.00, 0.48	0.011
CAD, %	0.37	0.17, 0.80	0.012	0.15	0.01, 2.32	0.176
Valvular heart disease, %	0.23	0.05, 1.07	0.062	0.67	0.07, 6.97	0.740
Smoking, %	2.79	1.57, 4.96	0.001	0.41	0.07, 2.48	0.334
Drinking, %	2.40	1.14, 5.05	0.021	0.96	0.18, 5.10	0.962
D-dimer, ug/ml	1.03	1.02, 1.03	<0.001	1.02	1.01, 1.03	0.043
LPA, mg/dl	1.23	1.13, 1.30	<0.001	1.21	1.06, 1.43	0.007

AAD, acute aortic dissection; Difference-S, difference of systolic blood pressure; Difference-D, difference of diastolic blood pressure; Right-D, the right diastolic blood pressure; CAD, coronary artery disease; LPA, lysophosphatidic acid. $P < 0.05$, Statistically different.

TABLE 3 | Diagnostic performance of AAD patients vs. others using LPA compared with D-Dimer.

	AUC	95% CI	Threshold	Sensitivity	Specificity	PLR	NLR	PPV	NPV
D-D, ug/ml	0.76	0.70–0.82	1.87	0.90	0.55	1.82	0.11	0.57	0.91
LPA, mg/dl	0.86	0.80–0.90	298.98	0.81	0.77	3.56	0.24	0.72	0.85
P for compare	0.041	-	-	-	-	-	-	-	-

D-D, d-dimer; LPA, lysophosphatidic acid. $P < 0.05$, Statistically different (DeLong test).

higher but no statistical difference between the two (Figure 2B). Logistic multiple regression analysis showed that the blood pressure differences, hypertension history, D-dimer, and LPA were independently associated with AAD ($P < 0.001$) (Table 2).

Pearson analysis showed that LPA level was positively associated with D-dimer, $p < 0.05$ (coefficient of 0.17 in AAD,

0.15 in AMI, and 0.24 in PE). There was no significant correlation in Normal (Supplementary Figure 2).

LPA Distribution

The box plots were used to analyze LPA levels in AAD patient plasma at different onset times (Supplementary Figure 3).

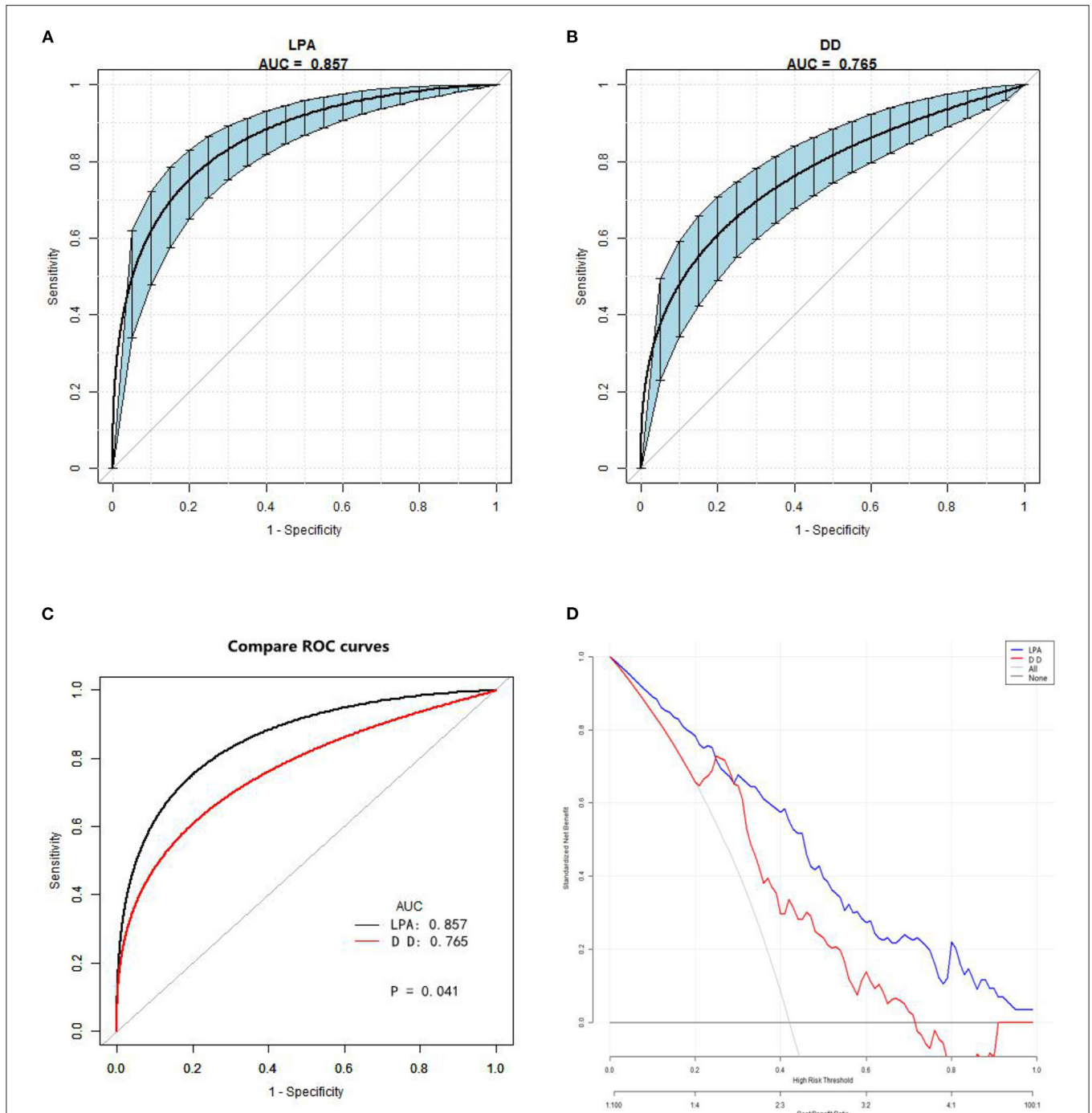


FIGURE 3 | Receiver operating characteristic and decision curve. **(A)** The AUC value of LPA predicting AAD. **(B)** The AUC value of D-dimer predicting AAD. Blue shading shows the bootstrap estimated 95% CI with AUC. **(C)** Comparison of ROC curves between D-dimer and LPA. The ROC curve of LPA is better than D-dimer (Delong test). **(D)** Decision curve for a theoretical distribution. Solid line: prediction model, LPA = blue, DD = red. Thin gray line: assume all patients have AAD. Black bottom line: assume no patients have AAD. The vertical axis displays standardized net benefit. The two horizontal axes show the correspondence between risk threshold and cost:benefit ratio. The graph gives the expected net benefit per patient associated with LPA and DD, with LPA performing better. LPA, lysophosphatidic acid; AAD, acute aortic dissection; AUC, area under the curve.

Based on the different onsets of symptoms in AAD patients, LPA seems to peak at 12 h and gradually decreased after 12 h, easing after 24 h ($P < 0.05$). The

number of chest pain patients at different symptoms onset-time was not statistically significant ($P = 0.148$) (Supplementary Table 3).

Diagnostic Performance for Discriminating AAD

The ROC analysis results indicated that D-dimer had an AUC of 0.76 (0.70–0.82), diagnosis threshold of 1.87 ug/ml, a sensitivity of 0.90, specificity of 0.55, and the negative predictive value of 0.91. LPA had an AUC of 0.85 (0.80–0.90), diagnosis threshold of 298.98 mg/dl, a sensitivity of 0.81, specificity of 0.77, and the negative predictive value of 0.85 (Table 3; Figures 3A,B). The ROC curve of LPA is better than D-dimer ($P = 0.041$, Delong test) (Figure 3C). The decision curve for a theoretical distribution showed that LPA had excellent standardized net benefits (Figure 3D).

DISCUSSION

This study, which included 174 suspected AAD patients and 30 healthy participants, found that LPA may be used for the clinical diagnosis of AAD. LPA, mainly produced by activated platelets, may be an early biomarker of the initiation of thrombosis and coagulation. Researches have shown that coagulation cascade activates platelets to release a large amount of lysophospholipids and autotaxin with phospholipase D activity stored in alpha particles at the same time. The two substances undergo a biochemical reaction to produce LPA, which increases the plasma concentration (14, 25, 26). LPA binding to its receptors (LPA1-6) on platelet surface activates platelets and forms a positive feedback reaction, alters platelet in morphology, promotes aggregation and thrombus stability (27–29). Moreover, LPA activates LPA1 and LPA3 expressed in vascular endothelial cells (30), promotes immune response and aggravate endothelial cell damage via G α i-RhoA-ROCK-NF- κ B dependent pathways (31). LPA also increases the expression of intracellular matrix metalloproteinase-2, which will remodel the extracellular matrix and reduce the aggregation of endothelial cells to promote the migration and aggregation of inflammatory cells, thereby damaging endothelial cells to activate the coagulation cascade (32).

We found that the magnitude of elevated LPA can distinguish patients with AAD from patients with AMI, PE, and the healthy within 48 h after symptom onset. AAD is a disease with high mortality due to severe damage to the aortic structure. There are also some biomarkers showing clinical prognosis including CRP (33), NT-pro BNP (34) and cardiac troponin (35). When aortic dissection occurs, disruption to the aortic media immediately changes aorta hemodynamics, then intramural hematoma expand (especially when the intimal layer is also disrupted) as the blood flow inside media (5). The tissue coagulation factor III directly exposed to the blood in the arterial smooth muscle activates the exogenous coagulation pathway and promotes the coagulation cascade (13). Platelets, an indispensable role in the coagulation cascade, are continuously activated by the LPC-ATX-LPA pathway to produce more LPA before the aortic dissection is surgically repaired (14, 36). Although some studies speculate that the half-life of LPA is only 2–3 min under the action of LPPs, the continuous existence of disruption to the aortic media and positive feedback may be a

reasonable explanation for the increase in plasma LPA in AAD patients (37, 38).

Our results suggested that the degree of the elevation of LPA levels is associated with the different magnitudes of vascular injury among AAD, AMI, and PE. Although LPA level in PE and AMI patients was higher than the healthy, there were still lower than AAD in our study. Substantial aortic hemodynamic changes significantly increased the circulating LPA level in the aorta (largest artery) compared with the small and medium blood vessels of pulmonary embolism and acute coronary syndrome. Studies have shown that LPA level is associated with the release location, releasing LPA directly and quickly to the aortic circulation may be another reason for the higher degree of AAD patients (39).

In addition, we speculated that LPA peaks at 12 h according to the symptoms of AAD patients, and our results also found that the threshold of LPA is 298.98 mg/dl, the specificity and AUC are 0.77 and 0.857, respectively, which are better than D-dimer ($P < 0.05$, Delong test). This means that as a marker of platelet activation, LPA ≥ 300 mg/dl indicates a high risk of AAD, and may be earlier than D-dimer. However, D-dimer has higher sensitivity and negative predictive value compared to LPA. As a fibrin degradation product in the circulation after thrombolytic fibrinolysis, D-dimer has been found to increase similarly in many diseases, including PE and AAD. In fact, D-dimer aids clinical diagnosis for PE only as a rule-out tool when the test result is negative (5).

To the best of our knowledge, this is the first study showing that LPA is associated with aortic dissection and could be a novel AAD biomarker. However, this study has some limitations. It is still unclear how LPA changes over time in AAD patients, a large-scale prospective multicenter study is needed to confirm the generalizability of the findings, the diagnostic validity, and the accuracy of this novel detection method since this was a single-center study. Second, the assay method used could provide an inconsistent absolute value for the LPA concentration, influencing the recommended cut-off level. Therefore, various detection methods should be accurately calibrated. Thirdly, this study did not include all undifferentiated chest pain patients, hence, patient selection could be biased. Finally, LPA < 300 mg/dl is difficult to rule out AAD in daily practice, and other diseases (ovarian cancer) (40) can also increase LPA levels. Therefore, further confirmatory diagnosis based on medical images is essential to prevent misdiagnosis in clinical practice.

CONCLUSION

LPA showed superior overall diagnostic performance to D-dimer in early AAD diagnosis may be a potential biomarker, but additional studies are needed to determine the rapid and cost-effective diagnostic tests in the emergency department.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: We are deeply sorry for this, because there

is still some research in progress for the time being. In order not to affect the following research, it is not convenient to disclose the data. Requests to access these datasets should be directed to 188212324@csu.edu.cn.

ETHICS STATEMENT

The hospital institutional review board of the Second Xiangya Hospital approved the study. The data collection and analysis followed the Ethics Committee of the institution and the Declaration of Helsinki. The Ethics Committee of the institution reviewed the patient consents, and the data were used only for research purposes.

AUTHOR CONTRIBUTIONS

XP and XC: drafted, revised, and reviewed the article. YZ and GY: conducted statistical analysis. ZH, HZ, ZP, WP, and ND: reviewed and revised the manuscripts. TG and MZ: organized the database. All authors significantly contributed to the conception, study design, execution, data acquisition, analysis, interpretation,

approved the final version, agreed on the journal, and are responsible for this study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fsurg.2021.789992/full#supplementary-material>

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