*Minireview*

# Challenges of applying circulating biomarkers for abdominal aortic aneurysm progression

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**Impact statement**

Currently, clinical management of abdominal aortic aneurysm (AAA) relies largely on AAA diameter and growth speed as prognostic parameters. These two parameters cannot sufficiently address a significant number of AAA for which unexpected life-threatening, rapid progression or rupture occurs. In the present review, literature was systematically reviewed in search of circulating biomarkers for AAA expansion. A total of 28 circulating biomarkers with varying prognostic values are summarized and discussed. However, the aforementioned biomarkers cannot be introduced to clinical use yet without large scale trials to verify their prognostic values. The present review summarized a group of potential circulating biomarkers that may predict AAA expansion and warrants further investigation and components analysis for prognostic model establishment.

## Abstract

As a prevalent potentially life-threatening condition, abdominal aortic aneurysm (AAA) presents increasing risk of rupture as its diameter grows. However, rapid progression and rupture may occasionally occur in smaller AAAs. Earlier surgery for patients with high risk of disease progression may improve the outcome. Therefore, more precise indicators for invasive treatment in addition to diameter and abdominal symptoms are demanded. This systematic review aimed to identify potential circulating biomarkers that may predict growth rate of AAA. Cochrane and PubMed library were searched (until August 2020) for researches which reported circulating biomarkers associated with AAA expansion, and 25 papers were included. Twenty-eight identified biomarkers were further classified into five categories (inflammation and oxidative stress, matrix degradation, hematology and lipid metabolism, thrombosis and fibrinolysis, and others), and discussed further with their correlation and regression analysis results. Larger prospective trials are required to establish and evaluate prognostic models with highest values with these markers.

**Keywords:** Abdominal aortic aneurysm, circulating biomarker, expansion, growth

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## Introduction

Abdominal aortic aneurysm (AAA) is a common aortic degenerative disease, and its pathological feature is aortic wall weakening and dilation.[1] Without appropriate treatment, AAA can irreversibly continue to develop and eventually lead to life-threatening rupture. Selective screening, early detection, and elective AAA repair have been implemented to reduce the mortality burden of AAA. Currently, the suggested indications for invasive treatment by surgical or endovascular aortic repair are large diameter (>5 cm in women or >5.5 cm in men).[2] Small, asymptomatic AAA is considered relatively safe from sudden rupture, and recommended close follow-up. However, small AAA diameters do not guarantee safety from progression or rupture, and occasional rupture or rapid growth of small sized AAA which leads to death is not uncommon.[3] Therefore, establishing other predictive biomarkers for aneurysm expansion may identify patients at high risk, indicate early intervention, prevent disease progression, and reduce morbidity and mortality.

Biomarkers may be cell, protein, peptide, gene, or metabolic products associated with clinically relevant biologic events, and biomarkers have been widely applied in disease detection, surveillance and intervention. Although many potential circulating biomarkers for AAA progression were identified with varying evidence level over the decades, few biomarkers were introduced to clinical practice, and more efforts are required to establish models of prognostic biomarkers. This update in a state-of-the-art review presents promising targets for further validation and clinical application, and may help physicians identify

patients at higher risk of disease progression and prompt timely intervention.

## Review of potential circulating biomarkers for AAA expansion

This systematic review observed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines. The Medline (PubMed) and the Cochrane library were searched (until August 2020) for researches which reported circulating biomarkers associated with AAA expansion. The following algorithm was applied: "((abdominal aortic aneurysm [MeSH Terms]) AND (biomarker [MeSH terms])) AND ((size) OR (expansion) OR (progression) OR (growth))". Only clinical studies were considered eligible. The exclusion criteria were: (1) articles on AAA without discussion on disease progression, (2) non-English articles, (3) non-human subjects, (4) reviews, (5) correspondence or editorials. From 281 abstracts on biomarkers and AAA growth, 40 full text unavailable, non-human, or non-English studies were excluded, and the remaining 241 abstracts were screened to include 25 articles on AAA expansion prediction. The included studies were full-text scrutinized, and two independent authors read the included articles, summarized, and cross-checked the related results. The potential biomarkers are classified and listed in Table 1, and the details of study population and statistical significance for each biomarker are summarized in Table 2.

In addition to the reviewed biomarkers which significantly correlated to AAA expansion rate, numerous other circulating biomarkers have been found correlated to AAA diameter, but evaluation with AAA expansion rate is either lacking or non-significant, and such biomarkers were not included in this review. Since AAA diameter is widely applied as predictor of AAA expansion, biomarkers correlating to AAA diameter may be promising markers of AAA progression too. Further evaluations with AAA expansion rates may identify new candidates for prognostic models.

**Table 1.** Classification of 28 reviewed predictive biomarkers for abdominal aortic aneurysm progression.

| Classification | Biomarkers |
|---|---|
| Inflammation and oxidative stress | MPO, TSP-1, APL, CRP, IGF-1, sTWEAK, PRX-1, TRX |
| Aortic wall matrix degradation | MMP-9, CTSB, CTSC, A1-at, tryptase, elastin peptides |
| Hematology and lipid metabolism | NGAL, Hba1c, WBC, TBil, TC, ApoB, HDL-C |
| Thrombosis and fibrinolysis | D-dimer, t-PA, TAT, PAP |
| Other | MicroRNAs, IgA-CP, cotinine |

MPO: myeloperoxidase; TSP-1: thrombospondin-1; APL: antiphospholipid antibodies; CRP: C-reactive protein; IGF-1: insulin-like growth factor 1; sTWEAK: soluble tumor necrosis factor-like inducer of apoptosis; PRX-1: peroxiredoxin-1; TRX: thioredoxin; MMP-9: matrix metalloproteinase-9; CTSB: cystatin B; CTSC: cystatin C; A1-at: $\alpha$1-antitrypsin; NGAL: neutrophil gelatinase-associated lipocalin; Hba1c: glycated hemoglobin; WBC: white blood cell; TBil: total bilirubin; TC: total cholesterol; ApoB: apolipoprotein B; HDL-C: HDL-cholesterol; t-PA: tissue-type plasminogen activator; TAT: tissue-type plasminogen activator; PAP: plasmin–antiplasmin complex; IgA-CP: IgA-antibodies against *Chlamydia pneumoniae*.

## Inflammation and oxidative stress

As well-investigated pathogenetic characteristics, levels of inflammation and oxidative stress may reflect AAA presence and progression. Multiple inflammation and oxidative stress related biomarkers have been investigated in association with AAA progression. C-reactive protein (CRP) is an inflammatory index with a long history of clinical application, widely used as marker for infection, inflammation, trauma, neoplasm, etc. It has been revealed that variation of CRP level significantly correlated with aneurysm expansion rate (OR 3.4, 95% CI 2.1, 5.6) in multivariate age-adjusted logistic model.[7] Insulin-like growth factor 1 (IGF-1) is known as predictive factor and mediator in cardiovascular disease, and serum IGF-1 positively correlated with the diameter of AAA ($r = 0.23$, $P = 0.016$) and its rate of expansion ($r = 0.27$, $P = 0.004$), which remained significant after adjusting for potential confounders.[8] Thrombospondin-1 (TSP-1) is an endogenous inhibitor of angiogenesis which regulates cell proliferation and plays a crucial role in inflammation. TSP-1 modulates vascular smooth muscle cell and fibroblast phenotype and preserves the extracellular matrix by inhibiting matrix metalloproteinase (MMP) activity. Krishna *et al*.[5] reported in a cohort of 276 men with AAA, wherein a negative correlation between AAA progression and serum TSP-1 concentration was revealed by Spearman correlation analysis ($\rho = -0.129$, $P = 0.033$). Antiphospholipid antibodies (APL) are autoimmune antibodies against phospholipids and their cofactors, and are related to atherosclerosis in patients with autoimmune diseases and asymptomatic carriers. Duftner *et al*.[6] reported that APL-positive AAA patients were more likely to present aneurysm expansion compared with APL-negative patients ($P = 0.041$ by Fisher's exact test). In logistic regression analysis adjusting for potential confounding factors such as established risk factors of aneurysm expansion, APL remained positively correlated with AAA growth (OR 9.4, 95% CI 1.0, 86.8, $P = 0.049$). As a type II transmembrane glycoprotein of the tumor necrosis factor superfamily, soluble tumor necrosis factor-like inducer of apoptosis (sTWEAK) circulates in plasma. Negative associations between sTWEAK level and AAA diameter ($r = -0.4$, $P = 0.008$) as well as aneurysm growth rate ($n = 79$, $r = -0.263$, $P = 0.031$) were observed in a five-year cohort. The association between sTWEAK concentrations and aneurysm expansion rate was confirmed independent in multivariate regression analysis ($\beta = -0.208$, $P = 0.046$).[9]

Myeloperoxidase (MPO), mainly expressed in neutrophils, is a major oxidative enzyme from the heme peroxidase family. Memon *et al*.[4] reported in a case–control study which included 133 AAA patients that MPO positively correlated with AAA expansion rate before and after adjusting for baseline aneurysm size in linear regression analysis (adjusted $\beta = 0.22$, $P = 0.013$). In receiver operator characteristic (ROC) analysis, the prognostic value of MPO was promising with a sensitivity of 80% and specificity of 59%, and area under the curve (AUC) was 0.71 (95% CI 0.61, 0.81). Peroxiredoxin-1 (PRX-1) can interact and modulate nicotinamide adenine dinucleotide phosphate activity by inactivating $H_2O_2$. In a cohort of 80 patients on five-year

**Table 2.** Summary of 28 reported circulating predictive biomarkers for abdominal aortic aneurysm progression.

| Biomarker | Study population | Statistical significance | References |
|---|---|---|---|
| Myeloperoxidase | 133 | $\beta = 0.22$, $P = 0.013$ | 4 |
| Thrombospondin-1 | 276 | $\rho = -0.129$, $P = 0.033$ | 5 |
| Antiphospholipid antibodies | 69 | OR 9.4, 95% CI 1.0, 86.8, $P = 0.049$ | 6 |
| C-Reactive protein | 435 | $R = 0.62$; $P = 0.05$ | 7 |
| Insulin-like growth factor 1 | 115 | $R = 0.27$, $P = 0.004$ | 8 |
| Soluble tumor necrosis factor-like inducer of apoptosis | 79 | $R = -0.263$; $P = 0.031$ | 9 |
| | | $\beta = -0.208$; $P = 0.046$ | |
| Peroxiredoxin-1 | 80 | $\rho = 0.3$, $P < 0.05$ | 10 |
| Thioredoxin | 78 | $\rho = 0.25$, $P = 0.027$ | 11 |
| Matrix metalloproteinase-9 | 46 | $R = 0.32$, $P < 0.05$ | 12 |
| | 36 | $R = 0.33$, $P = 0.01$ | 13 |
| Cystatin B | 133 | $\beta = 0.25$, $P = 0.007$ | 4 |
| Cystatin C | 36 | $R = -0.24$, 95%CI $-0.75$, $-0.05$ | 14 |
| $\alpha$1-Antitrypsin | 35 | $R = 0.55$, $P = 0.004$ | 15 |
| | 36 | $R = 0.42$, $P = 0.05$ | 13 |
| Tryptase | 100 | $R = 0.29$, $P = 0.005$ | 16 |
| Elastin peptides | 36 | $R = 0.51$, $P = 0.01$ | 13 |
| Neutrophil gelatinase-associated lipocalin | 40 | $\rho = 0.4$, $P = 0.01$ | 17 |
| Glycated hemoglobin | 319 | $\rho = -0.177$, $P = 0.002$ | 18 |
| White blood cell | 110 | OR 0.697, 95% CI 0.594, 0.800, $P = 0.002$ | 19 |
| Total bilirubin | 110 | OR 0.256, 95% CI 0.156, 0.355, $P < 0.001$ | 19 |
| Total cholesterol | 49 | $R = 0.38$, unadjusted $P = 0.011$ | 20 |
| Apolipoprotein B | 49 | $R = 0.41$, unadjusted $P = 0.005$ | 20 |
| HDL-cholesterol | 122 | $R = -0.18$, $P = 0.07$ | 21 |
| D-dimer | 237 | $\beta = 0.21$, 95% CI 0.09, 0.33 | 22 |
| | 33 | $R = 0.779$, $P < 0.001$ | 23 |
| | 96 | $\beta = 0.38$, 95% CI 0.001, 1.011 | 24 |
| | 299 | $R = 0.39$, $P < 0.001$ | 25 |
| | | $\beta = 0.29$, $P < 0.001$ | |
| Tissue-type plasminogen activator | 133 | $\beta = 0.21$, $P = 0.016$ | 4 |
| | 70 | $\rho = 0.37$, $P = 0.002$ | 26 |
| Thrombin–antithrombin complex | 237 | $\beta = 0.24$, 95% CI 0.19, 0.29 | 22 |
| Plasmin–antiplasmin complex | 96 | OR = 1.01, 95% CI 1.00, 1.02 | 24 |
| IgA-antibodies against *Chlamydia pneumoniae* | 70 | $\rho = 0.29$, $P = 0.006$ | 26 |
| Cotinine | 70 | $\rho = 0.24$, $P = 0.038$ | 26 |

follow-up, PRX-1 concentration significantly correlated with AAA growth rate ($r = 0.3$, $P = 0.01$).[10] PRX-1 concentration was indicative of AAA growth rate in ROC analyses, and its sensitivity and specificity were 63% and 64% at optimal cutoff points. As a crucial intracellular antioxidant enzyme, plasma thioredoxin (TRX) is up-regulated in coronary atherosclerosis patients. In a cohort of 78 patients, TRX significantly correlated to AAA growth rate ($\rho = 0.25$, $P = 0.03$).[11]

## Aortic wall matrix degradation

Aortic extracellular matrix proteolysis results in aortic wall weakening and dilation. MMPs, cysteine, and serine proteases play major roles in extracellular matrix degradation and AAA progression. A number of proteins and metabolites related to aortic wall degradation and remodeling in the serum were found prognostic of AAA progression. Cysteine proteases are associated with aortic wall degradation in AAA pathogenesis, and among them, cathepsin L is associated with vascular remodeling and elevated in patients with AAA. Cystatin B (CSTB) can inhibit cathepsin L. Memon *et al*.[4] found that CSTB is significantly associated with AAA growth rate as continuous variables before and after adjusting with baseline AAA diameter in linear regression analysis ($n = 133$, adjusted $\beta = 0.25$, $P = 0.007$). Tryptase is a serine protease mainly released from mast cells in allergic reaction. Zhang *et al*.[16] reported that in a 100-patient cohort, significant correlations between serum tryptase concentration and AAA annual growth rate were revealed and remained after adjusting for traditional risk factors of AAA ($r = 0.29$, $P = 0.005$). Cystatin C (CTSC) is another inhibitor of cysteine protease. On 4-year-follow-up of 36 male AAA patients, negative correlation between serum CTSC level and annual AAA expansion rate ($r = -0.24$, 95% CI $-0.75$, $-0.05$), and the correlation remained significant after adjusting for smoking, renal function, CRP level, diastolic blood pressure, age, and baseline aneurysm size.[14] MMPs are a group of key components in AAA pathogenesis, and MMP-9 is one of the most extensively studied factors. Circulating MMP-9 level positively correlated with AAA growth rate.[12,13] Human aortic wall contains a large content of elastin, and the amount and structure of elastin are varied in AAA. Therefore, it has been proposed to monitor elastic tissue degradation related pathological processes by measuring circulating elastin peptides. Alpha1antitrypsine ($\alpha$1-AT) is the major systemic elastase inhibitor. Lindholt *et al*.[13] reported in a cohort of 36 male patients that AAA expansion rate positively

correlated to serum elastin peptides ($r = 0.51$, 95% CI 0.20, 0.73), plasma MMP-9 ($r = 0.33$, 95% CI 0.01, 0.53), as well as α1-AT ($r = 0.42$, 95% CI 0.08, 0.67). In a study of 35 AAA patients, α1-AT positively correlated to AAA expansion in linear regression ($r = 0.55$, $P = 0.004$), and significant correlation remained after adjustment for age, sex, and active smoking.[15]

## Hematology and lipid metabolism

Traditional hematological and lipid metabolic parameters were revealed to have certain prognostic values, and these markers have the advantage of broad availability and relatively low additional cost. Kristensen *et al*.[18] evaluated the prognostic role of glycated hemoglobin (HbA1c) in a cohort of 319 patients, and concluded that HbA1c was significantly inversely associated with AAA expansion rate (Spearman $\rho = -0.177$, $P = 0.002$). Adjusted analyses demonstrated attenuated aneurysm expansion in patients with higher HbA1c level. This finding is consistent with establish theory that diabetes mellitus is a protective factor against AAA pathogenesis. However, the application of HbA1c as prognostic marker for AAA progression is limited to a smaller proportion of AAA patients with abnormal glucose metabolism. Vuruşkan *et al*.[19] conducted multivariate logistic regression analysis in 110 AAA patients and revealed that total bilirubin (TBil) level and white blood cells (WBCs) count were independently predictive of AAA rapid growth (>10 mm/y, $P < 0.001$ and $P = 0.002$, respectively). Deeg *et al*.[20] reported that in univariate analysis total cholesterol (TC; $r = 0.38$, unadjusted $P = 0.011$), as well as apolipoprotein B (ApoB; $r = 0.41$, unadjusted $P = 0.005$) were prognostic of aneurysm progression in a group of 49 patients. Burillo *et al*.[21] reported that in multiple linear regression analysis HDL-cholesterol (HDL-C) was an independent predictor of AAA progression ($n = 122$, $P = 0.008$).

Neutrophil gelatinase-associated lipocalin (NGAL) is a neutrophil-derived protein, but during inflammation or injury epithelial cells, hepatocytes and renal tubular cells may also release NGAL. The correlation between NGAL and AAA expansion has been reported with varying results. Ramos-Mozo *et al*.[17] reported positive correlation between NGAL level and AAA expansion rate by Spearman correlation test ($n = 40$, $r = 0.4$, $P = 0.01$) in retrospective study. The correlation remained significant in multivariate linear regression analysis after adjusting for age, sex, current smoking, arterial hypertension, dyslipidemia, heart disease, statin use, and creatinine level. However, analysis of two prospective cohort ($n = 40$ and $n = 100$ respectively) did not yield significant results. Non-significant correlation between plasma NGAL level and AAA growth rate was reported in another smaller cohort of 26 patients ($P = 0.34$).[27] It is suggested that the prognostic value of NGAL is unreliable, and further studies may reveal novel findings.

## Thrombosis and fibrinolysis

Several thrombosis and fibrinolysis-related markers have been associated with AAA growth. D-dimer is a well-studied prognostic maker for AAA growth with promising results. As a marker of the level of fibrin turnover, plasma D-dimer is significantly elevated in AAA, and positively correlated to AAA growth rate.[22–25] In a representative cohort of 299 patient, Golledge *et al*.[25] reported significant positive correlation between annual AAA expansion rate and rank-transformed D-dimer ($r = 0.39$, $P < 0.001$), which remained significant after excluding the effect of baseline AAA diameter. Significant positive association between rank-transformed D-dimer and AAA growth was revealed in multiple linear regression analysis ($\beta = 0.29$, $P < 0.001$). These studies demonstrated that plasma D-dimer may be of key prognosis value of AAA. Sundermann *et al*.[22] demonstrated in a cohort of 237 patients that both D-dimer and thrombin–antithrombin complex (TAT) were significant independent predictors of aneurysm expansion rate in multivariable regression models. Vega de Ceniga *et al*.[24] analyzed AAA growth as a dichotomous variable (AAA growth rate <2 mm/year versus >2 mm/year), and demonstrated weak association between plasmin–antiplasmin complex (PAP) and AAA growth (OR = 1.01, 95% CI 1.00, 1.02). Multiple studies examined tissue-type plasminogen activator (t-PA) and showed significant positive correlation with AAA expansion rate. Lindholt *et al*.[26] reported that in a cohort of 70 patients t-PA positively correlated with AAA annual expansion rate by Spearman's correlation analysis ($\rho = 0.37$, $P = 0.002$). Memon *et al*.[4] reported that linear regression analysis of t-PA levels in 133 AAA patients that t-PA was significantly associated with aneurysm expansion rate before and after adjusting for baseline aneurysm size (adjusted $\beta = 0.21$, $P = 0.016$). It was also significant in ROC curve analysis (AUC 0.62, 95% CI 0.51, 0.73, $P = 0.039$).

## Other

Other identified biomarkers assessed in patients with AAA include IgA-antibodies against *Chlamydia pneumoniae* (IgA-CP), cotinine, and miRNAs. It has been shown that *C. pneumoniae* is associated with atherosclerosis which shares many common pathogenetic characteristics with AAA, and serum antibodies are potential biomarkers of AAA expansion. Lindholt *et al*.[26] reported that in a cohort of 70 patients the annual AAA growth rate positively correlated with IgA-CP level ($\rho = 0.29$, $P = 0.006$) and serum cotinine level ($\rho = 0.23$, $P = 0.038$) by Spearman's correlation analysis. Wanhainen *et al*.[28] screened the levels of 172 circulating microRNAs of 170 AAA patients, and identified 20 differentially expressed microRNAs in rapid growing aneurysms, including miR-335-5p, miR-326, miR-125a-5p, miR-221-3p, miR-99a-5p, etc. Furthermore, diabetes, current smoker, miR-125a-5p, and miR-335-5p levels combined in AUC analysis presented 70% specificity and 80% sensitivity (AUC 0.84, $P < 0.001$).

## Conclusions

Aortic diameter is currently the major predictor of AAA progression and criterion for surgery. However, unexpected rapid growth or rupture may occur in a small proportion

of smaller aneurysms, leading to hemorrhage and death. To help improve current prognosis and intervention indication, we reviewed the literature and summarized 28 potential circulating biomarkers for AAA expansion. These biomarkers presented varying prognostic values, and some of them could be useful candidates in establishing prognostic models of higher prognostic values.

To predict risk of AAA expansion, numerous biomechanical and circulating markers have been studied, and AAA diameter is the most evident and widely accepted. Other image parameters of intraluminal thrombosis, 18F-FDG uptake, aortic wall stress, etc. also presented prognostic significance, and some of them are being considered in clinical practice. Multiple circulating biomarkers, as presented, are also under research to verify their specificity and sensitivity. According to sample size, significant outcomes and quality appraisal of the study, five prognostic markers with the highest potential for AAA growth are: AAA diameter, IgA-SP levels, serum elastin peptides, and 18F-FDG uptake.[29]

It is presumable that circulating biomarkers, unlike imaging and biomechanical markers that directly observe AAA lesion sites, may be easily affected by many factors such as the patients' overall condition, comorbidities, and treatment, and therefore they present certain difficulties with validation and broad application. However, it is also their comprehensiveness in reflecting overall conditions that makes promising predictors of disease progression tendency earlier than anatomical changes. Considering current challenges in applying novel biomarkers for AAA expansion in clinical practice, for example, lack of disease specificity, inability to cover all-cause AAA, an integrated prognostic model combining some of the aforementioned circulating or biomechanical markers may provide better clinical value. Large longitudinal cohort studies should be conducted to evaluate the prognostic value of any established models.

To sum up, this review identified a series of potential circulating biomarkers for the prognosis of AAA progression. Larger prospective trials are required to establish and evaluate prognostic models with highest values. In conclusion, a series of potential circulating biomarkers for AAA expansion have been identified, and may help improve decision making in AAA treatment practices.

## AUTHORS' CONTRIBUTIONS

All authors designed and conducted literature review, analyzed the data and reviewed the manuscript; LY and DY composed the manuscript, and YHZ provided critical reviews on the manuscript.

## DECLARATION OF CONFLICTING INTERESTS

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