



Current state-of-the-art and utilities of machine learning for detection, monitoring, growth prediction, rupture risk assessment, and post-surgical management of abdominal aortic aneurysms

Seungik Baek^{a,*}, Amirhossein Arzani^b

^a Department of Mechanical Engineering, Michigan State University, 2555 Engineering Building, East Lansing, MI 48824, USA

^b Department of Mechanical Engineering, Northern Arizona University, 15600 S. McConnell Dr. NAU bldg. 69, Flagstaff, AZ 86001, USA

ARTICLE INFO

Keywords:

Data-driven approaches
EVAR
Circulating biomarkers
Pulse wave imaging
Physics-based machine learning
Digital twin

ABSTRACT

Ultrasound imaging has long been playing a central role in detecting abdominal aortic aneurysms (AAAs). With a recent trend of reducing prevalence of AAAs, ultrasound screening is only recommended for men aged 65 to 75 years with previous smoking history, and a national level of a screening program for women is currently not recommended in the US. In the 2000s, several research groups demonstrated the utility of finite element stress analysis using patient-specific images, which was promising for an accurate assessment of the rupture risk, but physical models remain to be enhanced by considering patient variability and multi-physical characteristics. This review aims to provide a survey of emerging and alternative technologies and new methodologies, such as personalized medicine and data-driven approaches, that may make potential breakthroughs on detection of small AAAs, monitoring of patients during the follow-ups, prediction of AAA growth, assessment of the rupture risk, and post-surgical prognosis for AAA patient management.

1. Introduction

Abdominal aortic aneurysm (AAA) disease is one of the leading causes of death and several countries have national screening programs to help reduce deaths from AAAs and overall health cost (Jacomelli et al., 2016; Guirguis-Blake et al., 2019). In AAA screening programs, patient's aortic diameter is measured by ultrasound imaging and an AAA is diagnosed when its size is at least 3.3 cm. Once the patient is diagnosed, an individual is generally followed by surveillance scan with a duration of 3–12 months depending on the size of the maximum diameter. Surgical operations are then recommended when the maximum diameter is larger than 5.5 cm (Jacomelli et al., 2016). Although the criterion of maximum diameter 5.5 cm is commonly used to determine the surgical time, in the 2000s, several researchers suggested that the use of the finite element (FE) method in noninvasive assessment of AAA rupture risk is superior to that of maximum diameter criterion (Fillinger et al., 2003; Raghavan and Vorp, 2000; Wang et al., 2002; Bluetein et al., 2009; Doyle et al., 2009).

While those national screening programs have been beneficial to detecting patients early, during the last decade its prevalence has been decreased, partly due to reduced smoking, and there have been

challenges in expanding the national level of the screening program with ultrasonography (Owens et al., 2019; Sprynger et al., 2019; Watson et al., 2020). The current ultrasound screening also has drawbacks (Wilmink et al., 2002; Litmanovich et al., 2009) and deterministic models of mechanical stress analyses have some limitations (Conlisk et al., 2016; Polzer et al., 2021; Attarian et al., 2019). Many AAAs exhibit a nonlinear growth and their growth patterns are patient-specific and the prediction of AAA growth is challenging (Vega de Céniga et al., 2006; Kurvers et al., 2004). Specific biomechanical and biological factors influence the disease progression and local weakening (Golledge et al., 2007; Basalyga et al., 2004). Meanwhile, over the past decade, there has been a considerable shift in research direction, fueled by advanced mechanobiology, personalized medicine, and digital evolution, which provide a powerful complement to traditional ways of ultrasound screen/follow-up imaging. Biomechanical models offer an enhanced assessment of disease stage classification, growth prediction, and clinical decision-making for AAA patient management.

This review aims to provide a survey of the current state-of-the-art technologies and knowledge on detection, monitoring, growth prediction, rupture risk assessment, and post-surgical prognosis. The emerging machine learning methodology applicable to each of these problems is

* Corresponding author.

E-mail address: sbaek@egr.msu.edu (S. Baek).

<https://doi.org/10.1016/j.apples.2022.100097>

Received 4 November 2021; Received in revised form 23 March 2022; Accepted 24 March 2022

Available online 30 March 2022

2666-4968/© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

summarized, capitalizing new concepts, such as personalized, predictive medicine and digital twin, that may make potential breakthroughs in the AAA patient management.

2. Machine Learning (ML)

Machine learning (ML) is a collection of data-science tools for analyzing the relationship between input and output data as well as detecting significant patterns within complex datasets. Some traditional ML utilities are regression, dimensionality reduction, classification, and density estimation of datasets (Deisenroth et al., 2020). Various ML approaches have been rapidly gaining popularity in cardiovascular bioengineering and medicine to improve computational cardiovascular modeling speed/accuracy (Madani et al., 2019; Habibi et al., 2021; Dabiri et al., 2019), increase model credibility by quantifying computational model uncertainties (Schiavazzi et al., 2016; Eck et al., 2016; Maher et al., 2021), or facilitate identification of predictive biomarkers of disease progression and risk assessment (Heo et al., 2020; Liang et al., 2017; Weng et al., 2017; Detmer et al., 2020). Common ML techniques and their acronyms are listed at Table 1 (Koohy, 2018; Krittanawong et al., 2020; Al'Aref et al., 2019).

Although ML became popular because computation is abundant and cheap, gathering a large reliably-labeled human dataset relevant to biomedicine is challenging (Shaikhina et al., 2015; Seo et al., 2020; Chen et al., 2021). However, rich experiences in animal models and cardiovascular biomechanics models based on partial differential equations have helped us understand disease progression and risk assessment (Zhang et al., 2016; Humphrey and Holzapfel, 2011; Egidio et al., 2011). Over various fields, hybrid approaches of data-driven and physics-based ML have been proposed to reveal the physical process given with incompleteness of data and balance the prediction performance and computational cost (Liu et al., 2020; Gavrishchaka et al., 2019; Kissas et al., 2020).

Personalized medicine is an emerging concept which involves managing the health of patients based on their individual characteristics and identifying high-risk individuals (Tada et al., 2021). Precise disease classification and understanding of individual variations in disease pathology were aimed for the development of targeted therapeutics, driven by many national initiatives, where ML and artificial intelligence provide necessary tools to analyze dynamic patterns of health and disease and to create more efficient clinical models to tailor medical treatment for individuals (Blaus et al., 2015; Ginsburg and Phillips, 2018). Under the vision of precision medicine, “digital twin” of individual patients could be built to draw diagnosis and prognosis, monitor current health status and data, and provide an accurate projection of the pathways to restore health by model predictions (Corral-Acero et al., 2020; Hose et al., 2019).

Table 1
Common machine learning techniques and their acronyms.

Technique	Abbreviation	Category
Random Forest	RF	Supervised
Support Vector Machine	SVM	Supervised
Artificial Neural Network	ANN	Supervised & Unsupervised
Convolutional Neural Network	CNN	Supervised & Unsupervised
Principal Component Analysis	PCA	Dimensionality Reduction (unsupervised)
Linear Regression	LR	Supervised
Markov Model	MM	Unsupervised
Decision Tree	DT	Supervised
Gradient Boosting	GB	Supervised
Naive Bayes	NB	Supervised

3. Screening and detection

3.1. Current state-of-the-art

The US Preventive Services Task Force (USPSTF), which is the most updated in the US, recommends one time screening for AAA with ultrasonography in men aged 65 to 75 years with previous smoking history (Owens et al., 2019). Recent population-based studies in men older than 60 years have found an AAA prevalence of 1.2–3.3% and its prevalence has been reduced over time, in part, due to the decrease in smoking. Similarly, a fall in UK incidence (from 4.9–7.2% to 1.3%) has been reported in the recent studies of the National Abdominal Aortic Aneurysm Screening Programme (NAAASP) (Benson et al., 2016) and the Gloucestershire Aneurysm Screening Programme (GASP) (Oliver-Williams et al., 2018). With the current trend of reducing prevalence, screening of AAA with ultrasonography in women aged 65 to 75 years and whether a national program is beneficial for women is questionable (Owens et al., 2019; Sweeting et al., 2018). While the prevalence of AAAs in women is much lower than that of men, AAAs in women grow faster and are more likely to rupture at a smaller aortic diameter (Solberg et al., 2005; Soares Ferreira et al., 2018; Mofidi et al., 2007). There is still no consensus over the optimal screening and treatment for small AAAs in women.

While the ultrasonography screening program is recommended for the targeted group, there are still the other key groups with known AAA risk factors who are not screened. Meanwhile, many AAAs were found in the physical examination and alternative technologies have been explored to detect or screen for AAAs using low-cost means. Below is a brief summary of physical detection and alternative methods:

3.1.1. Focused palpation

Asymptomatic AAAs can be detected upon physical examination if abdominal palpation can reveal a pulsatile mass in or above the umbilical region (Aggarwal et al., 2011; Carpenter, 2005). The examination of palpation appears to be safe and has not been reported to induce rupture. Probability of detection increases with increasing aneurysm diameter, in which its sensitivity was reported ranging from 29% for AAAs of 3.0 to 3.9 cm to 50% and as high as 82% for AAAs of 5.0 cm or larger with a range of specificity 68–82% in the physical examination (Fink et al., 2002; Lederle and Simel, 1999).

3.1.2. Blood sample biomarkers

Circulating biomarkers have become attractive for diagnosing AAA due to their cost-effectiveness compared to ultrasound imaging. A few biomarkers (e.g., growth differentiation factor-15 (GDF-15), cystatin-B (CSTB), myeloperoxidase (Vergaro et al., 2020), desmosine (Mordi et al., 2019), insulin-like growth factor 1 (Guo et al., 2020), complement factor of C5a (Zagrapan et al., 2021), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) (Vezzoli et al., 2017)) have potentials for screening and prognosis. From an AAA screening study, ninety-one cardiovascular specific proteins in plasma samples were measured. The combination of GDF-15 and CSTB showed the best ability to discriminate AAA from non-AAA with a sensitivity of 80% and specificity of 52% (Memon et al., 2020).

3.1.3. Pulse wave imaging

Pulse wave imaging showed potentials to screen for and detect AAAs since previous studies (Kadoglou et al., 2012; Li et al., 2013; Nandlall et al., 2014) found that vascular stiffness of the aorta is altered during the growth and after endovascular surgery in humans. Particularly, implications on smart wearables provide a method for measuring pulse wave velocity (PWV) using circulatory waveform signals derived from multiple photoplethysmography (PPG) sensors, which allows an economic setting to estimate vascular stiffness (McCombie et al., 2006; Elshafeey et al., 2021). Li et al. (2016) used a fluid-solid interaction numerical model to show the relationship between the aneurysmal sac geometry and vessel stiffness to simulate the PWV and flow wave

propagation.

3.2. ML in screening and detection

There has been an exploration of ML using low-cost means such as utilizing previous history of patient-specific data and light sensor measurements to detect or select patients who have a high probability of AAA prevalence. For instance, Kerut et al. (2019) investigated the potential to detect AAA patients using neural networks from an AAA screening database of 10,329 patients who self-reported patient information (basic patient information, medical history, and smoking). The result of sensitivity analysis showed that the cohort of Caucasian males contributed most significantly to the accuracy of the ML algorithm, but it may not be reliable when evaluating non-Caucasian populations or Caucasian females. Another study from Li et al. (2018) tested a proof of concept of using a ML framework to integrate personal genomes and electronic health record data to screen for general population and provide quantitative and actionable guidelines on lifestyle to minimize disease risk. The developed framework, called HEAL (hierarchical estimate from agnostic learning), was constructed using ML and network analysis techniques, hierarchically modeling individual mutation effects and identifying mutational genes. HEAL not only identified disease-associated components in AAAs by aggregated learning from population genomes but also predicted disease status from personal genomes, which could potentially be developed into a clinically test for early screening of AAA.

Wang et al. (2021) tested the feasibility of ML-based pulse wave (PW) analysis for early detection of AAAs using a database of *in silico* PWs. They constructed a one-dimensional model of main arterial vessels in the systemic blood circulation and created three subsets of database of *in silico* PWs for baseline subset, increased global stiffness subset, and AAA subset. A recurrent neural network (RNN) was proposed to train and test using the peripheral PPG PW derived from the *in-silico* PW database and evaluate the prediction performance of detecting AAAs. The *in-silico* study predicted the magnitudes of the 5th and the 6th harmonics of the digital PPG PW to strongly influence various cardiovascular parameters in addition to the AAA size. By using the RNN, the *in-silico* analysis resulted in a sensitivity of 86.8% and a specificity of 86.3% in AAA detection. This study, however, used idealized vessel wall properties and morphological geometries and did not consider calcified or thrombus regions. The use of a virtual patient database was, then, extended for detecting major forms of arterial diseases, carotid arterial stenosis, subclavian artery stenosis, peripheral arterial disease, and AAAs with ML algorithms (RF, GB, NB, SVM, Logistic Regression, and Multi-layer Perception). The test results of best prediction performance were from the tree-based methods (RF and GB) (Jones et al., 2021). While the study used a virtual cohort of subjects, the test results were promising for AAA monitoring and screening through wearable devices.

4. Monitoring and assessment of disease status

4.1. Current state-of-the-art

Measuring the maximum diameter has a central role in AAA management and surgical recommendation, and other geometrical variables such as AAA volume (Lindquist Liljeqvist et al., 2016; Martufi et al., 2013), growth rate (Limet et al., 1991; Brown et al., 2003), thrombus (Parr et al., 2011; Haller et al., 2018), and asymmetry and tortuosity (Doyle et al., 2009) can be taken into account for improving the assessment of aneurysm development and rupture risk. The maximum diameter measurement, however, has not been standardized yet. In general, diameter measurement methodology is implemented according to four parameters: plane of acquisition, axis of measurement, position of calipers placement, and selected diameter (Long et al., 2012). The value may vary depending on the combinations of parameters, which can differ by up to 8 mm for an individual AAA (Matthews et al., 2021).

Although all parameters affect the diameter measurement, the plane of diameter acquisition (e.g., axial plane or the plane orthogonal to the centerline of an AAA) affects the measurement difference the most. Particularly, for the orthogonal maximum diameter measurement, it can depend on the construction of the centerline, which can be highly variable. For instance, an error of 5° in determining the orthogonal plane can lead to 15 mm of miscalculation in measuring maximum diameter. To reduce the variability in measurement, Gharahi et al. (2015) suggested exploiting a maximally inscribed sphere method to generate the centerline and measure the maximum axial, orthogonal, and spherical diameters. The axial diameter measurement determines the maximum diameter without generating the centerline, and the maximum orthogonal diameter represents the principal curvature of the vascular wall. The associated maximum diameters were correlated with the rupture risk assessment parameters such as peak wall stress (PWS) and peak wall rupture risk (PWRR) (Novak et al., 2017). Other factors that are influential to the measurements include posture and adjacent tissues (the vertebral columns, inferior vena cava). AAA tissues can be pressed by adjacent tissues affecting the maximum diameter measurement (Kwon et al., 2015).

While the maximum diameter is a convenient and important biomarker for clinical management, other physiological and biological features were sought to better estimate the disease process and detect early signs of adverse events during patient follow-up. In particular, the field of molecular imaging has been rapidly expanding over the past few decades to provide cellular activities related to pathological disease progression. Imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) identify process-specific and cell-specific probes that are associated with disease activities such as calcification and inflammation. Paramagnetic MRI agents (such as gadolinium) are widely used in clinical practice, where T2-weighted gadolinium-enhanced MRI delineates morphological regions such as blood, thrombus, and fibrous cap (Kramer et al., 2004; Forsythe et al., 2016). For more advanced technology, ultrasmall superparamagnetic particles of iron oxide (USPIOs) can visualize tissue inflammation. Focal areas of USPIO uptake were associated with a more rapid AAA expansion in a pilot study with 29 patients (Richards et al., 2011). Since PET has a lower spatial resolution, fusion techniques (PET-CT and PET-MRI) visualize a high intensity of macrophage activities using cell-specific PET tracers such as ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) and a novel marker of vascular calcification activities using PET tracer of ¹⁸F-sodium fluoride (¹⁸F-NaF) (Forsythe et al., 2016; Nchimi et al., 2014). These cellular and molecular imaging techniques may have the potential to provide better stratification of disease stages and assist in patient management.

Increased central artery stiffness is widely accepted as an indicator of cardiovascular risk and the associated differential hemodynamic forces account for local vascular remodeling through physio-pathological process (Dua and Dalman, 2010; Zieman et al., 2005; Boczar et al., 2021). PWV is a measure of arterial stiffness and higher levels of PWV were shown in AAA patients (Kadoglou et al., 2012). Konofagou and co-workers tested the utility of ultrasound imaging-based techniques to measure the regional PWV for monitoring and staging AAAs (Li et al., 2013; Nandlall et al., 2014; Li et al., 2011). Petterson et al. (2021) developed a workflow where multi-perspective biplane ultrasound imaging created a sparse, high resolution 3D map of wall motion and estimated wall elastic modulus via a personalized FE model using the 3D ultrasound imaging. Using a workflow of time resolved 3D ultrasound-based segmentation, Fonken et al. (2021) further implemented patient-specific fluid-structure interaction (FSI) simulations that estimate wall mechanics and hemodynamics variables such as time-averaged wall shear stress (TAWSS) and oscillatory shear index (OSI). The study found that incorporation of pre-stress in FSI significantly enhanced estimations of wall mechanics and hemodynamic variables.

Sonesson et al. (1997) developed an experimental setup to reduce the

pressure in a sealed chamber in the lower body while measuring the inner radius of the abdominal aorta *in vivo*. This lower-body negative pressure technique caused vasoconstriction and physical exercise caused the dilated condition. Using the experimental setup and the dataset, Gade et al. (2021) identified nonlinear mechanics of the aorta *in vivo* via altering smooth muscle activities, which has a potential for monitoring physical status of the aorta.

4.2. ML approaches in follow-up and monitoring

The “digital twin” concept could be used as a comprehensive framework for integrating ML, physics-based modeling, and follow-up data to create a continuously evolving digital representation of biological systems such as AAAs. A digital twin is defined as a virtual representation of its living counterpart (physical twin), and it is dynamically updated with new data to maintain a relevant representation of the physical twin (The AIAA, 2020; Niederer et al., 2021). A digital twin needs to facilitate decision-making, and therefore should be predictive. In the context of AAA follow-up monitoring, one could create a digital twin representation of AAA by creating a patient-specific hemodynamics model during baseline. Subsequently, predictive hemodynamic biomarkers such as structural stress and wall shear stress together with other relevant biomarkers could be used to simulate AAA growth and inform AAA monitoring strategies. Finally, the digital twin should be able to incorporate new imaging data during follow-up sessions to update its representation and remain predictive. Establishing such digital twins requires a synergistic blend of data-driven and physics-based modeling approaches. A similar workflow has been used by Chakshu et al. (2021) where data collected using wearable devices were

combined with 1D blood flow modeling and deep learning to create a digital twin representation of the cardiovascular system and monitor AAA severity (Fig. 1).

5. Growth prediction

5.1. Current state-of-the-art

AAA expansion rate is generally considered as a risk factor but it is still debatable whether the growth is directly connected to wall weakening or rupture risk (Sharp and Collin, 2003). Estimation of patient’s aneurysm growth is however important for patient’s management, particularly for deciding the time of surgery.

The mean expansion rate of AAAs ranges from 2.6 to 4.7 mm/year depending on the cohort groups (Vega de Céniga et al., 2006; Mofidi et al., 2007; Masuda et al., 1992; Bhak et al., 2015). Although AAA growth generally increases in their size (Powell et al., 2011; Bown et al., 2013), a high variability has been reported in the expansion rate of each AAA; some aneurysms found no expansion over several years, whereas others showed a rapid increase in size. The risk factors for increasing expansion rate were the initial diameter of aneurysms (Masuda et al., 1992), diabetic patients had a significantly smaller AAA growth rate than non-diabetics (Vega de Céniga et al., 2006), and intraluminal thrombus was associated with AAA growth (Parr et al., 2011; Zambrano et al., 2016). The pathophysiological processes of AAA growth involve degradation of elastin, thrombosis, inflammation, and lipid metabolism, which has been recognized from serum circulating and histological biomarkers (Deeg et al., 2016; Vega de Céniga et al., 2009; Flondell-Sif et al., 2010; Lindholt et al., 2011; Wanhainen et al., 2017). A systematic

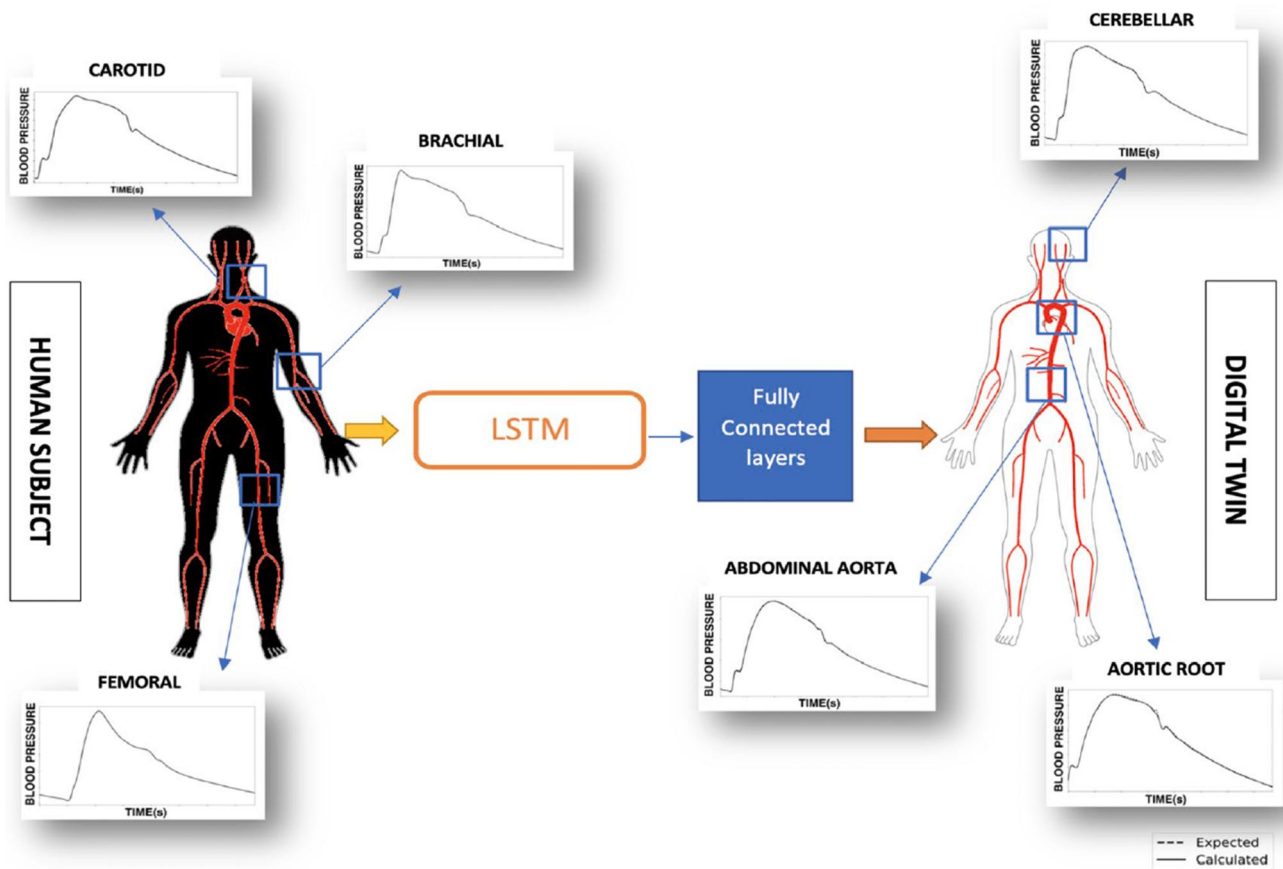


Fig. 1. Schematic workflow of one approach in creating a digital twin representing of the cardiovascular system. Blood pressure waveforms are measured at accessible locations as inputs and various waveforms are inversely estimated in the systemic circulation using ML with the aid of long short-term memory (LSTM) networks. The figure is reproduced from Chakshu et al. (Chakshu et al., 2021) under a Creative Commons Attribution (CC BY) license.

review and meta-analysis of 25 studies found the most significant association with AAA growth rates as biomarkers of D-dimers, LDL-C, HDL-C, TC, ApoB, and HbA1c (Nana et al., 2021). These biomarkers can be easily and cost-effectively implemented in clinical practice, and the recognized biomarkers, which are correlated to various stages of AAA progression could become attractive candidates for future studies of AAA growth prediction. Finally, patient-specific computational fluid dynamics models have shown a connection between near-wall hemodynamic parameters (e.g., TAWSS) and pathogenesis/growth (Arzani et al., 2014; Meyrignac et al., 2020; Zambrano et al., 2022; Tanweer et al., 2014; Salman et al., 2019).

5.2. ML in predicting AAA growth

A recent consensus has been reached that research priority may focus on obtaining an accurate prediction of AAA growth rate as a feasible task that is central for deciding the time of surgery (Lee et al., 2017). The new shift was motivated by recent papers that have demonstrated a proof of concept, which were promising for an enhanced prediction capability on AAA growth rate by using ML tools (Lareyre et al., 2020; Raffort et al., 2020). Through an effective surveillance strategy, the prediction of AAA growth can aid surgeons and specialists in better management of patients in a personalized manner.

ML techniques have been applied to predict future growth in individual patients using the retrospective sets of follow-up images and/or other variables. A majority of studies used morphological variables (e.g., diameter profiles, AAA volume, parameters related to ILT characteristics, and tortuosity) to train ML algorithms to predict AAA growth for a future time-point of one or two years (Akkoyun et al., 2020; Akkoyun et al., 2021; Zhang et al., 2020). Akkoyun et al. (2020) utilized a two-step Bayesian inference (a generalized linear model (GLM)) using an exponential growth function to calibrate against a dataset of AAA growth from 25 patients. For the first Bayesian inferences, the posterior distribution was obtained for the general AAA growth pattern of the whole population. Then the results were again used as the prior distributions for the second regression model to train with additional geometrical measurements and enhance the AAA growth prediction. The study found that the geometrical parameter, tortuosity, was a significant factor enhancing the prediction. The prediction error of the GLM method was 2.79 mm. Another study by Zhang et al. (2020) investigated the relationship between the characteristics of ILT and AAA expansion. A retrospective, follow-up CT image dataset of 26 AAA patients was classified into three stages (early, mild, severe, fatal) based on the maximum diameter and homogeneous multistate continuous-time Markov chain models. The study concluded that surgical intervention would be recommended when the ILT's areal fraction was larger than 60%. The other group of studies utilized other features with the morphological variables to predict growth. For instance, an ML technique (nonlinear kernel support vector regression) was applied to predict future AAA growth based on individual patients' baseline flow mediated dilatation (FMD) and AAA diameter as input variables for 94 patients (Lee et al., 2018). The algorithm predicted the individual's AAAs diameter within 2 mm error in 85 and 71% of patients at 12 and 24 months, respectively. Garcia-Garcia et al. (2017) used various data, clinical and morphometric, and mechanical stress characterization to exploit ML algorithms for predicting AAA growth rate. AAA's images were classified into three groups of slow, medium, and quick aneurysms and an ensemble of decision trees ('LPBoost') algorithm showed the best performance predicting the aneurysm growth rate.

Over the past two decades, various FE formulations were proposed by multiple groups presenting vascular growth models to simulate AAA shape evolution (Watton et al., 2004; Baek et al., 2006; Kuhl et al., 2007; Stevens et al., 2017; Grytsan et al., 2015). Several studies used FE models of growth and remodeling (G&R) for aortic tissue, characterizing homogenized aortic elements for mechanical behavior of main constituents (fibrous collagen, elastin, and smooth muscle cells), and simulated

long-term shape evolutions of AAAs (Baek et al., 2006; Zeinali-Davarani et al., 2011; Wilson et al., 2013, 2012; Baek and Humphrey, 2010; Zeinali-Davarani and Baek, 2012; Braeu et al., 2017, 2019; Martufi and Gasser, 2012). Recently, a few studies integrated these growth FE-based models with ML approaches. Baek and coworkers have obtained follow-up 118 CT scan images from 25 AAA patients and have investigated a general pattern of long-term shape evolution of AAAs. Based on those observations, it was found that an exponential function is superior to a linear one in predicting maximum diameter changes (Akkoyun et al., 2021). Further, they explored various data-driven ML models (GL, Bayesian inference, continuous-time Markov chain) (Akkoyun et al., 2020; Zhang et al., 2020; Do et al., 2019) and physics-based ML using the FE-based G&R model (Jiang et al., 2020; Zhang et al., 2019) to test the prediction of maximum diameter and AAA shape evolution for the cohort group (Fig. 2). Among different models, the physics-based ML using an FE-method G&R model (implemented in Bayesian calibration and deep learning) showed a significant reduction of errors in the prediction of aneurysm shape evolution compared to the data-driven models. The best prediction of AAA enlargement for 1 year was using a deep learning method where the average relative error was 3.1% (approximately about 2 mm error), which outperforms the classical mixed-effect model by 65% (Jiang et al., 2020).

The specific ML techniques of the growth prediction models and their accuracy performance are compared and summarized in Table 2.

6. Rupture risk assessment

6.1. Current state-of-the-art

The concept of rupture potential is central for disease risk assessment and clinical management of AAAs. The rupture potential index is, however, a more conceptual idea and there were several ways of implementation. The rupture potential index is generally defined by the maximum principal stress (or the von Mises stress) divided by the aortic wall strength for biomechanical risk assessment of aortic aneurysms (Raghavan and Vorp, 2000; Lu et al., 2007; Rissland et al., 2009). The superiority of peak wall stress (PWS) and peak wall rupture index (PWRI) over the criterion of the maximum transverse diameter have been shown in different studies using retrospective AAA images from patient groups (Erhart et al., 2015; Gasser et al., 2010; Ventatasubramanian et al., 2004; Truijers et al., 2007). More detailed comparisons between PWS and PWRI along with other physical/morphological indices can be found from recent studies (Leemans et al., 2017; Singh et al., 2021; Rengarajan et al., 2020).

While the image-based biomechanical stress analyses enable the prediction of rupture risk, the wall strength depends on patient-specific material properties that are not easy to estimate. Also, for the stress analysis, there can be improvements for the accurate prediction of rupture. The calculation of PWRI typically utilizes an isotropic material model, which may not be accurate for aortic tissues as many experimental studies have revealed that aortic wall strengths in the circumferential and axial direction are significantly different (Polzer et al., 2021; Teng et al., 2015; Kim et al., 2012; Liu et al., 2020). For instance, uniaxial tensile tests on aneurysmal tissues from 45 patients, harvested during AAA repair, were performed in circumferential and axial directions. The test results found that both the first Piola-Kirchhoff strength and ultimate tension were significantly higher in the circumferential direction (Polzer et al., 2021). In another study, 38 abdominal aortas harvested during autopsy were inflated up to their rupture. The AAAs ruptured at least higher than 590 mm Hg (mean = 1,035 mm Hg) and normal aortas were ruptured above 840 mm Hg (1,405 mmHg) (Gomes et al., 2021). One study investigated the influence of patient-specific AAA wall thickness on the predicted clinical outcomes. In 4 out of 8 patients, the unformed wall model underestimated stress by as much as 55%. In the remaining cases, it overestimated stress by up to 40% (Conlisk et al., 2016).

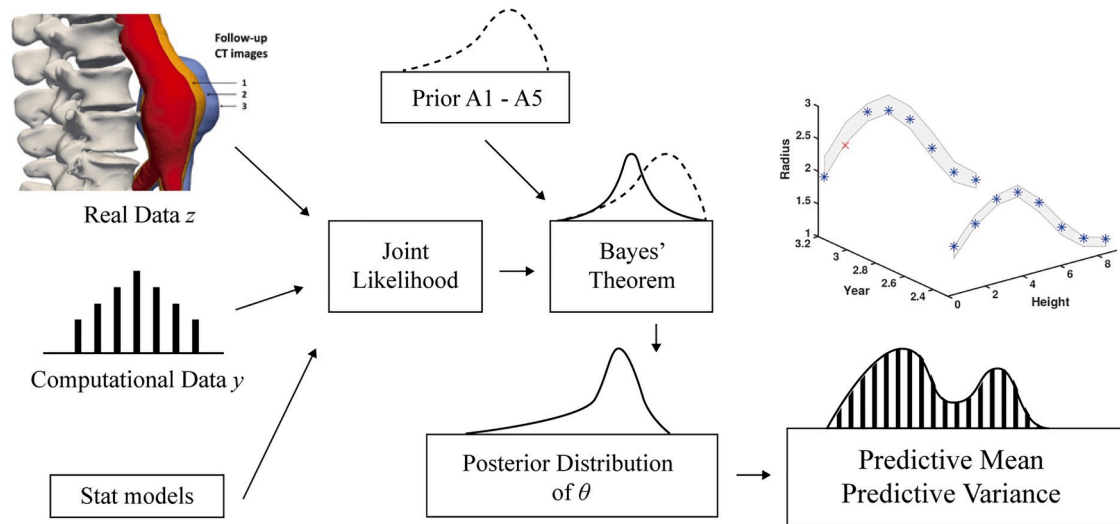


Fig. 2. A Bayesian calibration framework implemented to predict AAA growth with confidence range (adapted from Zhang et al., 2019).

Table 2

Comparison of different growth prediction studies using ML.

Paper	Aim	Method	Dataset	Training/testing	Features	Accuracy
Garcia-Garcia et al. (2017)	Classification of AAA growth groups	PCA, DT, SVM, and others	CTA images from 38 patients	No separate groups	Clinical, morphological, biomechanical, and texture features	Best result was from DT. Only one case was clinically missed for the classification.
Lee et al. (2018)	Prediction of AAA growth	Nonlinear SVM regression	94 patients	No separate groups	Max. AAA diameters and flow mediated dilation	Prediction of max. AAA diam. within 2mm error was 85% and 71% at 12 and 24 months
Do et al. (2019)	Prediction of AAA growth	Dynamic LR	Follow-up CT images from 7 patients	No separate groups	Point-clouds of AAA wall surfaces	The overall Hausdorff distance was 10.3mm (mean) and 3.64mm (SD)
Zhu et al. (2019)	Prediction of AAA growth	Statistical analysis	80 patients (with 41 followed)	No separate groups	ILT signal intensity of MRI	3-fold increase of growth rate compared with stable AAAs
Zhang et al. (2019)	Prediction of AAA growth	Bayesian LR	Follow-up CT scans from 4 patients	No separate groups	Inscribed sphere diameter	Most of relative errors of diameter growth prediction were less than 5%
Zhang et al. (2020)	Transition of disease progression	MM	Follow-up CT scans from 26 patients	No separate groups	Max diameter, ILT characteristics	ILT areal fraction was found as the most significant biomarker for predicting transitions
Akkoyun et al. (2020)	Prediction of rapid growing AAA	LR	Follow-up CT scans from 25 patients	No separate groups	Morphological characteristics	86% of scans were predicted in 95% CI cases
Jiang et al. (2020)	Prediction of AAA growth	Deep belief network	Follow-up CT scans from 20 patients	14/6	Inscribed sphere diameters	2.3-4.3% of relative prediction error at 12 months
Akkoyun et al. (2021)	Prediction of AAA growth	Statistics analysis, linear vs. exponential models	Follow-up CT scans from 25 patients	20/5	Morphological characteristics	Max diameter was predicted to 15 of 16 validation scans with a 95% CI
Stoecker et al. (2021)	Prediction of AAA growth	Extreme GB	10 patients CTAs	No separate patient groups	Image-derived geometric parameters	Mean relative error in predicting max. diameter growth was 10.5%
Liljeqvist et al. (2021)	Prediction of AAA growth	LR and SVM	189 patients (CT and CTA follow-up)	No separate groups	Geometric, biomechanical variables with sex, smoking and diabetes	Improved predictions of reaching surgical threshold and diameter growth rate

Moreover, other factors influencing rupture assessment were thrombus, calcified regions (Buijs et al., 2013), surrounding tissues (Kim et al., 2013), and other patient variables (sex, age, pre-deposited vulnerability, ethnicity) (Sweeting et al., 2012; Marcaccio and Schermerhorn, 2021). Forneris et al. (2021), therefore, suggested that an accurate prediction of a local wall weakening and aortic rupture should be taken into account in the presence of multifactorial, heterogeneous spatial factors. The study proposed an index of regional aortic weakness (RAW), which captures local changes in the tissue mechanical behavior and luminal hemodynamics, which were compared with qualitative and statistical analyses of microstructure and gene expression data. The new

approach was demonstrated to capture changes in the tissue mechanical behavior, microstructure, and gene expression, which account for the regional variability and tissue heterogeneity.

6.2. Statistical and ML approaches for rupture risk assessment

Although biomechanical indices such as PWS and PWRI based on FE modeling can be used for classifying the AAA groups (non-symptomatic/symptomatic or ruptured/intact), FE modeling has a deterministic nature, thus restricting the use of uncertainty for risk assessment. AAA rupture risk assessment is especially involved in a multitude of risk

factors from individual patients, and model constructions (e.g., segmentation, wall thickness, and boundary conditions) and the constitutive parameters are associated with uncertainties for the prediction capability (Seyedsalehi et al., 2015; Chen et al., 2013; Reeps et al., 2013).

Using the state-of-the-art deterministic biomechanical models, Polzer and Gasser (2015) proposed to enhance the prediction capability by incorporating probability density functions of wall thickness, wall strength, and peak wall stress, in which their uncertainties were integrated into the assessment of probabilistic rupture risk index (PRRI). Using 7 ruptured AAAs and 7 intact AAAs, their study found that PRRI was significantly higher in ruptured AAAs than intact AAAs, whereas PRRI showed a high sensitivity and specificity to discriminate between ruptured and intact AAA cases. Biehler et al. (2015) presented an uncertainty quantification framework based on multi-fidelity sampling and Bayesian formulation, where constitutive parameters of the aneurysmatic arterial wall were modeled as a univariate 3D, non-Gaussian random field taking into account inter-patient as well as intra-patient variations of the two parameters. However, because patient-specific parameters, such as wall thickness, wall strength, and constitutive properties, were not easily accessible, they instead utilized the well-developed regression models in a combination with noninvasively assessable, explanatory variables from basic patient information, medical history, laboratory test, and geometrical parameters (Biehler et al., 2017). Using a probabilistic biomechanical framework and a regression algorithm of selecting non-invasive features (similar to Biehler et al., 2017), Bruder et al. (2020) evaluated the PRRI for 18 asymptomatic and 18 symptomatic/ruptured patient groups, retrospectively. With 8 selected variables; maximum diameter, maximum thrombus thickness, AAA length, subrenal diameter, thrombocytes, hemoglobin, mean corpuscular hemoglobin, and mean corpuscular volume, they were able to differentiate the risk group from the asymptomatic group. They further showed that this method outperformed the other classifiers such as maximum diameter and traditional rupture potential indices.

Therefore, the maximum diameter may be insufficient in predicting AAA rupture risk, and integrated approaches using geometrical, physical, and biological data from follow-up imaging or monitoring can capture important features useful in assessing the rupture risk. A primary task is, therefore, to identify a set of key variables for morphological, biomechanical, and patient-specific variables from a multifactorial dataset. For this purpose, ML algorithms were implemented and tested to select predictive variables with discriminatory potential for rupture risk assessment. Using retrospective CT image datasets consisting of geometric, biomechanical, patient-specific information data, different ML algorithms tested the performance on the classification analysis discriminating the dataset between asymptomatic and symptomatic AAAs (Rengarajan et al., 2020) and between the group at risk of rupture and the group not at risk of rupture (Jalalahmadi et al., 2020). These ML classifications could provide selection of key markers and predict the rupture.

7. Post-procedural complications and prognosis

7.1. Current state-of-the-art

Surgical management options for AAAs are open surgical repair (OSR) and endovascular aneurysm repair (EVAR). A recent review of systematic and meta-analysis of perioperative results concluded that the minimally invasive operation procedure shows an improvement of short-term (30 days) mortality for EVAR compared with OSR, but for very long-term outcomes there has been no mortality difference between them (Li et al., 2019). Although there may be no difference in the long-term mortality, EVAR becomes the more preferable choice due to the less invasive nature of the procedure, resulting in advantages such as fewer cardiopulmonary complications and reduced lengths of stay in intensive care units, an important factor for the elderly population

(Salata et al., 2019). EVAR is, however, often associated with endograft-specific complications, including endoleak, graft migration, and fracture (Ultee et al., 2018). Endoleaks are the most commonly occurring complications following EVAR and, among five types of endoleaks, type I and II endoleaks are the most common and occur in 15-30% of patients in the first 30 days after the procedure. Type I endoleaks occur because of an incompetent seal at the proximal or distal endograft attached and type II endoleaks are characterized by persistent flow out of the residual aneurysm sac via patent aortic side branch vessels (Daye and Walker, 2018). Many type II endoleaks shrink and, hence, only about 20% of cases are needed for reinterventions (Biancari et al., 2015; Bryce et al., 2018). Nonetheless, owing to the relatively higher frequency of post-EVAR complications, patients are generally recommended for regular, long-term surveillance and early detection or significant features of their complications would be important for EVAR management. Risk factors of post-EVAR complications were reported as aneurysm sac enlargement, patent inferior mesenteric and lumbar arteries, and other patient-specific factors such as smoking and hypercholesterolemia (Müller-Wille et al., 2015; Guo et al., 2017; Laly et al., 2017). Patient-specific derived hemodynamics have also been linked to EVAR outcomes. For example, endoleak location corresponded to local peak wall stress on the endograft (Lu et al., 2016) and lowered aneurysm wall stress correlated to aneurysm shrinkage in follow-up (Molony et al., 2009). Nevertheless, managing EVAR complications still represents an unsolved clinical problem (Forbes, 2020). There have been several extensive reviews available on EVAR techniques, their complications, post-EVAR management, computational modeling, and pre- and post-EVAR vascular adaptation (Kim et al., 2019; Rengier et al., 2014; Roy et al., 2012; Kwon et al., 2011; Avril et al., 2021). The readers should refer to these references for more details.

7.2. ML in detection of endoleaks and post-surgical prognosis

Multiple studies have established the proof of concept for utilizing ML in detecting and differentiating endoleaks. Those groups used datasets of retrospective computed tomography angiography (CTA) to train ML algorithms (SVM Charalambous et al., 2021 and CNN Hahn et al., 2020; Talebi et al., 2020) to detect endoleaks and differentiate aggressive type II endoleaks. The performance of model prediction was more than 90% from those studies, and the ML-based approaches showed similar performance for endoleak diagnosis compared to those from specialists. The mortality risk of patients is associated with various factors and ML algorithms can aid medical staff in discriminating high risk of re-intervention and estimate in-hospital mortality. Attallah and Ma (2014) used a Bayesian neural network to predict re-intervention and classify the patients into high-risk and low-risk groups using a set of collected clinical conditions. Monsalve-Torra et al. (2016) grouped various data into four clusters: patient's basic data, clinical history, surgical data, and postsurgical data, and trained an ML algorithm (supervised ANN) to predict in-hospital mortality in patients after open surgery. The test results showed a predictive accuracy of 95%.

8. Closing remarks

Approximately 30% of asymptomatic small AAAs are discovered as a pulsatile abdominal mass on physical examination. Abdominal ultrasonography has been a choice for detecting AAAs because of its sensitivity and specificity but with a trend of reducing AAA prevalence over the past decade the decision to screen for AAAs is challenging for the national screening program. Alternative techniques such as blood circulating sample analysis and PWV measurement provide low-cost methods in detecting and identifying biomarkers that are correlated to AAA disease progression and prediction of its rupture. Genome sequencing analysis and molecular imaging techniques enable identifying key genetic components, process-specific and cell-specific markers. ML techniques provide synergy for improving clinical decisions by identifying

important morphological and biomarkers, classifying patients into high and low risk groups, and estimating the rupture risk of individual patients with a confidence range. Notably, physics-based ML models (FE modeling and vascular G&R models) play central roles in enhancing prediction capability for AAA growth and rupture risk assessment and were shown to outperform the pure data-driven ML models for small-size datasets.

While various ML approaches were proven to be effective for AAA detection and clinical management, ML in biomedical applications is still in its infancy and further studies are necessary before their routine use. Here, we suggest current limitations and, hence, potential future directions for the enhancement of ML methodology and physics-based modeling:

8.1. Development of an automatic pipeline from segmentation to FEM-based growth and stress analysis

Significant progress has been made in developing more accurate ML algorithms for medical image segmentation (Seo et al., 2020). For AAAs, multiple groups have investigated the feasibility of automatic segmentation of medical images including the aorta, aneurysm sac, intra-luminal thrombus using CT or CT angiograms to train and test CNN algorithms (Salvi et al., 2021; Lopez-Linares et al., 2018; Mohammadi et al., 2019; Brutti et al., 2022; Adam et al., 2021). These approaches were implemented based on deep learning CNN to extract geometric features. The first layers extract the low-level features such as edges, lines, and corners, and as the layers get deeper, the CNN increases in its complexity, identifying other portions of the images. However, deep neural networks require a large amount of training data and the methods are not yet fully validated, which is a main limitation. To deal with the patient morphology variability, new feature-based approaches via generating a set of synthetic data have been suggested within deep learning frameworks to enhance the accuracy of prediction and, more importantly, speed up the development of an automatic pipeline, from the segmentation process, morphological data analysis to FE-based growth and rupture risk analysis (Lareyre et al., 2019; Rengarajan et al., 2021).

8.2. Development of specific goal-driven ML techniques and integration toward the digital twin approach

This review summarized the high potential for alternative technologies on detection/monitoring of AAAs and data-driven/physics-based ML approaches, which are complementary to the traditional practice of ultrasound screening. Specific physical & morphological, biochemical, imaging, and genetic markers were recognized for different aims that will enhance surveillance strategies for patients, identify early signs of small aneurysm's rupture, provide post-surgical management, and enhance therapeutic treatments. Predictive ML technologies based on these markers could be ultimately integrated into health digital twins that enhance personalized treatments for the susceptible groups and AAA patients in the near future (Coorey et al., 2021).

8.3. Improvement of ML methodologies

ML frameworks still need improvement before being implemented in routine clinical practice. For instance, the developmental stages of new ML algorithms should be transparent and be tested with different ML algorithms using the same or similar set of independent variables. The selection of ML algorithms should be made based on the questions of interest and the structure of the dataset: how large the population is, how many cases exist, how many available variables there are, whether the data is longitudinal or not, if the clinical outcome is binary or time to event, etc. (Krittawong et al., 2020). There is, hence, a pressing need for standardizing ML methodologies (e.g., training/testing, validation, and evaluation metrics) (Kerut et al., 2019; Nana et al., 2021). The

developed ML algorithms can be also validated in large multicenter cohorts (and compared to other algorithms) to confirm their generalization to out of sample data (Lareyre et al., 2020).

8.4. Enhanced efficiency for physics-based modeling

Significant progress in understanding multi-physical biochemical characterizations of pathogenesis, G&R, and wall weakening by using computational modeling based on partial differential equations has been made, but these physical computational models require significant computational resources and time. Especially, considering the patient variability and various uncertainties, physics-based ML through traditional approaches becomes prohibitive for clinical practice. Therefore, multiple approaches such as surrogate/multi-fidelity modeling and physics-informed ML have been introduced and showed promise in various biomedical applications to reduce the computational cost and enable solutions to difficult problems (Ye et al., 2022; Jiang et al., 2021; Arzani et al., 2021; Liu et al., 2020). Expanding these models will be a high priority in improving physics-based ML for predictive.

AAA modeling applications.

In conclusion, the different identified biomarkers not only aid clinical decisions for early diagnosis, monitoring, growth prediction, and risk assessment but may also further guide intervention (lifestyle changes or targeted medicine) and provide better insights into the disease. We hope that this review will motivate improvement of technologies and ML approaches for detection, growth prediction, and risk assessment of AAA patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge the support, in part, by the National Heart, Lung, and Blood Institute of the National Institutes of Health (R01HL115185 and R21HL113857), the National Science Foundation (NSF) CAREER Award (CMMI-1150376), and NSF ECCS- 2103434.

References

- Adam, C., Fabre, D., Mougin, J., Zins, M., Azarine, A., Ardon, R., et al., 2021. Pre-surgical and post-surgical aortic aneurysm maximum diameter measurement: full automation by artificial intelligence. *Eur. J. Vasc. Endovasc. Surg.* 62 (6), 869–877.
- Aggarwal, S., Qamar, A., Sharma, V., Sharma, A., 2011. Abdominal aortic aneurysm: a comprehensive review. *Exp. Clin. Cardiol.* 16, 11–15.
- Akkoyun, E., Kwon, S.T., Acar, A.C., Lee, W., Baek, S., 2020. Predicting abdominal aortic aneurysm growth using patient-oriented growth models with two-step Bayesian inference. *Comput. Biol. Med.* 117, 103620.
- Akkoyun, E., Gharahi, H., Kwon, S.T., Zambrano, B.A., Rao, A., Acar, A.C., et al., 2021. Defining a master curve of abdominal aortic aneurysm growth and its potential utility of clinical management. *Comput. Methods Programs Biomed.* 208, 106256.
- Al'Aref, S.J., Anchouche, K., Singh, G., Slomka, P.J., Kolli, K.K., Kumar, A., et al., 2019. Clinical applications of machine learning in cardiovascular disease and its relevance to cardiac imaging. *Eur. Heart J.* 40, 1975–1986.
- Arzani, A., Suh, G.Y., Dalman, R.L., Shadden, S.C., 2014. A longitudinal comparison of hemodynamics and intraluminal thrombus deposition in abdominal aortic aneurysms. *Am. J. Physiol. Hear. Circ. Physiol.* 307 (12), H1786–H1795.
- Arzani, A., Wang, J.X.D., Souza, R.M., 2021. Uncovering near-wall blood flow from sparse data with physics-informed neural networks. *Phys. Fluids* 33 (7), 071905.
- Attallah, O., Ma, X., 2014. Bayesian neural network approach for determining the risk of re-intervention after endovascular aortic aneurysm repair. *Proc. Inst. Mech. Eng. Part H J. Eng. Med.* 228 (9), 857–866.
- Attarian, S., Xiao, S., Chung, T.C., Da Silva, E.S., Raghavan, M.L., 2019. Investigation of the observed rupture lines in abdominal aortic aneurysms using crack propagation simulations. *J. Biomech. Eng.* 141 (7), 071004.
- Avril, S., Gee, M.W., Hemmler, A., Rugonyi, S., 2021. Patient-specific computational modeling of endovascular aneurysm repair: state of the art and future directions. *Int. J. Numer. Method Biomed. Eng.* 37, e3529.

- Baek, S., Humphrey, J.D., 2010. Computational modeling of growth and remodeling in biological soft tissues: application to arterial mechanics. In: De, S., Guilak, F., Mofrad, M. (Eds.), *Computational Modeling in Biomechanics*. Springer, pp. 253–274.
- Baek, S., Rajagopal, K.R., Humphrey, J.D., 2006. A theoretical model of enlarging intracranial fusiform aneurysms. *J. Biomech. Eng.* 128 (1), 142–149.
- Basalyga, D.M., Simionescu, D.T., Xiong, W., Baxter, B.T., Starcher, B.C., Vyavahare, N. R., 2004. Elastin degradation and calcification in an abdominal aorta injury model: role of matrix metalloproteinases. *Circulation* 110 (22), 3480–3487.
- Benson, R.A., Poole, R., Murray, S., Moxey, P., Loftus, I.M., 2016. Screening results from a large United Kingdom abdominal aortic aneurysm screening center in the context of optimizing United Kingdom national abdominal aortic aneurysm screening programme protocols. *J. Vasc. Surg.* 301–304.
- Bhak, R.H., Wininger, M., Johnson, G.R., Lederle, F.A., Messina, L.M., Ballard, D.J., et al., 2015. Factors associated with small abdominal aortic aneurysm expansion rate. *JAMA Surg.* 150 (1), 44–50.
- Biancari, F., Mäkelä, J., Juvonen, T., Venermo, M., 2015. Is inferior mesenteric artery embolization indicated prior to endovascular repair of abdominal aortic aneurysm? *Eur. J. Vasc. Endovasc. Surg.* 50, 671–674.
- Biehler, J., Gee, M.W., Wall, W.A., 2015. Towards efficient uncertainty quantification in complex and large-scale biomechanical problems based on a Bayesian multi-fidelity scheme. *Biomech. Model. Mechanobiol.* 14 (3), 489–513 [Internet]Sep [cited 2016 Jan 14]Available from: <http://link.springer.com/article/10.1007/s10237-014-0618-0>.
- Biehler, J., Kehl, S., Gee, M.W., Schmies, F., Pelisek, J., Maier, A., et al., 2017. Probabilistic noninvasive prediction of wall properties of abdominal aortic aneurysms using Bayesian regression. *Biomech. Model. Mechanobiol.* 16 (1), 45–61.
- Blaus, A., Madabushi, R., Pacanowski, M., Rose, M., Schuck, R.N., Stockbridge, N., et al., 2015. Personalized cardiovascular medicine today: a food and drug administration/center for drug evaluation and research perspective. *Circulation* 132, 1425–1432.
- Bluestein, D., Dumont, K., De Beule, M., Ricotta, J., Impellizzeri, P., Verheghe, B., et al., 2009. Intraluminal thrombus and risk of rupture in patient specific abdominal aortic aneurysm-FSI modelling. *Comput. Methods Biomech. Biomed. Eng.* 12 (1), 73–81.
- Boczar, K.E., Boodhwani, M., Beauchesne, L., Dennie, C., Chan, K.L., Wells, G.A., et al., 2021. Aortic stiffness, central blood pressure, and pulsatile arterial load predict future thoracic aortic aneurysm expansion. *Hypertension* 77, 126–134.
- Bown, M.J., Sweeting, M.J., Brown, L.C., Powell, J.T., Thompson, S.G., 2013. Surveillance intervals for small abdominal aortic aneurysms: a meta-analysis. *JAMA J. Am. Med. Assoc.* 309 (8), 806–813.
- Braeu, F.A., Seitz, A., Aydin, R.C., Cyron, C.J., 2017. Homogenized constrained mixture models for anisotropic volumetric growth and remodeling. *Biomech. Model. Mechanobiol.* 16, 889–906.
- Braeu, F.A., Aydin, R.C., Cyron, C.J., 2019. Anisotropic stiffness and tensional homeostasis induce a natural anisotropy of volumetric growth and remodeling in soft biological tissues. *Biomech. Model. Mechanobiol.* 18, 327–345.
- Brown, P.M., Zelt, D.T., Sobolev, B., Hallett, J.W., Sternbach, Y., 2003. The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. *J. Vasc. Surg.* 37 (2), 280–284.
- Bruder, L., Pelisek, J., Eckstein, H.H., Gee, M.W., 2020. Biomechanical rupture risk assessment of abdominal aortic aneurysms using clinical data: a patient-specific, probabilistic framework and comparative case-control study. *PLoS One* 15, e0242097 (11 November).
- Brutti, F., Frantazzini, A., Finotello, A., Muller, L.O., Auricchio, F., Pane, B., et al., 2022. Deep learning to automatically segment and analyze abdominal aortic aneurysm from computed tomography angiography. *Cardiovasc. Eng. Technol.* <https://doi.org/10.1007/s13239-021-00594-z> [Internet]in press. Available from.
- Bryce, Y., Schiro, B., Cooper, K., Ganguli, S., Khayat, M., Lam, C.K., et al., 2018. Type II endoleaks: diagnosis and treatment algorithm. *Cardiovasc. Diagn. Ther.* 8, S131–S137.
- Buijs, R.V.C., Willems, T.P., Tio, R.A., Boersma, H.H., Tielliu, I.F.J., Slart, R., et al., 2013. Calcification as a risk factor for rupture of abdominal aortic aneurysm. *Eur. J. Vasc. Endovasc. Surg.* 46 (5), 542–548.
- Carpenter, C.R., 2005. Abdominal palpation for the diagnosis of abdominal aortic aneurysm. *Ann. Emerg. Med.* 45, 556–558.
- Chakshu, N.K., Sazonov, I., Nithiarasu, P., 2021. Towards enabling a cardiovascular digital twin for human systemic circulation using inverse analysis. *Biomech. Model. Mechanobiol.* 20 (2), 449–455.
- Charalambous, S., Klontzas, M.E., Kontopodis, N., Ioannou, C.V., Perisinakis, K., Maris, T.G., et al., 2021. Radiomics and machine learning to predict aggressive type 2 endoleaks after endovascular aneurysm repair: a proof of concept. *Acta Radiol.*, 2841851211032443. Online ahe.
- Chen, P., Quarteroni, A., Rozza, G., 2013. Simulation-based uncertainty quantification of human arterial network hemodynamics. *Int. J. Numer. Method Biomed. Eng.* 29 (6), 698–721.
- Chen, R.J., Lu, M.Y., Chen, T.Y., Williamson, D.F.K., Mahmood, F., 2021. Synthetic data in machine learning for medicine and healthcare. *Nat. Biomed. Eng.* 5, 493–497.
- Conlisk, N., Geers, A.J., McBride, O.M.B., Newby, D.E., Hoskins, P.R., 2016. Patient-specific modelling of abdominal aortic aneurysms: the influence of wall thickness on predicted clinical outcomes. *Med. Eng. Phys.* 38 (6), 526–537.
- Coorey, G., Figtree, G.A., Fletcher, D.F., Redfern, J., 2021. The health digital twin: advancing precision cardiovascular medicine. *Nat. Rev. Cardiol.* 18, 803–804.
- Corral-Acero, J., Margara, F., Marciniak, M., Rodero, C., Loncaric, F., Feng, Y., et al., 2020. The “digital twin” to enable the vision of precision cardiology. *Eur. Heart J.* 41, 4556–4564.
- Dabiri, Y., Van der Velden, A., Sack, K.L., Choy, J.S., Kassab, G.S., Guccione, J.M., 2019. Prediction of left ventricular mechanics using machine learning. *Front. Phys.* 7, 117.
- Daye, D., Walker, T.G., 2018. Complications of endovascular aneurysm repair of the thoracic and abdominal aorta: evaluation and management. *Cardiovasc. Diagn. Ther.* 8, S138–S156.
- Deeg, M.A., Meijer, C.A., Chan, L.S., Shen, L., Lindeman, J.H.N., 2016. Prognostic and predictive biomarkers of abdominal aortic aneurysm growth rate. *Curr. Med. Res. Opin.* 32 (3), 509–517.
- Deisenroth, M.P., Faisal, A.A., Ong, C.S., 2020. *Mathematics for Machine Learning. Mathematics for Machine Learning.* Cambridge Univ Pr.
- Detmer, F.J., Lücke, D., Mut, F., Slawski, M., Hirsch, S., Bijlenga, P., et al., 2020. Comparison of statistical learning approaches for cerebral aneurysm rupture assessment. *Int. J. Comput. Assist. Radiol. Surg.* 15 (1), 141–150.
- Do, H.N., Ijaz, A., Gharahi, H., Zambrano, B., Choi, J., Lee, W., et al., 2019. Prediction of abdominal aortic aneurysm growth using dynamical Gaussian process implicit surface. *IEEE Trans. Biomed. Eng.* 66 (3), 609–622. Mar 1.
- Doyle, B.J., Callanan, A., Walsh, M.T., Grace, P.A., McGloughlin, T.M., 2009. A finite element analysis rupture index (FEARI) as an additional tool for abdominal aortic aneurysm rupture prediction. *Vasc. Dis. Prev.* 6 (1), 114–121.
- Doyle, B.J., Corbett, T.J., Callanan, A., Walsh, M.T., Vorp, D.A., McGloughlin, T.M., 2009. An experimental and numerical comparison of the rupture locations of an abdominal aortic aneurysm. *J. Endovasc. Ther.* 16, 322–335 [Internet]Jun [cited 2011 Sep 29]Available from: <http://jevtonline.org/doi/abs/10.1583/09-2697.1>.
- Dua, M.M., Dalman, R.L., 2010. Hemodynamic influences on abdominal aortic aneurysm disease: application of biomechanics to aneurysm pathophysiology. *Vascul. Pharmacol.* 53 (1–2), 11–21.
- Eck, V.G., Donders, W.P., Sturdy, J., Feinberg, J., Delhaas, T., Hellevik, L.R., et al., 2016. A guide to uncertainty quantification and sensitivity analysis for cardiovascular applications. *Int. J. Numer. Method Biomed. Eng.* 32 (8), e02755.
- Egido, J., Zaragoza, C., Gomez-Guerrero, C., Martin-Ventura, J.L., Blanco-Colio, L., Lavin, B., et al., 2011. Animal models of cardiovascular diseases. *J. Biomed. Biotechnol.* 2011, 497841.
- Elshafey, A., Mhaimeed, O., Al Ani, J., Elshazly, M.B., 2021. Chapter 15-Wearable devices and machine learning algorithms for cardiovascular health assessment. In: Al'Aref, S.J., Singh, G., Baskaran, L., Metaxas, D. (Eds.), *Machine Learning in Cardiovascular Medicine*. Academic Press, pp. 353–370.
- Erhart, P., Hyhlík-Dürr, A., Geisbüsch, P., Kotellis, D., Müller-Eschner, M., Gasser, T.C., et al., 2015. Finite element analysis in asymptomatic, symptomatic, and ruptured abdominal aortic aneurysms: in search of new rupture risk predictors. *Eur. J. Vasc. Endovasc. Surg.* 49 (3), 239–245.
- Fillinger, M.F., Marra, S.P., Raghavan, M.L., Kennedy, F.E., 2003. Prediction of rupture risk in abdominal aortic aneurysm during observation: wall stress versus diameter. *J. Vasc. Surg.* 37, 724–732.
- Fink, H.A., Lederle, F.A., Roth, C.S., Bowles, C.A., Nelson, D.B., Haas, M.A., 2002. The accuracy of physical examination to detect abdominal aortic aneurysm. *Arch. Intern. Med.* 162 (6), 833–836.
- Flondell-Sit, D., Lindblad, B., Köbel, T., Gottsäter, A., 2010. Markers of proteolysis, fibrinolysis, and coagulation in relation to size and growth rate of abdominal aortic aneurysms. *Vasc. Endovascular Surg.* 44 (4), 262–268.
- Fonken, J.H.C., Maas, E.J., Nievergeld, A.H.M., van Sambeek, M., van de Vosse, F.N., Lopata, R.G.P., 2021. Ultrasound-based fluid-structure interaction modeling of abdominal aortic aneurysms incorporating pre-stress. *Front. Physiol.* 12, 717593.
- Forbes, T.L., 2020. Uncertainty persists around type II endoleaks. *J. Vasc. Surg.* 71, 1035, 1035.
- Forneris, A., Kennard, J., Ismaguilova, A., Shepherd, R.D., Studer, D., Bromley, A., et al., 2021. Linking aortic mechanical properties, gene expression and microstructure: a new perspective on regional weakening in abdominal aortic aneurysms. *Front. Cardiovasc. Med.* 8, 631790.
- Forsythe, R.O., Newby, D.E., Robson, J.M.J., 2016. Monitoring the biological activity of abdominal aortic aneurysms beyond ultrasound. *Heart* 102, 817. –24.
- Gade, J.L., Thore, C.J., Sonesson, B., Stålhand, J., 2021. *In vivo* parameter identification in arteries considering multiple levels of smooth muscle activity. *Biomech. Model. Mechanobiol.* 20 (4), 1547–1559.
- García-García, F., Metaxa, E., Christodoulidis, S., Anthimopoulos, M., Kontopodis, N., Correa-Londono, M., et al., 2017. Prognosis of abdominal aortic aneurysms: a machine learning-enabled approach merging clinical, morphometric, biomechanical and texture information. In: *Proceedings of the IEEE Symposium on Computer-Based Medical Systems*, pp. 463–468.
- Gasser, T.C., Auer, M., Labruto, F., Swedenborg, J., Roy, J., 2010. Biomechanical rupture risk assessment of abdominal aortic aneurysms: model complexity versus predictability of finite element simulations. *Eur. J. Vasc. Endovasc. Surg.* 40 (2), 176–185.
- Gavrishchaka, V., Senyukova, O., Koepke, M., 2019. Synergy of physics-based reasoning and machine learning in biomedical applications: towards unlimited deep learning with limited data. *Adv. Phys. X* 4, 1582361.
- Gharahi, H., Zambrano, B.A., Lim, C., Choi, J., Lee, W., Baek, S., 2015. On growth measurements of abdominal aortic aneurysms using maximally inscribed spheres. *Med. Eng. Phys.* 37 (7), 683–691.
- Ginsburg, G.S., Phillips, K.A., 2018. Precision medicine: from science to value. *Health Aff.* 37 (5), 694–701.
- Golledge, J., Clancy, P., Jamrozik, K., Norman, P.E., 2007. Obesity, adipokines, and abdominal aortic aneurysm: health in men study. *Circulation* 116 (20), 2275–2279.
- Gomes, V.C., Raghavan, M.L., Silva, L.F.F., Gomes, J., Silvestre, G.C., Queiroz, A., et al., 2021. Experimental study of rupture pressure and elasticity of abdominal aortic aneurysms found at autopsy. *Ann. Vasc. Surg.* 70, 517–527.
- Grytsan, A., Watton, P.N., Holzapfel, G.A., 2015. A thick-walled fluid-solid-growth model of abdominal aortic aneurysm evolution: application to a patient-specific geometry. *J. Biomech. Eng.* 137, 031008.

- Guirguis-Blake, J.M., Beil, T.L., Senger, C.A., Coppola, E.L., 2019. Primary care screening for abdominal aortic aneurysm: updated evidence report and systematic review for the US preventive services task force. *JAMA J. Am. Med. Assoc.* 322, 2219–2238.
- Guo, Q., Du, X., Zhao, J., Ma, Y., Huang, B., Yuan, D., et al., 2017. Prevalence and risk factors of type II endoleaks after endovascular aneurysm repair: a meta-analysis. *PLoS One* 12 (2), e0170600.
- Guo, S., Li, Y., Li, R., Zhang, P., Wang, Y., Gopinath, S.C.B., et al., 2020. High-performance detection of an abdominal aortic aneurysm biomarker by immunosensing. *Biotechnol. Appl. Biochem.* 67 (3), 383–388.
- Habibi, M., D'Souza, R.M., Dawson, S.T.M., Arzani, A., 2021. Integrating multi-fidelity blood flow data with reduced-order data assimilation. *Comput. Biol. Med.* 135, 104566.
- Hahn, S., Perry, M., Morris, C.S., Wshah, S., Bertges, D.J., 2020. Machine deep learning accurately detects endoleak after endovascular abdominal aortic aneurysm repair. *JVS Vasc. Sci.* 1, 5–12.
- Haller, S.J., Crawford, J.D., Courchaine, K.M., Bohannon, C.J., Landry, G.J., Moneta, G. L., et al., 2018. Intraluminal thrombus is associated with early rupture of abdominal aortic aneurysm. *J. Vasc. Surg.* 67 (4), 1051–1058.
- Heo, J., Park, S.J., Kang, S.H., Oh, C.W., Bang, J.S., Kim, T., 2020. Prediction of intracranial aneurysm risk using machine learning. *Sci. Rep.* 10 (1), 6921.
- Hose, D.R., Lawford, P.V., Huberts, W., Hellevik, L.R., Omholt, S.W., van-de-Vosse, F.N., 2019. Cardiovascular models for personalised medicine: where now and where next? *Med. Eng. Phys.* 72, 38–48.
- Humphrey, J.D., Holzapfel, G.A., 2011. Mechanics, mechanobiology, and modeling of human abdominal aorta and aneurysms. *J. Biomech.* 45, 805–814.
- Jacomelli, J., Summers, L., Stevenson, A., Lees, T., Earnshaw, J.J., 2016. Impact of the first 5 years of a national abdominal aortic aneurysm screening programme. *Br. J. Surg.* 103 (9), 1125–1131.
- Jalalahmadi, G., Helguera, M., Linte, C.A., 2020. A machine leaning approach for abdominal aortic aneurysm severity assessment using geometric, biomechanical, and patient-specific historical clinical features. *Proc. SPIE Int. Soc. Opt. Eng.* 11317, 1131713.
- Jiang, Z., Do, H.N., Choi, J., Lee, W., Baek, S., 2020. A deep learning approach to predict abdominal aortic aneurysm expansion using longitudinal data. *Front. Phys.* 7, 235.
- Jiang, Z., Choi, J., Baek, S., 2021. Machine learning approaches to surrogate multifidelity growth and remodeling models for efficient abdominal aortic aneurysmal applications. *Comput. Biol. Med.* 133, 104394.
- Jones, G., Parr, J., Nithiarasu, P., Pant, S., 2021. Machine learning for detection of stenoses and aneurysms: application in a physiologically realistic virtual patient database. *Biomech. Model. Mechanobiol.* 20 (6), 2097–2146.
- Kadoglou, N.P.E., Moulakakis, K.G., Papadakis, I., Ikonomidis, I., Alepaki, M., Lekakis, J., et al., 2012. Changes in aortic pulse wave velocity of patients undergoing endovascular repair of abdominal aortic aneurysms. *J. Endovasc. Ther.* 19 (5), 661–666.
- Kadoglou, N.P.E., Papadakis, I., Moulakakis, K.G., Ikonomidis, I., Alepaki, M., Moustardas, P., et al., 2012. Arterial stiffness and novel biomarkers in patients with abdominal aortic aneurysms. *Regul. Pept.* 179 (1–3), 50–54.
- Kerut, E.K., To, F., Summers, K.L., Sheahan, C., Sheahan, M., 2019. Statistical and machine learning methodology for abdominal aortic aneurysm prediction from ultrasound screenings. *Echocardiography* 36 (11), 1989–1996.
- Kim, J.H., Avril, S., Duprey, A., Favre, J.P., 2012. Experimental characterization of rupture in human aortic aneurysms using a full-field measurement technique. *Biomech. Model. Mechanobiol.* 11 (6), 841–853.
- Kim, J., Peruski, B.K., Hunley, S.C., Kwon, S.T., Baek, S., 2013. Influence of surrounding tissues on biomechanics of aortic wall. *Int. J. Exp. Comput. Biomech.* 2, 105–117.
- Kim, H.O., Yim, N.Y., Kim, J.K., Kang, Y.J., Lee, B.C., 2019. Endovascular aneurysm repair for abdominal aortic aneurysm: a comprehensive review. *Korean J. Radiol.* 20, 1247–1265.
- Kissas, G., Yang, Y., Hwuang, E., Witschey, W.R., Detre, J.A., Perdikaris, P., 2020. Machine learning in cardiovascular flows modeling: predicting arterial blood pressure from non-invasive 4D flow MRI data using physics-informed neural networks. *Comput. Methods Appl. Mech. Eng.* 358, 112623.
- Koohy, H., 2018. The rise and fall of machine learning methods in biomedical research. *F1000Research* 6, 2012.
- Kramer, C.M., Cerilli, L.A., Hagspiel, K., DiMaria, J.M., Epstein, F.H., Kern, J.A., 2004. Magnetic resonance imaging identifies the fibrous cap in atherosclerotic abdominal aortic aneurysm. *Circulation* 109 (8), 1016–1021.
- Krittanaowong, C., Virk, H.U.H., Bangalore, S., Wang, Z., Johnson, K.W., Pinotti, R., et al., 2020. Machine learning prediction in cardiovascular diseases: a meta-analysis. *Sci. Rep.* 10 (1), 16057.
- Kuhl, E., Maas, R., Himpel, G., Menzel, A., 2007. Computational modeling of arterial wall growth. *Biomech. Model. Mechanobiol.* 6, 321–331.
- Kurvers, H., Veith, F.J., Lipsitz, E.C., Ohki, T., Gargiulo, N.J., Cayne, N.S., et al., 2004. Discontinuous, staccato growth of abdominal aortic aneurysms. *J. Am. Coll. Surg.* 199 (5), 709–715 [Internet]Nov 1 [cited 2019 Jan 29]Available from: <https://www.sciencedirect.com/science/article/pii/S107275150401052X?via%3Dihub>.
- Kwon, S.T., Rectenwald, J.E., Baek, S., 2011. Intracac pressure changes and vascular remodeling after endovascular repair of abdominal aortic aneurysms: review and biomechanical model simulation. *J. Biomech. Eng.* 133, 011011.
- Kwon, S.T., Burek, W., Dupay, A.C., Farsad, M., Baek, S., Park, E.A., et al., 2015. Interaction of expanding abdominal aortic aneurysm with surrounding tissue: retrospective CT image studies. *J. Nat. Sci.* 1 (8), e150 [Internet]Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26636132>.
- Lalys, F., Daoudal, A., Gindre, J., Göksu, C., Lucas, A., Kaladji, A., 2017. Influencing factors of sac shrinkage after endovascular aneurysm repair. *J. Vasc. Surg.* 65, 1830–1838.
- Lareyre, F., Adam, C., Carrier, M., Dommer, C., Mialhe, C., Raffort, J., 2019. A fully automated pipeline for mining abdominal aortic aneurysm using image segmentation. *Sci. Rep.* 9 (1), 13750.
- Lareyre, F., Adam, C., Carrier, M., Raffort, J., 2020. Prediction of abdominal aortic aneurysm growth and risk of rupture in the era of machine learning. *Angiology* 71, 767, 767.
- Lederle, F.A., Simel, D.L., 1999. Does this patient have abdominal aortic aneurysm? *J. Am. Med. Assoc.* 281 (1), 77–82.
- Lee, R., Jones, A., Cassimjee, I., Handa, A., 2017. International opinion on priorities in research for small abdominal aortic aneurysms and the potential path for research to impact clinical management. *Int. J. Cardiol.* 245, 253–255.
- Lee, R., Jarchi, D., Perera, R., Jones, A., Cassimjee, I., Handa, A., et al., 2018. Applied machine learning for the prediction of growth of abdominal aortic aneurysm in humans. *EJVES Short Rep.* 39, 24–28.
- Leemans, E.L., Willems, T.P., Van Der Laan, M.J., Slump, C.H., Zeebregts, C.J., 2017. Biomechanical indices for rupture risk estimation in abdominal aortic aneurysms. *J. Endovasc. Ther.* 24 (2), 254–261.
- Li, R.X., Luo, J., Balaram, S.K., Chaudhry, F.A., Lantis, J.C., Shahmirzadi, D., et al., 2011. *In-vivo* pulse wave imaging for arterial stiffness measurement under normal and pathological conditions. In: *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society. EMBS*, pp. 557–570.
- Li, R.X., Luo, J., Balaram, S.K., Chaudhry, F.A., Shahmirzadi, D., Konofagou, E.E., 2013. Pulse wave imaging in normal, hypertensive and aneurysmal human aortas *in vivo*: a feasibility study. *Phys. Med. Biol.* 58 (13), 4549–4562.
- Li, H., Lin, K., Shahmirzadi, D., 2016. FSI simulations of pulse wave propagation in human abdominal aortic aneurysm: the effects of sac geometry and stiffness. *Biomed. Eng. Comput. Biol.* 7, 25–36.
- Li, J., Pan, C., Zhang, S., Spin, J.M., Deng, A., Leung, L.L.K., et al., 2018. Decoding the genomics of abdominal aortic aneurysm. *Cell* 174 (6), 1361–1372.
- Li, B., Khan, S., Salata, K., Hussain, M.A., de Mestral, C., Greco, E., et al., 2019. A systematic review and meta-analysis of the long-term outcomes of endovascular versus open repair of abdominal aortic aneurysm. *J. Vasc. Surg.* 70, 954–969.
- Liang, L., Liu, M., Martin, C., Elefteriades, J.A., Sun, W., 2017. A machine learning approach to investigate the relationship between shape features and numerically predicted risk of ascending aortic aneurysm. *Biomech. Model. Mechanobiol.* 16 (5), 1519–1533.
- Liljeqvist, M.L., Bogdanovic, M., Siika, A., Gasser, t.C., Hultgren, R., Roy, J., 2021. Geometric and biomechanical modeling aided by machine learning improves the prediction of growth and rupture of small abdominal aortic aneurysms. *Sci. Rep.* 11, 18040.
- Limet, R., Sakalikhassan, N., Albert, A., 1991. Determination of the expansion rate and incidence of rupture of abdominal aortic aneurysms. *J. Vasc. Surg.* 14 (4), 540.
- Lindholt, J.S., Martin-Ventura, J.L., Urbonavicius, S., Ramos-Mozo, P., Flyvbjerg, A., Egido, J., et al., 2011. Insulin-like growth factor i - a novel biomarker of abdominal aortic aneurysms. *Eur. J. Vasc. Endovasc. Surg.* 42 (5), 560–562.
- Lindquist Liljeqvist, M., Hultgren, R., Gasser, T.C., Roy, J., 2016. Volume growth of abdominal aortic aneurysms correlates with baseline volume and increasing finite element analysis-derived rupture risk. *J. Vasc. Surg.* 63 (6), 1434–1442.
- Litnanovich, D., Bankier, A.A., Cantin, L., Raptopoulos, V., Boisselle, P.M., 2009. CT and MRI in diseases of the aorta. *Am. J. Roentgenol.* 193, 928–940.
- Liu, Q., Liang, J., Ma, O., 2020. A physics-based and data-driven hybrid modeling method for accurately simulating complex contact phenomenon. *Multibody Syst. Dyn.* 50 (1), 97–117.
- Liu, M., Dong, H., Lou, X., Iannucci, G., Chen, E.P., Leshnowar, B.G., et al., 2020. A novel anisotropic failure criterion with dispersed fiber orientations for aortic tissues. *J. Biomech. Eng.* 142 (11), 111002.
- Liu, M., Liang, L., Sun, W., 2020. A generic physics-informed neural network-based constitutive model for soft biological tissues. *Comput. Methods Appl. Mech. Eng.* 372, 113402.
- Long, A., Rouet, L., Lindholt, J.S., Allaire, E., 2012. Measuring the maximum diameter of native abdominal aortic aneurysms: review and critical analysis. *Eur. J. Vasc. Endovasc. Surg.* 43, 515–524.
- Lopez-Linares, K., Aranjuelo, N., Kabongo, L., Maclair, G., Lete, N., Leskovsky, P., et al., 2018. Fully automatic segmentation of abdominal aortic thrombus in post-operative CTA images using deep convolutional neural networks. *Med. Image Anal.* 46, 202–214.
- Lu, J., Zhou, X., Raghavan, M.L., 2007. Inverse elastostatic stress analysis in pre-deformed biological structures: demonstration using abdominal aortic aneurysms. *J. Biomech.* 40 (3), 693–696.
- Lu, Y.H., Mani, K., Panigrahi, B., Hsu, W.T., Chen, C.Y., 2016. Endoleak assessment using computational fluid dynamics and image processing methods in stented abdominal aortic aneurysm models. *Comput. Math. Methods Med.* 2016, 9567294.
- Müller-Wille, R., Schötz, S., Zeman, F., Uller, W., Güntner, O., Pfister, K., et al., 2015. CT features of early type II endoleaks after endovascular repair of abdominal aortic aneurysms help predict aneurysm sac enlargement. *Radiology* 274, 906–916.
- Madani, A., Bakhty, A., Kim, J., Mubarak, Y., Mofrad, M.R.K., 2019. Bridging finite element and machine learning modeling: stress prediction of arterial walls in atherosclerosis. *J. Biomech. Eng.* 141 (8), 084502.
- Maher, G.D., Fleeter, C.M., Schiavazzi, D.E., Marsden, A.L., 2021. Geometric uncertainty in patient-specific cardiovascular modeling with convolutional dropout networks. *Comput. Methods Appl. Mech. Eng.* 386, 114038.
- Marcaccio, C.L., Schermerhorn, M.L., 2021. Epidemiology of abdominal aortic aneurysms. *Semin. Vasc. Surg.* 34 (1), 29–37.
- Martufi, G., Gasser, T.C., 2012. Turnover of fibrillar collagen in soft biological tissue with application to the expansion of abdominal aortic aneurysms. *J. R. Soc. Interface* 9 (77), 3360–3377.

- Martufi, G., Auer, M., Roy, J., Swedenborg, J., Sakalihasan, N., Panuccio, G., et al., 2013. Multidimensional growth measurements of abdominal aortic aneurysms. *J. Vasc. Surg.* 58 (3), 748–755.
- Masuda, Y., Takanashi, K., Takasu, J., Morooka, N., Inagaki, Y., 1992. Expansion rate of thoracic aortic aneurysms and influencing factors. *Chest* 102 (2), 461–466.
- Matthews, E.O., Pinchbeck, J., Elmore, K., Jones, R.E., Moxon, J.V., Gollidge, J., 2021. The reproducibility of measuring maximum abdominal aortic aneurysm diameter from ultrasound images. *Ultrasound J.* 13 (1), 13.
- McCombie, D.B., Reisner, A.T., Asada, H.H., 2006. Adaptive blood pressure estimation from wearable PPG sensors using peripheral artery pulse wave velocity measurements and multi-channel blind identification of local arterial dynamics. In: *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology*. New York, pp. 3521–3524.
- Memon, A.A., Zarrouk, M., Ågren-Witteschus, S., Sundquist, J., Gottsäter, A., Sundquist, K., 2020. Identification of novel diagnostic and prognostic biomarkers for abdominal aortic aneurysm. *Eur. J. Prev. Cardiol.* 27 (2), 132–142.
- Meyrignac, O., Bal, L., Zadrou, C., Vavasour, A., Sewon, A., Gaudry, M., et al., 2020. Combining volumetric and wall shear stress analysis from CT to assess risk of abdominal aortic aneurysm progression. *Radiology* 295 (3), 722–729.
- Mofidi, R., Goldie, V.J., Kelman, J., Dawson, A.R.W., Murie, J.A., Chalmers, R.T.A., 2007. Influence of sex on expansion rate of abdominal aortic aneurysms. *Br. J. Surg.* 94 (3), 310–314.
- Mohammadi, S., Mohammadi, M., Dehlaghi, V., Ahmadi, A., 2019. Automatic segmentation, detection, and diagnosis of abdominal aortic aneurysm (AAA) using convolutional neural networks and Hough circles algorithm. *Cardiovasc. Eng. Technol.* 10 (3), 490–499.
- Molony, D.S., Callanan, A., Kavanagh, E.G., Walsh, M.T., McGloughlin, T.M., 2009. Fluid-structure interaction of a patient-specific abdominal aortic aneurysm treated with an endovascular stent-graft. *Biomed. Eng. Online* 8, 24.
- Monsalve-Torra, A., Ruiz-Fernandez, D., Marin-Alonso, O., Soriano-Payá, A., Camacho-Mackenzie, J., Carreño-Jaimes, M., 2016. Using machine learning methods for predicting in-hospital mortality in patients undergoing open repair of abdominal aortic aneurysm. *J. Biomed. Inform.* 62, 195–201.
- Mordi, I.R., Forsythe, R.O., Gellatly, C., Iskandar, Z., McBride, O.M., Saratzis, A., et al., 2019. Plasma desmosine and abdominal aortic aneurysm disease. *J. Am. Heart Assoc.* 8 (20), e013743.
- Nana, P., Dakis, K., Brodis, A., Spanos, K., Kouvelos, G., 2021. Circulating biomarkers for the prediction of abdominal aortic aneurysm growth. *J. Clin. Med.* 10 (8), 1718.
- Nandall, S.D., Goldklang, M.P., Kalashian, A., Dangra, N.A., D'Armiento, J.M., Konofagou, E.E., 2014. Monitoring and staging abdominal aortic aneurysm disease with pulse wave imaging. *Ultrasound Med. Biol.* 40 (10), 2404–2414.
- Nchimi, A., Cheramy-Bien, J., Gasser, T.C., Namur, G., Gomez, P., Seidel, L., et al., 2014. Multifactorial relationship between 18F-fluoro-deoxy-glucose positron emission tomography signaling and biomechanical properties in unruptured aortic aneurysms. *Circ. Cardiovasc. Imaging* 7, 82–91.
- Niederer, S.A., Sacks, M.S., Girolami, M., Willcox, K., 2021. Scaling digital twins from the artisanal to the industrial. *Nat. Comput. Sci.* 1 (5), 313–320.
- Novak, K., Polzer, S., Krivka, T., Vlachovsky, R., Staffa, R., Kubicek, L., et al., 2017. Correlation between transversal and orthogonal maximal diameters of abdominal aortic aneurysms and alternative rupture risk predictors. *Comput. Biol. Med.* 83, 151–156.
- Oliver-Williams, C., Sweeting, M.J., Turton, G., Parkin, D., Cooper, D., Rodd, C., et al., 2018. Lessons learned about prevalence and growth rates of abdominal aortic aneurysms from a 25-year ultrasound population screening programme. *Br. J. Surg.* 105 (1), 68–74.
- Owens, D.K., Davidson, K.W., Krist, A.H., Barry, M.J., Cabana, M., Caughey, A.B., et al., 2019. Screening for abdominal aortic aneurysm: US preventive services task force recommendation statement. *JAMA J. Am. Med. Assoc.* 322, 2211–2218.
- Parr, A., McCann, M., Bradshaw, B., Shahzad, A., Buttner, P., Gollidge, J., 2011. Thrombus volume is associated with cardiovascular events and aneurysm growth in patients who have abdominal aortic aneurysms. *J. Vasc. Surg.* 53 (1), 28–35 [Internet]. Jan [cited 2014 Jun 6]. Available from: <http://www.sciencedirect.com/science/article/pii/S0741521410018689>.
- Pettersson, N., Sjoerdsma, M., van Sambeek, M., van de Vosse, F., Lopata, R., 2021. Mechanical characterization of abdominal aortas using multi-perspective ultrasound imaging. *J. Mech. Behav. Biomed. Mater.* 119, 104509.
- Polzer, S., Gasser, T.C., 2015. Biomechanical rupture risk assessment of abdominal aortic aneurysms based on a novel probabilistic rupture risk index. *J. R. Soc. Interface* 12 (113), 20150852.
- Polzer, S., Man, V., Vlachovsky, R., Kubíček, L., Krafek, J., Staffa, R., et al., 2021. Failure properties of abdominal aortic aneurysm tissue are orientation dependent. *J. Mech. Behav. Biomed. Mater.* 114, 104181.
- Powell, J.T., Sweeting, M.J., Brown, L.C., Gotensparre, S.M., Fowkes, F.G., Thompson, S.G., 2011. Systematic review and meta-analysis of growth rates of small abdominal aortic aneurysms. *Br. J. Surg.* 98, 609–618.
- Raffort, J., Adam, C., Carrier, M., Lareyre, F., 2020. Fundamentals in artificial intelligence for vascular surgeons. *Ann. Vasc. Surg.* 65, 254–260.
- Raghavan, M.L., Vorp, D.A., 2000. Toward a biomechanical tool to evaluate rupture potential of abdominal aortic aneurysm: identification of a finite strain constitutive model and evaluation of its applicability. *J. Biomech.* 33, 475–482.
- Reeps, C., Maier, A., Pelisek, J., Härtl, F., Grabher-Meier, V., Wall, W.A., et al., 2013. Measuring and modeling patient-specific distributions of material properties in abdominal aortic aneurysm wall. *Biomech. Model. Mechanobiol.* 12 (4), 717–733.
- Rengarajan, B., Wu, W., Wiedner, C., Ko, D., Multuk, S.C., Eskandari, M.K., et al., 2020. A comparative classification analysis of abdominal aortic aneurysms by machine learning algorithms. *Ann. Biomed. Eng.* 48 (4), 1419–1429.
- Rengarajan, B., Patnaik, S.S., Finol, E.A., 2021. A predictive analysis of wall stress in abdominal aortic aneurysms using a neural network model. *J. Biomech. Eng.* 143 (12), 121004.
- Rengier, F., Geisbüsch, P., Schoenhagen, P., Müller-Eschner, M., Vosschenrich, R., Karmonik, C., et al., 2014. State-of-the-art aortic imaging: part II - applications in transcatheter aortic valve replacement and endovascular aortic aneurysm repair. *Vasa* 43 (1), 6–26.
- Richards, J.M.J., Semple, S.I., MacGillivray, T.J., Gray, C., Langrish, J.P., Williams, M., et al., 2011. Abdominal aortic aneurysm growth predicted by uptake of ultrasmall superparamagnetic particles of iron oxide: a pilot study. *Circ. Cardiovasc. Imaging* 4 (3), 274–281.
- Rissland, P., Alemu, Y., Einav, S., Ricotta, J., Bluestein, D., 2009. Abdominal aortic aneurysm risk of rupture: patient-specific FSI simulations using anisotropic model. *J. Biomech. Eng.* 131, 31001.
- Roy, D., Kauffmann, C., Delorme, S., Lerouge, S., Cloutier, G., Soulez, G., 2012. A literature review of the numerical analysis of abdominal aortic aneurysms treated with endovascular stent grafts. *Comput. Math. Methods Med.* 2012, 820389.
- Salata, K., Hussain, M.A., De Mestral, C., Greco, E., Aljabri, B.A., Mamdani, M., et al., 2019. Comparison of outcomes in elective endovascular aortic repair vs open surgical repair of abdominal aortic aneurysms. *JAMA Netw. Open* 2 (7), e196578.
- Salman, H.E., Ramazanli, B., Yavuz, M.M., Yalcin, H.C., 2019. Biomechanical investigation of disturbed hemodynamics-induced tissue degeneration in abdominal aortic aneurysms using computational and experimental techniques. *Front. Bioeng. Biotechnol.* 7, 111.
- Salvi, A., Finol, E., Menon, P.G., 2021. Convolutional neural network based segmentation of abdominal aortic aneurysms. In: *Proceedings of the 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society*, pp. 2629–2632.
- Schiavazzi, D.E., Arbía, G., Baker, C., Hlavacek, A.M., Hsia, T.Y., Marsden, A.L., et al., 2016. Uncertainty quantification in virtual surgery hemodynamics predictions for single ventricle palliation. *Int. J. Numer. Method Biomed. Eng.* 32 (3), e02737.
- Seo, H., Badiei Khuzani, M., Vasudevan, V., Huang, C., Ren, H., Xiao, R., et al., 2020. Machine learning techniques for biomedical image segmentation: an overview of technical aspects and introduction to state-of-art applications. *Med. Phys.* e148–e167.
- Seyedsalehi, S., Zhang, L., Choi, J., Baek, S., 2015. Prior distributions of material parameters for Bayesian calibration of growth and remodeling computational model of abdominal aortic wall. *J. Biomech. Eng.* 137 (10), 101001 [Internet]. Available from: <http://biomechanical.asmedigitalcollection.asme.org/article.aspx?doi=10.1115/1.4031116>.
- Shaikhina, T., Lowe, D., Daga, S., Briggs, D., Higgins, R., Khovanova, N., 2015. Machine learning for predictive modelling based on small data in biomedical engineering. *IFAC-PapersOnLine* 48, 469–474.
- Sharp, M.A., Collin, J., 2003. A myth exposed: fast growth in diameter does not justify precocious abdominal aortic aneurysms repair. *Eur. J. Vasc. Endovasc. Surg.* 25 (5), 408–411.
- Singh, T.P., Moxon, J.V., Gasser, T.C., Gollidge, J., 2021. Systematic review and meta-analysis of peak wall stress and peak wall rupture index in ruptured and asymptomatic intact abdominal aortic aneurysms. *J. Am. Heart Assoc.* 10 (8), e019772.
- Soares Ferreira, R., Gomesoliveira, N., Oliveira-Pinto, J., Van Rijn, M.J., Ten Raa, S., Verhagen, H.J., et al., 2018. Review on management and outcomes of ruptured abdominal aortic aneurysm in women. *J. Cardiovasc. Surg.* 59, 195–200 (Torino).
- Solberg, S., Singh, K., Wilsaard, T., Jacobsen, B.K., 2005. Increased growth rate of abdominal aortic aneurysms in women. The tromsø study. *Eur. J. Vasc. Endovasc. Surg.* 29 (2), 145–149.
- Sonesson, B., Vernersson, E., Hansen, F., Länne, T., 1997. Influence of sympathetic stimulation on the mechanical properties of the aorta in humans. *Acta Physiol. Scand.* 159 (2), 139–145.
- Sprynger, M., Willems, M., Van Damme, H., Drieghe, B., Wautrecht, J.C., Moonen, M., 2019. Screening program of abdominal aortic aneurysm. *Angiology* 70 (5), 407–413.
- Stevens, R.R.F., Grytsan, A., Biasetti, J., Roy, J., Liljeqvist, M.L., Gasser, T.C., 2017. Biomechanical changes during abdominal aortic aneurysm growth. *PLoS One* 12 (11), e0187421.
- Stoecker, J.B., Eddinger, K.C., Pouch, A.M., Jackson, B.M., 2021. Image-derived geometric characteristics predict abdominal aortic aneurysm growth in a machine learning model. *Lecture Notes in Computer Science*. Springer, pp. 35–45 (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics).
- Sweeting, M.J., Thompson, S.G., Brown, L.C., Powell, J.T., 2012. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. *Br. J. Surg.* 99 (5), 655–665.
- Sweeting, M.J., Masconi, K.L., Jones, E., Ulug, P., Glover, M.J., Michaels, J.A., et al., 2018. Analysis of clinical benefit, harms, and cost-effectiveness of screening women for abdominal aortic aneurysm. *Lancet* 392 (10146), 487–495.
- Tada, H., Fujino, N., Nomura, A., Nakanishi, K., Hayashi, K., Takamura, M., et al., 2021. Personalized medicine for cardiovascular diseases. *J. Hum. Genet.* 66, 67–74.
- Talebi, S., Madani, M.H., Madani, A., Chien, A., Shen, J., Mastrodicasa, D., et al., 2020. Machine learning for endoleak detection after endovascular aortic repair. *Sci. Rep.* 10 (1), 18343.
- Tanweer, O., Wilson, T.A., Metaxa, E., Riina, H.A., Meng, H., 2014. A comparative review of the hemodynamics and pathogenesis of cerebral and abdominal aortic aneurysms: lessons to learn from each other. *J. Cerebrovasc. Endovasc. Neurosurg.* 16 (4), 335–349.
- Teng, Z., Feng, J., Zhang, Y., Huang, Y., Sutcliffe, M.P.F., Brown, A.J., et al., 2015. Layer- and direction-specific material properties, extreme extensibility and ultimate

- material strength of human abdominal aorta and aneurysm: a uniaxial extension study. *Ann. Biomed. Eng.* 43 (11), 2745–2759.
- The AIAA digital engineering integration committee. digital twin : definition & value. *An AIAA and AIA Position Paper*. 2020.
- Truijers, M., Pol, J.A., SchultzeKool, L.J., van Sterkenburg, S.M., Fillinger, M.F., Blankensteijn, J.D., 2007. Wall stress analysis in small asymptomatic, symptomatic and ruptured abdominal aortic aneurysms. *Eur. J. Vasc. Endovasc. Surg.* 33 (4), 401–407.
- Ultee, K.H.J., Büttner, S., Huurman, R., Bastos Gonçalves, F., Hoeks, S.E., Bramer, W.M., et al., 2018. Editor's choice – systematic review and meta-analysis of the outcome of treatment for Type II endoleak Following endovascular aneurysm repair. *Eur. J. Vasc. Endovasc. Surg.* 56, 794–807.
- Vega de Céniga, M., Gómez, R., Estallo, L., Rodríguez, L., Baquer, M., Barba, A., 2006. Growth rate and associated factors in small abdominal aortic aneurysms. *Eur. J. Vasc. Endovasc. Surg.* 31 (3), 231–236 [Internet]Mar [cited 2014 Jun 6]Available from. <http://www.sciencedirect.com/science/article/pii/S1078588405006210>.
- Vega de Céniga, M., Esteban, M., Quintana, J.M., Barba, A., Estallo, L., de la Fuente, N., et al., 2009. Search for serum biomarkers associated with abdominal aortic aneurysm growth - a pilot study. *Eur. J. Vasc. Endovasc. Surg.* 37 (3), 297–299.
- Ventatasubramanian, A.K., Fagan, M.J., Mehta, T., Mylankal, K.J., Ray, B., Kuhan, G., et al., 2004. A comparative study of aortic wall stress using finite element analysis for ruptured and non-ruptured abdominal aortic aneurysms. *Eur. J. Vasc. Surg.* 28, 168–176.
- Vergaro, G., Del Corso, A., Franzini, M., Emdin, M., 2020. Biomarkers for growth prediction of abdominal aortic aneurysm: a step forward(?). *Eur. J. Prev. Cardiol.* 27, 130–131.
- Vezzoli, M., Bonardelli, S., Peroni, M., Ravanelli, M., Garrafa, E., 2017. A simple blood test, such as complete blood count, can predict calcification grade of abdominal aortic aneurysm. *Int. J. Vasc. Med.* 2017, 1370751.
- Wang, D.H., Makaroun, M.S., Webster, M.W., Vorp, D.A., 2002. Effect of intraluminal thrombus on wall stress in patient-specific models of abdominal aortic aneurysm. *J. Vasc. Surg.* 36, 598–604.
- Wang, T., Jin, W., Liang, F., Alastruey, J., 2021. Machine learning-based pulse wave analysis for early detection of abdominal aortic aneurysms using in silico pulse waves. *Symmetry* 13 (5), 804 (Basel).
- Wanhainen, A., Mani, K., Vorkapic, E., De Basso, R., Björck, M., Länne, T., et al., 2017. Screening of circulating microRNA biomarkers for prevalence of abdominal aortic aneurysm and aneurysm growth. *Atherosclerosis* 256, 82–88.
- Watson, J.D.B., Gifford, S.M., Bandyk, D.F., 2020. Aortic aneurysm screening using duplex ultrasound: choosing wisely who to examine. *Semin. Vasc. Surg.* 33 (3–4), 54–59.
- Watton, P.N., Hill, N.A., Heil, M., 2004. A mathematical model for the growth of the abdominal aortic aneurysm. *Biomech. Model. Mechanobiol.* 3, 98–113.
- Weng, S.F., Reps, J., Kai, J., Garibaldi, J.M., Qureshi, N., 2017. Can machine-learning improve cardiovascular risk prediction using routine clinical data? *PLoS One* 12 (4), e0174944.
- Wilmink, A.B.M., Forshaw, M., Quick, C.R.G., Hubbard, C.S., Day, N.E., 2002. Accuracy of serial screening for abdominal aortic aneurysms by ultrasound. *J. Med. Screen.* 9 (3), 125–127.
- Wilson, J.S., Baek, S., Humphrey, J.D.D., 2012. Importance of initial aortic properties on the evolving regional anisotropy, stiffness and wall thickness of human abdominal aortic aneurysms. *J. R. Soc. Interface* 9, 2047–2058.
- Wilson, J.S., Baek, S., Humphrey, J.D., 2013. Parametric study of effects of collagen turnover on the natural history of abdominal aortic aneurysms. *Proc. R. Soc. A Math Phys Eng. Sci.* 469 (2150), 20120556.
- Ye, D., Zun, P., Krzhizhanovskaya, V., Hoekstra, A.G., 2022. Uncertainty quantification of a three-dimensional in-stent restenosis model with surrogate modelling. *J. R. Soc. Interface* 18, 20210864.
- Zagrapan, B., Eilenberg, W., Scheuba, A., Klopff, J., Brandau, A., Story, J., et al., 2021. Complement factor C5a is increased in blood of patients with abdominal aortic aneurysm and has prognostic potential for aneurysm growth. *J. Cardiovasc. Transl. Res.* 14 (4), 761–769.
- Zambrano, B.A., Gharahi, H., Lim, C.Y., Jaber, F.A., Choi, J., Lee, W., et al., 2016. Association of intraluminal thrombus, hemodynamic forces, and abdominal aortic aneurysm expansion using longitudinal CT images. *Ann. Biomed. Eng.* 44 (5), 1502–1514.
- Zambrano, B.A., Gharahi, H., Lim, C.Y., Lee, W., Baek, S., 2022. Association of vortical structures and hemodynamic parameters for regional thrombus accumulation in abdominal aortic aneurysms. *Int. J. Numer. Method Biomed. Eng.* 38 (2), e3555.
- Zeinali-Davarani, S., Baek, S., 2012. Medical image-based simulation of abdominal aortic aneurysm growth. *Mech. Res. Commun.* 42, 107–117.
- Zeinali-Davarani, S., Sheidaei, A., Baek, S., 2011. A finite element model of stress-mediated vascular adaptation: application to abdominal aortic aneurysms. *Comput. Methods Biomech. Biomed. Eng.* 9, 803–817.
- Zhang, Y., Barocas, V.H., Berceci, S.A., Clancy, C.E., Eckmann, D.M., Garbey, M., et al., 2016. Multi-scale modeling of the cardiovascular system: disease development, progression, and clinical intervention. *Ann. Biomed. Eng.* 44 (9), 2642–2660.
- Zhang, L., Jiang, Z., Choi, J., Lim, C.Y., Maiti, T., Baek, S., 2019. Patient-specific prediction of abdominal aortic aneurysm expansion using bayesian calibration. *IEEE J. Biomed. Health Inform.* 23, 2537–2550. Jan 30.
- Zhang, L., Zambrano, B.A., Choi, J., Lee, W., Baek, S., Lim, C.Y., 2020. Intraluminal thrombus effect on the progression of abdominal aortic aneurysms by using a multistate continuous-time Markov chain model. *J. Int. Med. Res.* 48 (11), 1–12.
- Zhu, C., Leach, J.R., Tian, B., Cao, L., Wen, Z., Wang, Y., et al., 2019. Evaluation of the distribution and progression of intraluminal thrombus in abdominal aortic aneurysms using high-resolution MRI. *J. Magn. Reson. Imaging* 50 (3), 994–1001.
- Zieman, S.J., Melenovsky, V., David, A.K., 2005. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler. Thromb. Vasc. Biol.* 25, 932–943.