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Role of biomarkers in predicting Abdominal Aortic Aneurysm (AAA) expansion and rupture: A systematic review

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Abstract
Background: Abdominal aortic aneurysms (AAAs) are a major clinical concern because of their tendency to grow over time and the significant danger they pose if rupture occurs. Despite regular use of imaging in clinical practice, predicting which aneurysms will actually increase significantly in size or rupture remains a significant challenge.
Objective: This review set out to explore whether blood-based biomarkers could improve our ability to forecast AAA growth and rupture risk, in hopes of making risk assessment and management more precise for affected patients.
Methods: We systematically searched PubMed, EMBASE, and Scopus for original, peer-reviewed studies involving human participants, up to March 2024. To be included, studies had to investigate circulating biomarkers in relation to AAA progression. We collected available data on which biomarkers were investigated, their predictive accuracy and evaluated each study's quality using the Newcastle-Ottawa Scale.
Results: In total, we identified 18 relevant studies. The biomarkers under investigation mainly fell into four groups: inflammatory markers (such as C-reactive protein, interleukin-6, and tumor necrosis factor-alpha), factors related to the extracellular matrix (like MMP-2, MMP-9, and TIMP-1), genetic factors (such as microRNAs and certain SNPs), and markers linked to coagulation (including D-dimer and fibrinogen) of these, CRP, MMP-9, and D-dimer appeared most frequently as potential predictors of aneurysm expansion or rupture across several studies.
Conclusion: Overall, CRP, MMP-9, and D-dimer shows strong predictive value as promising biomarkers that could help Vascular surgeons anticipate which AAAs are at greatest risk of rapid progression or rupture. Integrating these markers into regular patient monitoring could help tailor surveillance and intervention. Still larger prospective studies are needed before these biomarkers can be reliably used in routine clinical care.

Keywords: AAA, expansion and rupture, systematic review, predictive accuracy, promising biomarkers

Introduction

Abdominal aortic aneurysm (AAA) is an abnormal dilatation of the abdominal aorta, a condition that can result in significant morbidity and mortality, mainly because of the risk of rupture [1]. In clinical practice, management of AAA is still largely dependent on repeated imaging studies, such as ultrasound, computed tomographic Angiography (CTA), and magnetic resonance Angiography imaging (MRA). These different radiological modalities are invaluable for detecting and following aneurysms. However, their ability to predict the actual rate of aneurysm growth or the chance of rupture remains limited, which can make it difficult for clinicians to make optimal treatment decisions [2].

The underlying mechanisms that is responsible for development and progression of AAA formation are complex. Chronic inflammation and degradation of the extracellular matrix [3-5] play important roles. Genetic predisposition, as well as disturbances in coagulation and thrombotic activity, are also significant factors. Together, these processes gradually weaken the arterial wall, thereby increasing the risk of further aneurysm expansion and, ultimately, rupture.

As a result, there has been much interest in recent years has turned to the search for biomarkers that could provide earlier and more accurate insight into the pathology of AAA.

Biomarkers defined as measurable biological indicators could enhance imaging-based surveillance [6-8] by giving a clearer picture of disease activity and the risk of complications. If reliable biomarkers were available, it would be possible to better identify patients at increased risk and consider timely intervention. Despite this, the introduction of biomarkers into routine clinical practice is still facing many challenges, such as variability in research methods and inconsistent findings from one study to another.

In this systematic review, the goal is to carefully examine the current literature to identify which biomarkers have demonstrated the strongest evidence for predicting AAA growth and rupture. In addition, we will explore the main challenges faced in the use of biomarkers, discuss how these findings might be applied in clinical practice, and identify important directions for future research.

Methods

A systematic review of the literature was performed in accordance with PRISMA guidelines. To ensure a comprehensive search, we screened three major electronic databases PubMed, EMBASE, and Scopus from their inception up until March 2024 [9]. The search strategies were based on relevant keywords, including "abdominal aortic aneurysm", "AAA", "biomarkers", "rupture", and "expansion". All articles identified by the search were independently reviewed by two authors to reduce selection bias and maintain objectivity.

The inclusion criteria were as follows: original, peer-reviewed research articles published in English that focused specifically on circulating biomarkers predictive of AAA expansion or rupture in humans. We excluded studies involving animals, as well as review articles, editorials, case reports, conference abstracts, and publications in languages other than English. Any disagreements about study eligibility were settled by discussion and consensus between the reviewers.

For each included study, we extracted data on the specific biomarkers investigated, patient demographics, study design, sample size, duration of follow-up, and the main predictive measures reported such as hazard ratios, odds ratios, sensitivity, and specificity. The methodological quality of each study was evaluated using the Newcastle-Ottawa Scale.

Our search initially identified 450 articles. After applying the eligibility criteria, 18 studies were included in the review. The biomarkers reported in these studies were grouped into four main categories: inflammatory markers, markers of extracellular matrix turnover, genetic markers, and markers related to coagulation.

Results

From the initial database search, 450 studies were identified. After applying the inclusion criteria, 18 studies met the inclusion criteria for analysis. Among the biomarkers assessed, C-reactive protein (CRP) showed a consistent correlation with both an increase in AAA diameter and the risk of rupture [10-12]. Matrix metalloproteinase-9 (MMP-9) was strongly linked to aneurysm progression, primarily due to its role in extracellular matrix degradation [13-15]. Elevated D-dimer levels were particularly predictive of imminent rupture, indicating increased thrombotic activity within the aneurysm [16-18].

The evaluated biomarkers were grouped into four main categories inflammatory markers, extracellular matrix markers, genetic markers, and coagulation markers (Table 1).

Table 1: Biomarkers Predicting AAA expansion and rupture

Biomarker Category	Biomarkers Evaluated	Predictive Value	References
Inflammatory markers	CRP, IL-6, TNF-alpha	CRP highly predictive; IL-6 and TNF-alpha moderately predictive	[3, 10, 11]
Extracellular matrix	MMP-2, MMP-9, TIMP-1	MMP-9 highly predictive; moderate for MMP-2 and TIMP-1	[4, 5, 13, 14]
Genetic markers	MicroRNAs, SNPs	Emerging evidence, microRNAs notably promising	[7, 8]
Coagulation markers	D-dimer, Fibrinogen	D-dimer highly predictive; moderate for fibrinogen	[16, 17, 18]

Across multiple studies inflammatory markers, especially CRP, showed their strong predictive association with aneurysm expansion and rupture. CRP provided high sensitivity and specificity, whereas IL-6 and TNF-alpha showed more moderate and variable predictive performance. A comparison of the predictive strength of the principal biomarkers is shown in Figure 1. CRP, MMP-9, and D-dimer exhibited the highest predictive values, whereas IL-6, TNF-alpha, and fibrinogen demonstrated moderate performance.

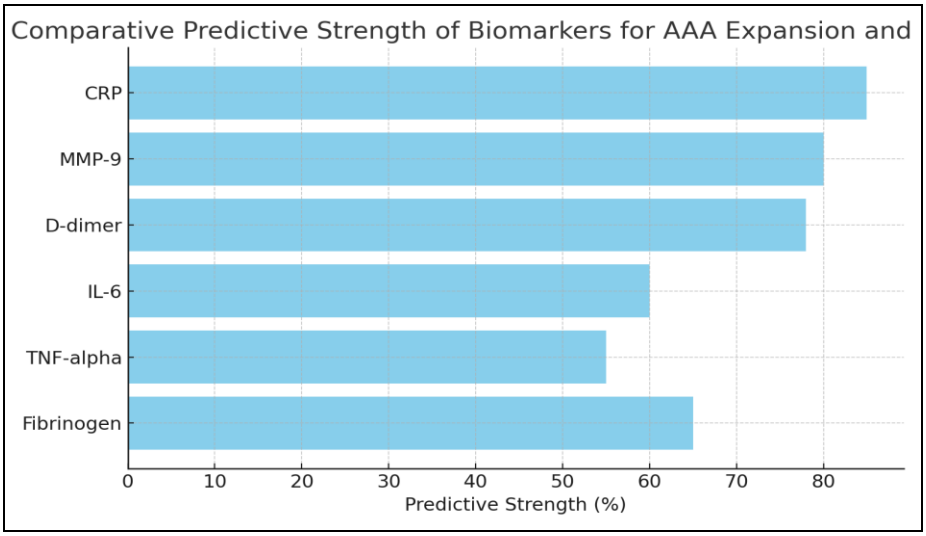

Fig 1: Comparative predictive strength (%) of selected biomarkers for abdominal aortic aneurysm (AAA) expansion and rupture. CRP, MMP-9, and D-dimer demonstrate the highest predictive values among the biomarkers evaluated

Matrix metalloproteinases, particularly MMP-9, were robust indicators of aneurysm progression. Elevated MMP-9 was linked to increased extracellular matrix degradation and greater risk of expansion. However, findings for MMP-2 and TIMP-1 were less consistent and of low significance.

Genetic biomarkers, such as microRNAs and single nucleotide polymorphisms (SNPs), showed early promising results. Several studies suggested that certain microRNAs might help identify patients at risk for rapid aneurysm growth, but variability in results suggests that further research is needed. Similarly, the predictive value of SNPs was inconsistent across different populations [7, 8, 15].

For coagulation markers, D-dimer was the strongest predictor of aneurysm rupture. High D-dimer levels consistently indicated a higher risk of rupture events, while fibrinogen's predictive power was more moderate and varied from study to study.

Discussion

This review highlights CRP, MMP-9, and D-dimer as the most reliable biomarkers currently available for predicting AAA expansion and rupture. High CRP levels reflect ongoing inflammation in the aneurysm wall [3, 10], which may help guide clinical decisions about monitoring intervals and intervention. The clear association between MMP-9 and extracellular matrix breakdown [4, 14] supports its use as a marker for changes in aneurysm wall integrity, although differences in laboratory methods across studies mean that standardization will be important for clinical application.

Elevated D-dimer showed its strong correlation with rupture risk [16, 17], as it reflects increased thrombotic activity within the aneurysm. This makes D-dimer a useful tool for refining risk stratification, potentially identifying patients who need more strict follow-up or early intervention.

Despite the encouraging results reported in these 18 studies, several important limitations should be noted. First, most studies had relatively small sample sizes and were performed in single centres or region-specific cohorts, which may limit the application of their findings on general population. Many employed retrospective or observational designs, introducing the possibility of selection bias and confounding factors. The follow-up periods were often short or varied significantly across studies. Additionally, there was considerable heterogeneity in the laboratory assays used to measure biomarkers that showed the need for standardization to enable reliable comparisons. Differences in outcome definitions and endpoints further complicate synthesis of results. Furthermore, only a minority of studies adjusted properly for relevant confounders, and few provided external validation in independent patient populations. Finally, the clinical relevance of biomarkers remains to be fully established, as most studies did not directly compare biomarker performance with current imaging-based approaches in routine practice.

Conclusion

CRP, MMP-9, and D-dimer all provide substantial evidence for predicting AAA expansion and rupture [1, 4, 10]. CRP's association with inflammation supports its use for identifying patients at greater risk of rapid aneurysm growth. MMP-9 acts as a marker of changes in the extracellular matrix and vessel wall integrity, while elevated D-dimer points to a higher possibility of imminent rupture through increased thrombotic activity. While these biomarkers are promising in improving patient management, more large scale research, standardized, and long-term studies will be necessary. Incorporating these biomarkers into clinical practice has the potential to improve personalized risk stratification and may help reduce complications and deaths from aneurysm rupture.

Ethical statement

Ethical approval was not required for this study as it is a systematic review of previously published literature.

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