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Numerical Approach for The Evaluation of Hemodynamic Behaviour in Peripheral Arterial Disease: A Systematic Review

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ABSTRACT

Reduced blood flow to the lower extremities causes peripheral arterial disease (PAD), which is caused by atherosclerotic plaque in the arterial wall. If this impairment is not treated, it will result in severe vascular diseases like ulceration and gangrene. Previous research has shown that while evaluating the pathology of the peripheral artery, the assumption of the model geometry significantly impacts the uncertainty of the stenosis area. However, more work needs to be done to understand the interaction between mechanical better and flow conditions in the peripheral artery using a separate computer model of the cardiovascular system. This paper reviews the numerical approach on pre- and post-treatment of hemodynamic behavior in peripheral arterial disease (PAD). The goal of this study was to thoroughly examine the most recent developments with the application of computational studies in PAD from 2017 to 2022. While FSI investigation highlights the behavior of both the fluid and structure domains (blood and artery) during the numerical analysis of blood flow, CFD simulations primarily focus on the fluid domain (blood) behavior. Out of 92 research publications, 19 were appropriate for this assignment. This thorough study divides the publications into the categories of CFD, and FSI approaches. The results were then reviewed in accordance with the wall characteristic, analytical method, geometry, viscosity models, and validation. This paper summarizes the parameters of geometrical construction, viscosity models, analysis methods, and wall characteristics taken into consideration by the researchers to identify and simulate the blood flow in the stenosis area. These parameters are summarised in this study. Additionally, it could offer systematic data to help future studies produce better computational analyses.

1. Introduction

Peripheral Arterial Disease (PAD) in the lower limbs of the body has affected more than 200 million people globally [1-3]. The PAD prevalence cases recorded constantly increasing especially in the elderly for the past 15 years, indicating the high burden to the healthcare systems [4]. Among

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the risk factors for PAD are diabetes, smoking, hypertension, hyperlipaemia, heart disease and stroke [5].

Majority of PAD patients are asymptomatic, but many also have intermittent claudication, which can cause numbness, cramping, or pain in the legs when walking or ascending stairs. If PAD is not treated, the patient may experience lifestyle-altering leg ulcers, gangrene, and eventually amputation [6]. Atherosclerosis is the primary cause of the obstruction of blood supply, which causes the impairment (Figure 1). As a result of the build-up of lipids, cholesterol, and other compounds in the artery wall, atherosclerosis is the development of a substance known as plaque. Particularly, the profunda femoris artery, a branch of the femoral artery and a component of the external iliac arteries, is where it is most likely to happen [7].

Low wall shear stress (WSS) in specific areas of the arteries encourages the build-up of substances by reducing the atheroprotective genes on the arterial wall and in the same time promoting the atherogenic ones that will lead to plaque formation [1,3]. Dead foam cells, macrophages, smooth muscle cells, and extracellular matrix are present in the plaque [8]. The accumulation of plaques will narrow the arterial inner diameter, reducing the wall compliance (increased arterial stiffness) [9]. In situations of high grade stenosis, the local blood flow may change from laminar to turbulent in the downstream area [10,11]. The narrowing phenomenon also disrupts the nearby normal blood flow. An abrupt increase in WSS on the endothelium layer may cause the plaque to break and produce a blood clot, which may reduce blood flow to the lower reaches of peripheral arteries.

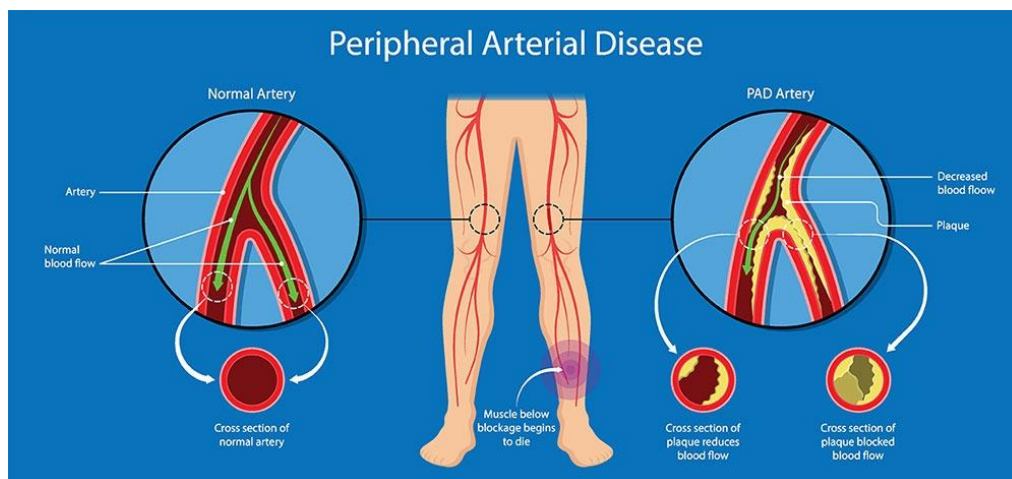


Fig. 1. Schematic diagram of atherosclerosis in the lower limbs of the body causing peripheral arterial disease (PAD) [12]

Patients with severe PAD and large plaque diameters may be advised to undergo endovascular therapy in addition to taking generic drugs such as aspirin, clopidogrel, and statins [13]. Patients may be referred to surgeons for open surgical atherectomy intervention or for invasive procedures like angioplasty and stenting [6,14,15]. Generally, there are two methods of endovascular therapy i.e., invasive and non-invasive techniques. Stent implantation is usually performed to open-up the narrowed artery and prevent it from happening again. widen the affected arteries from narrowing again. Figure 2 depicts the state of an artery with stenosis after stent placement. For minor and long/medium lesions, stenting and angioplasty are advised [2]. One of the advanced ways in percutaneous transluminal angioplasty (PTA) to totally relieve the constriction by "leave nothing behind" strategy is the use of drug-coated balloons and bioresorbable stents [16]. After stent implantation, arterial stiffness may change due to a reduction in axial elongation, although this has no impact on the average arterial curvature [17]. Additionally, these implantations limit the artery's

axial shortening and result in decreased flow velocity during leg flexion [18]. For femoropopliteal artery, the long-term primary patency after endovascular treatment remains low with rates around 25% [19]. The development of restenosis may strongly happen after 6-12 months follow-up on the treated area [20,21].

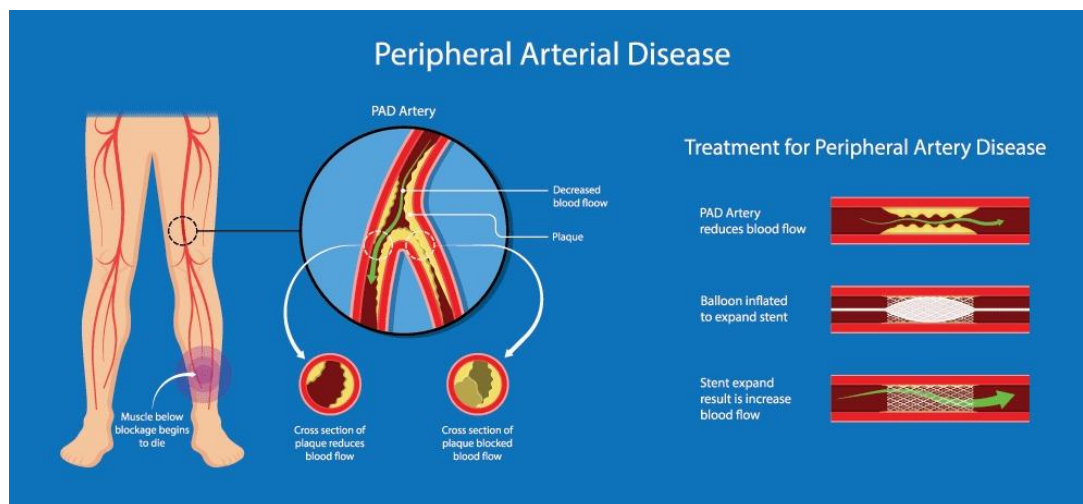


Fig. 2. Treatment for peripheral artery disease (PAD) [22]

Previous studies claims that their working models have yet to achieve the expected results in term of its precision [18,23,24]. They nevertheless need to occasionally take into account restrictions when choosing variables such geometry types, viscosity models (whether Newtonian or non-Newtonian), types of flows, boundary conditions at the entrance and outflow of the artery, and the solver used to solve its governing equations. In order to comprehend how the PADs behave, it is essential to reveal and enhance those assessments before moving forward with the inquiry. The discussion of choosing parameters will be expanded upon in the next section.

This paper presents a systematic review of important recent research articles from 2017 to 2021 in the investigation of blood hemodynamic in PAD using computer simulation analysis. This work aims to demonstrate the methods applied to the computer modelling and investigation of this phenomenon. Future research may benefit from a better approach from the systematic review in order to provide computational analyses with more effect.

2. Methodology

This systematic review was performed according to an agreed predefined protocol. The review was conducted and presented according to the statement standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [25].

2.1 Search Strategy

The literature was searched up to October 31, 2022, using the Boolean operators AND, OR, and NOT along with the keywords "Peripheral Artery Disease," "Atherosclerosis," "Computational Fluid Dynamics," and "Fluid Structure Interaction." Science Direct, PubMed, and Scopus are among the search databases.

2.2 Eligibility Criteria

Search references were gathered and arranged according to their research importance in accordance with PRISMA principles. First, the database's articles were categorised by filtering according to article category and restricting the year of publication to 2018 and later. The remaining papers were then manually evaluated for quality and topical relevance through the reading of abstracts and conclusions. The exclusion criteria were restricted to the following: (1) full texts in languages other than English; (2) kinds of arteries that do not exist from hip to toe (lower limb extremities); (3) studies on animals; and (4) accessibility of the articles in the database. After screening, 19 articles were found that could have their content's uniqueness evaluated in full. In several of the studies by the same author, when a meta-analysis technique was used to address these problems, it was discovered that the information and findings were insufficient.

3. Results

Out of the 92 research publications, 19 have been found to be eligible for this work after duplicates were removed and papers were excluded after reading the abstracts. This thorough analysis was done to divide the publications mainly into two groups: CFD approaches and FSI approaches. While FSI investigation highlights the behaviour of both the fluid and structural domains (blood and artery) during numerical analysis of blood flow, CFD simulations primarily focus on the behaviour of the fluid domain (blood).

3.1 Study Characteristic

Possible relevant article papers were found after using the screening methodology for this study through systematic review in accordance with PRISMA criteria, as shown in Figure 3. 18/19 (94%) of the included papers were exclusively CFD works, whereas 1/19 (6%) were FSI works.

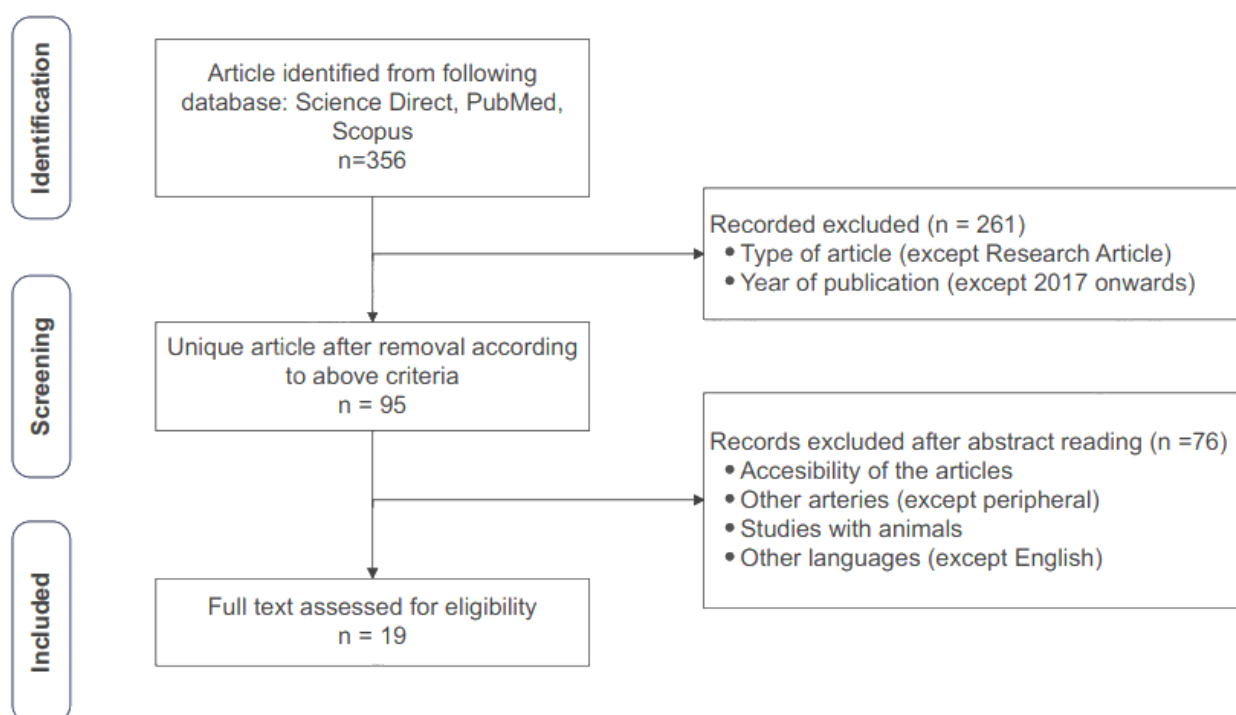


Fig. 3. Flowchart of the systematic review

Thus, Table 1's categories provide a summary of the review's findings [26]. Classification was carried out to draw attention to the crucial variables examined in the pre- and post-processing simulation methods for PAD research in the corresponding articles. The several types of geometry models that were used for pre-processing parameters were first discussed, then the geometry model source, the analysis technique, and finally an explanation of the different types of viscosity models and wall features that were considered during simulation. The post-processing parameter was noted in the category of "Validation procedure." The technique employed in the study to evaluate the reliability and excellence of the simulation results is represented by this category. Validation techniques may change depending on the author's preferences and considerations.

Table 1
 Summary of CFD and FSI studies in peripheral arteries disease [26]

Article	Geometry	Image Source	Analysis Platform	Viscosity Model	Wall Characteristic	Validation Method
CFD Studies						
Xu <i>et al.</i> , [27]	Patient-specific (stenosis, bending, branching)	MRA (MIMICS)	CFD (Scientific report of comparison between CFD data and UDV result)	Newtonian	Rigid	Ultrasound Doppler
Salman and Yazicioglu [23]	Patient-specific (stenosed)	CTA (MIMICS)	CFD (Analysis of skin response to identify the location of stenosis)	-	Single layer structured (FEA)	-
Corti <i>et al.</i> , [1]	Idealised (healthy SFA)	-	CFD-FLUENT	non-Newtonian (Carreau)	Rigid	-
Colombo <i>et al.</i> , [2]	Patient-specific (stented)	CTA (CAD)	CFD-FLUENT	non-Newtonian (Carreau)	Rigid (based on ABM Framework)	-
Gogineni and Ravigururajan [7]	Idealised (bifurcation)	-	CFD-FLUENT	Newtonian	Rigid	-
Gökgöl <i>et al.</i> , [18]	Patient-specific (stented, kinking)	CTA (MIMICS)	CFD-CFX	Newtonian	Rigid	-
Desyatova <i>et al.</i> , [28]	Patient-specific (aging, FPA)	CTA	CFD-CFX	Newtonian	FEA (Abaqus)	-
Donadoni <i>et al.</i> , [29]	Patient-specific (stenosed)	USA	CFD-CFX	non-Newtonian (Carreau-Yasuda)	Compliant	-
Gu <i>et al.</i> , [30]	Idealised (peripheral ECMO)	-	CFD based on Finite Element Method	Newtonian	Rigid	Clinical data
Ferrarini <i>et al.</i> , [31]	Patient Specific (FPA)	CTA	CFD-FLUENT	Newtonian, non-	Rigid	-

				Newtonian (Carreau)		
Donadoni <i>et al.</i> , [32]	Patient-specific (vein graft failure)	CTA (Scan IP)	CFD-CFX	Newtonian	Rigid	Clinical data
Wood <i>et al.</i> , [33]	Patient-specific (curvature, tortuosity)	MRA (MIMICS) USA (HDI Lab, MATLAB)	CFD-CFX	Newtonian	Rigid	-
Li <i>et al.</i> , [34]	Patient-specific (tortuosity)	CTA (MIMICS)	CFD-CFX	Newtonian	Rigid	-
McGah <i>et al.</i> , [35]	Patient-specific (curvature)	USA (MATLAB)	CFD-FLUENT	-	Rigid	-
Colombo <i>et al.</i> , [36]	Idealised (FPA)	-	LS-DYNA (ALE)	Newtonian	Rigid	-
Colombo <i>et al.</i> , [37]	Patient-specific (stented, SFA)	CTA	CFD-FLUENT	non-Newtonian (Carreau)	Rigid	Experimental data
Gökgöl <i>et al.</i> , [38]	Patient-specific (FPA)	OCT	LS-DYNA	Newtonian	Rigid	Clinical data
Corti <i>et al.</i> , [39]	Idealised (FA)	-	CFD-FLUENT	non-Newtonian (Carreau)	Rigid	Clinical data
FSI Studies						
Wang <i>et al.</i> , [40]	Patient-specific (stenosed)	CTA (MIMICS)	CFD-FLUENT, One-Way	non-Newtonian (Carreau)	nonlinear, homogenous, and hyperelastic material	-

CAD – Computer Aided Design; MIMICS – Materialise Interactive Medical Image Control System; CTA – Computed Tomography Angiography; MRA – Magnetic Resonance Angiography; USA – Ultrasound Angiography; OCT – Optical Coherence Tomography; FEA – Finite Element Analysis; ECMO - Extracorporeal Membrane Oxygenation; ALE – Arbitrary Lagrangian Eulerian

3.2 Geometry Construction

In order to get a qualitative outcome in the investigation of peripheral blood flow, the choice of PAD geometrical configuration is essential in the early stages of simulation. Idealized and patient-specific model geometries are the two types of geometries most frequently utilised. Patient-specific (13/19) as opposed to idealised model (5/19) has been employed more frequently out of the 19 papers (CFD and FSI). Furthermore, a comparative study (1/19) was carried out using an idealised and patient-specific model.

3.3 Medical Images

The patient-specific models from the available research papers are found to often use CTA image sources (9 out of 19 articles), followed by USA (2 out of 19 articles), while MRA and OCT is least likely to be used among the examined studies. However, several studies done by Wood *et al.*, [33] have used more than one image source. The typical imaging method used in clinical diagnosis is described in Table 2.

Table 2
 The comparison of stenosis diagnosis method [41,42]

Method	Hemodynamic data	Anatomic Measurements	Time consumption	Resolution	Risk
Computed Tomography Angiography (CTA)	No	Yes	Low	High	Radiation exposure
Magnetic resonance Angiography (MRA)	Yes	Yes	High	Low	-
Ultrasound Angiography (USA)	No	Yes	High	High (have depth limit)	Imaging modality (operator and patient dependent)

3.4 Characteristics of Peripheral Artery

The network of arteries from hip to toe makes up most of the peripheral arterial system. The Iliac Artery (IA), which later split into the internal and exterior iliac arteries as seen in Figure 4, is the starting point for the Peripheral Artery (PA) construction. The external iliac artery continues as the femoral artery (FA), a significant artery in the thigh. FA is made up of the Superficial Femoral Artery (SFA), which connects to the lower branch of the Profunda Femoral Artery (PFA), also known as the Deep Femoral Artery, and the Common Femoral Artery (CFA) (DFA). From the distal end of the FA, SFA goes down the medial thigh to the knee, where it is terminated by the Popliteal Artery (PA), which continues to the lower boundary of the popliteus muscle. Peroneal Tibial Artery, also known as Fibular Artery, is located at the lowest extremities of Posterior Tibial Artery and performs comparable responsibilities to ATA to give blood to the lower compartment of the leg.

A smooth blood flow along the hip to toe area also depends on the size and length of peripheral arteries. Additionally, those criteria were discovered to vary in humans depending on a variety of variables, including age group, gender, body size, and leg side. Table 3 summarises findings from Shahrulakmar *et al.*, [26] the size and length of the arteries involved in the peripheral system from earlier studies, focusing primarily on the relationship between gender and side of the leg.

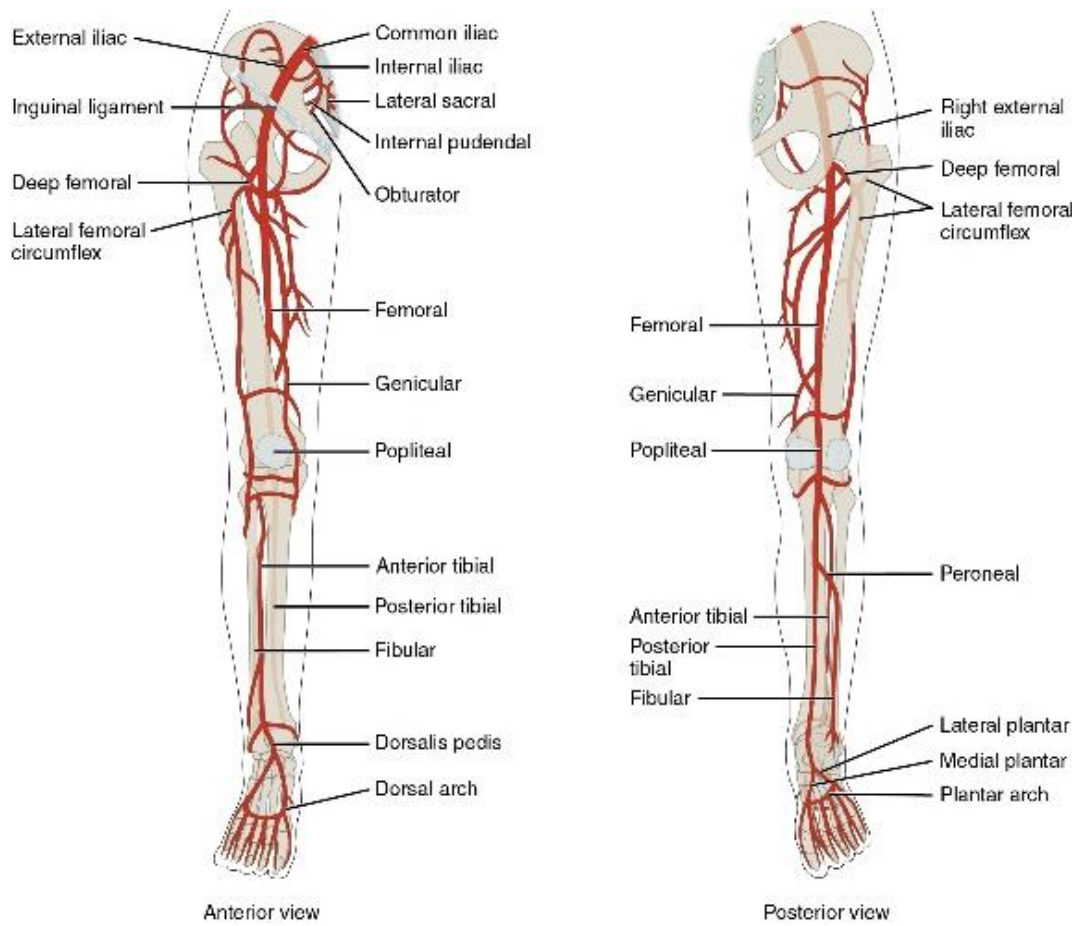


Fig. 4. Vascular anatomy of lower limb arteries [43]

Table 3
 Summary of peripheral arterial sizes [26]

Article	Gender / Side of leg	FA		CFA		PFA		SFA		PA		PTA		ATA		Peroneal	
		L (mm)	D (mm)	L (mm)	D (mm)	L (mm)	D (mm)	L (mm)	D (mm)	L (mm)	D (mm)	L (mm)	D (mm)	L (mm)	D (mm)	L (mm)	D (mm)
Avolio [44]	-	127	4.8	-	-	126	4.6	-	-	94	4.0	161	3.6	25 & 150	2.6 & 2.0	159	2.6
Valerio <i>et al.</i> , [45]	-	-	-	-	9.4 ± 1.3	-	-	-	-	-	-	-	-	-	-	-	-
Lorbeer <i>et al.</i> , [46]	Right	-	-	-	8.03 ± 1.17	-	-	-	5.94 ± 0.91	-	5.34 ± 0.95	-	3.09 ± 0.38	-	3.36 ± 0.46	-	3.10 ± 0.45
	Left	-	-	-	8.12 ± 1.2	-	-	-	5.93 ± 0.93	-	5.43 ± 0.91	-	3.09 ± 0.38	-	3.43 ± 0.46	-	3.08 ± 0.39
Wolf <i>et al.</i> , [47]	Male	-	-	-	9.3 ± 1.1	-	-	-	7.3 ± 1.0	-	6.9 ± 0.9	-	-	-	-	-	-
	Female	-	-	-	8.4 ± 0.8	-	-	-	6.2 ± 2.7	-	6.0 ± 0.6	-	-	-	-	-	-
Sandgren <i>et al.</i> , [48]	Male	-	-	-	9.8	-	-	-	-	-	-	-	-	-	-	-	-
	Female	-s	-	-	8.2	-	-	-	-	-	-	-	-	-	-	-	-
Spector and Lawson [49]	-	-	-	-	6.6 ± 1.2	-	4.9 ± 0.9	-	5.2 ± 1.2	-	-	-	-	-	-	-	-
Li <i>et al.</i> , [50]	-	354	4.8	-	-	-	-	-	-	188	4.0	322	3.6	25 & 300	2.6 & 2.0	318	2.6

L – Length; D – Diameter; FA – Femoral Artery; CFA – Common Femoral Artery; PFA – Profunda Femoris Artery; SFA – Superficial Femoral Artery; FPA – Femoralpopliteal Artery; PA – Popliteal Artery; PTA – Posterior Tibial Artery; ATA – Anterior Tibial Artery; Prox. – Proximal; Dist. - Distal

3.5 Viscosity Model

In PAD numerical works, 10 of 19 prior research articles presumed blood flow to be a Newtonian fluid, whereas 7 papers propose a non-Newtonian viscosity model. Similarly, one study outlines a comparative study using both Newtonian and non-Newtonian viscosity models, whereas the remaining papers make no assumptions regarding the kind of blood flow considered. Carreau and Carreau-Yasuda are two further models of non-Newtonian viscosity that are presented. 6/7 studies considered Carreau model and 1/7 study included Carreau-Yasuda model in their studies. Table 4 displays the equations describing these models as well as the common values used to simulate blood rheology.

Table 4

Viscosity models used to model blood rheology condition (with adaptation from Lopes *et al.*, [51])

Model	Equation	Parameters
Newtonian	$\mu = \mu_{\infty}$	$\mu_{\infty} = 0.0035 \text{ Pa}\cdot\text{s}$
Power Law	$\mu = k(\dot{\gamma})^{n-1}$	$k = 0.017$ $n = 0.708$
Quemada	$\mu = \mu_p \left(1 - \frac{1}{2} \frac{k_0 - k_{\infty} \sqrt{\frac{\dot{\gamma}}{\gamma_c}}}{1 + \sqrt{\frac{\dot{\gamma}}{\gamma_c}}} H_t \right)^{-2}$	$\mu_p = 0.0012 \text{ Pa}\cdot\text{s}$ $k_0 = 4.33$ $k_{\infty} = 2.07$ $\gamma_c = 1.88 \text{ s}^{-1}$
Carreau – Yasuda	$\mu = \mu_{\infty} + (\mu_0 - \mu_{\infty}) [(1 + \lambda \dot{\gamma})^2]^{\frac{n-1}{q}}$	$\mu_0 = 0.056 \text{ Pa}\cdot\text{s}$ $\lambda = 1.902 \text{ s}\mu_{\infty}$ $\mu_{\infty} = 0.00345 \text{ Pa}\cdot\text{s}$ $n = 0.22q$ $q = 1.25$
Casson	$\mu = \left\{ \sqrt{\frac{\tau_0}{ \dot{\gamma} }} [1 - e^{(-m\dot{\gamma})}] + \sqrt{\mu_0} \right\}^2$	$\mu_0 = 0.004 \text{ Pa}\cdot\text{s}$ $\tau_0 = 0.004 \text{ Pa}$ $m = 100$

3.6 Analysis Platform

Table 1 contains 15 research that utilised CFD methodology in PAD investigations. CFD involves several applications, including commercial softwares such as ANSYS CFD, Comsol-Multiphysics, Autodesk CFD, STAR-CCM, and SolidWorks Flow Simulation, as well as Open-Source codes such as Visual-CFD, simFlow, OpenFoam, SimScale, HARVEY, etc. Fluent and CFX from ANSYS Inc. are the most often used commercial CFD software for modelling blood flow.

3.7 FSI Techniques

The FSI investigations combines CFD and FEA to analyse fluid and structural behaviour, as well as how they interact and impact one another. Previously, blood flow prediction models were based on rigid geometries that required the arterial lumen to be reconstructed and partitioned, resulting in reasonably precise results that could be provided in a short amount of time [52,53]. Nonetheless, numerous additional variables must be considered, including the elasticity structure of the artery wall and the stresses it endures as a result of atherosclerosis, as well as changes in material characteristics as the atherosclerotic lesion proceeds [54]. As a result, improved discretization methodologies, domain coupling techniques, and mesh interaction types are applied in fluid and solid

domain problem solution using FSI [55]. Besides, FSI also important specially after interventions which permanently change local biomechanics such as stenting and bypass grafting [56,57].

4. Discussion

4.1 Geometry Constructions

According to Xu *et al.*, [27], a patient-specific model reflects a more intricate structure for stenosis, branching, and bifurcation and indirectly affects the distribution of Wall Shear Stress (WSS). This structure also advances the hemodynamic research, which is affected by alterations in a particular lesion of the sick geometry. However, in another situation shown by Colombo *et al.*, [36] the effect of leg movement was examined by simulating hip rotation, knee flexion, and the full gait cycle on FPA hemodynamic with an idealised model. The intricacy of the patient-specific model, according to the author, will make it difficult to include it in this study. Additionally, as per the clinical standard imaging technique, CTA and MRA also ignore the leg bending throughout the imaging process.

Therefore, using an idealised model and accounting for pertinent boundary conditions in line with patient-specific data also clearly identifies essential components that affect the phenomena. Strong evidence is provided by Colombo *et al.*, [36] and Ferrarini *et al.*, [31] and others that patient-specific boundary conditions are more accurate in leg flexion investigations and directly guarantee the lack of irrational results. According to Colombo *et al.*, [37], also discussed that due to limited resolution of CT and the metallic artefacts created by the stent in post-operative CT scans, viewing the stent struts and immediately rebuilding a 3D model of the stent is not possible. In addition, Salman and Yazicioglu [23] looked into the site of stenosis by measuring the skin's sensitivity to sound vibrations along the inner artery wall of peripheral arteries. Using the hyper-elastic Ogden and Mooney-Rivlin method, the hyper-elastic of skin, fat, artery, and muscle describe the relationship between stress and strain. In the meanwhile, the Maxwell technique is used to simulate the behaviour of viscoelastic soft body tissue. The study's findings indicate that the sum of amplitude reaches its highest value close to the site of the stenosis.

CTA is a technique that produces inside body X-ray pictures with high contrast and resolution while also injecting contrast agent [58]. According to Xu *et al.*, [27] the existence of stenosis may be misinterpreted by the curvature's silhouette in CTA images [59]. The MRA scanning method, in contrast to CTA, generates detailed pictures with a high magnetic field, and blood works as its own contrast agent. Using real-time PC-MRA to create a 4D flow pattern, the MRA technique is also advantageous [58]. It does, however, take more time to acquire and analyse the pictures and is a relatively more complicated process. Other than CTA and MRA, another often utilised source image in non-invasive approach is USA. USA images are generated by sound wave frequency to scan part of the body. Wood *et al.*, [33] compared MRA data with USA data and found that USA data had superior measurement accuracy of the calculated circular diameter of SFA than the MRA approach. The analysis was performed with custom-written Matlab 7.0.4 software and HDI Lab 1.9 (ATL-Phillips) (The Mathworks, Natick, MA). Using MRA pictures from an L12-5 linear array transducer and an ATL HDI 5000 ultrasound machine, the outcomes of MRA in the USA were compared in terms of diameter measurement accuracy (ATL Phillips, Bothell, WA). USA is recognised to be a low-cost technology, but Lopes *et al.*, [51] also reported that USA that the accuracy of the method is still greatly impacted by the competence and knowledge of the operator. Furthermore, imaging of unusual anatomical circumstances, such as extensively stenosed carotid vessels, is limited in the USA, resulting in the lowest prevalence rate [60].

In general, there are two types of geometry construction: patient-specific models and idealised models. By using MRA and CTA methods, realistic geometry for a patient-specific model can be reconstructed. These geometries must be more crucially rebuilt as the necessary model for the computer analysis. This method will ensure that arterial behaviour and mechanical structure are not overlooked.

4.2 Characteristics of Peripheral Artery

Avolio [44] and Li *et al.*, [50] reports general length of 127 mm and 354 mm with same diameter of 4.8 mm for FA. While other researchers report specific size data for CFA in the range of 6.6 mm to 9.4 mm (diameter) and range of 5.2 mm to 7.3 mm (diameter) for SFA. There are also limited data available for PFA where length found is 126 mm and diameter fall in between 4.6mm to 4.9mm. Next, the length of PA is 94 mm to 188 mm and the diameter changes from proximal to distal of PA from 6.2 mm to 4.2 mm accordingly. Lastly, in tibia region, the diameter of arteries lay in the range of 3.09 mm to 3.6 mm (PTA), 2.0 mm to 3.43 mm (ATA) and 2.6 mm to 3.10 mm (Peroneal) respectively.

Findings also shows that gender draws changes in the size of arteries in human. The artery size in male subjects is larger compared to female subjects. For an example, Wolf *et al.*, [47] states the diameter of CFA in male is 9.4 mm while in female 7.8 mm. Significant difference also found in the size of other arteries such as SFA and PA as shown in Table 3. Apart from gender, factor such as side of leg, right and left leg also shows different arterial size for every individual. Lorbeer *et al.*, [46] describes that for side of leg the comparison has to be carried out for each type of artery accordingly. This is because certain artery found to be bigger on right leg and vice versa for others. Meanwhile, PTA shows similar diameter of 3.09 mm for both side of leg. Age and body size another two factors which affect the arterial size. Sandgren *et al.*, [48] conclude that as the trend of age and body sizes increases, the arterial length and diameter also becomes larger.

4.3 Viscosity Model

According to Ameenuddin *et al.*, [61], blood consists of erythrocytes, leukocytes, and thrombocytes suspended in plasma. The haematocrit is the volume fraction in which erythrocytes compose at around 45 percent of total blood volume. Although it is recognised that plasma is a Newtonian fluid, the entire fluid exhibits non-Newtonian features, particularly in capillaries. Topps and Elliott [62] were the first to characterise the shear-thinning behaviour of blood. They established that viscosity reduces as shear and strain rates increases.

Most arterial simulation studies utilise a Newtonian model to mimic blood flow. This Newtonian blood assumption is a significant inaccuracy in approximations of blood flow modelling [63]. Even though plasma is a fully Newtonian fluid, narrow channels such as capillaries display non-Newtonian behaviour due to variations in the viscosity of the blood flow [64]. Several studies like Guerciotti and Vergara [64], Kumar *et al.*, [65], Lee *et al.*, [66], and Urevc *et al.*, [67] have discovered distinct change between Newtonian and non-Newtonian results, especially in local hemodynamics due to decreased velocities at stenosed regions. This contributes to a decrease in shear rates in the region downstream of the stenosis, resulting in an increase in viscosity [10]. These findings show that it may be suitable to mimic blood as a non-Newtonian fluid in simulations of peripheral blood flow. In addition, few non-Newtonian models are utilised to predict shear-induced blood thinning [68]. As a generalised non-Newtonian flow behaviour, the Power law model technique is the most used rheology for constructing empirical relationships due to its simplicity. On the contrary, Power Law model has two shortcomings: first, it fails to depict the linear shear-strain connection at extremely low and very high

shear rates, which are typical for most actual systems, and second, the viscosity curve becomes unique at the vanishing shear limit. Next, Casson model, is a well-known mathematical model used specifically to evaluate small arteries at low shear rates. Subsequently, Carreau or Carreau-Yasuda model, a four-parameter model suited to a broad range of shear rates, is afterwards offered when there is a significant deviation from the previous models [69]. Moreover, this model was designed to behave as a Newtonian fluid at high and low shear rates and as a Power law fluid in the intermediate shear phase [51]. No model representing the viscosity of blood has been approved by all researchers.

Various computational analysis findings on various viscosity model assumptions have also been presented in studies. Vu *et al.*, [70] evaluated the Newtonian model against non-Newtonian models in branchial arterial system, by using Power Law, Carreau, and Casson models, and provided quite compelling hemodynamics predictions for each approach. The size of the recirculation zone obtained differs dramatically between each observed model. The wall shear stress of the Carreau model is greater than that of the Newtonian model by 14% for continuous flow and 17% for pulsatile flow [69]. Pulsatile flow data indicate that the Newtonian model is close to the power law model, but the Casson model is comparable to the Carreau model.

In summary, Newtonian or non-Newtonian models of viscosity must be taken into account while analysing blood flow. Findings from Ferrarini *et al.*, [31] states that both Newtonian and non-Newtonian models provide almost identical results in both popliteal geometry models, except when the magnitude of the TAWSS is relatively small ($<0.4\text{Pa}$). In this latter case the Newtonian model gives lower values of TAWSS than the non-Newtonian one [15]. Essentially, the Newtonian model is the simplest and most practical approach to evaluate constant viscosity, but it does not completely match the viscosity of blood in nature. On the other hand, non-Newtonian considerations are more relevant due to the incorporation of viscosity variability based on blood flow in the arterial environment. However, the Newtonian blood treatment should be a good choice in general but the viscosity model consideration strongly depends on whether they need or does not need to include consideration of WSS in their study respectively.

4.4 Analysis Platform

CFD is a significant tool to illustrate the flow behaviour in vitro experiments that relate with vascular hemodynamic. Over the last 20 years, researchers have performed CFD analysis on set of vascular remodelling mechanisms that result in the development of atherosclerosis. CFD has been a key tool for analysing various endovascular treatment approaches and evaluating the development of endovascular devices [2,19,21,71]. In the field of PADs research, the element of pathobiological processes can be explored using the right analysis platform to examine the blood flow and the wall structure deformation in correlation with the artery behaviour [7,16-18,23,24,27,28,72].

Two commercially available solvers in ANSYS, Fluent and CFX, are primarily utilised for their unique capacities to analyse arterial blood flow. The pre-processor, solver, and post-processor can all be used by Fluent simultaneously in a single window. The grid quality in CFX is much more forgiving when it comes to meshing, focusing on the cell-vertex node that separates each element into sub-volumes. Additionally, since iterative methods are used to solve the governing equations in CFD, convergence is a significant difficulty. It is common to look for residuals that are below a certain threshold as well as specific local and global flow characteristics that stabilised, while different research use different convergence criteria [58]. Both Fluent and CFX can assess the data at several monitor points to see how accurate the convergence is. In these cases, CFX outperformed Fluent in terms of usability and clarity. While fluent needs more repetitions, it is computationally efficient, and

it is feasible to tell if the solution is converging or diverging at the first stages of a simulation. Additionally, Fluent can resolve axisymmetric model simulations while CFX can only do 3D simulations. Fluent can also execute simulations in both 2D and 3D [73].

Fluent and CFX are competent solver that can solve most flow analyses according to the need of the user. For inexperienced CFD users, there is a thorough description on how CFD software would aid users to tackle the Navier–Stokes equations rather than depending on commercialised CFD code [52,74]. The robust CFD simulation has the capability to be a useful tool in treatment decision-making systems [27]. LS-DYNA is another commercial software used to examine blood flow modelling under dynamic boundary conditions. Gökgöl *et al.*, [38] investigated the hemodynamic impact of endovascular therapy by using LS-DYNA on the flow behaviours of femoralpopliteal arteries (FPA) while Colombo *et al.*, [36] used LS-DYNA with Arbitrary Lagrangian-Eulerian (ALE) on an idealised model of FPA to perform computational fluid dynamics analysis by simulating hip rotation, knee flexion, and the full movement of walking. The findings of these studies indicate that this software is extremely cost-effective and adequate for assessing large and complex models. In addition, the practicality of integrating diverse software in an integrated system such as adaption of MATHLAB ABM into CFD simulation as carried by Corti *et al.*, [39] may become the sole viable method to support the hundreds of simulations required for ambiguity and sensitivity studies, as well as calibration.

Historically, the computational requirements of three-dimensional computational fluid dynamics (CFD) models of blood flow were excessively consumed memory and computationally complicated to calculate blood flows in arteries accurately. However, the use of high-performance computing resources and development of new massively parallel simulation Open-Source code frameworks have recently progressed toward solving these limitations. For example, HARVEY is hemodynamic code that includes the Lattice Boltzmann Method (LBM) to resolve the unsteady Navier-Stokes equations [75]. This is attributable to the scaling's effectiveness to which boundary conditions in complex structures are addressed. However, the simulation in this framework still considers the vessel wall as a rigid wall.

Overall, there are many available software to analyse modelling of blood flow in arterial system like peripheral artery. However, each software has its own advantages and shortcomings which can be select by the user according to their research requirements. Besides, inclusion of Open-Source codes also reduces the shortcomings of the existing software which consequently improves the accuracy of the results obtained.

4.5 Rigid Wall Assumptions toward Their Works

According to Xu *et al.*, [27], a change in WSS distribution can easily cause rupture and the development of calcified plaque. This implies that the primary reason for atherosclerosis is hardened plaque. Due to the framework's rigid wall presumption, the displacement of the artery wall generated by blood is omitted, hence the correlation between geometric characteristics and WSS change remains unknown.

Desyatova *et al.*, [28] performed the analysis by separating the solid and fluid analyses in order to achieve simplicity and computational effectiveness. Although the consequences of fluid-structure interaction are minimal in terms of qualitative outcomes, it may have significant effects in terms of quantitative outcomes. Another investigation was conducted to ascertain the distribution and severity of hemodynamic disturbances by taking into account the compliance wall with various SFA geometry. Hence, distinct findings obtained through both investigations where the assumption of

compliance wall able to quantify the displacement of the artery wall under hemodynamic stress might have a significant influence on the study's conclusions.

It is well acknowledged that WSS and related parameters like Wall Shear Stress Temporal Gradient (WSSTG) and Oscillatory Shear Index (OSI) play a major role in the progression of femoral artery atherosclerosis [15]. One study on femoral artery showed that the arterial wall compliance had a negligible impact on the local hemodynamics [76]. The flow parameters and WSS field of a compliant femoral artery bifurcation model were compared to those of a rigid model using an internal FSI system. The research's findings indicate that near the SFA bifurcation, small changes in Time-Averaged Wall Shear Stress (TAWSS) and larger differences in WSSTG were discovered. Wall motion only slightly effect the velocity field. This study suggests that wall compliance at the femoral artery bifurcation does not significantly modify factors previously identified as critical in the development of arterial disease; nevertheless, longer arterial segments must be simulated to see the influence of wall motion on tortuosity. Data indicate that compliance makes particular sections of the femoral artery bifurcation more susceptible to the onset of disease by increasing the regions of high OSI and WSSTG.

Overall, rigid wall assumptions can reduce the computational cost whereas compliant wall assumptions are essential for producing realistic simulation results. In light of their studies on artery structure and blood flow, researchers should determine the appropriate wall assumption to produce accurate and relevant outcome of study.

4.6 FSI Technique

The majority of recent CFD studies, however, used idealised geometry and the CTA/MRA reconstruction method to analyse the arterial wall compliance on the local blood hemodynamic, which has a direct impact on blood behaviour [16-18]. Assessment alone, in contrast, could not illustrate the real rigid wall characterization. The Fluid-Structure Interaction (FSI) approach, which combines Finite Element Analysis and CFD, can be used to get around these restrictions (FEA). The analysis of fluid behaviour, structural behaviour, and their interactions with one another is possible thanks to numerical methods between the fluid domain and the structure domain [57,58,77,78]. Additionally, it can lessen the degree of ambiguity around the growth of stenosis locations. The doctor will be further assisted in providing an appropriate treatment plan for patients with PAD by combining all the criteria with actual patient-specific datasets.

The monolithic technique, which meshes both domains and solves them mathematically as a single entity, is one of the discretization approaches [56,79]. The main benefit of this technique is that the boundary conditions are virtually contained in the mathematical model, allowing the use of a single discretization scheme. It is also more accurate in resolving multi-physical phenomena [80-82]. One of the key disadvantages of this strategy is that code development becomes extremely problem-specific, resulting in a loss of generality. In order to solve the algorithms, competency is also required.

Another alternative is partitioned technology, which solves fluid and solid domains using separate meshing and governing equations. Both domains have strong independent solutions. It is, nevertheless, prone to mistakes during discretization and meshing due to convergence inaccuracy. Partitioned processes incur greater computing costs as compared to monolithic approaches. A coupling mechanism is also required to communicate interface data between the two domain solvers. The two primary types of coupling approaches used to overcome this problem are one-way and completely coupled two-way [56,83]. In a One-way FSI analysis, both domains are solved in series, and the solution of one domain is used as a boundary or starting condition in the second.

While this study has the advantage of being easy to construct and using fewer computer resources, it may not fully reflect the fluid-structural interaction [84,85]. In a fully-coupled two-way FSI investigation, the two domains are solved concurrently, with each iteration defining and achieving convergence for the fluid and solid domains [84,86]. When the one-way FSI approach fails, the fully linked two-way methodology is used to address the relevant problem. Conforming and non-conforming meshes, on the other hand, are also important in the FSI approach. The boundary condition for fluid and solid domain treatment in conforming mesh technique is physical, but it is not physical in non-conforming mesh approach. Arbitrary Lagrangian Eulerian (ALE), and Deformed Spatial Domain/Stabilised Space Time (DSD/SST) are extensively used approaches in conforming mesh [87-89]. The fluid and structural domains, for example, are linked using a coupling technique, such as the ALE approach, in which one domain's mesh is allowed to deform in order to conform to the restrictions of the other domain [84,85,90].

The domains in non-conforming mesh method are addressed by applying single meshing in the governing equations themselves. Some of the ways that have been developed in this field are the Immersed Boundary Method (IBM), the Immersed Interface Method (IIM), the Coupled-Momentum method, and the Direct Forcing method [76,89,92]. Similarly, IBM has seen an increase in application, where it is often utilised in heart valve simulations due to the thin valve leaflets experiencing significant structural deformation [90,93-96]. Because the structural mesh is integrated inside the larger model mesh, re-meshing and mesh deformation are avoided [90,94,97].

The FSI technique is still considered futuristic, and most researchers are not very interested in these approaches to lower limb research. Only a few studies have focused at other arteries besides the carotid and coronary arteries. Wang *et al.*, [40] conducted 1/19 FSI tests on stenosed femoral artery to assess hemodynamic performance with multiple plaques (calcified and lipid plaques) utilising Mooney-Rivlin material property. Besides, Nematzadeh [98] also discussed regarding Mooney-Rivlin model which performed better mechanically in generation of stress-strain distribution compared to Ogen model. These models were suitable for describing peripheral artery performance and smart stent behaviour while taking material qualities, strain level, and friction coefficient into account throughout the interaction process. Johari *et al.*, [57] indicate FSI findings related to minimal wall displacement of the bifurcation and the stented area where the rigid-wall model might overstate the region of low TAWSS, which could contribute to the development of neointimal hyperplasia and the development of restenosis.

Despite patient-specific geometries, the existence of restriction is evident due to the complex composition of the artery wall, which includes smooth muscle cells, elastin, and collagen fibrils [40]. Furthermore, FSI must still adhere to various boundary requirements that limit output precision in a manner similar to that of a realistic vascular model [31,34,36].

4.7 Validation and Verification

It is of utmost importance that CFD hemodynamic studies be verified and validated. An evaluation of the computational model's accuracy in numerical terms is referred to as "verification". Usually, this process needs to be done in the presence of an analytical model solution. Instead, the process of validating a computer model involves finding and gauging how closely it resembles reality. Verification must occur before validation while developing innovative hemodynamic models. The simulation is said to have been validated if there are small and acceptable differences between the results of the simulation and the real data, and if the experimental data's uncertainties are also small. The distinction between validation and verification was made clear by Roache [99] and Babuska and

Oden [100], who defined validation as "solving the right equations" and verification as "solving the equations properly".

In line with the current ASME Standard for Verification and Validation in Computational Fluid Dynamics and Heat Transfer, it is also stated that "There can be no validation without experimental data," and that the data can be produced through in vivo or in vitro investigations. According to Prantil *et al.*, [101] in their book "Lying by Approximation: The truth about Finite Element Analysis," modelling validation using theoretical or experimental data is necessary to get reliable simulation results.

Some researchers, including Schumann *et al.*, [17], Gökgöl *et al.*, [16], Desyatova *et al.*, [28], and McGah *et al.*, [35], recommended further research on clinical datasets or experimental data in the scenario of leg flexion brought on by stent implantation to assess the consistency of their findings. Combining computational models with longitudinal patient scans can help demonstrate complex hemodynamic properties, their importance in determining long-term morphologic changes, and most importantly clinical outcomes. In research paper by Donadoni *et al.*, [32], the model validation was carried out against a patient-specific, unique clinical dataset by detecting the locations of restenosis in the CT scans from the patient, and then compared them against the simulated results.

Furthermore, a typical strategy among academics is to use already-existing in vivo data to test numerical models. Publicly available research has the advantages of being simple to get, inexpensive, taking less time to carry out specific experiments, not requiring ethical approval, and being able to be compared to many databases [41]. It is possible to directly or indirectly compare the simulation output to the actual in vivo data. The indirect comparison strategy is either (a) the CFD user modifies the initial boundary conditions and/or geometry to match existing clinical data, or (b) the CFD user compares the published research to the original simulation findings [102,103]. For example, Xu *et al.*, [27] acquired the Ultrasound Doppler measured velocities from the previous research to validate the evaluation of hemodynamics which serves as a complement for therapeutic decision-making to prevent the overestimation or underestimation of the anatomical evaluation.

However, there are two different ways to go about the verification process. The initial approach investigates the output's sensitivity to the elements on the changing quality level of the meshed domain. By concentrating on the sizes of residual error, this mesh sensitivity test evaluates whether the number of mesh components can effectively capture the flow pattern. The second method, on the other hand, concentrates on and assesses governing equation solver issues. As an alternative, the direct comparative technique has a high degree of validity since it builds a 3D structure and pathway for the CFD simulation based on the unique data and boundary conditions of the patient [104]. A comparison between the reaction and the patient's initial data is then made. The drawback of this technique is that it takes time to collect patient imaging data from CTA or MRA, extract and rebuild data for modelling, obtain ethics clearance, then enrol and obtain consent from patients [41].

5. Conclusion

Cardiovascular disease known as peripheral artery disease affects the lower body by reducing the lumen patency of blood vessels. The use of computer software to mimic the circumstances in the afflicted region is now possible thanks to recent technologies. However, because of how blood behaves and the peculiarities of arteries wall, accurate representation of the conditions due to the behaviour of blood and the characteristics of arteries wall. In order to identify and simulate the blood flow in the stenosis area, the researchers took into account a number of geometrical constructions, viscosity model, analysis technique, and wall characteristic features. These parameters

are summarised in this study. The techniques used to validate the identification and simulation are also discussed in this paper.

Overall, this study demonstrates the current efforts in the computational analysis of PAD. The findings can help researchers to develop a better computational analysis that can assist for early diagnosis of PAD diseases, and appropriate therapeutic approach.

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