AI-powered assessment of biomarkers for growth prediction of abdominal aortic aneurysms

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ABSTRACT

Objective: The purpose of this study was to employ biomechanics-based biomarkers to locally characterize abdominal aortic aneurysm (AAA) tissue and investigate their relation to local aortic growth by means of an artificial intelligence model.

Methods: The study focused on a population of 36 patients with AAAs undergoing serial monitoring with electrocardiogram-gated multiphase computed tomography angiography acquisitions. The geometries of the aortic lumen and wall were reconstructed from the baseline scans and used for the baseline assessment of regional aortic weakness with three functional biomarkers, time-averaged wall-shear stress, in vivo principal strain, and intra-luminal thrombus thickness. The biomarkers were encoded as regional averages on axial and circumferential sections perpendicularly to the aortic centerline. Local diametric growth was obtained as difference in diameter between baseline and follow-up at the level of each axial section. An artificial intelligence model was developed to predict accelerated aneurysmal growth with the Extra Trees algorithm used as a binary classifier where the positive class represented regions that grew more than 2.5 mm/year. Additional clinical biomarkers, such as maximum aortic diameter at baseline, were also investigated as predictors of growth.

Results: The area under the curve for the constructed receiver operating characteristic curve for the Extra Trees classifier showed a very good performance in predicting relevant aortic growth (area under the curve = 0.92), with the three biomechanics-based functional biomarkers being objectively selected as the main predictors of growth.

Conclusions: The use of features based on the functional and local characterization of the aortic tissue resulted in a superior performance in terms of growth prediction when compared with models based on geometrical assessments. With rapid growth linked to increasing risk for patients with AAAs, the ability to access functional information related to tissue weakening and disease progression at baseline has the potential to support early clinical decisions and improve disease management. (JVS—Vascular Science 2023;4:100119.)

Clinical Relevance: Disease progression and tissue weakening in AAAs are complex and multifactorial processes linked to rapid growth and increased risk of adverse clinical outcomes. Serial monitoring is key in the management of AAAs and can be improved by accessing functional information at baseline to predict rapid growth in individual patients.

Keywords: Abdominal aortic aneurysms; Artificial intelligence; Computational fluid dynamics; Growth; In vivo strain; Thrombus

Current clinical practice relies on the monitoring of an abdominal aortic aneurysm (AAA) size and growth, with surgical intervention recommended when complications arise or a threshold size is reached. This approach has proven limitations, with rupture occurring in small aneurysms and larger aneurysms undergoing repair at an advanced stage of disease likely to result in poorer clinical outcomes.[1,2] From a structural point of view, disease progression and aortic wall weakening are associated with rapid growth and increased risk of rupture.[3,4] Therefore, accurate estimate of aortic weakening could help identifying risk for rapid growth in individual aortas

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providing an essential tool to improve risk stratification and disease management.

Given the multifactorial nature of AAA progression, a multifactorial assessment linked to the local AAA pathophysiology is essential to improve the current standard of care. In this regard, biomechanics-based approaches have shown potential in the functional characterization of individual aortas and the estimate of aortic wall weakening.[5-8] Specifically, the role of disturbed hemodynamics (ie, low wall-shear stress) and thick intraluminal thrombus (ILT) has been investigated, showing association with disease progression and aortic expansion.[9-11] Similarly, from a structural perspective, the assessment of local wall deformability can provide an insight into the regional weakening of the aortic wall, with elevated strain potentially suggesting a weaker tissue.[12]

The present study proposes the use of an artificial intelligence (AI) model to investigate a compound measure, the Regional Aortic Weakness (RAW) (patent WO2021059243A1),[7] as a surrogate of aortic weakening and its relation to local aortic growth for a population of patients with AAAs under serial monitoring.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** The characterization of aortic tissue by means of biomechanics-based biomarkers showed very good performance (area under the curve = 0.92) in the artificial intelligence-based prediction of faster than average growth for 36 patients with abdominal aortic aneurysms under serial monitoring. The biomechanics-based biomarkers of aortic weakening were found to be critical features contributing to local growth.
- **Take Home Message:** The ability to access functional information related to aortic weakening and disease progression at baseline and evaluate the tendency to grow for individual aortas has the potential to benefit patient monitoring and enable precision-based aortic care.

METHODS

Study population and region of interest. The research protocol for this single center retrospective study was approved by the University of Calgary Conjoint Health Research Ethics Board (CHREB - Ethics ID #REB21-0043). The subject of the study was a population of patients with AAAs (age 18+ year old, no known genetic abnormalities) who were monitored with at least two electrocardiogram (ECG)-gated multiphase computed tomography angiography (CTA) acquisitions (image resolution, 0.7 × 0.7 × 2.0 mm) during a minimum surveillance time of 8 months between 2016 and 2021. A total of 36 patients met the inclusion criteria of the study protocol.

The region of interest for the analysis was defined as the abdominal aorta, specifically from below the celiac artery to the common iliac bifurcation, which were used as landmarks to ensure evaluation of the same portion of the artery at baseline and follow-up. The aortic wall and lumen for each patient were segmented semi-automatically[13] from both the baseline and follow-up CTAs, and the 3D geometry of both structures was extracted as a triangulated surface mesh by using the imaging software Simpleware ScanIP (Synopsys).

Baseline analysis of aortic weakness: a compound measure. The aortic wall and lumen geometries obtained from the baseline scan were used for the baseline assessment of aortic weakness with three biomarkers, the time-averaged wall-shear stress (TAWSS), the in vivo principal strain, and the ILT thickness.

Specifically, the geometry of the aortic lumen was discretized into tetrahedral elements and used as computational domain for computational fluid dynamic (CFD) simulations of blood flow performed in Fluent (Ansys) by using the SIMPLE algorithm as described in detail in a previous publication.[7] The blood was modeled as an incompressible Newtonian fluid with constant density, whereas the aortic wall (blood interface) was assumed to be rigid (no slip condition). From the simulation of a full cardiac cycle, the TAWSS was obtained as a quantifier of disturbed flow patterns (low TAWSS).[7]

The reconstructed geometry of the aortic wall was used to estimate in vivo aortic strain from ECG-gated multiphase CTA images with in-house ViTAA software. The triangular surface mesh of the aortic wall served as 3D feature-tracking model to measure nodal displacements on successive images throughout the cardiac cycle by means of an optical-flow algorithm.[7,14] The in vivo strain was obtained directly from the nodal displacements of the mesh model and did not require any modeling assumptions (ie, constitutive model for the aortic wall or ILT).

Finally, the aortic wall surface mesh was used in combination with the lumen surface mesh to measure the ILT thickness, defined as the local distance between the two geometries.

The workflow of the study methods is shown in Fig 1.

AI-based growth prediction. An AI model was developed to predict accelerated aneurysmal growth, defined as higher than 2.5 mm/year based on average aortic growth,[15] using the patients' baseline and first follow-up scans. Data preparation involved registering each patient's abdominal aorta acquired at baseline to the follow-up acquisition. The surface mesh defining each aorta was then subdivided in 96 patches (12 axial sections and 8 circumferential sections perpendicularly to the

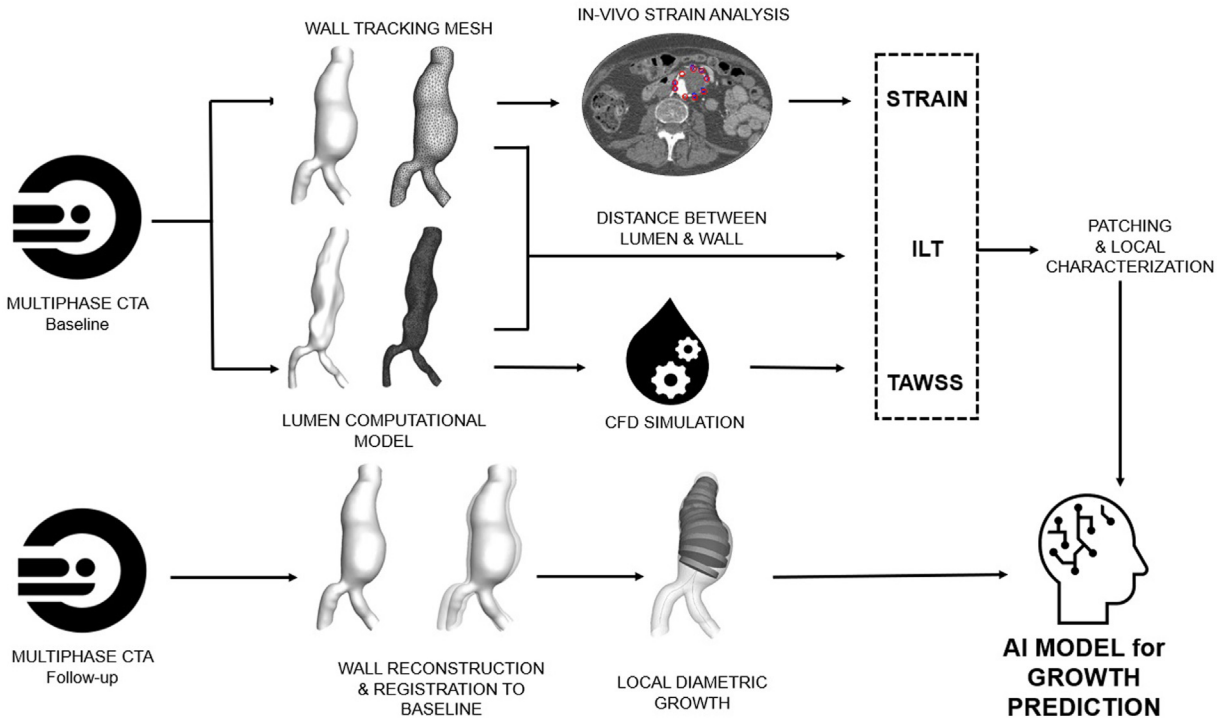

Fig 1. Workflow of the study methodology. *AI*, Artificial intelligence; *CFD*, computational fluid dynamics; *CTA*, computed tomography angiography; *ILT*, intraluminal thrombus; *TAWSS*, time-averaged wall-shear stress.

aortic centerline), where the three obtained biomarkers, or RAW components, (TAWSS, strain, and ILT) were encoded as a regional (patch) average to achieve a local characterization (Fig 2). The local diametric growth was calculated as difference in diameter at the level of each axial section (Fig 3) following registration.

Over the 36 patients (3456 patches), 3147 patches were used for AI modeling, whereas 309 patches, randomly distributed among the patients, were excluded due to quality check failures in the diametric growth calculator, usually occurring near the aortic bifurcation into the iliac arteries. The Extra Trees algorithm was used as a binary classifier, where the positive class represented patches that grew more than 2.5 mm/year.[16] Prior to training the algorithm, Boruta feature selection was used to select relevant features.[17] A stratified 70%/30% train/test dataset split at the patient level (25 patients used for training and 11 patients for testing) was implemented to evaluate the performance of the algorithm.[18] The training and inference were done at the patch level within each patient, with the train/test split based on random sampling of the patients. A 10-fold cross-validation was performed on the training set, whereas the 30% leave out set was used as a pure validation set. As such, a patient's patch samples were not permitted from being in both training and testing sets to avoid label leakage.[19] The training dataset was used to train the Extra Trees model, and the test dataset was used to evaluate its performance in terms of receiver operating characteristic (ROC) area under the curve (AUC).[20] All analyses were conducted using Python programming language and the scikit-learn library.[21]

Additional biomarkers derived from clinical and demographic information, such as maximum aortic diameter at baseline, age, biological sex, weight, height, family history of AAA, smoking history, heart disease, hypertension, chronic obstructive pulmonary disease, and diabetes mellitus were also investigated as predictors of growth.

RESULTS

The AAA study population (n = 36; mean age, 77 ± 7 years; 89% males) presented a mean maximum aortic diameter at baseline of 47.2 ± 5.7 mm and a median surveillance time between CT scans of 12 months (range, 8-31 months). Patients' demographic and clinical information are summarized in Table.

Of the total 3147 patches, evaluated according to local diametric growth, 728 patches (23%) showed accelerated growth above the relevant threshold at the follow-up assessment. The maximum growth rate for individual aortas occurred at the location of maximum baseline diameter in only two patients (6%).

Patients with a larger baseline maximum diameter (≥50 mm) did not demonstrate significant difference in terms of local diametric growth, regional ILT thickness, or regional strain when compared with the patients

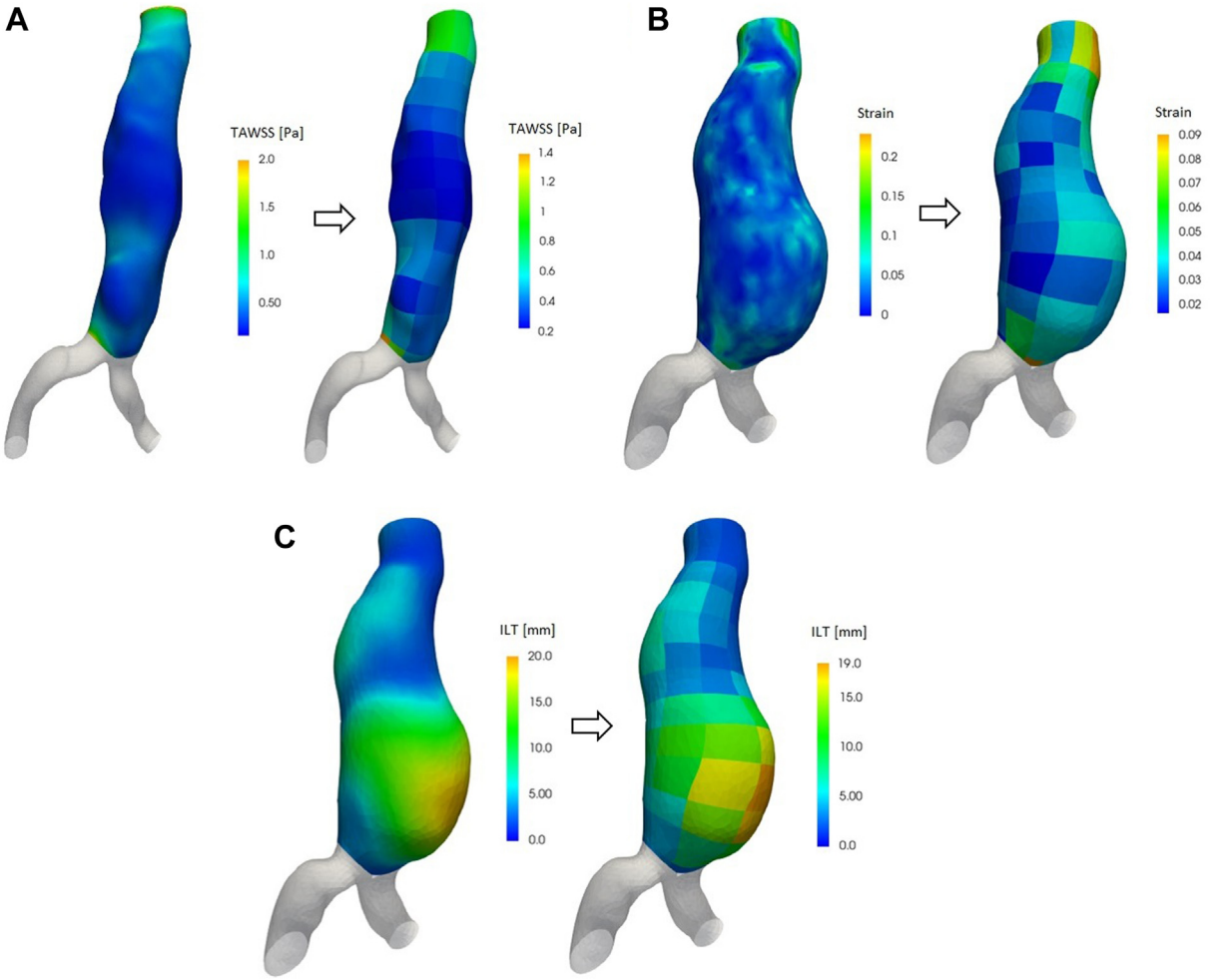

Fig 2. Distribution of the time-averaged wall-shear stress (*TAWSS*) on the lumen surface **(A)** and distribution of the strain **(B)** and intraluminal thrombus (*ILT*) **(C)** on the wall surface for a case example. Each panel shows the nodal distribution of the variable on the left and the patch-based encoding for local characterization on the right.

with a smaller baseline maximum diameter (<50 mm). A significant difference between the two subsets was found for the TAWSS, with patients with larger baseline maximum diameter showing significantly lower regional TAWSS (mean regional TAWSS, 0.59 ± 0.37 Pa vs 0.78 ± 0.48 Pa; $P < .001$).

Among the patients in the smaller baseline maximum diameter subset, patients with faster diametric growth (> median of the maximum per patient annual growth rates) showed significantly higher regional ILT thickness (mean regional ILT, 4.87 ± 3.37 mm vs 3.71 ± 2.77 mm; $P < .001$) and significantly lower regional TAWSS (mean regional TAWSS, 0.49 ± 0.38 Pa vs 0.83 ± 0.48 Pa; $P < .001$). Among the patients in the larger baseline maximum diameter subset, on the other hand, patients with faster diametric growth (> median of the maximum per patient annual growth rates) showed significantly higher regional ILT thickness (mean regional ILT, 5.31 ± 3.57 mm vs 4.96 ± 3.62 mm; $P < .001$), whereas no significant differences were found for the regional strain and TAWSS.

The AUC for the constructed ROC curve for the Extra Trees classifier was statistically greater than 0.5 (AUC = 0.92, with micro and macro AUC equal to 0.94 and 0.92, respectively) (Fig 4), showing a good performance of the model in predicting relevant aortic growth.

Shapley Additive exPlanations (SHAP) dependence plots are presented to shows the contribution and importance of the explored biomarkers to the growth prediction (Fig 5 and 6).[22] The three biomechanics-based biomarkers, or component of the RAW index (ie, TAWSS, strain, and ILT)[7] were found to be critical features contributing to local growth, with the TAWSS playing the most important role in the model prediction. The additional clinical biomarkers were found to have a lesser effect on the growth prediction.

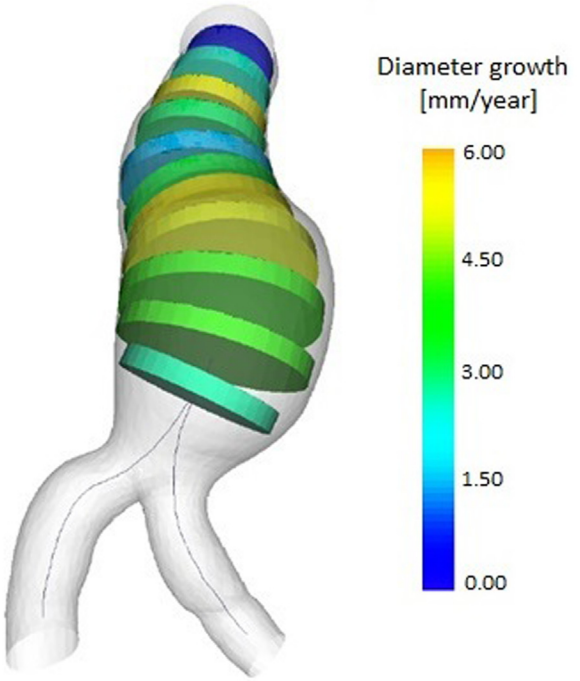

Fig 3. Example of regional growth assessed as a measure of local diameter change, determined by registering the reconstructed geometries at baseline and follow-up scan and comparing the diameters at multiple sections perpendicular to the aortic centerline. The aortic centerline is shown as a black line along the length of the aorta.

DISCUSSION

The present work focused on AI-based faster than average growth prediction for a retrospective population of patients with AAAs under serial monitoring. Faster than average aortic growth has been demonstrated in multiple previous studies to contribute to negative clinical events including aortic rupture and can be used as a surrogate marker for aortic risk.[3,4] A combined in vivo fluid dynamics and strain analysis approach was used to derive a compound measure of RAW from ECG-gated multiphase CTA baseline scans and characterize individual aortas on a regional level. The present approach for faster than average growth prediction integrates multiple functional biomarkers with the ability to capture the multifactorial and local nature of AAA pathophysiology. Each biomarker involved in the compound measure, along with clinical biomarkers, was used as feature to train and test an AI model for the prediction of local diametric growth based on the Extra Trees Classifier algorithm. Other tree-based approaches, such as Random Forest, were also assessed and resulted in good performance; the Extra Trees Classifier was the top performing classifier. Neural network-based approaches performed poorly, which is not uncommon for tabular datasets; similarly logistic regression showed poorer performance (AUC = 0.77).

Table. Clinical and demographic information for the study population

Variable	Patients (n = 36)
Male	32 (89)
AAA family history	2 (6)
Smoking	27 (75)
Heart disease	16 (44)
HTN	8 (22)
COPD	19 (53)
DM	9 (25)
Max diameter ≥50 mm	11 (30)

COPD, Chronic obstructive pulmonary disease; *DM*, diabetes mellitus; *HTN*, hypertension.
Data are presented as number (%).

The performance of the Extra Trees Classifier, assessed with a ROC curve and SHAP dependence plots, showed that the in vivo functional and local characterization of the aortic tissue provides predictive information in terms of local aortic growth, with the three critical biomarkers being objectively selected as the main predictors of faster than average growth.

The TAWSS was selected as the most important feature in the model prediction, followed by the ILT and the strain. Shear stresses are known to have an essential role in regulating the physiology and pathophysiology of the endothelium with effects on vascular function. Literature on AAAs has consistently implicated low TAWSS as a driver of aortic expansion and rupture, as well as ILT deposition.[7,9,23] In the context of mechano-sensing and mechano-transduction, the wall-shear stress represents the signal to which the endothelial cells and the aortic tissue respond and adapt in the long term. Therefore, this biomarker carries a high predictive power in terms of aortic weakening and faster than average growth prediction, as confirmed by its major contribution to the present model. Similarly, the presence and amount of ILT has been associated with increased local inflammation and hypoxia affecting the structural integrity of the tissue, which in turn promotes weakening and disease progression.[11,24,25] A relationship between ILT and aortic aneurysm rupture location has also been demonstrated.[26] Although the TAWSS and ILT seem to intuitively have more predictive power due to their effect on the remodeling of the aortic tissue, the in vivo strain can inform directly on the actual state of structural degradation as it reflects the local deformation of the wall. An elevated strain can be indicative of structural weakening when it is not caused by a direct action of the blood impinging on the aortic wall, which would also result in elevated local TAWSS. For this reason, the combined approach provides a functional and local characterization of the aortic tissue, with all three biomechanics biomarkers contributing to growth prediction.

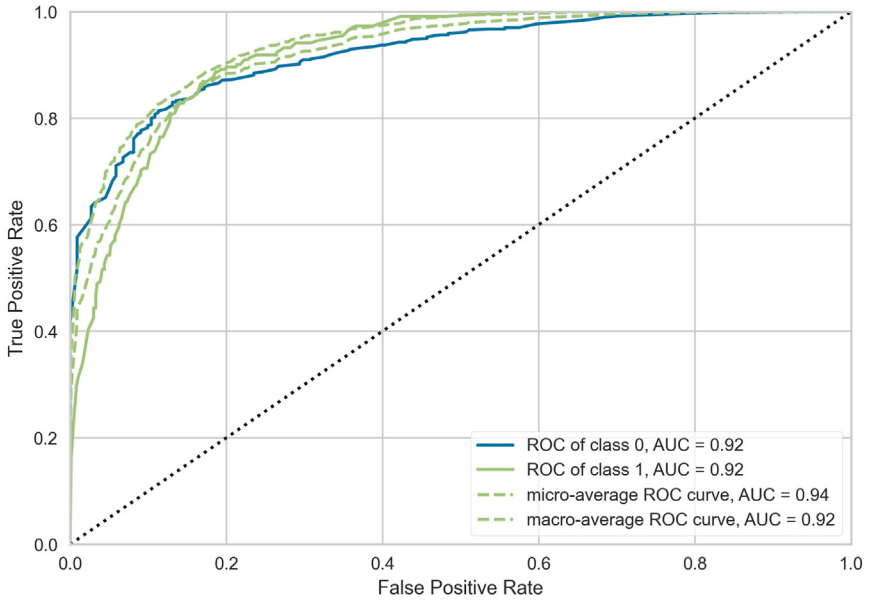

Fig 4. Receiver operating characteristic (*ROC*) curves for the Extra Trees Classifier with reported area under the curve (*AUC*). The Extra Trees algorithm was used as a binary classifier where the positive class represented patches with diameter growth ≥2.5 mm/year. A Boruta feature selection was used to select relevant features.

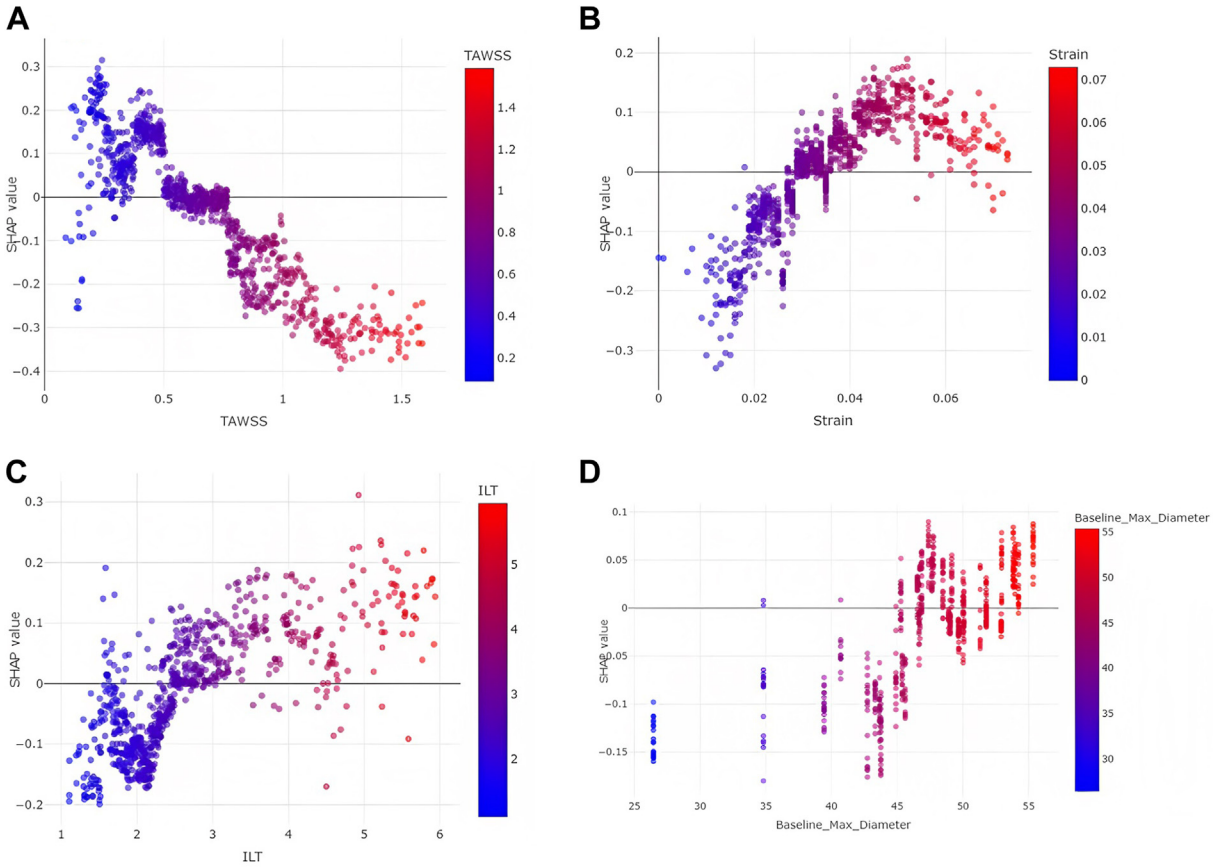

Fig 5. Shapley Additive exPlanations (*SHAP*) dependence plots showing the effect of each of the biomechanics-based biomarkers on the growth prediction. Time-averaged wall-shear stress (*TAWSS*) **(A)**, strain **(B),** and intraluminal thrombus (*ILT*) **(C),** and the maximum aortic diameter at baseline **(D)**.

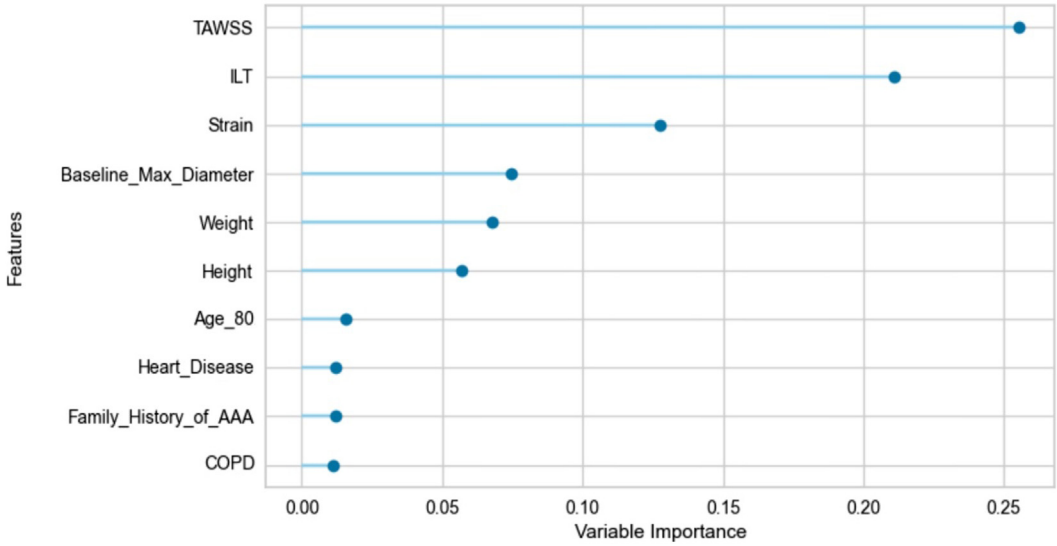

Fig 6. Shapley Additive exPlanations (*SHAP*) summary plot showing the importance of all the features contributing to the model prediction. *AAA*, Abdominal aortic aneurysm; *COPD*, chronic obstructive pulmonary disease; *ILT*, intraluminal thrombus; *TAWSS*, time-avereaged wall-shear stress.

The use of features based on the functional and local characterization of the aortic tissue resulted in a superior performance in terms of faster than average growth prediction when compared with models mostly based on geometrical assessments.[27-29] The morphology and morphological changes in the aorta play a role in disease progression, but they fail to fully characterize the aortic tissue from a functional perspective and to account for the local processes and high level of heterogeneity in the aortic tissue. This aspect is further highlighted by the finding that maximum growth rates occurred at the location of maximum baseline diameter in only two cases, showing the importance of assessing individual aortas at the local level to fully characterize the aortic tissue and its localized weakening. Aortic geometry and biomechanics are strictly connected; for example, a larger maximum aortic diameter may contribute to a higher level of stress in the aorta and a more disturbed blood flow. However, only a local biomechanical assessment can inform on the actual state of weakening and, therefore, propensity for faster than average growth, of each individual aorta. Additionally, the current biomechanical approach presents the advantage of the in vivo strain estimate being free from assumptions on the mechanical behavior of the aortic tissue and ILT that was required for prior models using finite element analysis. This limitation has affected biomechanics-based indices of aortic growth and/or rupture in the past, hindering their performance, which was often reported as providing little to no added value to geometric assessment.[28-30]

The objective of the study was to explore the ability of the present method to predict growth and AAA evolution within 1 year given the common clinical practice of follow-up scans at 6 months to 1 year. Future work will focus on expanding the investigation and growth prediction over a longer surveillance period. Additionally, future research efforts will aim at achieving a generalized applicability of the presented methodology to different imaging modalities and imaging protocols currently adopted for the clinical monitoring of AAAs.

The described methodology relies on a patching system with multiple patches defined for each axial section and diametric growth measurement. This aspect would raise an issue of nonindependent measures when looking at associations between local variables and local growth. The present work, however, focused on developing a predictive model and making predictions in new patients. Although these correlations among observations may make predictions optimistic in the training sample, the reported AUC refers to the performance of the model in predicting faster than average growth in a randomly sampled group of test patients that were not included in the training sample.

The interpretation of this work should take into consideration the limitations. The study population was small, especially in the context of training and testing of AI models and was based on a single-center cohort. The local diameter growth assessment was not significantly affected by interobserver variability in image segmentation but was limited by the image resolution likely to affect the estimate of growth rates. The use of rigid wall assumption for CFD simulations was chosen to resolve the main flow features in the context of highly heterogeneous material properties for the aortic wall

and ILT.[31] Nonetheless the use of a rigid wall assumption is a limitation to the current methods. Finally, although the retrospective nature of the study presents a potential for bias in patients' selection, the definition of the study cohort and the assessment of each baseline scan was performed without any prior knowledge of aortic growth or clinical outcomes. Due to the retrospective nature of the study, there was limited access to clinical and demographic data: information on smoking history was limited and did not allow for a subcategorization of the study population (ie, active vs former smokers), pharmacological data (eg, use of antiplatelets or statins), and data regarding race/ethnicity of the patients were not collected.

CONCLUSIONS

The present characterization of aortic tissue by means of biomechanics-based biomarkers showed very good performance in the AI-based prediction of faster than average growth for a population of patients with AAAs under serial monitoring. The current approach provides functional insight into the multifactorial essence of AAA pathophysiology and accounts for its local and heterogeneous nature. The functional biomarkers were objectively selected as the main contributors to relevant aortic growth.

With continuous and rapid growth linked to increasing risk for patients with AAAs, access to information on disease progression becomes essential for improved disease management. The ability to access functional information related to tissue weakening and disease progression at baseline for individual aortas has the potential to benefit patient monitoring, risk stratification, and treatment selection, and to optimize precision-based aortic care.

AUTHOR CONTRIBUTIONS

Conception and design: MB, RM, EDM
Analysis and interpretation: AF, MB, PF
Data collection: AF, RB
Writing the article: AF
Critical revision of the article: AF, RB, MB, PF, RM, EDM
Final approval of the article: AF, RB, MB, PF, RM, EDM
Statistical analysis: MB, PF
Obtained funding: MB, EDM
Overall responsibility: EDM

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