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Biomarkers in aortic dissection: Diagnostic and prognostic value from clinical research

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Abstract

Aortic dissection is a life-threatening condition for which diagnosis mainly relies on imaging examinations, while reliable biomarkers to detect or monitor are still under investigation. Recent advances in technologies provide an unprecedented opportunity to yield the identification of clinically valuable biomarkers, including proteins, ribonucleic acids (RNAs), and deoxyribonucleic acids (DNAs), for early detection of pathological changes in susceptible patients, rapid diagnosis at the bedside after onset, and a superior therapeutic regimen primarily within the concept of personalized and tailored endovascular therapy for aortic dissection.

Keywords: Aortic dissection; Biomarker; Protein; Cell-free DNA; miRNA; Inflammation; Lipid-metabolism

Introduction

Aortic dissection (AD) is caused by a proximal tear in the intimal layer of the aorta or bleeding of vasa vasorum within the aortic wall, which contributes to and perpetuates the separation of the layers of the aortic wall. The intimal flap extends in both antegrade and retrograde directions and progresses to affect side-branch arteries. Normal blood flowing into the false lumen causes symptoms of ischemia and complications such as internal organ malperfusion, aortic valve insufficiency, heart failure, cardiac tamponade, and death.[1] The mortality of acute AD increases by 1%–3% per hour before the intervention or medical treatment and reaches up to 21% for 1 day and 74% for 7 days.[2] AD is likely to be misdiagnosed or overdiagnosed because of its rarity and concomitant comorbidities that often mask the primary symptoms.

Currently, the diagnosis of AD relies on imaging examinations, such as computed tomography angiography (CTA), which provides an in-depth understanding of the anatomical structure of the aortic wall with the advantages of being easily available, having a shorter scanning time, and being able to evaluate the whole aorta and branch vessels.[3] However, due to the large radiation dose of enhanced computed tomography (CT), contrast agent-induced nephropathy, and failure to provide an aortic function or dynamic evaluation, imaging can be applied only under certain circumstances. Moreover, patients with an increased genetic risk of AD may not present aortic dilatation, which restricts imaging examination as a means of a screening method for AD in the general population, making it more necessary to develop valuable early stage biomarkers for AD.

The holy grail of biomarkers is to reliably screen high-risk patients, rapidly identify or exclude this disease, and accurately assess disease prognosis during follow-up in a cost-effective and resource-efficient manner, and even brings the entire field of AD management into the mainstream of chronic disease management.[4] Broadly speaking, candidate biomarkers include proteins, ribonucleic acids (RNAs), and deoxyribonucleic acids (DNAs), the majority of which are still under preclinical investigation. This article aims to summarize these candidate biomarkers, elucidate their roles in AD diagnosis, progression prediction, and prognostic evaluation, and anticipate their transformation into clinical practice.

Protein as a Biomarker of Diagnosis and Prognosis in AD

Over the past few years, biomarker-selecting methods have changed from those based on the understanding of

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pathogenesis to a now common alternative method through a series of proteomics screening techniques, including gel electrophoresis, mass spectrometry, and multiple antibody array techniques. In the wake of advanced proteomics technologies providing unexampled opportunities to accelerate the discovery of biomarkers at the molecular level, cytokines, enzymes, and cytoskeletal proteins are found to actively participate in the pathophysiological condition at the early stage or acute phase of AD, hence, are proposed as reliable biomarkers for diagnosis and prognosis [Table 1].

D-dimer

D-dimer, originally found as a fibrin degradation product, is elevated in the blood during active fibrosis in clinically common diseases such as deep vein thrombosis, myocardial infarction, cerebral infarction, pulmonary embolism, and malignant tumors. It was not until 2009, however, that proof for this hypothesis was provided in the prospective multicenter International Registry of Acute Aortic Dissection Substudy on Biomarkers (IRAD-Bio) study, which demonstrated that the cut-off level of 500 ng/mL, which was widely used to rule out pulmonary embolism, can also accurately exclude AD during the first 24 h after onset with a sensitivity of 97%, specificity of 59%, negative and positive likelihood ratios of 0.06 and 2.58, respectively [Table 1].[5] Acute AD was considered to be excluded with a sensitivity of 100%, when D-dimer levels were <100 ng/mL.[6] In addition, elevated D-dimer levels >1600 ng/mL would rule in AD within the first 6 h after onset.[5] The aortic dissection detection risk score (ADD-RS) was historically proposed as a primary screening tool with a high sensitivity of 95.7%,[7] while D-dimer was further introduced as a secondary marker for patients with low ADD-RS. A study from Italy verified that negative D-dimer levels, which was <500 ng/mL, had a sensitivity of 100% to rule out AD patients with the ADD-RS of 0.[8]

In addition, D-dimer presented a sensitivity of 93.5%, and a specificity of 63.2% for the detection of patients with the acute aortic syndrome (AAS), with a negative predictive value (NPV) of 98.9%.[9] The diagnostic accuracy of the aortic dissection detection risk score plus D-dimer for acute aortic syndromes (ADvISED) study showed a similar result: a positive D-dimer result had an overall sensitivity of 96.7% and a specificity of 64% to diagnose AAS. The combination of intermediate and low ADD-RS and D-dimer levels <500 ng/mL showed a failure rate of 3.3%, whereas D-dimer was not discriminatory in patients with a higher ADD-RS.[10]

Nevertheless, owing to the short biological half-life (<8 h), it has limited power to detect subacute or chronic AD, which might prevent it from being widely used in the clinic.

Recent studies have confirmed that increased D-dimer levels following endovascular repair in the thoracic aorta were associated with less overall survival and more severe complications.[11] The sensitivity and specificity for prediction of in-hospital mortality were 87.19% and 64.70%, respectively, when D-dimer was over 5.92 μg/mL [Table 1].[12] The average D-dimer level at 9 μg/mL from before to after intervention treatment during hospitalization was an independent risk factor for in-hospital death.[13] Although not statistically significant, the IRAD-Bio study also found postoperative false lumen patency in type A dissections to be associated with higher level of D-dimer.[5] In conclusion, the significance of D-dimer as a prognostic marker for AD appears in the near future.

Inflammatory markers

The initial focus on the comprehension of what roles inflammatory responses and factors play in cardiovascular diseases arose from the observation and experiment that many facets of phenotypes could be simulated by the known biological effects of proinflammatory cytokines. Increasing evidence indicates that the innate immune response pathway consisting of the inflammasome NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3), interleukin (IL)-1 to IL-6, the C-reactive protein (CRP), and fibrinogen derived from liver was involved in cardiovascular disorders and thus that specific inflammatory cytokines might have a profound role in their early diagnosis.

IL-6

IL-6 was a crucial cytokine of innate immune responses that participates in a series of physiological or pathophysiological conditions related to immune cell proliferation, differentiation, and regulation. Circulating IL-6 levels in patients with acute AD were considerably increased than those in normal controls.[14–17] Post-implantation syndrome (PIS), which occurred in 15.8% of patients after endovascular treatment, was associated with higher peak value of IL-6 than non-PIS patients.[18] Furthermore, the IL-6 level in plasma of the non-survival AD group was higher than that of the survival group. The cut-off value of the IL-6 level for the prediction was 18.36 pg/mL, with a sensitivity and a specificity of 87.4% and 70.8%, respectively [Table 1].[19] A similar trend was reported in which the IL-6 level and tumor necrosis factor α (TNF-α) level in plasma were significantly elevated in AD. The time intervals of the levels of IL-6 and TNF-α increasing to peak were shorter than those of CRP.[20] The dynamically changed IL-6 levels in AD climbed steadily after onset and peaked 1–2 days, followed by a gradual slide to normal range during the next 2 months.[14] The relatively wide time window improves its diagnostic and prognostic accuracy in clinical applications.

IL-10

IL-10 concentrations were confirmed six to seven times higher in AD plasmas than all other diagnoses, such as thoracic aortic aneurysm (TAA), acute myocardial infarction (AMI), or pulmonary embolism (PE), collectively. IL-10 individually presented a superior performance for AD diagnosis with a sensitivity of 55.0% and

Table 1: Summary of the sensitivities and specificities of biomarkers alone or in combination in AD at the cut-off values with the respective time windows.

Biomarkers	Concentration	Time (h)	Sensitivity (%)	Specificity (%)
D-dimer for diagnosis	500 ng/mL	24	97	59
	1600 ng/mL	6	100	NR
D-dimer for in-hospital mortality	5.92 μg/mL	NR	87.19	64.70
IL-6	18.36 pg/mL	NR	87.4	70.8
IL-10	20 ng/L	NR	55	98
CRP for in-hospital death	14.30 mg/L	NR	87.10	53.85
CP	36.82 mg/dL	NR	90.6	92.9
sST2	34.6 ng/mL	NR	99.1	84.9
	40.0 ng/mL	NR	87.7	91.3
Combination of ANGPTL8, hs-CRP, and D-dimer	NR	NR	98.46	79.49
sLOX-1	150 pg/mL	NR	89.5	94.3
smMHC	2.5 ng/mL	3/12/24	90.9/90/85	98/97/97
	10 ng/mL	NR	NR	100
Calponin				
Acidic calponin	2.3 ng/mL	6/24	50/58	87/72
Basic calponin	159 ng/ml	6/24	63/50	73/66
Polycystin	357.33 pg/mL		85.7	75.6
Calcium-binding protein S100	1.10 ng/mL	NR	84.4	85.5
IMA	79.35 U/mL	24	80.6	84.8
MMP8	3.6 ng/mL	NR	100.0	9.5
MMP9	20 ng/mL	NR	96.2	16.2
sELAF	NR	NR	64.0	98.8
	97.07ng/mL	NR	82.86	NR
sELAF for open or partially open pseudolumen	285.4 ng/mL	NR	88.9	99.8
TNC for in-hospital death	>103.4 ng/mL	NR	83.87	83.33
Combination of TNC and D-dimer	NR	NR	90.30	86.6
ACAN	14.3 ng/mL	NR	81	97
miR-15a	NR	NR	75.7	100
miR-23a	NR	NR	91.9	85.7
let7b	NR	NR	79.4	92.9
US33-5p	NR	NR	73.5	85.7
4-miRNA panel	NR	Within 48 h	93.33	86.67
miR-25	1.353	after onset	86.67	93.33
miR-29a	1.354	NR	93.33	93.33
miR-155	1.457	NR	73.33	86.67
miR-26b	0.500	NR	73.33	86.67
circMARK3	1.497	NR	90.0	86.7
circMARK3 and miR-1273-3p	0.4807	NR	93.3	86.7
DNA methylation pattern	NR	NR	86	75

ACAN: Aggrecan; AD: Aortic dissection; ANGPTL8: Angiopoietin Like 8; CP: Ceruloplasmin; CRP: C-reactive protein; DNA: Deoxyribonucleic acid; FC: Fold change; hs-CRP: High sensitive C-reactive protein; IL: Interleukin; IMA: Ischemia-modified albumin; LDL: Low-density lipoprotein; miRNA: MicroRNA; MMP: Matrix metalloproteinase; NR: Not reported; RNA: Ribonucleic acid; sELAF: Soluble elastin fragments; sLOX-1: Soluble form of lectin-like oxLDL receptor 1; smMHC: Smooth muscle myosin heavy chain; sST2: Soluble suppression of tumorigenesis-2; TNC: Tenascin-C.

a specificity of 98.0%, with the cut-off value of 20 ng/L [Table 1], enabling itself to be a potential biomarker to AD and accurately discriminate suspected AD, AMI, and PE.[21]

CRP

CRP, stimulated by several cytokines in the acute phase of inflammation, was recommended as the first choice of inflammation marker in clinical diagnosis and treatment. Studies have pointed toward a clear association between plasma CRP levels at hospital admission and long-term adverse events in patients with AD. The short-term mortality significantly increased as the CRP value exceeded 6.3 mg/L.[22] When CRP exceeded 14.30 mg/L, the sensitivity and specificity for forecasting in-hospital mortality were 87.10% and 53.85%, respectively.[12] In addition, the CRP level over 15 mg/L was a vital risk factor for poor prognosis [Table 1].[23]

Ceruloplasmin (CP)

CP, a multicopper oxidase family member, is mainly synthesized and largely released in acute phase reactions.[24] A previous study pointed out that though CRP was regarded as the gold standard, serum CP might be helpful in detecting and monitoring chronic inflammation, and elevated CP levels are associated with an increased incidence of abdominal aorta aneurysm,[25] heart failure,[26] atrial fibrillation,[27] as well as cardiovascular risk in chronic dialysis.[28] Serum CP evidently increased and was positively related to CRP or platelet levels. The area under the curve (AUC) for the diagnosis of AD was 0.929 at the cut-off value of 36.82 mg/dL, with a sensitivity of 90.6% and a specificity of 92.9% [Table 1 and Figure 1]. Furthermore, serum CP was increased in cases with thrombosed false lumen than those with patent false lumen cases, suggesting that higher CP exposed patients to raised risk of thrombosed false lumen. Therefore, CP can act as a candidate biomarker for the diagnosis of AD and the risk factor for thrombosed false lumen.[29]

Soluble suppression of tumorigenesis-2 (sST2)

sST2 was primarily involved in inflammatory processes and T-cell-mediated immune responses. As a soluble cytokine receptor with a large molecular weight, sST2 was quite stable in the circulation and was considered a more precise biomarker of inflammation. Wang *et al*[30] corroborated that sST2 was a more valuable biomarker than D-dimer to exclude the diagnosis of AD. sST2 showed increased levels in acute AD than either in myocardial infarction or in pulmonary embolism. sST2 at a cut-off level of 34.6 ng/mL yielded a sensitivity of 99.1% and a specificity of 84.9% [Table 1], as well as positive predictive value (PPV) and NPV of 68.7% and 99.7%, respectively, with the area under curve (AUC) of 0.97 for sST2 [Figure 1]. It was also reported that sST2 showed the highest accuracy of 90.1% with a sensitivity of 87.7% and a specificity of 91.3%, and a positive predictive value of 77.1% and a positive likelihood ratio of 10.1% at a cutoff level of 40 ng/mL, which might also support a role in positive prediction [Figure 1]. The level of sST2 peaked at approximately 24 h after symptom onset.

Adipokine adiponectin

There was growing evidence that the perivascular adipose tissue surrounding the vasculature played a role in modulating inflammation and vascular tone via the regional release of adipokines.[31] The pleiotropic adipokine adiponectin, such as angiopoietin like 8 (ANGPTL8) and ANGPTL2, down-regulated the expression of inflammatory cytokines in abdominal aortic aneurysm.[32–34] Increasing ANGPTL8 levels in the blood resulted in a higher odds ratio as an independent risk factor for AD and were positively correlated with hs-CRP and aortic diameter. The AUC for ANGPTL8 was 0.746, while the AUC for the combination of ANGPTL8, D-dimer, and hs-CRP was 0.927, with a sensitivity of 98.46% and a specificity of 79.49% [Table 1 and Figure 1].[32]

Lipid metabolism-related markers

Low-density lipoprotein (LDL)

LDL played an active role in promoting foam cell formation, and inducing proliferation, migration, and pheno-

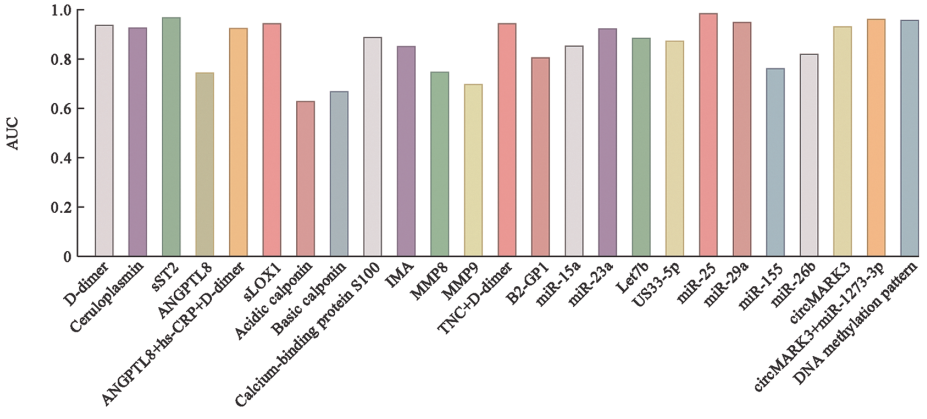

Figure 1: The AUC of biomarkers for the diagnosis of AD. AD: Aortic dissection; ANGPTL 8: Angiopoietin Like 8; AUC: Area under the curve; GP1: glycoprotein1; hs-CRP: High sensitive C-reactive protein; IMA: Ischemia-modified albumin; LDL: Low-density lipoprotein; miR: MicroRNA; MMP: Matrix metalloproteinase; RNA: Ribonucleic acid; sLOX-1: Soluble form of lectin-like oxLDL receptor 1; sST2: Soluble suppression of tumorigenesis-2; TNC: Tenascin-C.

typic switching of vascular smooth muscle cell in the initiation and progression of atherosclerosis.[35] A soluble form of lectin-like oxLDL receptor 1 (sLOX-1) was generated by being cleaved at the membrane-proximal extracellular domain from LOX-1, the major oxLDL receptor located in the endothelial cells. A majority of studies had confirmed the performance of sLOX-1 in terms of determining the severity of stable coronary artery disease and acute coronary syndrome.[36–39] sLOX-1 levels was considerably higher in the AD and acute coronary syndrome (ACS) patients than in control and that in AD group were even substantially higher compared with the ACS group. The AUC for sLOX-1 at optimal threshold of 150 pg/mL to differentiate AD from ACS was 0.946 [Figure 1], with a sensitivity of 89.5% and a specificity of 94.3% [Table 1], while that of cardiac troponin T (cTnT) was merely 0.580.[40] Further multicenter studies are required to identify the diagnostic accuracy for sLOX-1 and in combination with D-dimer in large sample sizes.

Lysophosphatidylcholine (LPC)

LPC was a fundamental cell signaling molecule that is produced through the phospholipase A2 acting on phosphatidylcholine. Sphingomyelins (SM) and ceramides were interrelated through the "sphingomyelinase-ceramide pathway", and the latter were products of SM hydrolysis under the action of the enzyme sphingomyelinase.[41] The sphingomyelinase-ceramide pathway generally contributes to pro-inflammatory, pro-oxidative, and pro-apoptotic processes, such as promoting vascular smooth muscle cell calcification,[42,43] leading to atherosclerosis, aging, and other cardiovascular events.[44–46] SMs, typically SM C16:0 and SM C24:1 predominated in the normal blood.[47] A general increase in the amount of total SM levels in AD was uncovered through the metabolic profiles of ascending thoracic aortic wall tissue.[48] Meanwhile, LPCs and sphingolipids, including sphingosine, phytosphingosine, SM, and ceramide, were identified to differ between the AD groups and the control.[49] LPC levels were remarkably diminished in both the Stanford type A and type B AD, while sphingolipids were only reduced in the Stanford type A AD. The identification of potential biomarkers for the diagnosis of AD and discrimination between type A and type B AD might be facilitated by combining these two families of metabolites.

Homocysteine (Hcy)

Hcy was an intermediate product during the process of the physiologically biosynthesizing the amino acids cysteine and methionine. A clear association between total Hcy and the presence of coronary and peripheral vascular disease had been pointed out in recent studies.[50] Hcy, as an independent risk factor for atherosclerosis,[51] mediates the formation of cardiovascular disease by different mechanisms, including promoting vascular smooth muscle cells (VSMCs) proliferation, triggering endothelial dysfunction and oxidative stress, inducing synthesis and deterioration of collagen, and launching an inflammatory response.[52] A recent study prospectively confirmed the efficacy of Hcy levels in predicting adverse cardiovascular disease events.[53] Patients with aortic dilatation or AD were characterized by higher levels of serum Hcy than those with mild cardiovascular manifestations. Total Hcy was evidently higher in Marfan's syndrome patients who have severe cardiovascular manifestations *vs.* patients with mild manifestations.[54]

Smooth muscle cell markers

Smooth muscle myosin heavy chain (smMHC), a specific smooth muscle protein, was released from impaired aortic medial smooth muscle cell during the initial and progression of AD and reached a concentration 20 times higher followed by a rapid decline to the normal range. The smMHC value in serum, first reported in AD, greatly increased within 24 h of onset and exceeded 7 ng/mL until 24 h after onset, which was 5–10 times higher than controls, following a substantial decrease to a normal value after 24 h.[55]

Another study showed that the sensitivity and the specificity of the smMHC at a cut-off level of 2.5 ng/mL within the first 12 h was 90% and 97%, respectively [Table 1].[56] While within 3 h after onset, the elevated levels of circulating smMHC showed a sensitivity of 90.9% and a specificity of 98%. Levels of smMHC exceeding 10 ng/mL showed 100% specificity for AD. Furthermore, smMHC level was significantly increased in patients with proximal lesions than in distal lesions, which interestedly showed decreased levels (<2.5 ng/mL). Chances were that smMHC was lower in patients with distal lesions, probably because less smooth muscle exists in the abdominal aorta than in the thoracic aorta. The receiver operating characteristic (ROC) curve confirmed its superior sensitivity for proximal lesions than for distal lesions within 3–6 h after onset and thereafter,[57] presenting a potential value in locating the lesions.

Creatine kinase-BB isozyme

Creatine kinase-BB isozyme, which also reflected aortic smooth muscle damage, was found to be 7- or 8-fold higher in AD patients than in normal controls. It peaked at 6 h after onset with a longer time window than that of smMHC.[58]

Calponin

Calponin, troponin-like protein of smooth muscle, analogous to cardiac troponins present in myocardial ischemia or necrosis had caught the eyes of researchers. Patients with AD have acid and basic calponin levels elevated in both proximal and distal aortic diseases. The acidic calponin at the cut-off point of 2.3 ng/mL and basic calponin with optimum values of 159 ng/mL showed a sensitivity of 50% and specificity of 87%, and a sensitivity of 63% and specificity of 73% during the first 6 h, respectively. Calponin presented a relatively long time, with a sensitivity of 58% and specificity of 72% for acidic calponin, a sensitivity of 50% and specificity of 66% for basic calponin in the initial 24 h, and an acceptable NPV but a disappointing PPV [Figure 1

and Table 1].[5] A meta-analysis involving four studies pointed to a strong relationship between elevated troponin levels, which was present in 26.8% of patients with AD, and a high risk of short-term death during hospitalization.[59] Collectively, calponin exhibited promising potential in the diagnosis of AD and is presently being pursued with hopes of its clinical application and bedside practice.[3]

Polycystin 1 (PC1)

PC1, predominately expressed in both endothelial cells and smooth muscle cells, casts a fundamental role in maintaining the structural stability and functional integrity of the vessel wall.[60–63] Serum PC1 was increased in patients with AD than in other diseases or healthy subjects, with a sensitivity of 85.7% and a specificity of 75.6%, at the cut-off value of 357.33 pg/mL [Table 1].[64]

Cardiac markers

N-terminal pro-brain natriuretic peptide (NT-proBNP)

NT-proBNP was a well-established diagnostic and prognostic biomarker in patients with heart failure. Although NT-proBNP showed no superiority in the early diagnosis of acute AD in the emergency setting,[65] higher levels of NT-proBNP also were independently associated with in-hospital mortality. NT-proBNP levels >647 pg/mL indicated the occurrence of postoperative heart failure in patients with AD.[66] In addition, a higher sensitivity in predicting in-hospital death was achieved with the combination of NT-proBNP levels and aortic diameters.[67]

Calcium-binding protein S100

Calcium-binding protein S100 had various biological functions and involves in cell proliferation and differentiation, protein phosphorylation, and transcription factor regulation via the regulation of intracellular calcium ions.[68] The calcium-binding protein S100A1, one of the S100 protein families, was reported as a pivotal regulator of myocardial systolic and diastolic functions.[69] S100A1 was regarded as an early diagnostic marker of ischemic coronary artery disease.[70] The concentration of S100A1 was further elevated in patients with AD, typically in AD complicated by aortic regurgitation, pericardial effusion, or in-hospital death. When the plasma concentration of S100A1 was 1.10 ng/mL, the sensitivity for the diagnosis of AD was 84.4%, and the specificity was 85.5% [Table 1].[71]

Ischemia-modified albumin (IMA)

IMA was an extensively investigated diagnostic marker of the early stage of myocardial ischemia in patients.[72] However, IMA lacked diagnostic specificity, resulting in a high proportion of false positives.[73,74] Studies had found elevated IMA in a wide range of diseases, including acute coronary syndrome,[75] chronic liver and kidney diseases,[76] malaria,[77] and preeclampsia.[78] IMA tended to be positively correlated to time from symptom onset at baseline.[79] Patients with poor prognosis exhibited higher levels of IMA within 24 h from the onset, indicating that IMA was an independent risk factor for in-hospital mortality with the best threshold of 79.35 U/mL. The AUC at this IMA level was 0.854, while the sensitivity and specificity to anticipate in-hospital death were 80.6% and 84.8%, respectively [Figure 1 and Table 1].[80]

Extracellular matrix markers

The vessel wall extracellular matrix (ECM) was a dynamic structure, which was instrumental in regulating vascular function in healthy and pathophysiological conditions.[81] The vascular ECM was composed of structural proteins, such as collagens and elastin, and non-structural proteins, including glycoproteins, proteoglycans, growth factors, and proteases. The collagen and elastin remained to be the most principal ECM proteins in the arterial wall, though the composition of ECM varies along the aortic wall layers and longitudinal directions. The balance of structural proteins regulated by proteolytic enzymes matrix metalloproteinases (MMPs) and their inhibitors tissue inhibitors of metalloproteinases (TIMPs) has been a hotspot in the field of aneurysms.[82] Recently, a growing number of studies have focused on the role of non-structural proteins, especially proteoglycans.[83–85]

Matrix metalloproteinases (MMPs)

MMPs mainly involved in the aortic remodeling have been extensively studied in the past several years. MMP-2 and TIMP-2 were reported to be significantly lower in the AD group.[85] Whereas the expression of MMP-1 and MMP-9 was increased in patients with aneurysm and AD compared with healthy controls, and higher MMP-2 and MMP-9 expressions were typically recorded in AD than in aneurysm.[86] Increased MMP-9 levels were also observed in the subacute phase of medically treated type B AD.[84] Plasma levels of MMP-8 and MMP-9 were closely related, and both MMP-8 and MMP-9 showed a stronger association with D-dimer. For MMP-8, the AUC for patients with AD was 0.75 *vs.* all controls, 0.75 *vs.* aortic aneurysm, 0.67 *vs.* inflammatory disease, and 0.82 *vs.* acute coronary syndrome. Plasma MMP-8 had a sensitivity of 100.0% and a specificity of 9.5% at a cut-off of 3.6 ng/mL. For MMP-9, the AUC for patients with AD was 0.70 *vs.* all controls, 0.77 *vs.* aortic aneurysm, 0.69 *vs.* inflammatory disease, and 0.73 *vs.* acute coronary syndrome. Plasma MMP-9 had a sensitivity of 96.2% and a specificity of 16.2% at a cut-off of 20.0 ng/mL [Table 1]. Furthermore, a combination of MMP-8 and D-dimer increases the AUC of the ROC curve in predicting acute AD, representing a promising marker to accurately rule out AD.[87]

Soluble elastin fragments (sELAF)

sELAF, degraded by proteolytic enzymes, were released into the plasma when a great number of elastic fibers in the vascular wall rupture. Its dynamic change with

confounding factors had made it difficult for clinical application in the present.[3] Elastin showed an average diagnostic performance with a sensitivity of 64.0%, a specificity of 98.8%, PPV of 94.1%, and NPV of 98.1% [Table 1]. Another study implied that sELAF had a better diagnostic sensitivity of 82.86% at a cut-off value of 97.07 ng/mL.[64] The elevated plasma sELAF level increased as early as 0.7 h after onset and was sustained for 72 h, which might be considered an effective diagnostic marker. The increased sELAF at the cut-off value of 285.4 ng/mL can effectively predict an open or a partially open false lumen of AD patients with a sensitivity of 88.9% and a specificity of 99.8% [Table 1].[88] A combination of smMHC and sELAF showed high sensitivity and specificity in the diagnosis of AD, but these tests were regarded as not practical in clinical emergency scenarios.[89]

Tenascin-C (TNC)

TNC was an ECM glycoprotein that can be synthesized by a broad set of cell types, exhibiting a main function of de-adhesion and cell proliferation promotion in the response to inflammatory mediators and mechanical stress. Elevated TNC level was identified in aortic aneurysm, pulmonary arterial hypertension, and restenosis patients.[90] TNC levels were positively correlated with the maximal aortic diameter and the degree of histological damage to the aortic wall.[91] A recent study showed that serum TNC levels were increased in patients with AD, and TNC levels were correlated with the peak hs-CRP and D-dimer levels on the seventh day after onset.[92] TNC levels reached the top point at 12–24 h and diminished to normal in the next 24 h. The serum TNC level was significantly higher in non-survivors than survivors, showing the potential of being an independent risk factor in predicting in-hospital death among patients with acute AD. ROC analysis showed that the AUC of TNC was comparable to that of D-dimer and superior to that of CRP in predicting in-hospital death at the cut-off point TNC >103.4 ng/mL, with a sensitivity of 83.87% and specificity of 83.33% [Table 1]. The AUC of TNC combined with D-dimer reached up to 0.946, with a sensitivity of 90.30% and a specificity of 86.60% [Figure 1 and Table 1],[12] indicating that TNC can enhance the ability of D-dimer to evaluate the short-term prognosis of acute AD.

Aggrecan (ACAN)

ACAN, a major proteoglycan, was significantly increased at a 4- to 5-fold higher concentration compared to the controls and maintained elevated levels for 72 h after onset without major fluctuations. The optimum discrimination limit of 14.3 ng/mL resulted in a specificity of more than 97% and a sensitivity of 81%, as well as a PPV and NPV of 72.7% and 98%, respectively [Table 1].[93]

Vinculin

Vinculin was a crucial cytoskeletal protein located at focal adhesions involved in mediating the mechanochemical pathway of the cytoskeleton in cell component and ECM.[94,95] It contributed to abnormal proliferation, adhesion, and vascular smooth muscle cells switching from contractile to the synthetic phenotype. Synthetic VSMCs could secrete excessive MMPs, resulting in an imbalanced state of MMPs and TIMPs and elastin proteolysis in the outer layer of the aortic wall.[96] Vinculin increased significantly among the differential proteins in AD (15.8 ng/mL) than in AMI patients (8.6 ng/mL) than healthy volunteers (5.3 ng/mL). The concentration of vinculin increased swiftly in the early stage after onset (often <12 h) and then remained at a high level for 48 h in patients with AD, indicating a satisfactory time window.[97]

Other proteins

TGF-β

TGF-β was a signaling molecule that binds to fibrillin-1, an ECM protein encoded by the *FBN1* gene. The deficiency of fibrillin-1 can affect the overactivation of TGF-β, giving rise to an abnormal TGF-β bioavailability in Marfan patients.[98] The TGF-β level was elevated at 24.5 ng/mL, which was approximately 5-fold higher, in non-Marfan patients within 24 h of symptom onset. Approximately 2-fold elevations were observed in type A AD (28.5 ng/mL) compared with type B AD (14.4 ng/mL).[99]

Osteoprotegerin (OPG) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)

An elevated OPG/TRAIL ratio was identified as the best predictor of overall, 30-day, and post-30-day mortality, with a hazard ratio of 2.32. Two cut-off OPG/TRAIL ratio values can categorize the mortality of patients into low-risk (OPG/TRAIL ratio <4) and high-risk (OPG/TRAIL ratio >33).[100]

Beta-2 glycoprotein1 (β2-GP1)

β2-GP1 mainly participated in the immune system through direct interaction with membrane toll-like receptors, promoting activation of endothelial cells and expression of proinflammatory cytokines.[101] The AUC of B2-GP1 for diagnosing AD was 0.81 [Figure 1], indicating that B2-GP1 might be a potential biomarker.[102]

Uric acid

Uric acid was an end-product of purine nucleotide degradation. It was closely related to many conditions, such as hypertension, dyslipidemia, obesity, and impaired glucose metabolism. Uric acid levels were higher in patients with AD than in controls.[103–106] Moreover, hyperuricemia was reported to be independently associated with the risk of AD.[107,108] In addition, a meta-analysis of seven case–control studies confirmed no significant difference between type A and type B AD.[109]

RNA as a Biomarker of Diagnosis and Prognosis in AD

MicroRNA (miRNA)

miRNA was an endogenous non-coding RNA molecule that orchestrates gene expression at the transcriptional and posttranscriptional levels via targeting mRNA for cleavage or translational repression.[110] In recent years, a plethora of evidence suggested that miRNAs, which were strikingly stable in plasma,[111] played crucial roles in the pathologic processes of cardiovascular diseases.[112,113]

miR-29

The miR-29 family, comprising miR-29a, miR-29b, and miR29c, are essential regulators of ECM homeostasis, with targets in elastin,[114] collagens, and MMPs.[115] miR-29a expression was up-regulated in patients with bicuspid aortic valve-thoracic aneurysm, a disease that progressively enlarges and predisposes tissue to acute AD in the aortic concavity,[116–118] while a decline was shown in the convexity with demonstrated regional differences,[117] suggesting that miR-29a might play a role in adapting the thoracic aorta to the environment of hemodynamic stress created by the bicuspid aortic valve. Nevertheless, miR-29a was declined in aortic tissue obtained during open chest surgery both before[119] and after dissection.[120]

miR-30

miR-30 family members were involved in the development of multiple organs and tissues, including the heart, blood vessels, intestinal tract, and malignant tumor. Up-regulated expression of miR-30 promotes the occurrence and progression of AD, which possibly aims at LOX, suggesting a potential role of miR-30a as a strong regulator of LOX in aortic VSMCs.[121]

miR-143/145

miR-143/145 were two of the best-characterized miRNAs in cardiovascular conditions, which collaboratively played a crucial role in VSMC differentiation and phenotype switching.[122–124] Contractile VSMC populations in the aorta were maintained, with miR-145 promoting contractile gene expression and miR-143 inhibiting synthetic gene expression,[123] therefore, contributing to structural modifications of the aorta.[120] Recently, Jing *et al*[89] verified that circulating miRNAs were novel potential biomarkers for the diagnosis of AD.

miRNA panel

Four miRNAs (miR-15a, miR-23a, let7b, and US33-5p) were significantly increased in the AD group compared with the control group. ROC analysis for miR-15a exhibited a sensitivity of 75.7% and specificity of 100%, for miR-23a presented a sensitivity of 91.9% and specificity of 85.7%, for let7b showed a sensitivity of 79.4% and specificity of 92.9%, and for US33-5p revealed a sensitivity of 73.5% and specificity of 85.7%. The AUCs for four miRNAs were 0.855, 0.925, 0.887, and 0.815, respectively.

Another four miRNAs, including miR-25, miR-29a, miR-155, and miR-26b, may also serve as potential biomarkers for diagnosing AD patients. When compared with healthy controls, patients with AD had significantly higher expression of miR-25, miR-29a, and miR-155, while miR-26b was markedly diminished. ROC analysis for miR-25 exhibited a sensitivity of 86.67% and specificity of 93.33%, for miR-29a presented a sensitivity of 93.33% and specificity of 93.33%, for miR-155 showed a sensitivity of 73.33% and specificity of 86.67%, and for miR-26b revealed a sensitivity of 73.33% and specificity of 86.67% [Table 1]. The 4-miRNA panel showed a sensitivity of 96%, a specificity of 100%, and an AUC of 0.995, with an optimal cut-off value of 46.50%. In the following single-blind trial, the 4-miRNA panel reliably exhibited a sensitivity of 93.33%, specificity of 86.67%, and AUC of 0.973 [Figure 1].[125]

The differential expression profile of miRNAs yielded a series of upregulated expressed circulating miRNAs, incorporating miR-4313, miR933, miR-1281, and miR-123831, whose accuracy is currently under clinical verification in a large sample of AD patients and controls.[126]

circMARK3

The preliminary landscape of circRNA expression profiles suggested that circMARK3, the upstream regulatory molecule of tyrosineprotein kinase Fgr, was differentially expressed in the occurrence and development of AD. The ROC of serum circMARK3 as a biomarker for AD presented a sensitivity of 90.0%, specificity of 86.7% [Table 1], and AUC of 0.934 at a cut-off value of 1.497 [Figure 1]. The AUC of the combination of circMARK3 and miR-1273-3p was 0.9644, with the cutoff value of 0.4807 and the corresponding sensitivity of 93.3% and specificity of 86.7%, respectively [Figure 1 and Table 1].[127]

Recent studies had highlighted the potential application of non-coding RNA-regulated processes in the pathogenesis of AD. However, comparison of the conclusions among different studies presented a low consistency of differentially regulated miRNAs. There were possible reasons. First, a circulating miRNA profile may differ depending on different confounding factors such as population, sex, presence of comorbidities, medication history, the nature of the sample, and collection methods.[128–130] Such confounding factors should be clarified and controlled during study design and statistical analysis to minimize potential bias. Second, it can be difficult to determine whether miRNA up- or down-regulation has a causal effect in terms of AD development or, oppositely, results from a compensatory mechanism to regulate. While animal models that allow detailed mechanistic approaches would provide some insight.

DNA as a Biomarker of Diagnosis and Prognosis in AD

Cell-free DNA (cfDNA) from plasma heralds a revolution in the battle against cancer.[131] It was rapidly

emerging as a significant and minimally invasive adjunct to standard tumor biopsies and, in some diseases, even a potential alternative approach.[132] Each cfDNA fragment harbors molecular markers of its cellular origin, such as DNA methylation status.[133]

Although based on a minority of patient samples, recent studies had suggested a high degree of consistency among DNA alterations detected in between arterial walls and plasma samples from the same patient, in which researchers see the potential of blood test to distinguish AD from other diseases. Methylation of the CpG site significantly increased in the promoter of MMP2 in the AD group.[134] The DNA methylation landscape supported that AD was associated with an inflammatory vascular remodeling process and a dedifferentiated smooth muscle cell phenotype.[135] Moreover, a different methylation profile in AD patients who underwent surgery and healthy controls presented numerous differentially methylated regions (DMRs) enriched in the areas of vasculature and heart development. A prediction model was built based on the maximal 50 differentially methylated regions (DMRs) with methylation variance for cfDNA from plasma to evaluate the DNA methylation pattern as a biomarker in AD diagnosis. A high sensitivity of 86% and specificity of 75% [Table 1] were achieved with the AUC of 0.96 [Figure 1].[136] The results suggested the potential of cfDNA leveraging informative methylation patterns to be a non-invasive biomarker for screening heritable thoracic aortic disease, predicting disease before the symptoms fully manifest, indicating the clinical characteristics of subtype classification, and then accordingly guiding the timing of intervention, treatment and prognosis management for individual aortopathy.

These results shed light on the value of genetic diagnosis in hereditary connective tissue diseases. The link between genetic variants and various phenotypes might enhance our ability to stratify individuals based on their genetic profile. Although the time-consuming genetic test might not be suitable for the detection of AD in the acute phase,[67] they were very valuable in predicting patients with high risk and were conducive to determining the etiology of AD and differentially diagnosing hereditary diseases associated with AD, which contributed to AD prevention in future generations.

Conclusion

Biomarkers play an important role in the diagnosis and prognosis of multiple diseases. Recent scientific innovations and cutting-edge technologies have provided unprecedented opportunities to detect key factors involved in the pathogenesis and progression of AD, and an increasing number of biomarkers with potential clinical translational value have been identified. There are no ideal biomarkers available for clinical diagnosis or prognostic assessment of AD currently, and there is an urgent need for multicenter, large-sample randomized clinical trials to provide evidence for clinical practice with the aim of monitoring pathological changes in genetically susceptible patients in the pre-disease stage, rapidly confirming or ruling out disease at early onset, predicting disease progression, assessing disease prognosis, and providing personalized treatment strategies for endovascular treatment of AD.

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Conflicts of interest

None.

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