



# **A CORRELATION BETWEEN PATIENT SPECIFIC CEREBRAL ANEURYSM WALL HISTOLOGY, MICRO CT AND COLLAGEN PARAMETERS WITH CFD AND FSI STUDIES.**

**Dr. BHUSHAN SADASHIV AKHADE**

**PDF CEREBROVASCULAR NEUROSURGERY THESIS**

**2024**

**SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND  
TECHNOLOGY, TRIVANDRUM**

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**A CORRELATION BETWEEN PATIENT SPECIFIC CEREBRAL  
ANEURYSM WALL HISTOLOGY, MICRO CT AND  
COLLAGEN PARAMETERS WITH CFD AND FSI STUDIES.**

A THESIS SUBMITTED BY

**Dr BHUSHAN SADASHIV AKHADE**

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND  
TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

**PDF CEREBROVASCULAR NEUROSURGERY**

**2024**

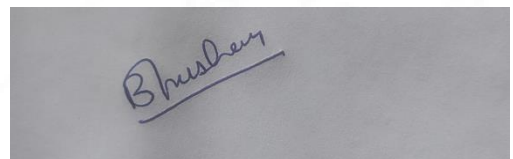
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### CERTIFICATE

I Dr Bhushan Sadashiv Akhade hereby certify that I had personally carried out the work depicted in the thesis titled, “**A CORRELATION BETWEEN PATIENT SPECIFIC CEREBRAL ANEURYSM WALL HISTOLOGY, MICRO CT AND COLLAGEN PARAMETERS WITH CFD AND FSI STUDIES**”.

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

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Date-16/12/2024

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The thesis entitled, “**A CORRELATION BETWEEN PATIENT SPECIFIC CEREBRAL ANEURYSM WALL HISTOLOGY, MICRO CT AND COLLAGEN PARAMETERS WITH CFD AND FSI STUDIES**” was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

Clearance was obtained from the Institutional Ethics Committee for carrying out the study.(IEC/841/MARCH-2023)

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## **APPROVAL OF THESIS**

The thesis entitled

**“A CORRELATION BETWEEN PATIENT SPECIFIC CEREBRAL ANEURYSM WALL  
HISTOLOGY, MICRO CT AND COLLAGEN PARAMETERS WITH CFD AND FSI  
STUDIES”**

Submitted by

**Dr Bhushan Sadashiv Akhade**

for the degree of

**PDF Cerebrovascular Neurosurgery**

Of

**SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY,  
TRIVANDRUM**

is evaluated and approved by

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(External Examiner)

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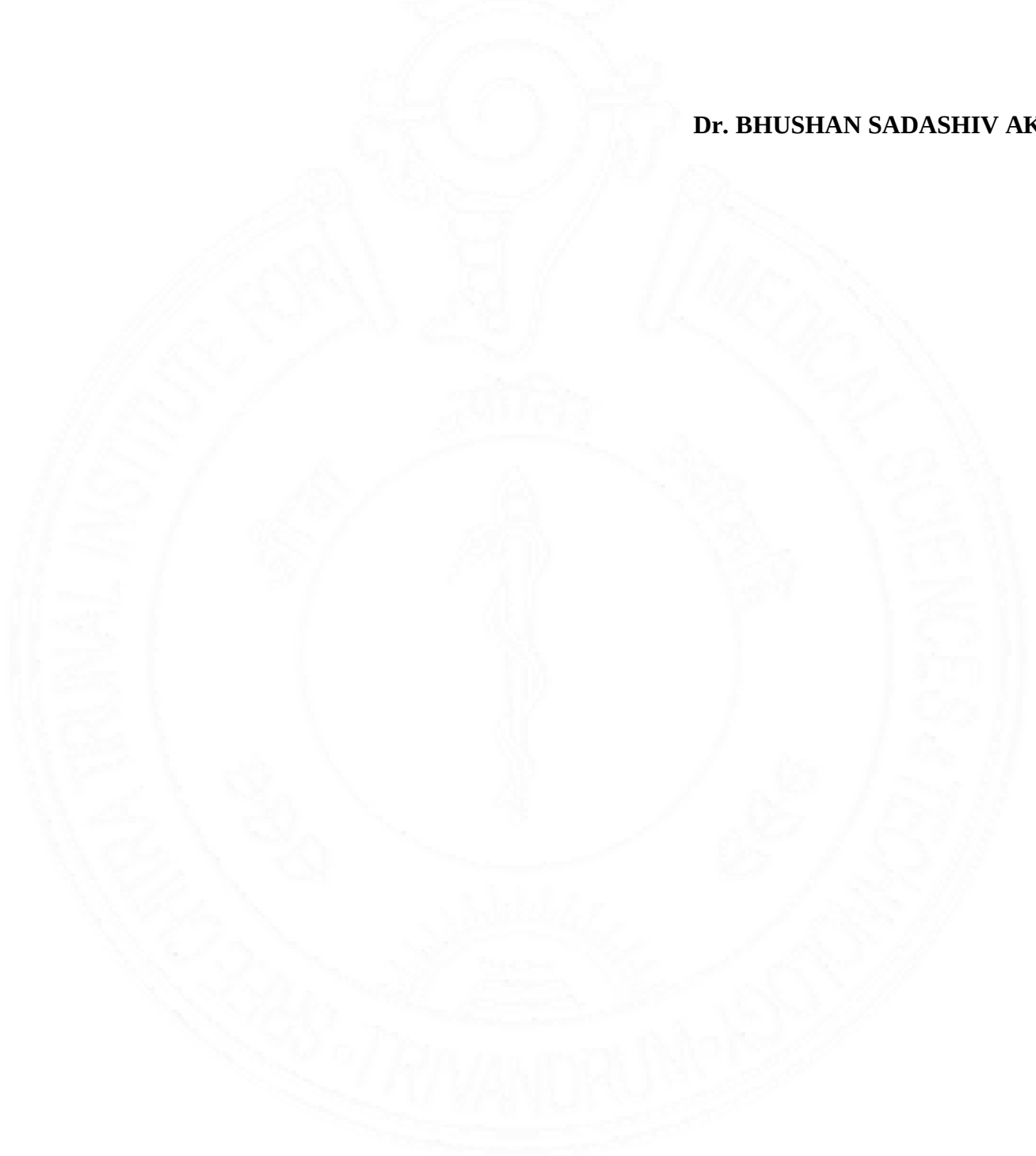
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**Dr. BHUSHAN SADASHIV AKHADE**



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## LIST OF ABBREVIATIONS

| Abbreviation | Full Form                               |
|--------------|-----------------------------------------|
| 1. IA        | Intracranial Aneurysms                  |
| 2. FSI       | Fluid Structure Interaction Simulations |
| 3. CFD       | Computational Fluid Dynamics            |
| 4. IVUS      | Intravascular ultrasound                |
| 5. ROI       | Region of Interest                      |
| 6. VIF       | Variance inflation factor               |
| 7. ALE       | Arbitrary Lagrangian Eulerian           |
| 8. CTA       | Computed Tomographic Angiography        |
| 9. UWT       | Uniform Wall Thickness                  |
| 10. PWT      | Patient-specific Wall Thickness         |

## SYNOPSIS

# **A CORRELATION BETWEEN PATIENT SPECIFIC CEREBRAL ANEURYSM WALL HISTOLOGY, MICRO CT AND COLLAGEN PARAMETERS WITH CFD AND FSI STUDIES.**

**Background and Aim:** Cerebral aneurysms occur as balloon-like out-pouchings in an artery, which commonly develop at the weak curved regions and bifurcations. When aneurysms are detected, understanding the risk of rupture is of immense clinical value for better patient management. Towards this, Fluid Structure Interaction (FSI) studies can improve our understanding of the mechanics behind aneurysm initiation, progression, and rupture. Performing hemodynamic analysis using an accurate computational model that is closer to the actual biological milieu could yield clinically useful rupture risk predictions. Currently, the geometric model for the CFD studies rely on imaging the flow domain using Computed Tomographic Angiography (CTA) or Digital Subtraction angiography (DSA), which limits accurate discerning of the vessel wall thickness for FSI studies. The present study combines both the shape information of the 3D lumen model (as it existed in vivo), which is accurately rendered through the CTA, in conjunction with the wall thickness information extracted from histo-pathological 2D images, Micro CT and collagen parameters of wall of the aneurysm. Further, perform fluid-structure interaction (FSI) simulations on the aneurysm using patient-specific heterogeneity of the wall

**Methods:** 3 D geometric model of the blood-flow domain of an anterior communicating artery aneurysm is extracted from the CTA of a patient who underwent surgical clipping of the aneurysm. During surgery, after the aneurysm was safely clipped, the fundus of the aneurysm beyond the clip was cut and extracted. This was carefully preserved and sliced to obtain the wall thickness variation of the hoop at various axial sections. In this study, a novel methodology

of combining multi-modal image data is developed to geometrically render the 3D model of the Cerebral aneurysm. The wall thickness extracted from the histological 2D cross-sectional images of the aneurysm is encapsulated around the 3D lumen model obtained from CT Angiographic data. To this end, a wall thickness transfer algorithm is developed to accurately reconstruct the patient specific aneurysm wall thickness variation for the FSI simulations.

**Results:** The blood flow domain obtained from the CT angiography along with the histopathological images, accurately reconstructs the 3D aneurysm as it existed in vivo. Various 3D model generation challenges have been addressed in unifying the two different imaging modalities. Since the aneurysm has been accurately discerned with wall thickness information, fluid-structure interaction (FSI) based simulations are performed to assess the utility of patient-specific wall aneurysm model vis-a-vis uniform wall model for the aneurysm

**Conclusion:** The rendered patient-specific aneurysm wall model with its thickness variation, as it existed in vivo was obtained. Patient-specific fluid-structure interaction (FSI) simulations show that, this approach is highly valuable for an accurate rupture risk analysis of cerebral aneurysms

**KEYWORDS:** Image analysis, Computational modelling, Geometric modelling, Aneurysms, Mesh generation

## INTRODUCTION



## 1. INTRODUCTION

Sub Arachnoid hemorrhage is acute neurosurgical emergency with significant morbidity and mortality. Approximately 3–5% of the population has unruptured intracranial aneurysms (UIAs)(Etminan and Rinkel, 2017). Unfortunately, most UIAs will never rupture, and the anticipated yearly rupture rate is only 0.25%(Korja and Kaprio, 2016). The natural history and variety of UIAs make it difficult to draw a consensus among Neurosurgeons regarding the surgical indications for UIAs.

Cerebral arteries are different in its structure from extracranial vessels i.e., due to their lack of external elastic lamina and thinner adventitial tissue. The study into the pathogenesis continues to date because of the multifactorial nature of the disease. Irregularities in the aneurysm wall has been significantly associated with wall instability. Therefore, it is necessary to make a multidimensional prediction of the rupture risk of an aneurysm. An major determinant in the development, rupture, and creation of intracranial aneurysms (IAs) is the inflammatory response of the aneurysm wall. When inflammatory cells invade the aneurysm wall, they produce chemicals that cause the wall structure to collapse. In the event that the aneurysm wall's repair is unable to withstand the inflammatory damage, the aneurysm expands and its wall eventually becomes thinner<sup>3</sup>. This process, when combined with the ongoing hemodynamic effects, will cause the aneurysm wall to rupture, resulting in a subarachnoid haemorrhage (SAH). Intraoperative observation is the only reliable method to determine thick, moderate, and very thin translucent tissue regions on aneurysm wall. The risk of rupture can be predicted to a certain extent by investigating the change in the thickness of the aneurysm wall. However, it is challenging to directly measure or investigate the thickness of the aneurysm wall, and there have been few studies performed in this area.

In the present study we propose to validate the use of assumption of cerebral aneurysmal wall thickness with help of patient specific micro CT imaging, histopathology and Collagen composition and its orientation in resected dome of cerebral aneurysm.

## **AIMS & OBJECTIVES**

## **AIMS AND OBJECTIVES**

1. To study the properties of collagen and its orientation in the cerebral aneurysm wall.
2. To assess the validity of CT Angiography guided assumed cerebral aneurysm wall thickness assessment using patient specific post resection dome wall thickness using micro CT evaluation.
3. To assess the validity of CT Angiography guided assumed cerebral aneurysm wall thickness assessment using patient specific post resection dome wall thickness histopathology evaluation.
4. To formulate a relationship between the orientation and properties of collagen fibres in aneurysm wall, the hemodynamic stress parameters and rupture point of cerebral aneurysm with help of histopathology, and Micro CT

## REVIEW OF LITERATURE



## REVIEW OF LITERATURE

Multiple well known risk factors are contributing to the formation, growth, and rupture of IAs such as genetics, age, hypertension, smoking, size, and site of the aneurysms (UCAS Japan Investigators et al., 2012). However, the actual mechanisms that lead to an aneurysm rupture are not well understood yet.

Predicting the future behavior of cerebral aneurysms was the target of several studies in recent years. When an unruptured cerebral aneurysm is diagnosed, the physician has to decide about the treatment method. Often more giant aneurysms are diagnosed at higher risk of rupture and are candidates for intervention. However, several clinical and morphological parameters are introduced as risk factors. Therefore, some small size aneurysms with a higher growth rate and rupture risk may be missed.

Treatment method of unruptured aneurysm depends on the aneurysm size. The ISUIA study and the UCAS study both concluded that size is a significant risk factor for rupture.(UCAS Japan Investigators et al., 2012; Wiebers et al., 2003) In both ISUIA and UCAS studies, aneurysms smaller than 7 mm have been associated with very low risk profiles for rupture(Wiebers et al., 2003) Aneurysms below the threshold size of 7 mm still account for a noticeable number of ruptures(Robertson et al., 2015).Therefore, it is necessary to be aware of the future behavior of the aneurysm. Estimating the 3D flow pattern and stress distribution and predicting the disease's progression trend may be possible by measurement of wall thickness by patient specific cerebral aneurysm wall histology, Micro CT and collagen parameters with CFD and FSI studies.

These studies can help surgeons to decide about the best treatment method and prevent unnecessary interventions.

It is not possible to study the true natural history of UIAs in future prospective follow-up cohorts

Risk factors for aneurysmal rupture include aneurysm size and aneurysm site, with higher risks for larger aneurysms and aneurysms in the posterior circulation (Juvela et al., 2000; UCAS Japan Investigators et al., 2012; Wiebers et al., 2003). Various other factors like multiple aneurysms, (UCAS Japan Investigators et al., 2012) female sex, (Wermer et al., 2007) young age, (UCAS Japan Investigators et al., 2012) and cigarette smoking (Juvela et al., 2000) have been suggested as risk factors

The treatment decisions of unruptured IAs may improve to a large extent with an accurate prediction model based on the different types of risk factors aiming to identify patients with a high risk of aneurysmal rupture. (Detmer et al., 2018) Treatment of unruptured IAs would be indicated when the risk of rupture from natural history is higher than the risk of treatment and follow-up.

Despite great progress in methodological developments and many studies using patient specific data, there are still significant controversies about the precise governing processes and divergent conclusions from apparently contradictory results.

Cerebral arteries are structurally and functionally different from the extra cranial vessels. They have a specific wall organization with absence of external elastic lamina and a thinner adventitial tissue.<sup>3</sup> Various studies have been conducted over the years in order to understand pathogenesis of development of intracranial aneurysms, its relation to the vessel wall morphology and its natural history and progression. However, the study into the pathogenesis continues to date because of the multifactorial nature of the disease. The aneurysm formation is essentially initiated by the disruption of the internal elastic lamina which is followed by the remodelling of the wall. Continuous ongoing processes of remodelling and degeneration will continue as the aneurysm wall grows.<sup>4</sup>

Irregularities in the aneurysm wall has been significantly associated with wall instability.<sup>5</sup> Collagen fibres are seen in both adventitial layer and the tunica media.<sup>6</sup> In the aneurysm wall, it has been seen that different diameter of collagen fibres exist in the luminal and abluminal parts of the wall.<sup>7</sup> Also, the orientation of the collagen fibres differs in the aneurysmal wall when compared to the normal cerebral

arteries. A study by Hackenberg et al<sup>8</sup> used a mathematical model with the help of C<sup>14</sup> and studied the collagen turnover rate and mean age of collagen in the aneurysmal walls. It was noted that the mean collagen turnover rate was higher than 2600% per year and the mean age of collagen was less than 2 weeks in patients with intracranial aneurysms.<sup>8</sup>

#### Collagen adaption:

The basic adaptive response of the collagen fibres is of growth and remodelling. The aneurysm develops as elastin degrades and hence the collagen fibre adapts to restore its strain to the hemostatic value. The growth and atrophy of the collagen fibres in turn has its effect on the enzymes which maintain the collagenous matrix of the vessel wall.<sup>9</sup>

Various studies investigating the association between the wall shear stress and the risk of rupture of an aneurysm have been done using the computational fluid dynamics. Using CT angiography, digital subtraction angiography or MR TOF, Computational Fluid Dynamics (CFD) and Fluid Structure Interaction Analysis (FSI) helps create a 3D model of blood flow. When the wall strength is lower than the hemodynamic forces, rupture of an aneurysm occurs.<sup>10</sup> Often mechanical strength of the aneurysm wall varies from patient to patient and also within the aneurysm dome itself. Hence the site of rupture is variable in each aneurysm. Cebal et al<sup>11</sup> demonstrated that the collagen fibre diameter is larger when the wall shear stress increased whereas the orientation of collagen fibres was more coherent in regions with normal wall shear stress or even low wall shear stress. Once the internal elastic lamina is damaged, it is the collagen fibres of the adventitia which are the main load bearing structure. Hence, the collagen thickness and orientation variability with its relationship to the shear stress of the flow in the aneurysm becomes important for its growth and its rupture. Experimentally, it is noted that high levels of wall shear stress at the curves is noted to induce the endothelial cells to produce MMP-9. As noted by various studies; matrix

metalloproteinases play an essential role in the pathogenesis of the aneurysm. it was also noted that high wall shear stress progressively leads to the dolichoectatic changes in the blood vessels. <sup>12</sup>

Aneurysm dome wall thickness is a poorly documented feature in the study of aneurysm pathogenesis and the clinical assessment of rupture risk. Histological assessment has shown that the aneurysm wall undergoes a dynamic process of destructive remodeling and dysregulation, featuring de-cellularization and apoptosis, collagen reorganization, degeneration of the internal elastic lamina and elastin fragmentation, de-endothelialization, thrombus formation and inflammatory infiltration. Some aspects of this process may be focal in nature as a result of the local release of inflammatory destructive enzymes and endothelium derived factors, such as nitric oxide and prostaglandin I<sub>2</sub>. The ultimate consequence is a heterogeneous tissue distribution observable on surgical exploration of thick, intermediate and thin translucent regions of the aneurysm wall. Many observed aneurysms possess clearly defined loci of translucency suggestive of focal weakness, potentially influencing local material stiffness and yield stress, predisposing these regions to rupture. Wall thickness is highly variable between and within aneurysms and has been reported as ranging from 16 to 400 micrometer, with the majority between 30 and 200 micrometer.<sup>4</sup> Several studies have attempted to describe a continuum through which different stages of the aneurysm ageing process can be observed and identified based on aneurysm size, level of calcification and intraoperative appearance. These attempts to describe intraoperative findings of the aneurysm wall thickness have resorted to subjective or qualitative description (such as entirely thick, thin or a combination) and have lacked quantitative analysis. Given the risks associated with both rupture and treatment, we need improved methods of stratifying rupture risk. In practice, treatment selection hinges on only several epidemiological and morphological parameters (e.g., aneurysm size, location, and patient age). Thinning of aneurysm wall thickness (AWT) has previously been associated with aneurysm rupture and may represent an additional parameter by which to guide treatment decisions. Till date, many studies have been undertaken to assume the Aneurysmal wall thickness(AWT). They include use of microscopic images, resolution, pixelage and

colour of the aneurysm, and high resolution images. CT angiography and MRI based studies have been described. Image resolution of the same is poor to reconstruct vessel/aneurysm wall thickness for Fluid Structure Interface studies. Previously histopathological examination of cross sectional samples of resected dome have been used. But due to shear factor associated with use of microtome in histopathological specimens have led to limitation of measurement of vessel thickness.

By methodically applying the Laplace equation, Bazilevs et al.(Bazilevs et al., 2009) created a changeable vessel wall thickness for a blood vessel lumen in three dimensions. For the three distinct sections of the diseased blood artery, Valencia et al.(Valencia et al., 2013) conducted FSI tests using three different thicknesses. In order to determine whether wall stress analysis in a basilar artery bifurcation was necessary, VoB et al. (Voß et al., 2016) compared various artificial wall generation techniques. Using optical coherence tomography, VoB et al.(Voß et al., 2016) subsequently removed a vascular bifurcation of the circle of Willis postmortem and scanned it. After these photos were integrated to create a 3D model, the local wall thickness was resolved. FSI analysis was used to compare this model with models that had constant or diameter-dependent wall thickness. Based on experimental results, Torii et al.(Torii et al., 2009) modelled the aneurysm wall with a significantly lower uniform thickness of 0.05 mm and the arteries with a uniform thickness of 0.3 mm. In order to investigate the wall strains and deformations following a traumatic brain injury (TBI), Razaghi et al.(Razaghi et al., 2019) have modelled a cerebral aneurysm.

By running patient-specific FSI simulations, they have found that TBI-induced concentrated stresses increase the likelihood of rupture. Combining the patient-specific wall and lumen to create a 3D model was first done by Cebal et al.(Cebal et al., 2018; Cebal and Raschi, 2013). Micro-CT imaging of a resected aneurysm wall tissue placed on a 3D-printed model of the in vivo aneurysm lumen or fluid-domain (blood) imaged by a 3D rotational angiography (RA) imaging modality before surgery was the basis of their methodology. Nevertheless, based on the landmark (bleb) in the aneurysm, subjective

assumptions were made for aligning the fluid domain with the wall. The wall and fluid domain models produced by various imaging modalities may not always be able to be reliably aligned, especially in spherical aneurysms.

In order to create a 3D aneurysm wall geometry from clearly resolved cross-sectional histopathology pictures of surgically removed intracranial aneurysm slices, Niemann et al. (Niemann et al., 2021) developed a pipeline. Through the expansion of each cross-section to a circle, the aneurysm wall was created into a spherical shape for their investigation. The aneurysm lumen, however, can actually take many other forms, such as blebs or undulations. The aneurysm model could be enhanced by in vivo lumen shape information, it was noted. Because the arteries are more anatomically similar to cylindrical geometries, Glaber et al. (Virtual Inflation of the Cerebral Artery Wall for the Integrated Exploration of OCT and Histology Data - Glaßer - 2017 - Computer Graphics Forum - Wiley Online Library, n.d.) inflated a cerebral artery-wall cross-section into a circular shape, which served as the model for their investigation.

However, the lumen shape as it was in vivo cannot be preserved by the wall thickness acquired from surgically resected IAs. Niemann et al. (Niemann et al., 2021) have addressed this gap by combining lumen and wall data to create a more accurate model. Using 2D histologic image data and the virtually inflated 3D micro-CT image data to form fit the pre-operative angiographic data, they have integrated the multimodal wall and lumen data to create an enhanced 3D geometric model for intracranial aneurysms. In order to make the inner border of the aneurysm wall as level as the lumen in the preoperative angiographic imaging, the Iterative Closest Point Algorithm (ICP) was employed. However, utilising the algorithm's assistance, it is necessary to evaluate the accuracy of the aneurysm shape preservation and the wall thickness heterogeneity preservation after inflation. Glaber et al.'s method (Virtual Inflation of the Cerebral

Artery Wall for the Integrated Exploration of OCT and Histology Data - Glaßer - 2017 - Computer Graphics Forum - Wiley Online Library, n.d.) was applied to the aneurysm wall inflating.

Using other imaging modalities to generate an in vivo reference value is quite challenging. The few wall visualisation modalities that are now available are either impractical or difficult to use. Additionally, there are other ethical issues that must be resolved. There are currently only case reports and case studies describing intraluminal OCT usage in human cerebral aneurysms, and no intraluminal OCT is authorised for use in the cerebral vasculature (Ku et al.(Pasarikovski et al., 2020)). Despite being documented in the literature, intravascular ultrasonography (IVUS) has a low resolution for the cerebral vasculature (more than 1500 micrometres). Signal dropout behind calcium because the measurement is hampered by the ultrasonic beam's inability to pass through calcium. IVUS imaging is therefore restricted to tiny vessels(Athanasίου et al., 2011). On the other hand, there is disagreement in imaging protocols regarding 3T and 7T MRI modalities' ability to objectively quantify aneurysm wall enhancement because of factors like heart cycle pulsation-induced blurring ( Tian et al (Visualizing wall enhancement over time in unruptured intracranial aneurysms using 3D vessel wall imaging - Tian - 2019 - Journal of Magnetic Resonance Imaging - Wiley Online Library, n.d.), Hadad et al (Hadad et al., 2023), and Kleinloog et al(Kleinloog et al., 2018) and others. Although the walls of cerebral aneurysms are sometimes very diverse, with thick, atherosclerotic, or hypoplastic sections next to extremely thin ones, the majority of CFD studies of aneurysms assume solid walls.

Using conventional clinical imaging to resolve these sub-millimeter thicknesses is challenging. The material characteristics of these areas can also vary greatly. Because of this, the majority of fluid-structure modelling of cerebral aneurysms has traditionally depended on presumed homogeneous wall properties, making it seldom patient-specific, as Steinman and Pereira (Steinman and Pereira, 2019) highlighted.

## **MATERIALS AND METHODS**



## MATERIALS AND METHODS

Clinical history and demographic details i.e., age, sex, presence of comorbidities such as hypertension, diabetes and smoking are collected. Imaging of the patients with ruptured cerebral aneurysms will be studied. 3D model of DSA or CT angiography of the intracranial vessels containing the aneurysm is developed from the existing imaging. Further these images will be used to calculate the Hemodynamic Stress parameters in the various parts of the aneurysm i.e., Neck, body and dome as well as the probable site of rupture. CFD and FSI analysis to be done.

Patients are operated as per institutional protocol and the aneurysm dome beyond the placement of the aneurysm clip is excised.

The excised wall will be further examined by polarise microscopy. The content of collagen and orientation will be studied at different parts of the wall. Representative reconstruction based on the collagen properties of the aneurysm wall will be rendered.

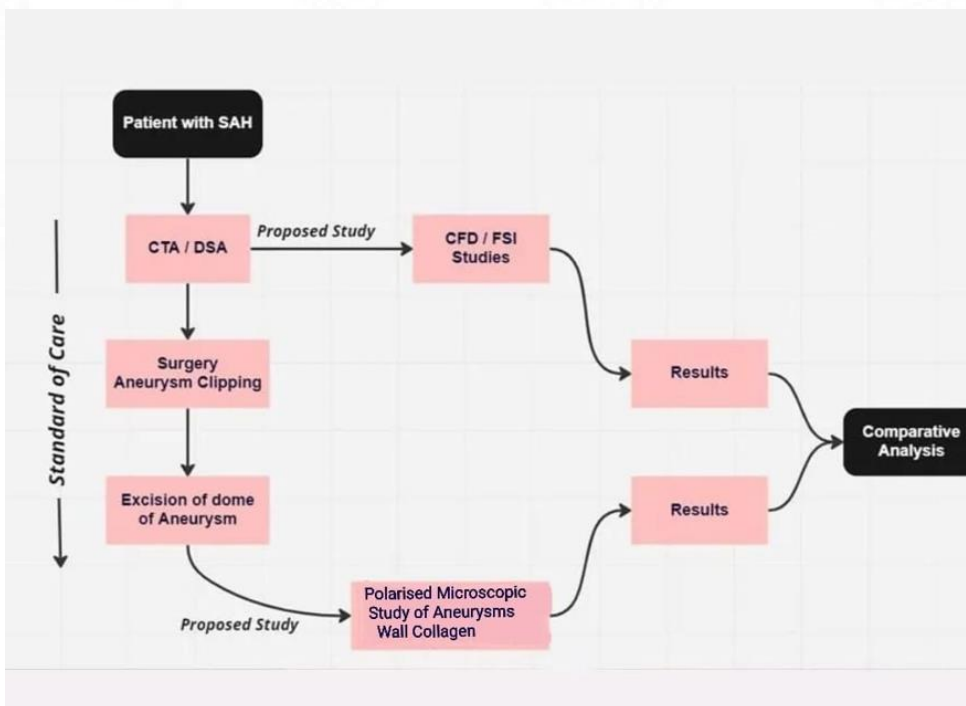


Figure 1- Flowchart for polarized microscopic study of aneurysm wall collagen parameters.

Another resected dome of aneurysm gross specimen will be sent to Department of Pathology, SCTIMST where it will be embedded in paraffin box. This embedded gross specimen of resected aneurysm will be evaluated using Micro computed tomography to assess the geometry and dimensions of the same. The patient specific actual wall thickness will then be calculated. The Assumed thickness of wall will be compared using micro CT based patient specific wall thickness assessment.

The relationship between the hemodynamic stress parameters at different parts of the aneurysm wall and its corresponding collagen properties and its orientation will be investigated in detail.

The histopathological image stack used in this work was obtained after performing the surgical clipping procedure for a female patient. The resected anterior cerebral artery aneurysm was acquired with the consent of the patient and approval by the institute's ethics committee. The haemotoxylin and eosin (H&E) stained aneurysm tissue was filled with a gel foam sponge such that the aneurysm wall encapsulates the lightweight foam without significantly altering the original shape of the aneurysm. Subsequently, the aneurysm was sliced, starting from the apex to the base, with a microtome such that consecutive slices were 200  $\mu\text{m}$  apart. These slices were imaged using a microscope (see Figure. 2). These images had a resolution of  $3840 \times 3072$  pixels. Each image accurately shows the wall thickness variation at that particular cross-section of the aneurysm slice, whilst the shape of the slice is expectantly deformed due to the histological process of cutting and preparing samples for image acquisition.

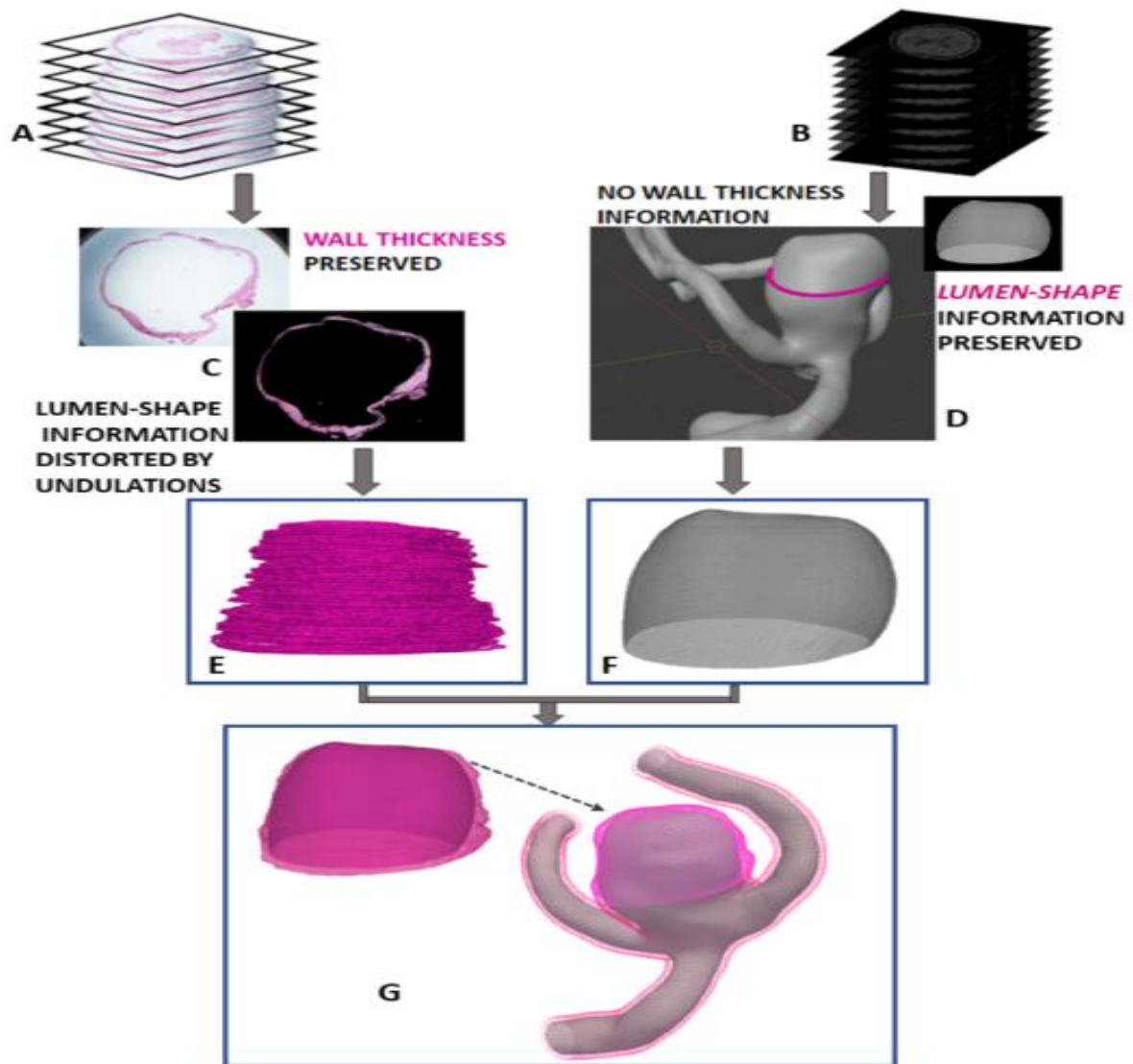


Figure 2: A) Histological 2D image stack of Resected Aneurysm dome B) CT Angiographic 2D image stack of slices in the axial plane C) A particular Histological slice showing the cross-sectional wall thickness of the aneurysm and the corresponding segmented 2D image D) 3D segmentation of the Lumen from CT Angiographic images E) Axially stacked 2D segmented images. F) 2D Slices of the 3D lumen G) 3D wall model rendered by Combining the wall thickness around the lumen

### **Slicing of Aneurysm-lumen 3D model**

1. The 3D model of the aneurysm lumen alone is sliced from the dome-apex to base such that, the shape of the generated lumen-slices match with the histological wall-slices with a one-to-one correspondence. This shape matching of slice pairs enable combining the wall thickness from the histological slice to its shape matched lumen slice, preserving their iso-surface shape. In essence, the slices are reconstructed such that, the in vivo shape and volume are conserved by the seamless continuity between successive slices. The binary images generated by slicing the 3D model were of resolution 1280 x 720 pixels (see Figure.3)

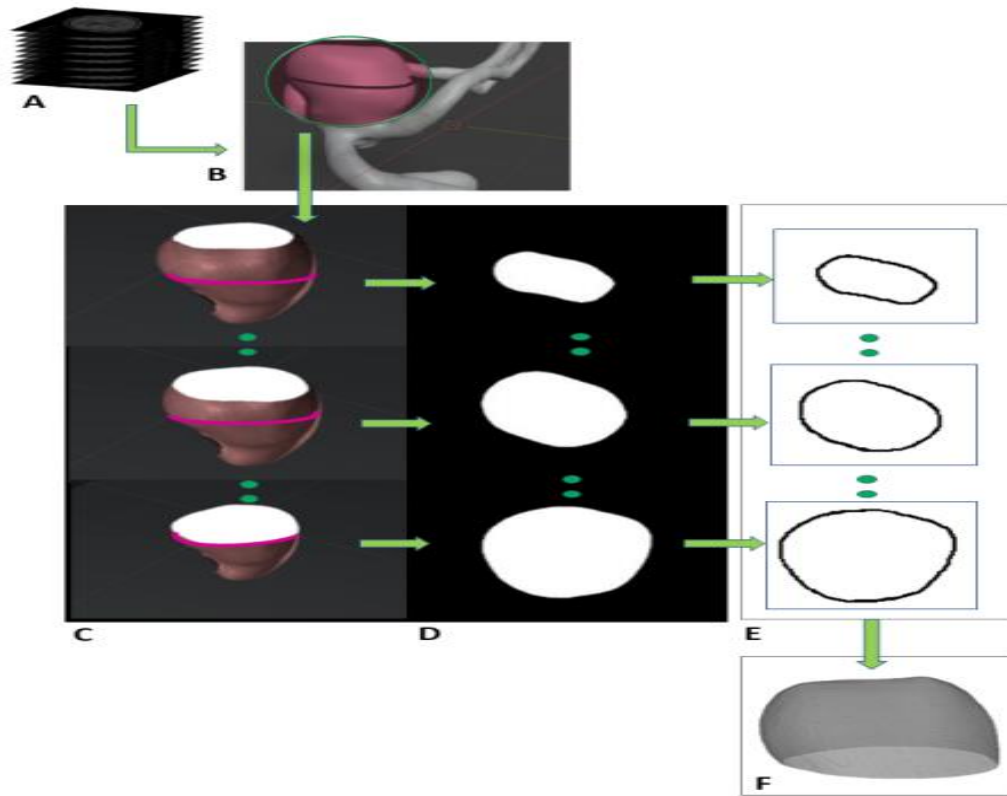


Figure 3: A) CT Angiographic Image stack of whole brain B) Segmented 3D geometry of the Aneurysmal-lumen along with its arterial-lumen C) Generation of lumen slice images top, middle and bottom (3D view) D) Lumen-slice Binary images top, middle and bottom E) Boundary detection from Binary Images to obtain the Aneurysm Lumen contours F) Stacked contours that form an accurate domain of the lumen

2. Contour generation from slices The cross-sectional image slices of the 3D image model for the lumen are cropped to a size 238 x 191 pixels so as to keep them in the same image-scale as that of the corresponding histologic wall-slice images. A sobel operator is applied on the binary image of every slice to obtain the contour of the lumen for that specific slice as shown in Figure.3. 2.3. Contour Shape Matching and

thickness transfer 200 Under in vivo conditions, the boundary of the lumen and its wall inner boundary are one and the same. The histologic images were processed to obtain the cross-sectional wall inner-outer boundary contours ( $C_i$  and  $C_o$ )

CT Angio 3D model (aneurysm lumen) was sliced digitally to obtain the crosssectional lumen contours( $C_l$ ). The aneurysm-lumen was sliced only at a particular angle of orientation with respect to the z axis, and sliced at  $\phi = 38^\circ$  as shown in Figure 4. For any other angle  $\phi$ , the flow-domain slices will result in a totally different set of shapes for the lumen slices which do not match with the corresponding histologic slices (see Figure 4). Additionally, the deflated wall images have shape and size changes, resulting in hindrance in establishing spatial correspondence between any slice-pair from histology to CT Angio directly (Figure 5 C1). Therefore geometric transformations, such as rotation, scaling and translation is performed on the wall-contour images such that, a minimum Hausdorff distance is achieved (Figure 5 C2). The small step sized rotations and translations are applied to obtain a minimum Hausdorff distance(Figure 6), which establishes perfect shape match and correspondence. To confirm the shape-match between histologic and CT Angio slice-contour images, the shape co-ordinates (x, y) are plotted for wall inner-boundary contour (histology) and the lumen contour (CT Angio). The contour shape represented by the shape co-ordinates ( ( $x_o, y_o$ ) - outer; ( $x_i, y_i$ ) - inner; ( $x_l, y_l$ ) - lumen) are plotted with respect to  $\theta_k$  (the sectoring angle around the contours). Since the plots of the shape co-ordinates for wall inner boundary and lumen do not match (Figure 5 A1 and A2), the Fourier descriptors are computed for those shape co-ordinates, as it provides the summary of the histological wall shape outpacing the undulations. When the Fourier coefficients are obtained for the histologic wall-inner boundary contour in the transformed frequency domain, the summary of the shape is deduced in the spatial domain. The undulation free shape descriptors for the wall inner boundary, now matches with the corresponding lumen contour shape(Figure 5 B1 - B3). In this way, the shape match is validated by using the Fourier Descriptors, The inner contour is warped ([42] and [43]) onto its shape-matched lumen contour to compute the subtle geometric transformations undergone by the aneurysm wall-slice due to the histological methods of tissue processing.

After warping the wall inner contour onto the shape matched lumen contour, a gradual reduction in Hausdorff distance facilitates spatial correspondence between the wall-lumen slice pair (Figure 5 C1 and C2). Since the inner area of the aneurysm wall slice is slightly less than the inflated lumen slice area, by normalising the wall inner-contour enclosed area from  $A_i$  to  $A^*_i$  with the lumen-contour area from  $A_l$  to  $A^*_l$  respectively, the proportionately normalised thickness area  $A^*_t$  from histology is combined around the normalised lumen.

3. Contour sectoring with points Due to the inherent drawbacks of tissue processing methods, the sliced aneurysm wall may have undulations which are clearly visible in each histology derived wall inner contour( $C_i$ ), whereas the corresponding CT angio derived lumen contour( $C_l$ ) is smooth. This scenario makes it difficult to obtain a spatial correspondence between the wall and the lumen. Therefore, using a sectorised wall boundary, the thickness was extracted from the wall at all its sector-points outpacing the undulations to combine it with the CT angio-derived lumen boundary, which is also sectorised into the same number of points (see Figure 7 A). This is achieved by picking up an equal number of points, uniformly by sectoring the wall inner-outer contours ( $C_i$  &  $C_o$ ) and lumen contour( $C_l$ ), such that  $P_o = P_i = P_l$  (the complete methodology is schematically presented in Figure 7). The equal number of sectorised points are on each contour, preserves the thickness between  $C_o$  and  $C_i$  which can be extracted at all the sectorised pair points,  $P_o$  and  $P_i$  and transferred around the spatially corresponding lumen contour's sector point,  $P_l$ . (see Figure 7 B). This can be repeated for all the matching contours between the histologic slices and lumen slices, which provide wall-thickness point cloud around them Figure 13 images G.

### 2.3.2. Extraction and transfer of thickness

The distance vector is computed between each boundary point on the outer periphery ( $P_o(\theta_k)$ ) and the inner contour ( $P_i(\theta_k)$ ). The distance  $x_t$  and  $y_t$  pixels are scaled proportionately based on the scale factor, the area ratios between the wall inner boundary to the lumen and added to  $P_l(\theta_k)$ , to obtain the thickness transferred at  $P_t(\theta_k)$ . See Figure 8

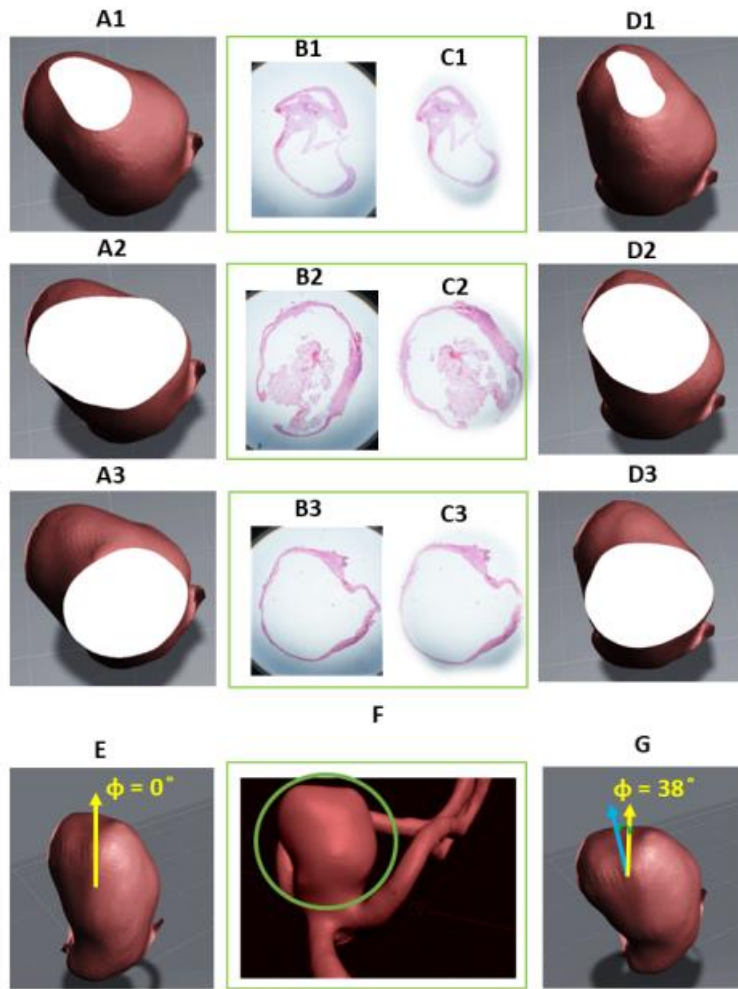


Figure 4: The angle between the central axis of the geometry and the z axis is  $\phi$ . A1-A3) Flow-domain / aneurysm-lumen slices for : E) Flow-domain sliced at an angle  $\phi = 0^\circ$  with respect to the z axis, shows no match D1-D3) Flow-domain / aneurysm-lumen slices for : G) Flow-domain sliced at an angle  $\phi = 38^\circ$  with respect to the z axis, shows perfect match with histologic slices (C1-C3 Rotated versions of original B1-B3). F) The complete flow-domain wherein the aneurysmal-lumen is highlighted by green circle.

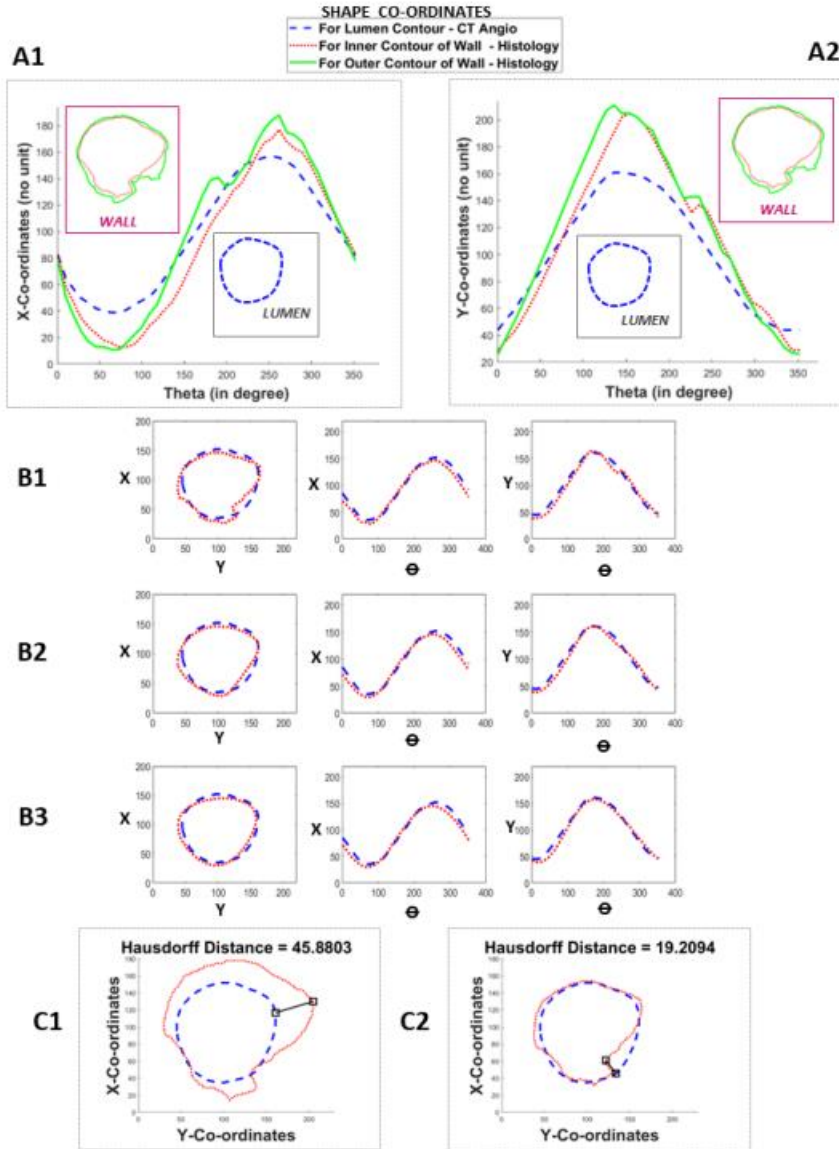


Figure 5: A1, A2) Variation of shape co-ordinates (x, y) histology derived wall-contours (preserve thickness - green & red) vs CT Angio derived Lumen-contour (preserves in vivo shape - blue) B1) shape matching with the Actual number of Shape coordinates that define the contour-shape (After image-warping the inner contour over the lumen contour), B2 and B3) Shape matching with a reduced number of Fourier Descriptors, C1) Superimposed inner contour over lumen contour to understand the geometric differences between the wall inner boundary(red-dotted) & lumen boundary(blue-dashed), C2) Warping the inner contour over the lumen contour to reverse the geometric transformation

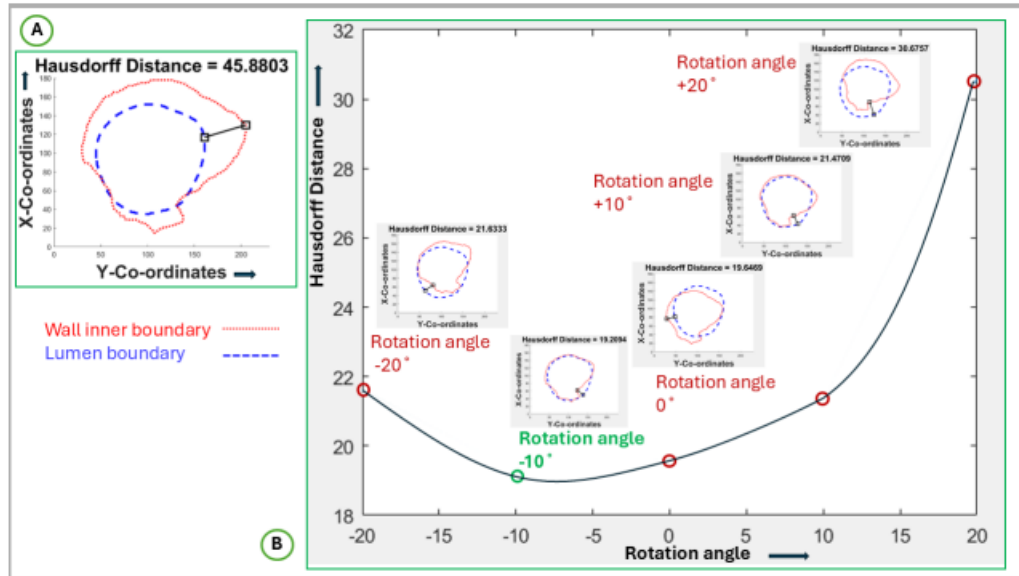


Figure 6: A) Original alignment of contours (wall inner boundary and lumen boundary). B) Geometric Transformation for wall inner boundary to match lumen boundary (Alignment match for gradual in-plane rotations of the Wall inner boundary to fit on the Lumen boundary)

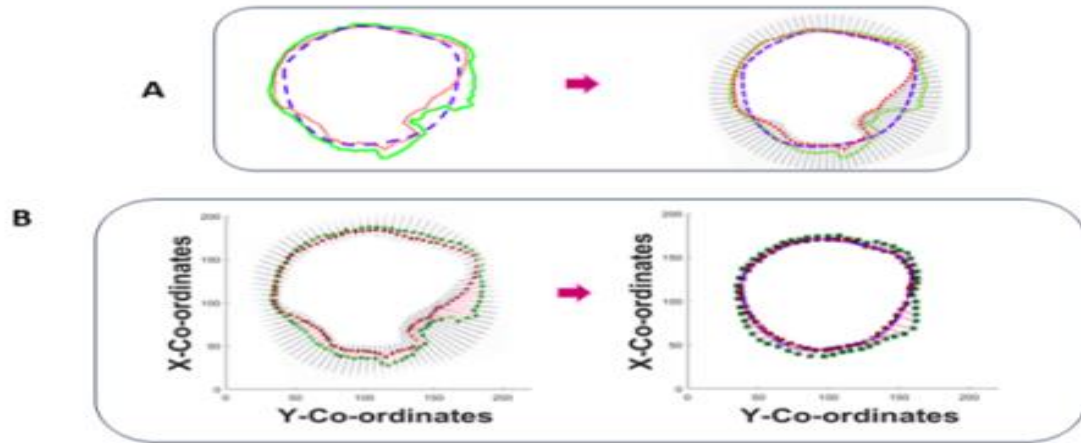


Figure 7: A) The Shape co-ordinates of the Inner, Outer & matched Lumen Contours are selected by uniformly/evenly dividing them around the loci as  $n$  sectors obtained from the GCF of Actual number of Shape co-ordinates between the inner, outer and lumen matched set of contours, B) The Distance metric between the Shape co-ordinates at every inner-outer sector-point pairs representing wall-thickness values at those points are transferred around the lumen at the spatially corresponding sector points

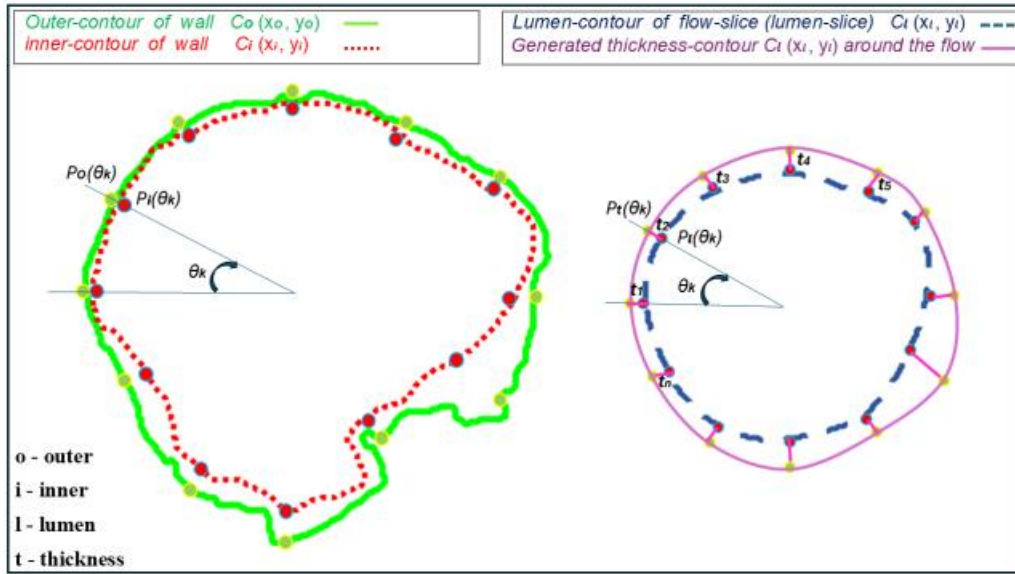


Figure 8: Thickness measured around the sector points on the histologic wall-contours & transferred around the lumen-contour at the spatially corresponding sector points.

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|               |                                                                                                                   |
|---------------|-------------------------------------------------------------------------------------------------------------------|
| <b>Input</b>  | Number of sectors $n \in \mathcal{R}$ ,                                                                           |
|               | Inner Contour of boundary points $\mathcal{C}_i$ ,                                                                |
|               | Outer Contour of boundary points $\mathcal{C}_o$ ,                                                                |
|               | Lumen contour from the CT $\mathcal{C}_l$ ,                                                                       |
| <b>Output</b> | Array of position vectors for points on the outer wall for CT based lumen for a slice $\vec{X}_t \in \mathcal{R}$ |

---

- 1:  $\theta \leftarrow \text{linspace}(0, 2\pi, n)$  {Equally spaced array of angles of size  $n$ }
- 2:  $P_i \leftarrow \mathcal{C}_i(xi, yi)$  { Get ' $n$ ' Shape co-ordinates for inner contour}
- 3:  $P_o \leftarrow \mathcal{C}_o(xo, yo)$  { Get ' $n$ ' Shape co-ordinates for outer contour}
- 4:  $P_l \leftarrow \mathcal{C}_l(xl, yl)$  { Get ' $n$ ' Shape co-ordinates for lumen contour from CT }
- 5:  $\mathcal{A}^*_i \leftarrow \text{Area}(\mathcal{C}_i)$  {Area enclosed by inner contour}
- 6:  $\mathcal{A}^*_l \leftarrow \text{Area}(\mathcal{C}_l)$  {Area enclosed by lumen contour}
- 7:  $\text{Scalefactor} \leftarrow \sqrt{\mathcal{A}^*_l / \mathcal{A}^*_i}$
- 8: **for** each angle  $\theta_k$  in  $\theta$  **do**
- 9:    $\vec{X}_i \leftarrow P_i(\theta_k)$  {Position vector of point on inner contour at angle  $\theta_k$ }
- 10:    $\vec{X}_o \leftarrow P_o(\theta_k)$  {Position vector of point on outer contour at angle  $\theta_k$ }
- 11:    $\vec{X}_l \leftarrow P_l(\theta_k)$  {Position vector of point on lumen contour at angle  $\theta_k$ }
- 12:    $\vec{T}_k \leftarrow (\vec{X}_o - \vec{X}_i) / \text{Scalefactor}$  { Extract and scale the thickness at a given sector }
- 13:    $\vec{X}_{t,k} \leftarrow \vec{X}_l + \vec{T}_k$  { Transfer the thickness at the spatially corresponding sector }
- 14: **end for**

---

Table 1: Wall Thickness Transfer Algorithm

The algorithm involves thickness extraction from all sector points around the wall and combining it with the spatially corresponding sector points on the lumen as described in Table 1. Since the 3D volume of a slice is obtained from a respective 2D image, there is a loss in the axial thickness information. The total number of histologic slice images obtained from microtome cutting followed by microscopic imaging was only 49, while the CT angio based blood-flow domain was 560 (smaller axial thickness preserves the shape of the lumen better). To start with, every histologic image slice was duplicated with an equivalent

ratio between the total number of lumen slices and the total number of histologic slices. As expected, it resulted in a textured surface during 3D reconstruction of the wall geometry (Figure 9 A and B). Therefore, Spline interpolation was used to obtain smooth texture for the outer surface of the wall as shown in Figure 9.

#### **4. Volume Rendering and Smoothing**

The histological 2D images provide the planar wall-thickness detail for every cross-sectional slice of the resected aneurysm tissue but do not account for the axial variations in wall thickness. From the base to the top, the height of the blood flow domain enclosed by the resected aneurysm wall tissue was measured to be around 11 mm, while the number of slices used to preserve the lumen shape post the 3D slicing was around 560. To render the complete 3D geometry(wall plus lumen), of the resected aneurysm, the number of slices per mm ( $\approx 51$  slices/mm) is used along with the number of pixels/mm (10 pixels/mm) so as to compute each lumen-slice height (0.02mm). The blood flow domain(lumen) alone preserves the 3D morphological shape within its continuous slices, acquired during the slicing of the lumen's 3D model. The volume rendering software enables the volume in 3D by stacking up the lumen images, which encompasses the wall thickness details. The histological wall images were uniformly duplicated to match the CT angio derived lumen slices, resulting in a rough and stacked surface (see Figure 9). Therefore, a smoothing step is required to smoothen the discrete thickness around the lumen. The post-smoothing 3D aneurysm geometry, (see Figure 9), exhibits a smooth surface that satisfies the necessity of a smoother surface mesh.

#### **5. Mesh Generation**

A 3D Mesh of the reconstructed aneurysm wall (wall thickness plus lumen shape Figure 10 A) is placed on the 3D surface mesh of the blood flow domain to ensure a good fit, and an outer mesh is created over them that undergoes the sculpting process [44, 45, 46, 47] to preserve the thickness heterogeneity 300 (see Figure 10 B). The average thickness measured around the reconstructed aneurysm wall is set as the wall

thickness for the rest of the geometry extending up to the arteries (Figure 10 C). The final 3D outer and inner mesh representing the wall thickness around the entire blood flow domain enclosed by the aneurysm and the associated arteries is the final 3D geometry (Figure 10 D). Volume mesh is generated for the fluid and solid domains using tetrahedral and prism elements. Prism layers are added near the vessel surface to capture the boundary layer physics accurately, with the inner core filled with tetrahedral elements. Two different views of meshing, surface-based as well as a close-up view are shown in Figure 11.

## 6. Fluid Structure Interaction

Over the meshed geometry, coupled fluid-structure interaction (FSI) effects are resolved by duly accounting for the two-way influences between the fluid flow(blood flow) and the deformable structure(wall). Fluid-structure interaction (FSI) resolves the interaction effects between the blood flow and the arterial wall, as the flowing fluid modifies wall deformation. To resolve these influences, the Arbitrary Lagrangian Eulerian (ALE) approach is adopted for the coupling between the fluid and wall structure. In ALE formulation, the fluid flow equations are solved in the Eulerian reference frame, and the solid equations are solved in the Lagrangian reference frame. The flowing fluid is assumed to be laminar, incompressible, and Newtonian, which can be modeled using the Navier-Stokes equation. Simulations are performed using finite element-based commercial solver(Introduction to COMSOL Multiphysics, n.d.). In this solver, the governing equations that are numerically solved are, continuity and linear momentum conservation are,

$$\nabla \cdot \mathbf{V} = 0 \quad (1)$$

$$\rho \left( \frac{\partial \mathbf{V}}{\partial t} \right) + ((\mathbf{V} - \mathbf{V}_m) \cdot \nabla) \mathbf{V} = -\nabla P + \mu \nabla^2 \mathbf{V} \quad (2)$$

Where ' $\mathbf{V}$ ' is the velocity field vector, ' $\mathbf{V}_m$ ' is the mesh velocity,  $P$  is the fluid pressure, ' $\rho$ ' is the density of the incompressible fluid, and ' $\mu$ ' is the dynamic viscosity of the fluid. Additionally, the equation for the wall deformation is coupled to the Navier-stokes equations to solve the wall deformations as,

$$\rho_s \left( \frac{\partial^2 \mathbf{y}}{\partial t^2} \right) = \nabla \cdot \boldsymbol{\sigma} + \mathbf{F}_b \quad (3)$$

Where ' $y$ ' refers to the wall displacement, ' $F_b$ ' is the body force acting on the structure, ' $\rho_s$ ' is the density of the vessel wall, and ' $\sigma$ ' is the Cauchy stress tensor. Here, the fluid flow equations are solved in a deforming mesh domain having mesh velocity  $V_m$ . Hyperelastic smoothing ensures smooth deformation of the fluid mesh based on the boundary constraints. The solid wall boundary is subjected to pressure and viscous forces from the fluid side. The solid wall is free to move, and the fluid mesh deforms freely according to the wall displacements. Two-way coupling is employed for the FSI simulations, and the interface has the same velocities for the fluid and solid domains. Furthermore, the dynamic forces at the interface are identical but act in opposite directions. The direct solver PARDISO solves the fluid and solid equations simultaneously using a fully coupled approach and uses the Newton-Raphson method to linearize the non linear equations. The damping factor is adjusted such that, the residual errors at each iteration converge with an absolute tolerance value set to 0.001. The flow domain uses the P2+P1 discretization technique, while Quadratic Lagrange is adopted for the solid domain. The generalized- $\alpha$  method is used for temporal discretization with a strict initial time-step of 0.0001

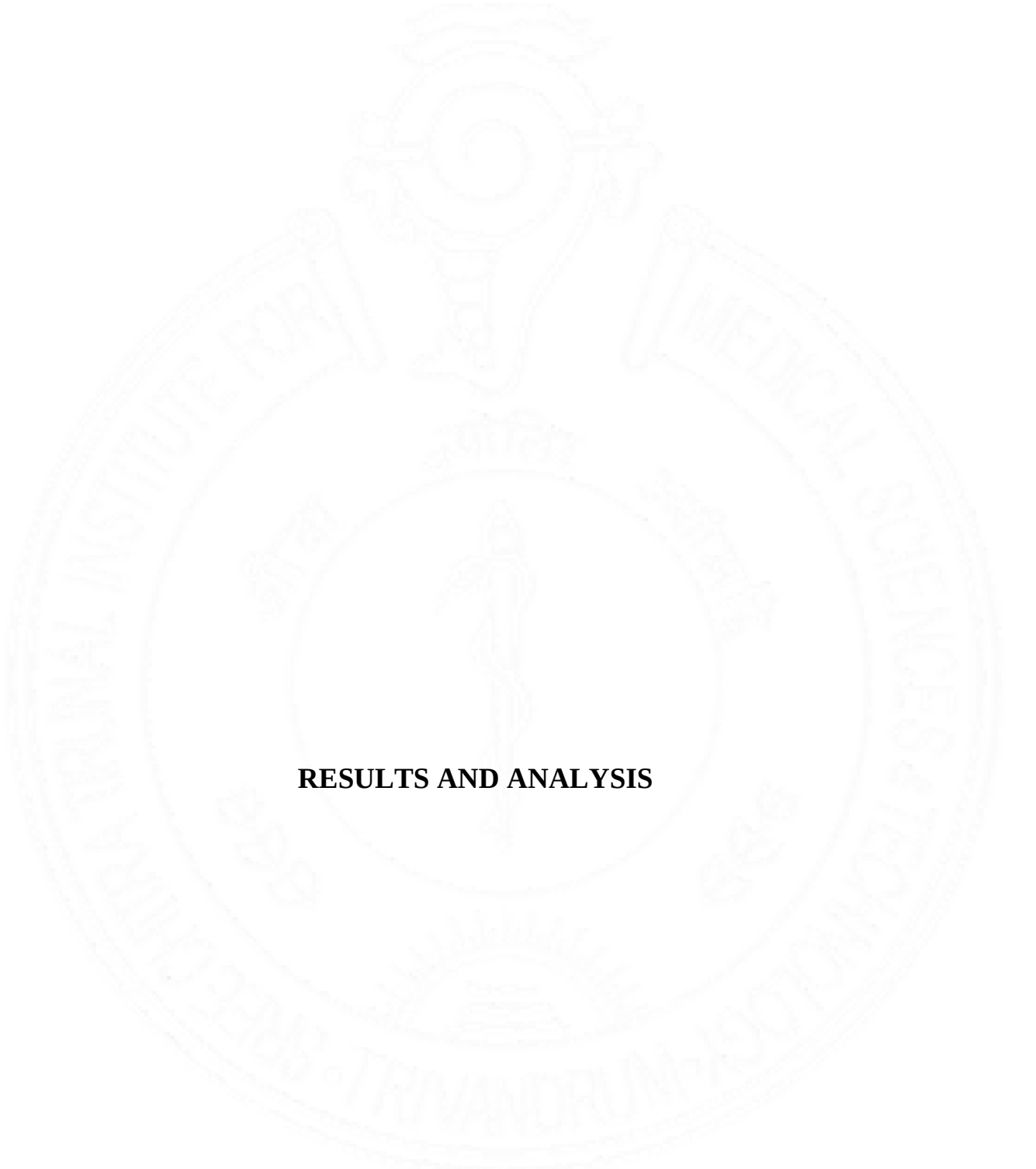
Aneurysm walls exhibit non-linear hyper-elastic properties (A fully-coupled fluid-structure interaction simulation of cerebral aneurysms | Computational Mechanics, n.d.; Sanchez et al., 2014). However, an earlier study by Lee et al (Lee et al., 2012) showed that the linear-elastic material model could represent the trends in displacement patterns and high flow velocities (Lee et al., 2012). 350 The present study assumes the arterial wall to be a linear elastic material that simplifies the modeling complexities and reduces the computational cost. Blood has a density of 1050 Kg/m<sup>3</sup> and a dynamic viscosity of 0.0035 Pas. The arterial wall structure has a density of 1100 Kg/m<sup>3</sup> with Young's modulus value equal to 1 MPa and Poisson's ratio of 0.49 (Lee et al., 2012). The transient pulsatile waveform is provided at the inlet cross-section. The reference pressure at the outlet is considered to be zero. There is a no-slip boundary condition for the fluid wall, and the solid wall is set with zero traction. Mesh metrics for coarse, medium and fine meshes are presented in Table 3. The GCI values are shown in Table 4 to assure that the FSI simulations are reliable and grid independent (Journal of Fluids Engineering, 2008)

| Metrics                    | Coarse(c) | Medium(m) | Fine(f)   |
|----------------------------|-----------|-----------|-----------|
| Global cell size(minimum)  | 0.064     | 0.048     | 0.036     |
| Global cell size (maximum) | 0.32      | 0.24      | 0.18      |
| Refinement factor (r)      | 1.3       | 1.3       | 1.3       |
| First cell height (h)      | 0.04      | 0.02      | 0.01      |
| Inflation layers           | 3         | 5         | 7         |
| Prism growth ratio         | 1.12      | 1.12      | 1.12      |
| Number of Elements         | 4,54,728  | 8,02,605  | 11,27,880 |

Table 2: Mesh metrics for coarse, medium and fine meshes

| Parameter         | Coarse(c) | Medium(m) | Fine(f) | GCI(f,m) | GCI(m,c)      |
|-------------------|-----------|-----------|---------|----------|---------------|
| $WSS_{max} @ t_1$ | 5.02      | 6.69      | 6.83    | 2.75%    | <b>0.225%</b> |
| $WSS_{max} @ t_2$ | 23.26     | 27.21     | 28.47   | 8.512%   | <b>2.587%</b> |
| $WSS_{max} @ t_3$ | 8.19      | 11.06     | 11.95   | 14.6%    | <b>4.187%</b> |
| $WSS_{max} @ t_4$ | 4.48      | 5.53      | 5.82    | 9.062%   | <b>2.375%</b> |

Table 3: Grid Convergence Index (GCI)



## **RESULTS AND ANALYSIS**

## RESULTS AND ANALYSIS

The present study essentially unified multi-modal imaging data obtained from two distinct modalities. CTA images along with histopathological slices were used to accurately reconstruct wall thickness heterogeneity as it existed in vivo. However, it is equally important to estimate the efficacy of the wall thickness transfer algorithm as well as the accuracy of the present approach.

### 1. Segmentation Accuracy

In the Figure 13, images A1 - A5 are randomly selected slices from histology and images B1 - B5 are the segmented versions of the aneurysm wall crosssection. It is observed that the K-means clustering algorithm combined with the sectoring algorithm has performed a satisfactory segmentation and sectoring preserving the thickness measures for further steps in the pipeline (Figure 12).

### 2. Sectoring Efficiency

The method of uniform sectoring of the contours (outer-inner contours from histology and lumen contour from CT Angio) into an equal number of sector points 'n', results in 3 distinct sectoral arc lengths that enable spatially precise thickness transfer from the histology derived wall-contour sector-point pairs to the spatially corresponding locations around the lumen-contour points. Moreover, due to some undulations present in the wall boundaries, their respective contours were larger than the spatially corresponding matching lumen-contour. This resulted in an improper fit, if the wall contours were directly wrapped around the lumen-contour for any given wall-lumen matched slice-pair between histology and CT Angio. However, by uniformly sectoring the 3 contours with an equal number of sector points, spanning around their respective contour perimeters, the spatial correspondence between histologic and CT Angio contours is achieved for enabling an accurate thickness transfer.

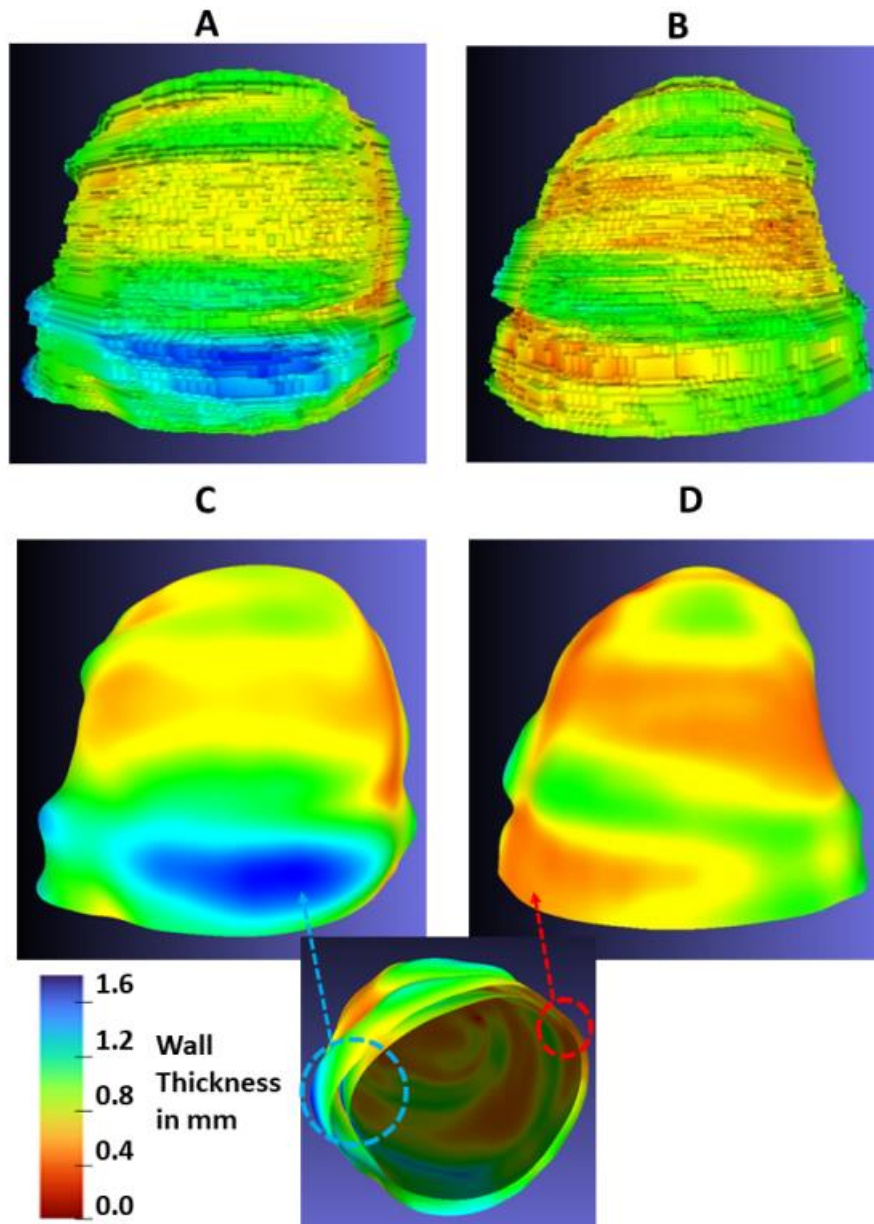


Figure 9: 3D rendered aneurysm wall outer boundary A) with rough surface-mesh showing Maximum thickness (blue) regions (front view) B) with rough surface-mesh showing Minimum thickness (red) regions (back view) C) with Smoothed Surface-Mesh showing Maximum thickness (blue) regions (front view) D) with Smoothed Surface-Mesh (red) showing Minimum thickness regions (back view)

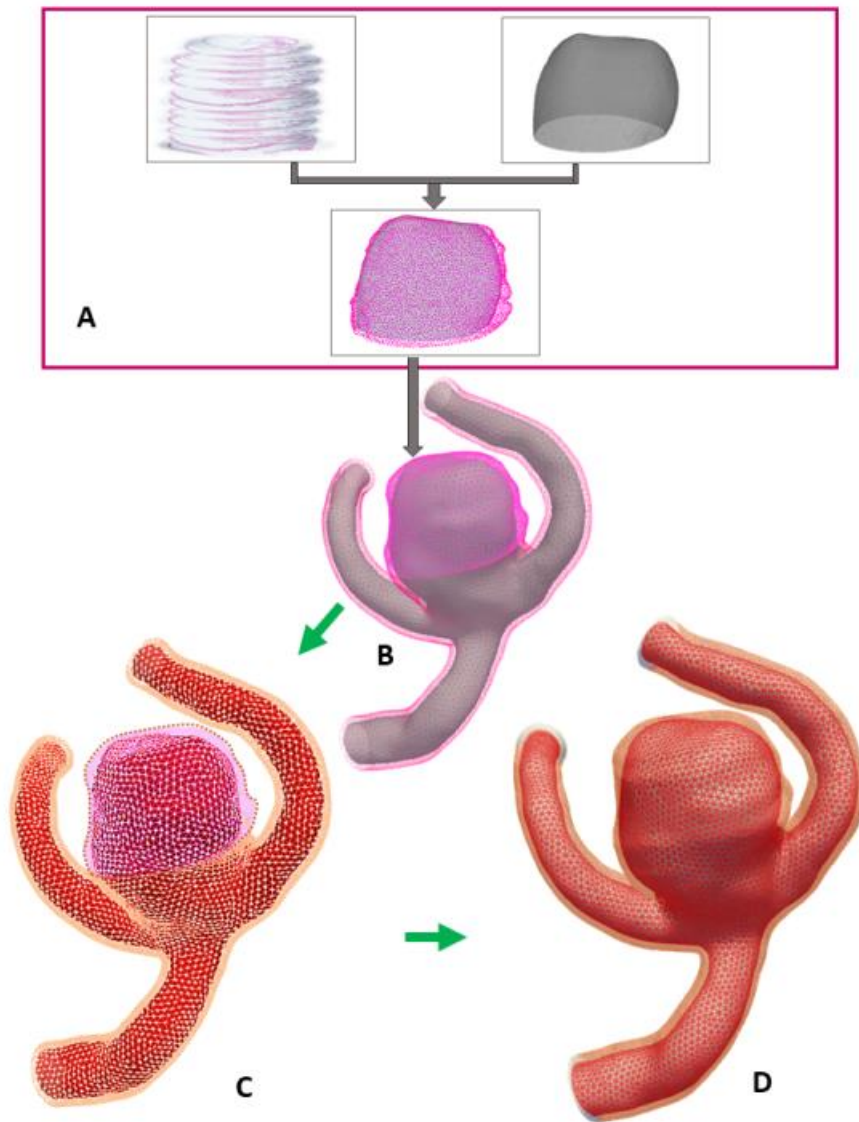


Figure 10: A) Wall thickness information from Histological slices + shape information from CT-derived blood-flow-domain/lumen slices to obtain the Point Cloud for representing the wall-thickness values transferred around the lumen B) A 3D Mesh of the reconstructed aneurysm wall (wall thickness + lumen shape) is being placed on the 3D mesh of the blood flow domain to ensure the perfect fitting C) Average thickness measured around the reconstructed aneurysm wall is used to computationally create the wall thickness-mesh for the rest of the blood flow domain extending up to the arteries D) Final 3D outer and inner Mesh representing the wall thickness around the entire blood flow domain enclosed by the aneurysm and the associated arteries.

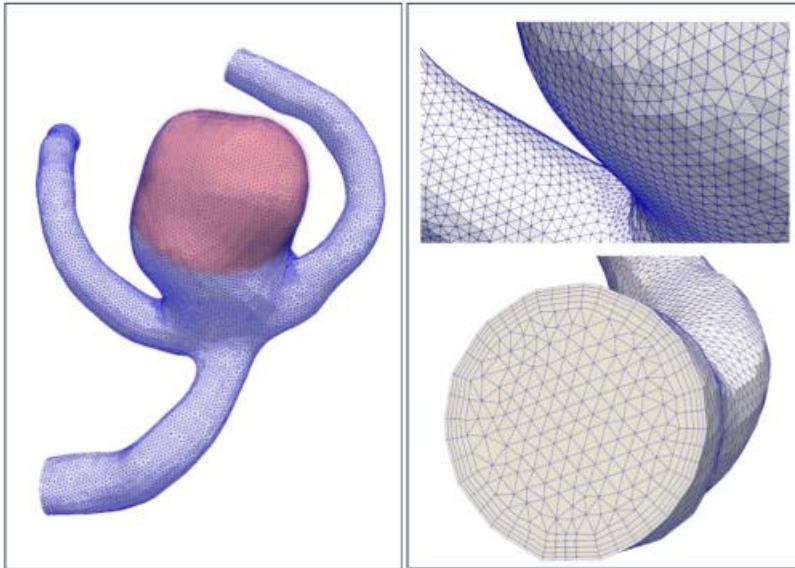


Figure 11: Surface mesh as well as close-up view of the neck branch and the outlet

### 3. 3D-geometry Reconstruction Efficiency

The spatially sectorized discrete points holding the thickness data around the lumen data-points (Figure 13 images C1 -C5) are joined using a string element that is used in image processing methods (Radial Decomposition of Disks and Spheres - ScienceDirect, n.d.) to connect the points (Figure 13 D1 - D5). Now, all the lumen contour images holding the transferred thickness values representing the wall around them are stacked up in the axial plane, to obtain the 3D geometric model of the resected aneurysm. The integration of all the thickness-melded lumen-slices (Figure 13 images D1 - D5) to obtain the synthesized geometry is presented in Figure 13 image H. The final smoothed version of the 3D reconstructed aneurysm wall 13 image I is virtually sliced to ensure that the instilled thickness heterogeneity is revealed at those selected random slices (see Figure 13 image E1-E5). To compare and validate the discrete thickness values that were extracted from a histologic slice

(Figure 13 images A2 and B2) against the transferred thickness values around the corresponding shape-matched lumen slice (Figure 13 C2), the cross-sectional plane pertaining to that slice in the finally reconstructed 3D geometry of the resected aneurysm model is identified and observed (Figure 13 E2). It is inferred that the thickness extracted from a histologic slice is comprehensively transferred around the corresponding lumen slice, which is obviously reflected in the corresponding cross-sectional plane from the finally reconstructed 3D model of the resected aneurysm. In the Figure 13 for any randomly selected plane, the horizontal series of images, for instance, A3 - E3 can be observed to infer qualitatively, that the thickness heterogeneity is preserved all the way from histology to CT Angio. While Figure 14 gives the quantitative 2D Mapping of the wall thickness values from Histologic Wall contours (Figure 13 images A1-A4) to CT Angio Lumen contours (Figure 13 images C1-C4) for those randomly selected slices. High correlation co-efficient values and lower mean error percentages amply exemplify the quantitative validation for the thickness transfer from histologic wall contours to CT Angiographic lumen contours.

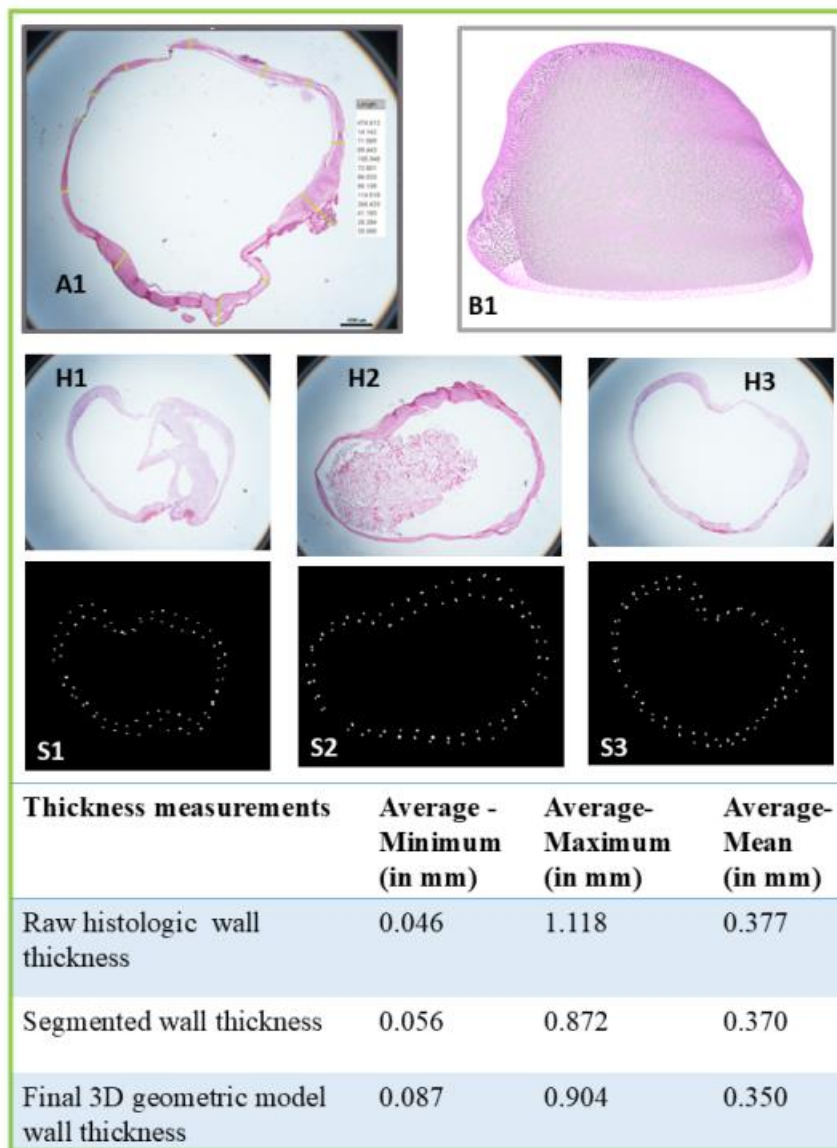


Figure 12: Raw Manual Thickness data measurements (A1) vs Extracted wall Thickness data measurements (H1-H3 : Random Histologic images, S1-S3 : Segmented versions) vs Final 3D wall geometry thickness measurements (B1)

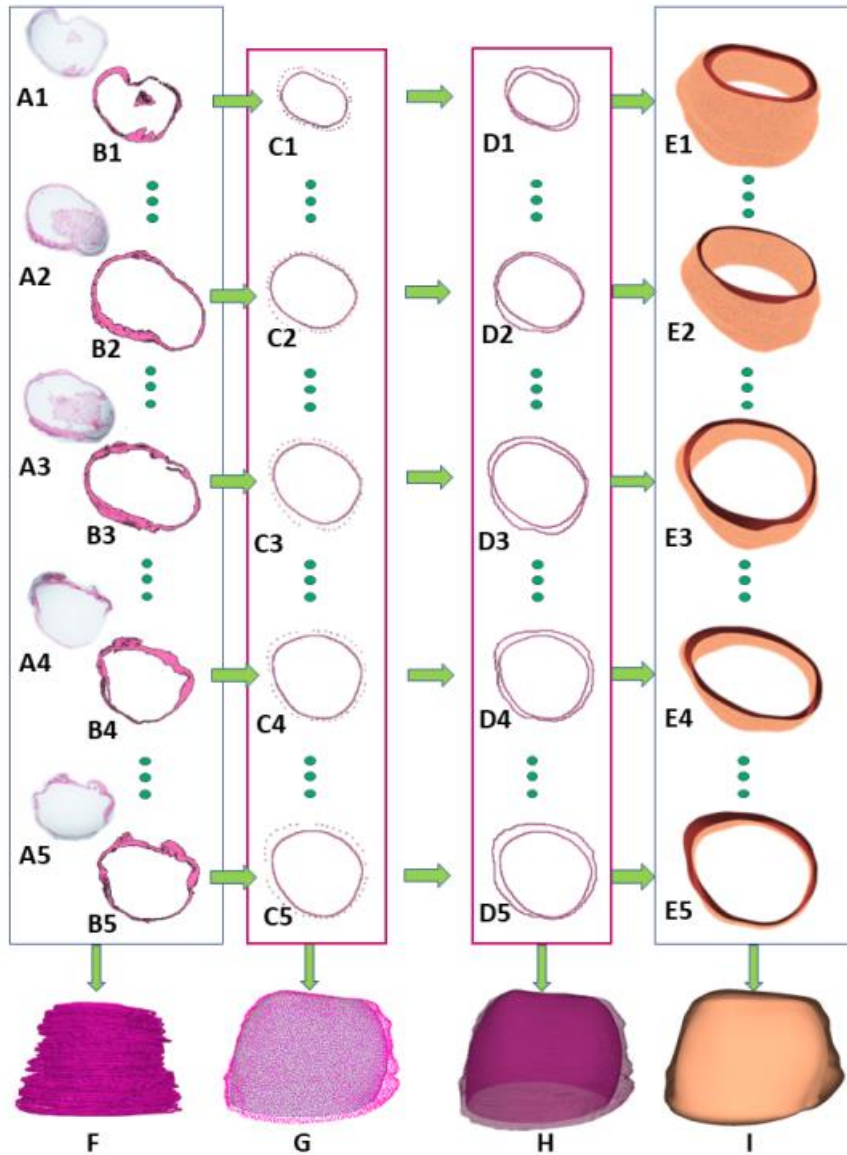


Figure 13: A1-A5) Histologic slices B1-B5) Wall segmentation from slices C1-C5) Transferring thickness at sector points around the lumen-contours D1-D5) Joining the thickness points E1- E5) Slice appearance revealing the thickness heterogeneity at various planes axially F) Volume rendered from segmented images G)Point cloud showing the transferred thickness around the lumen H) Rough volume rendering I) Smooth volume rendered by stacking E1-E5

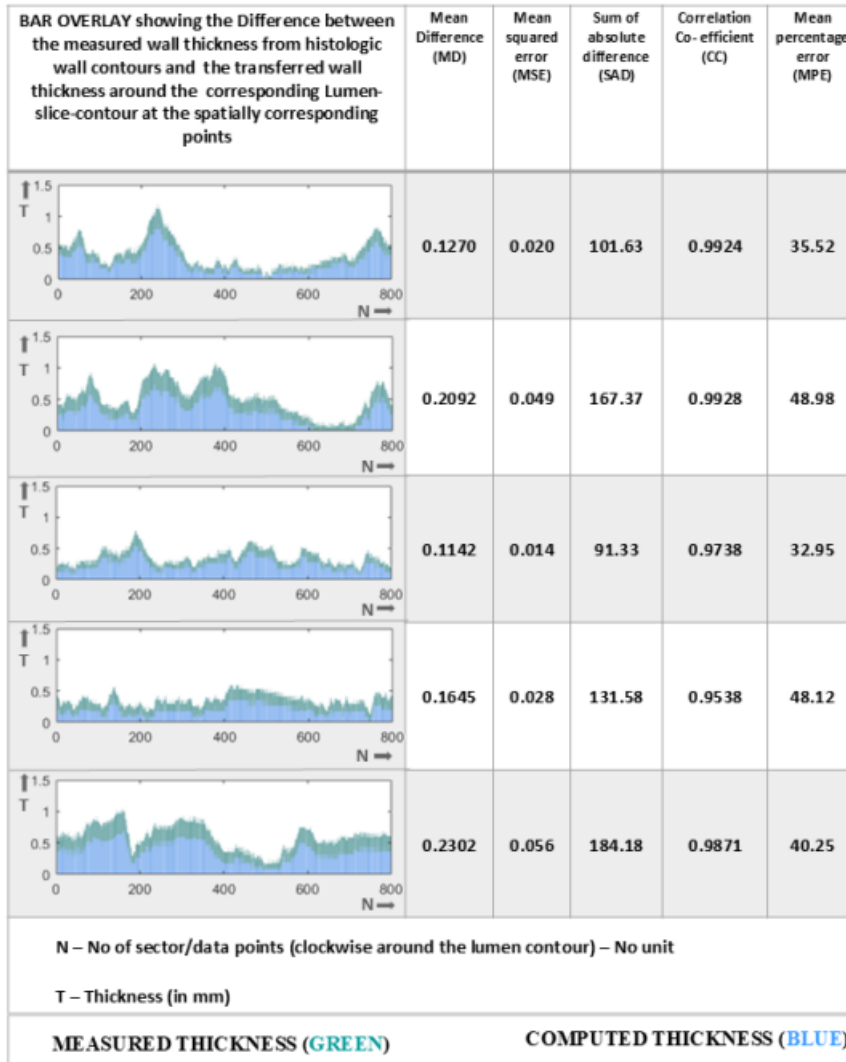


Figure 14: 2D Mapping of wall thickness from Histologic Wall contours to CT Angio Lumen contours

#### 4. Patient Specific Wall Thickness Measurements

Each thickness data that is measured as a distance vector between the inner and outer contour sector-points (shape co-ordinates for outer sector point  $Co(x_o, y_o)$  & inner sector point  $Ci(x_i, y_i)$ ) from a histologic slice is transferred in a clockwise fashion around the spatially corresponding lumen sector points (shape co-ordinates for a sector point in a lumen contour  $Cl(x_l, y_l)$  in the corresponding shape-matched lumen slice. At various slices of the rendered aneurysm wall (Figure 13 images C1 - C5), the maximum thickness value

spanned between 0.6 mm to 1.5 mm, similarly, the minimum thickness values at various slices of the aneurysm wall ranged between 0.1 mm to 0.4 mm (Figure 15).

## 5. Wall Thickness Conservation

The elasticity provided by the gel foam sponge embedded within the resected aneurysm wall before it underwent microtomy was efficient enough to almost retain the same amount of inflation, analogous to the blood-volume that originally prevailed in vivo. Area normalization was performed for all slice-contours of the wall and lumen. Since slices are made of equal width in the axial direction, the thickness area conservation (precise transfer of measured thicknesses from histology to the final 3D model) for every slice, in turn, has ensured volume conservation. However, it is to be noted that various effects, such as shrinkage distortion due to tissue processing, slicing, and imaging, make the exact conservation highly challenging. Figure 16 presents over all reconstructed volume of the wall and CT angio projected wall volume. The associated differences from the present algorithm was observed to be with in acceptable limits.

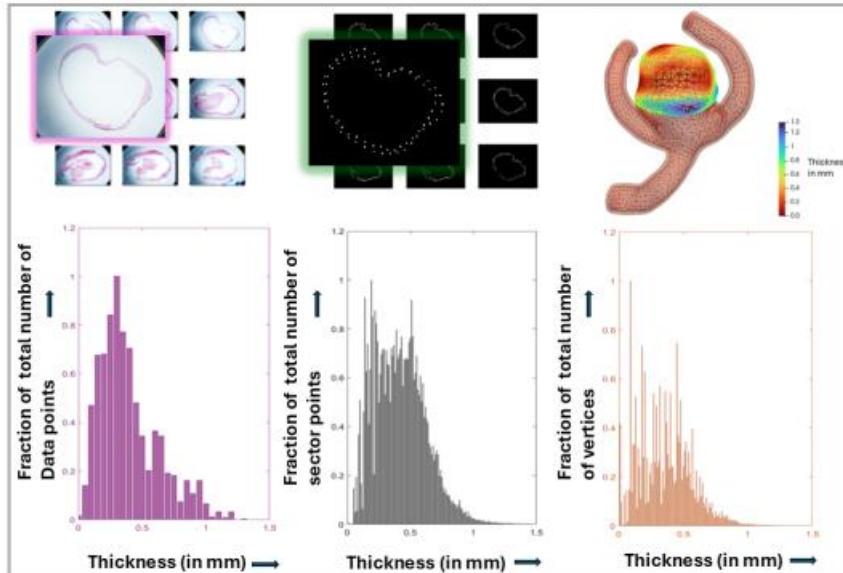


Figure 15: Histogram of randomly measured wall thickness at various stages of the pipeline a) Raw ground truth manual measurements at various data points b) extracted thickness measurements from segmented images at all sector points c) 3D thickness contour measure

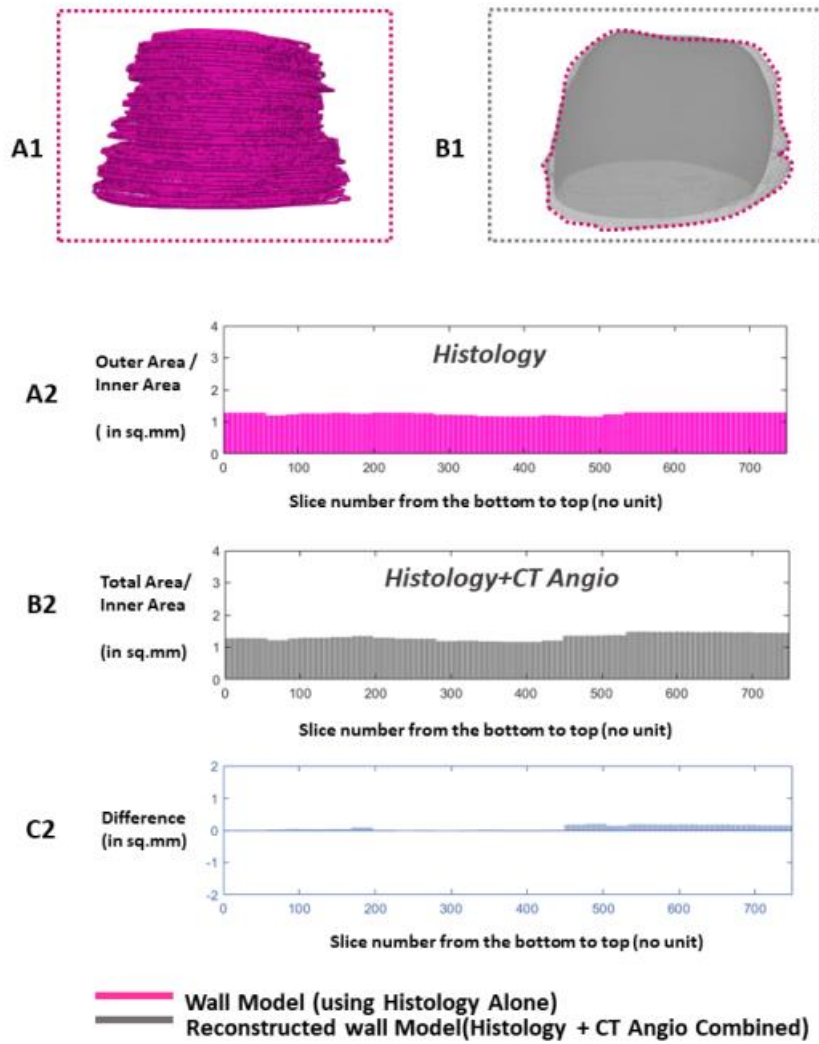


Figure 16: Wall Volume Conservation A1) Wall model(using Histology Alone) B1) Reconstructed wall model(Histology + CT Angio Combined) A2) Area ratios for each slice (using Histology Alone) B2) Area ratios for each slice (Histology + CT Angio Combined) C2) Difference between the area ratios.

## 6. Fluid Structure Interaction Simulations

Numerical simulations are performed by accounting for two different wall thickness constructions, viz. a uniform wall and patient specific wall. These two models are subjected to fluid-structure interaction studies to compare and contrast the difference between the two approaches. The reconstructed patient

specific cerebral aneurysm model, using the proposed multi-modal registration methodology of combining the 3D lumen shape information from Computed Tomographic Angiography (CTA) and the wall thickness data from histopathological images, was compared against the uniform wall thickness model developed for the same aneurysm. The uniform wall thickness (UWT) model was incorporated with a uniform defined thickness around the aneurysm lumen of about 0.6 mm and the patient-specific wall thickness (PWT) reconstructed from histologic 450 slices using the algorithm discussed in the manuscript had its own wall thickness heterogeneity. FSI Simulation results on these two models revealed that thin walled regions in the PWT model experienced higher pressure compared to thick walled regions as shown in Figure 17. In the biomechanical perspective, Wall Shear Stress (WSS) is the haemodynamic parameter of interest when the solid (wall) and fluid (blood) is combined. Moreover, Wall shear stresses in the aneurysm influences endothelial response and hence, the inner layer of the wall is affected. It is observed that UWT model underestimate the hemodynamic forces. Considerable differences are noticed in the pressure and wall shear stresses observed between the UWT and PWT models. Aneurysm cannot withstand the higher stress and ruptures when arterial wall loses its structural integrity. Thinner wall regions experience higher stresses and displacements for the same internal pressure than thicker wall regions, leading to concentrated strain in those areas. The maximum wall stresses for the UWT model is 13.6 kPa, while for the PWT model is 48.4 kPa. The maximum wall displacements for the UWT model is 58.5  $\mu\text{m}$ , while for the PWT model is 162  $\mu\text{m}$  (see Table 2 ). It is observed that the uniform thickness model underestimates the prediction of the biomechanical stresses and wall displacements (see Figure 18 and 19)

| <b>Hemodynamic Results</b> | <b>UWT</b>         | <b>PWT</b>        |
|----------------------------|--------------------|-------------------|
| Maximum Wall Stresses      | 13.6 KPa           | 48.4 KPa          |
| Maximum Wall Displacements | 58.5 $\mu\text{m}$ | 162 $\mu\text{m}$ |

Table 4: Quantified Hemodynamic Results - comparison between uniform and patient-specific models

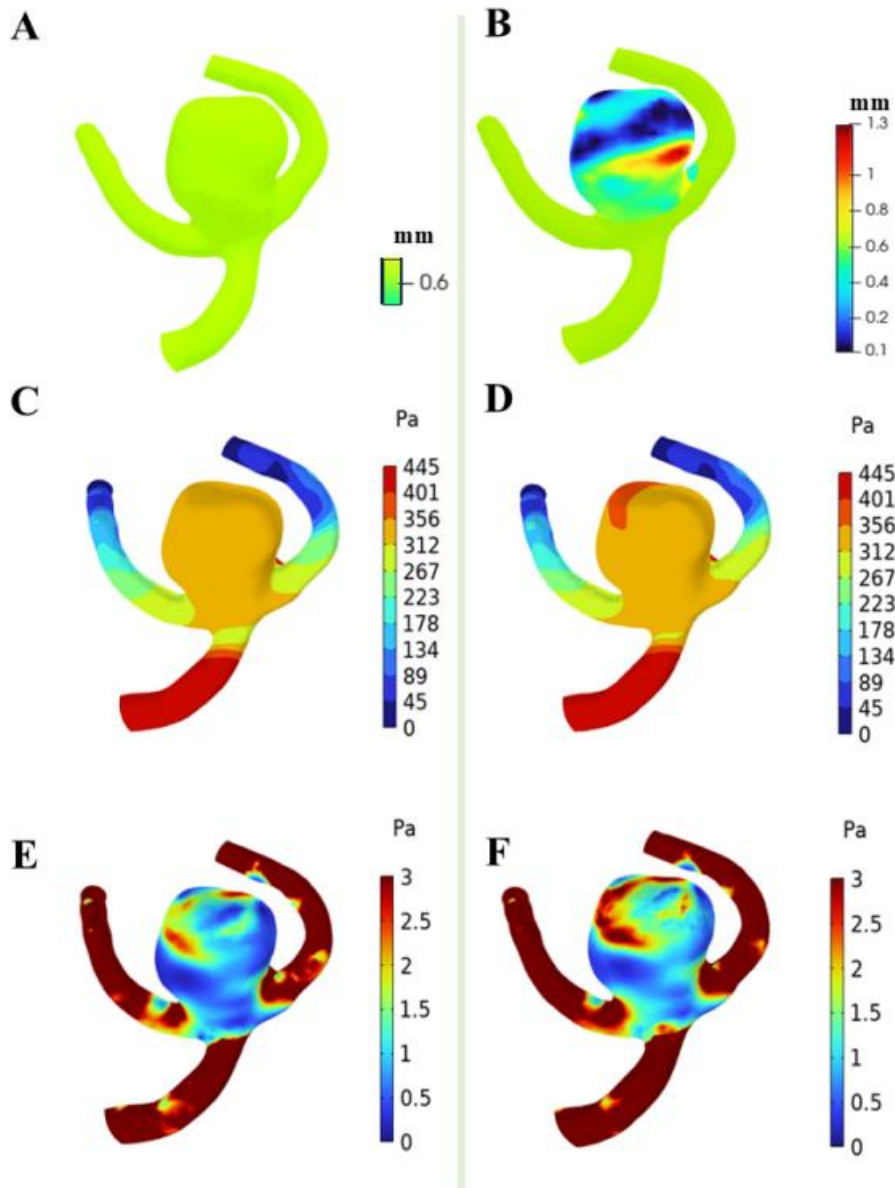


Figure 17: A) Uniform Wall Thickness (UWT) Contours B) Patient-specific Wall Thickness (PWT) contours . Pressure at peak systole for: C) UWT D) PWT. Wall Shear Stress contours (WSS) at peak systole for: E) UWT F) PWT.

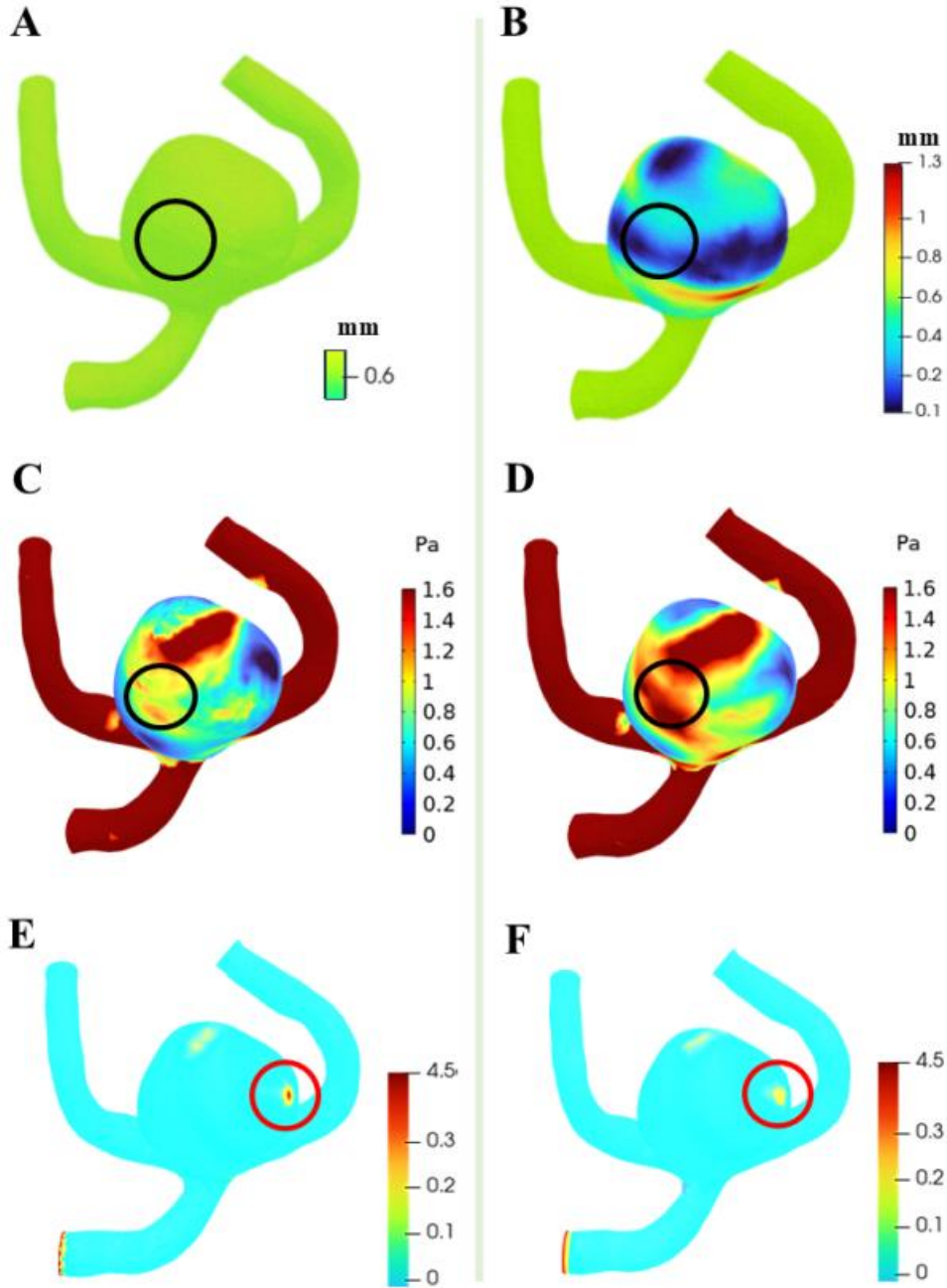


Figure 18: A) Uniform Wall Thickness (UWT) Contours B) Patient-specific Wall Thickness (PWT) contours . Time-Averaged Wall Shear Stress (TAWSS) contours at peak systole for: C) UWT D) PWT. Oscillatory Shear Index (OSI) contours at peak systole for: E) UWT F) PWT.

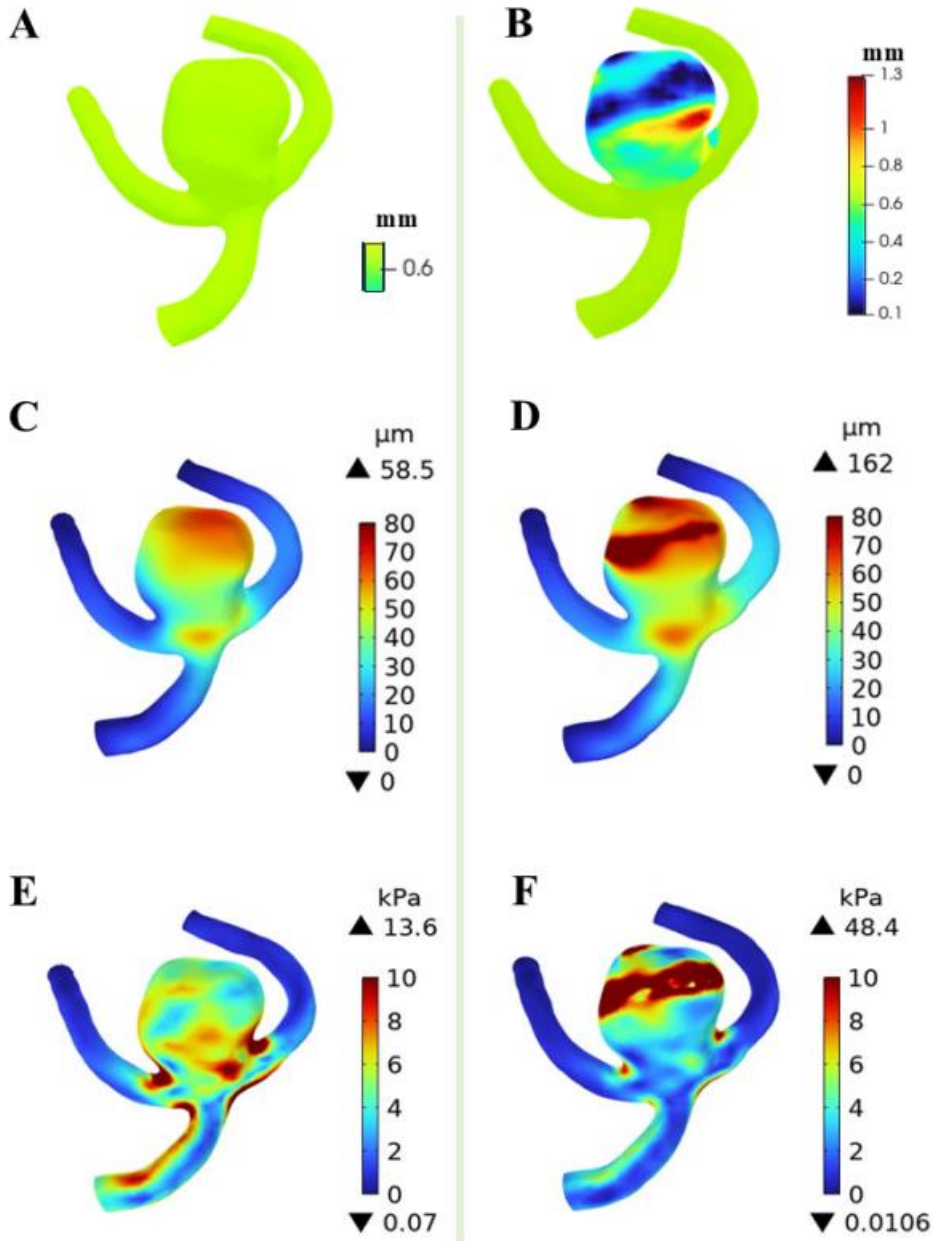


Figure 19: A) Uniform Wall Thickness (UWT) Contours B) Patient-specific Wall Thickness (PWT) contours . Wall displacements at peak systole for: C) UWT D) PWT. Von Mises stresses at peak systole for: E) UWT F) PWT.

The results of wall thickness measurement with the help of micro CT and collagen parameters study with the help of polarised microscopy are under process and will be accessed as a continuation study once completed

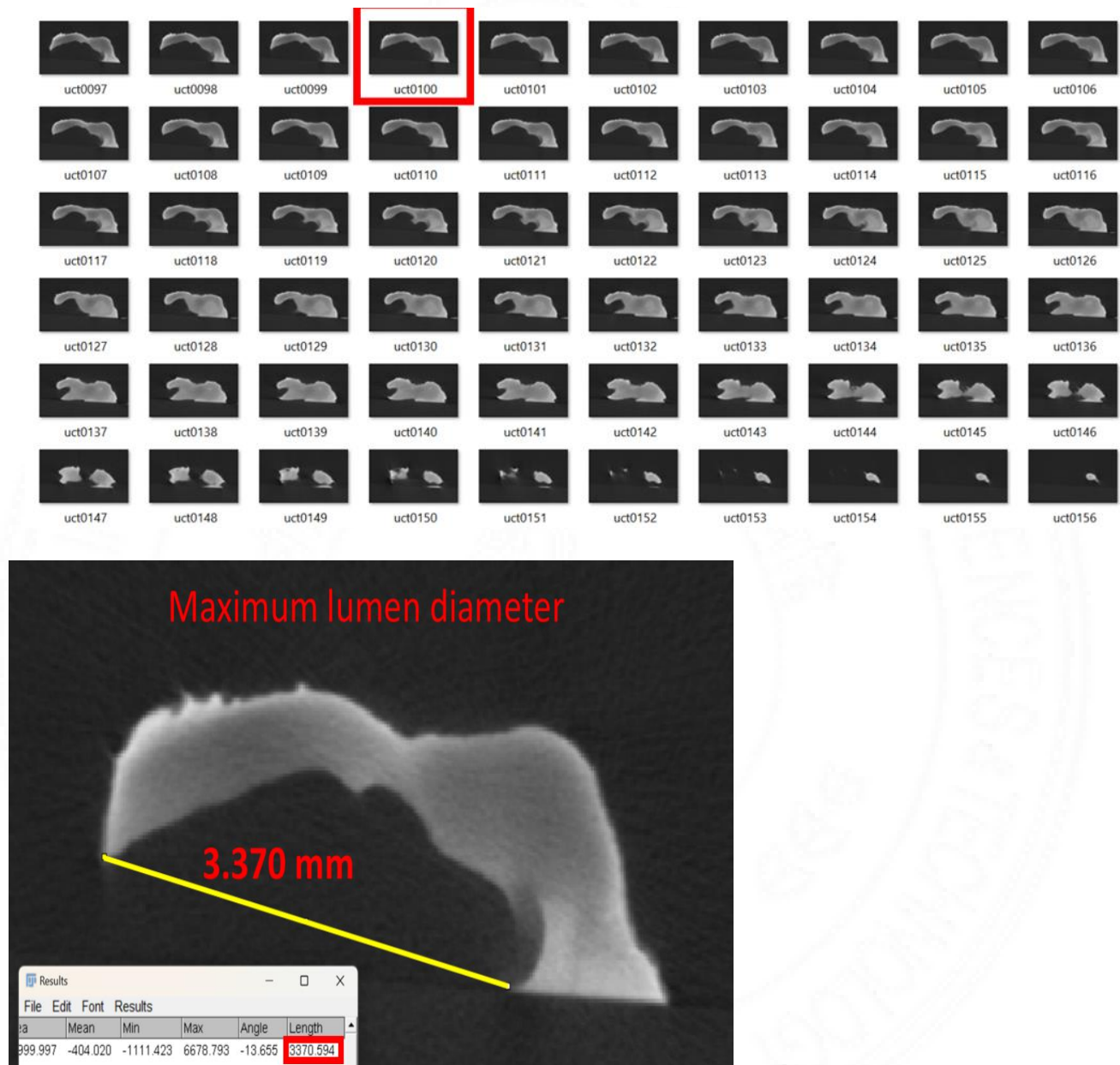


Fig 20 – Micro CT assessment of the wall of cerebral aneurysm

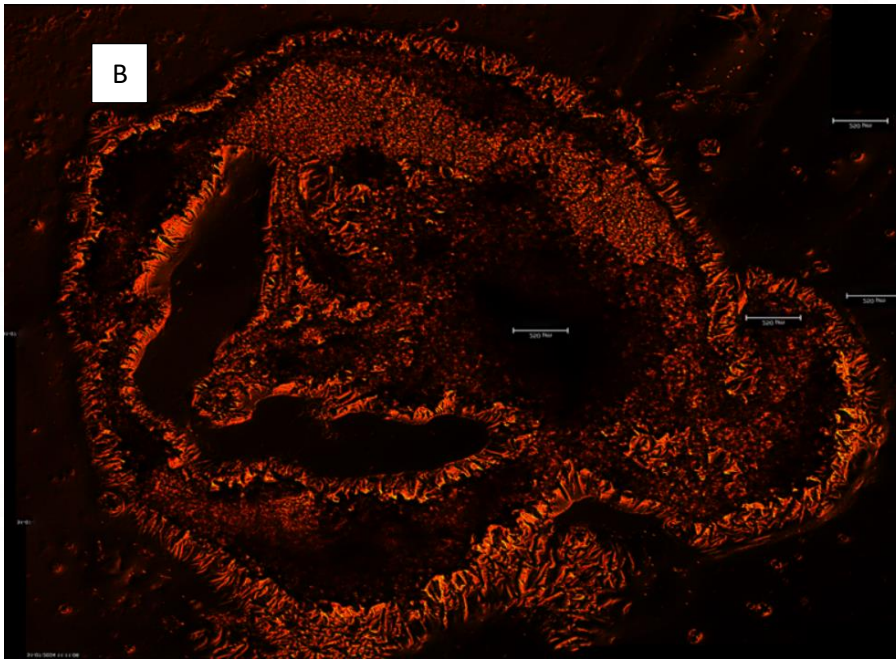
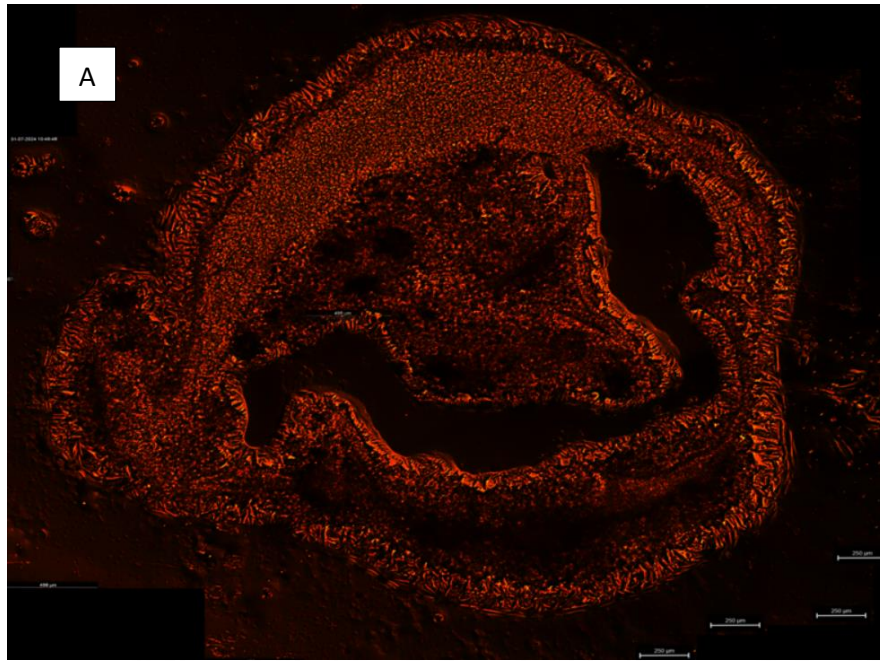


Fig 21 – Polarised microscopy assessment of the wall of cerebral aneurysm

## DISCUSSION



## Discussion

1. Patient specific cerebral aneurysm model Glaber et al (Virtual Inflation of the Cerebral Artery Wall for the Integrated Exploration of OCT and Histology Data - Glaßer - 2017 - Computer Graphics Forum - Wiley Online Library, n.d.) inflated a cerebral artery-wall cross-section into a circular shape, as the arteries are morphologically closer to cylindrical shapes, using ex vivo specimens. Although, this approach may be suitable for an artery, it cannot be applied for an aneurysm which usually manifests in various random shapes. In the pipeline put forth by Niemann et al (Niemann et al., 2021) the aneurysm wall has been inflated into a spherical shape, by expanding each cross-sectional slice to a circle. It was pointed out in their study that, in vivo information of the lumen shape could improve the aneurysm model. Compared against these models, our pipeline's key contribution is accounting for both, the wall thickness heterogeneity and the cerebral aneurysm lumen shape that are patient-specific, in the finally reconstructed 3D aneurysm model

Very few studies have attempted the actual patient-specific aneurysm wall thickness measurement variations in the literature. An earlier study made by Abruzzo et al (Abruzzo et al., 1998) measured the wall thicknesses of ruptured human IAs and found an average value of 0.51 mm. More recent studies have also found similar values. Studies performed by Costalat et al (Costalat et al., 2011) and Robertson et al (Robertson et al., 2015), found the aneurysm averaged thickness to be around 0.2 to 0.3 mm (having a minmax range of 0.1 to 0.6 mm). In a similar study, Cebal et al (Cebal et al., 2015) found an average aneurysm sample thickness of 0.247 mm. On the other hand, according to Robertson et al (Robertson et al., 2015), intracranial arteries have a larger mean thickness with  $0.60 \pm 0.12$  mm and  $0.51 \pm 0.08$  mm in the basilar and middle cerebral arteries, respectively. We have observed the wall thickness to vary between 0.1 to 1.5 mm from our histopathological measurements. This range further corroborates the earlier studies.

## 2. Comparative assessment of UWTM and PWTM based on FSI

In the literature, FSI studies have been performed on idealized geometries towards understanding disease-specific modelling, aneurysm progression, and risk of rupture (Drewe et al., 2017; Gao et al., 2013; Wang

and Li, 2011). Computational simulation results are likely to be accurate if the wall geometry and boundary conditions are patient specific(Steinman and Pereira, 2019). Since resolving vessel wall thickness is not feasible with the available traditional 500 imaging techniques, the research community has typically assumed constant wall thickness for modelling the cerebral aneurysm based on autopsy studies (Ingall et al., 2000). Earlier FSI studies estimated the biomechanical stresses using uniform wall thickness for cerebral aneurysm models(Philip et al., 2022; Sanchez et al., 2014; Torii et al., 2009). However, uniform wall thickness approach may not accurately represent aneurysm wall tissue, leading to limitations in estimating the stress distributions and subsequent rupture risk assessment. Other studies on aneurysms analyse the flow and wall characteristics of patient-specific wall thickness reconstructed from micro CT data (Cebral et al., 2016; Voß et al., 2016). These results show that patient-specific models inferred higher stresses at rupture sites. These studies highlight that, a patient-specific wall thickness modeling of an aneurysm is essential for enhancing the accuracy and reliability of fluid-structure interaction (FSI) simulations. One of the biggest research gap unnoticed throughout these literature noteworthy cerebral aneurysm models, is that a patient specific model can be procured for only an aneurysm with obviously noticeable landmarks like blebs, or thrombus etc. On the contrary, most cerebral aneurysms are uniform in shape, much closer to a sphere with every slice of it resembling subtly varying shapes close to a circle, but not actually a circle. With the aid of Fourier descriptor approximation, the wall and lumen can be registered better than the methods used previously in the literature, which primarily focussed on the first step of fixing the landmark. This study is the first to address the registration of a cerebral aneurysm wall with its in vivo state of lumen for uniformly shaped aneurysms, which do not have blebs or landmarks, posing a huge challenge to objectively unifying the multi-modal imaging and then, performed patient specific fluid-structure interaction simulations.

## **Conclusion and Future work**



## **Conclusion and Future work**

Present study proposed a novel methodology to geometrically reconstruct a 3D model of a cerebral aneurysm, using multi-modal image data. This methodology accurately accounts for the patient-specific wall thickness heterogeneity as well as the patient-specific lumen shape. An algorithm is developed for holistically combining the in vivo CT angio data with the histopathological images containing the wall thickness information to obtain the 3D model. The reconstructed near-realistic patient-specific 3D model of the aneurysm would be a valuable first step in the study of aneurysms and their associated hemodynamics using fluid-structure interaction studies. FSI simulations performed clearly show the significant differences between the uniform wall thickness model and the patient-specific wall-lumen combined model. The Uniform wall thickness model was found to underestimate the biomechanical stresses and wall displacements, compared to the patient-specific model. The wall thickness heterogeneity of the reconstructed patient-specific model could aid in linking the identified critically thin regions of interest with the haemodynamic parameters, which are useful in the rupture risk analysis of cerebral aneurysms.

The comparative results of histopathology, Micro CT, and collagen assessment will help more precisely in the rupture risk analysis of cerebral aneurysms than any standalone modality.

## **Limitations**

In the present study, the histological 3D volume of a slice is obtained from a respective 2D image, which resulted in the loss of slope information associated with the axial thickness, fails to capture the wall thickness variation along the slope in the axial direction of that slice. Although obtaining finer slices will

increase the accuracy, the enormous number of slices will make the process technically demanding and time-consuming. Volume conservation of wall thickness could not be exactly obtained between the histopathological slices, which have undergone ex vivo variations due to shrinkage, deformations due to slicing, 550 etc. With the aid of apriori estimates, such volume conservation deficit could be bridged. Although the focus of the present study is to combine multi-modal image data as well as 2D histopathological slices, fluid-structure interaction simulations are performed to demonstrate the utility of the present approach. Since the present study is patient-specific, a higher number of cases is needed to understand the robustness of the proposed approach to better understand the thickness heterogeneity. The lumen-to-thickness ratio ranging from smaller to bigger variations or different aneurysm tissue materials (blebs, calcification) etc., would enable greater confidence and robustness to the procedure discussed.

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## ANNEXURES:

### CURRICULUM VITAE

|                                                                                                                                                                                                                   |                                                                                                                                     |             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-------------|
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| Date of Birth (dd/mm/yy)                      01/04/90                                                                                                                                                            |                                                                                                                                     | Sex: Male   |
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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Telephone (Residence): -                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                   | Email : <a href="mailto:bhushanakhade01@gmail.com">bhushanakhade01@gmail.com</a>                         |
| Academic Qualifications (Most recent qualification first)                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                   |                                                                                                          |
| Degree/Certificate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Year                                              | Institution                                                                                              |
| MCh Neurosurgery                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 2023                                              | SCTIMST,TRIVANDRUM,KERALA                                                                                |
| MS GENERAL SURGERY                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 2019                                              | LTMMC AND LTMGH, SION, MUMBAI, INDIA                                                                     |
| MBBS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 2015                                              | DR SC GMC, NANDED, MAHARASHTRA, INDIA                                                                    |
| Details of professional registration : (Travancore Cochin Medical Council, including Registration Number and Year of Registration) - 80887, Year – 2021.<br>Maharashtra Medical Council- 2015/06/3198                                                                                                                                                                                                                                                                                                                 |                                                   |                                                                                                          |
| Current and previous positions (most recent position first)                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                   |                                                                                                          |
| Month and Year                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Title                                             | Institution                                                                                              |
| JANUARY 2024- DECEMBER 2024                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | PDF<br>CEREBROVASCULAR<br>SURGERY                 | SREE CHITRA TIRUNAL<br>INSTITUTE OF MEDICAL<br>SCIENCES AND TECHNOLOGY,<br>THIRUVANANTHAPURAM,<br>INDIA. |
| JANUARY 2021- DECEMBER 2023                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | SENIOR RESIDENT,<br>NEUROSURGERY                  | SREE CHITRA TIRUNAL<br>INSTITUTE OF MEDICAL<br>SCIENCES AND TECHNOLOGY,<br>THIRUVANANTHAPURAM,<br>INDIA. |
| JULY 2019 – JULY 2020                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | SPECIALITY<br>MEDICAL OFFICER,<br>GENERAL SURGERY | ESIS HOSPITAL, KANDIVALI,<br>MUMBAI                                                                      |
| MAY 2016 – MAY 2019                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | JUNIOR RESIDENT,<br>GENERAL SURGERY               | LTMMC AND LTMGH, SION,<br>MUMBAI, INDIA                                                                  |
| Brief summary of relevant research experience:<br>1.Cisternal, vascular, and parenchymal landmarks in amygdalohippocampectomy for mesial temporal sclerosis: an index case with learnings from 820 resections<br>2.Technical and Morphometric Comparisons Between Vertical and Horizontal Functional Hemispherotomies-A Juxtaposed 2D Video Analysis: 2-Dimensional Operative Video<br>3.Influence of Wall Thickness on the rupture risk of a patient-specific cerebral aneurysm: A Fluid-structure interaction study |                                                   |                                                                                                          |

- 4.Review of CFD Based Simulations to Study the Hemodynamics of Cerebral Aneurysms
- 5.Hemodynamic investigation of hemorrhagic stroke treatment options for a patient-specific aneurysm using a porous medium model
- 6.Influence of morphological parameters on hemodynamics in internal carotid artery bifurcation aneurysm.

Current project/s at hand:

- 1.Guidelines on the management of Moyamoya angiopathy and proposal for an upgraded staging system
- 2.Can Murray's Law help in identifying rupture propensity of small bifurcation aneurysms?
- 3.Comparative spatio-temporo-prognostic ablatodynamics for recrudescence epilepsy networks-LiTT versus other ablative therapies
- 4.Do steroids alter the dynamics of colloid cyst with hydrocephalus: A Case report.
5. Intra Dural Extra medullary Spinal Metastasis- A Rare Presentation of a Case

Presentation at National and International conferences

- 1.Murray's Law to predict the variations in bifurcation geometry aneurysms- 1 st prize in award paper presentation at SGPGI Neurosurgery Foundation Day Celebration,Lucknow 2024
- 2.An unusual cause and management of Trigeminal Neuralgia- at Neurovascon Jaipur 2024
- 3.Rupture Status prediction, based on the morphology and hemodynamic parameters of cerebral aneurysms: a machine learning based study- 3rd International Rhoton Society Meeting 2023,Istambul,Turkey.
- 4.Endovascular ACOM aneurysm coiling leading to blindness- Is surgical salvage an option?- Travancore Neurocon,Trivandrum, 2022

|                                                                                                       |                                                              |
|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| <p>Signature:</p>  | <p>Date: 01/12/2024</p> <p>Place:<br/>THIRUVANANTHAPURAM</p> |
|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|

## APPENDIX A- INSTITUTIONAL ETHICS COMMITTEE APPROVAL

 श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम  
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया  
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM  
Thiruvananthapuram - 695 011, Kerala, India  
(An Institute of National Importance under Govt. of India)  
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

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**Institutional Ethics Committee**  
(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/841/MARCH-2023 30.03.2023

**Dr. Jayanand Sudhir**  
Additional Professor  
Department of Neurosurgery  
SCTIMST, Thiruvananthapuram

Dear Dr. Jayanand Sudhir,

The Institutional Ethics Committee reviewed your project titled "COMPUTATIONAL FLUID DYNAMICS BASED TOOLS TO THE AID OF CLINICAL DECISION MAKING IN THE MANAGEMENT OF INTRACRANIAL ANEURYSMS (IEC/841)" on 28<sup>th</sup> March 2023.

**The following documents were reviewed:**

Original submission

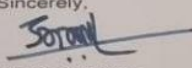
1. Covering Letter addressed to the Member Secretary, IEC, SCTIMST dated 29.03.2023 regarding the inclusion of two Co-Principal Investigators in the study- Dr. Bhushan Sadashiv Akhade and Dr. N. Ram Kishan
2. Covering Letter addressed to the Member Secretary, IEC, SCTIMST dated 09.01.2023
3. Copy of IEC Approval letter dated 31.08.2021
4. IEC Application Form
5. CV of Co-Principal Investigators – Dr. Bhushan Sadashiv Akhade and Dr. N. Ram Kishan
6. Consent of Co-Principal Investigators – Dr. Bhushan Sadashiv Akhade and Dr. N. Ram Kishan

**The IEC Review Criteria**  
The study fulfils the expedited criteria from ethics review criteria vide section 9.1 of the Standard Operating Procedures (August 2021) of the SCTIMST-IEC

**IEC Decision**  
The IEC approved the conduct of the study in the present form.

**Remarks:**  
The Institutional Ethics Committee expects to be provided a copy of the final report/publication.

There was no member of the study team who participated in voting / decision making process.  
The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,  
  
**Dr. G. Srinivas**  
Member Secretary, IEC

**MEMBER SECRETARY**  
INSTITUTIONAL ETHICS COMMITTEE (IEC)  
SCTIMST, THIRUVANANTHAPURAM



## **APPENDIX B - PAPERS AND POSTERS FROM THIS THESIS**

- **NEUROVASCON 2022, RAIPUR :**

RUPTURE STATUS PREDICTION BASED ON THE MORPHOLOGY OF CEREBRAL ANEURYSM - **Paper presentation**

- **3<sup>RD</sup> INTERNATIONAL RHOTON SOCEITY MEET 2023, ISTANBUL, TURKEY :**

RUPTURE STATUS PREDICTION BASED ON THE MORPHOLOGY OF CEREBRAL ANEURYSM - ePOSTER

- **SGPGI Neurosurgery Foundation Day Celebration,Lucknow 2024**

Murray's Law to predict the variations in bifurcation geometry aneurysms- 1 st prize in award paper presentation

## APPENDIX C – TABLES & SCORES USED IN STUDY

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|               |                                                                                                                    |
|---------------|--------------------------------------------------------------------------------------------------------------------|
| <b>Input</b>  | Number of sectors $n \in \mathcal{R}$ ,                                                                            |
|               | Inner Contour of boundary points $\mathcal{C}_i$ ,                                                                 |
|               | Outer Contour of boundary points $\mathcal{C}_o$ ,                                                                 |
|               | Lumen contour from the CT $\mathcal{C}_l$ ,                                                                        |
| <b>Output</b> | Array of position vectors for points on the outer wall for CT based lumen for a slice $\vec{X}_t \in \mathcal{R}$  |
| 1:            | $\theta \leftarrow linspace(0, 2\pi, n)$ {Equally spaced array of angles of size $n$ }                             |
| 2:            | $P_i \leftarrow \mathcal{C}_i(xi, yi)$ { Get 'n' Shape co-ordinates for inner contour }                            |
| 3:            | $P_o \leftarrow \mathcal{C}_o(xo, yo)$ { Get 'n' Shape co-ordinates for outer contour }                            |
| 4:            | $P_l \leftarrow \mathcal{C}_l(xl, yl)$ { Get 'n' Shape co-ordinates for lumen contour from CT }                    |
| 5:            | $\mathcal{A}^*_i \leftarrow Area(\mathcal{C}_i)$ {Area enclosed by inner contour }                                 |
| 6:            | $\mathcal{A}^*_l \leftarrow Area(\mathcal{C}_l)$ {Area enclosed by lumen contour }                                 |
| 7:            | $Scalefactor \leftarrow \sqrt{\mathcal{A}^*_l / \mathcal{A}^*_i}$                                                  |
| 8:            | <b>for</b> each angle $\theta_k$ in $\theta$ <b>do</b>                                                             |
| 9:            | $\vec{X}_i \leftarrow P_i(\theta_k)$ {Position vector of point on inner contour at angle $\theta_k$ }              |
| 10:           | $\vec{X}_o \leftarrow P_o(\theta_k)$ {Position vector of point on outer contour at angle $\theta_k$ }              |
| 11:           | $\vec{X}_l \leftarrow P_l(\theta_k)$ {Position vector of point on lumen contour at angle $\theta_k$ }              |
| 12:           | $\vec{T}_k \leftarrow (\vec{X}_o - \vec{X}_i) / Scalefactor$ { Extract and scale the thickness at a given sector } |
| 13:           | $\vec{X}_{t,k} \leftarrow \vec{X}_l + \vec{T}_k$ { Transfer the thickness at the spatially corresponding sector }  |
| 14:           | <b>end for</b>                                                                                                     |

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**Table1-** Wall Thickness Transfer Algorithm

| Metrics                    | Coarse(c) | Medium(m) | Fine(f)   |
|----------------------------|-----------|-----------|-----------|
| Global cell size(minimum)  | 0.064     | 0.048     | 0.036     |
| Global cell size (maximum) | 0.32      | 0.24      | 0.18      |
| Refinement factor (r)      | 1.3       | 1.3       | 1.3       |
| First cell height (h)      | 0.04      | 0.02      | 0.01      |
| Inflation layers           | 3         | 5         | 7         |
| Prism growth ratio         | 1.12      | 1.12      | 1.12      |
| Number of Elements         | 4,54,728  | 8,02,605  | 11,27,880 |

Table 2- Mesh metrics for coarse, medium and fine meshes

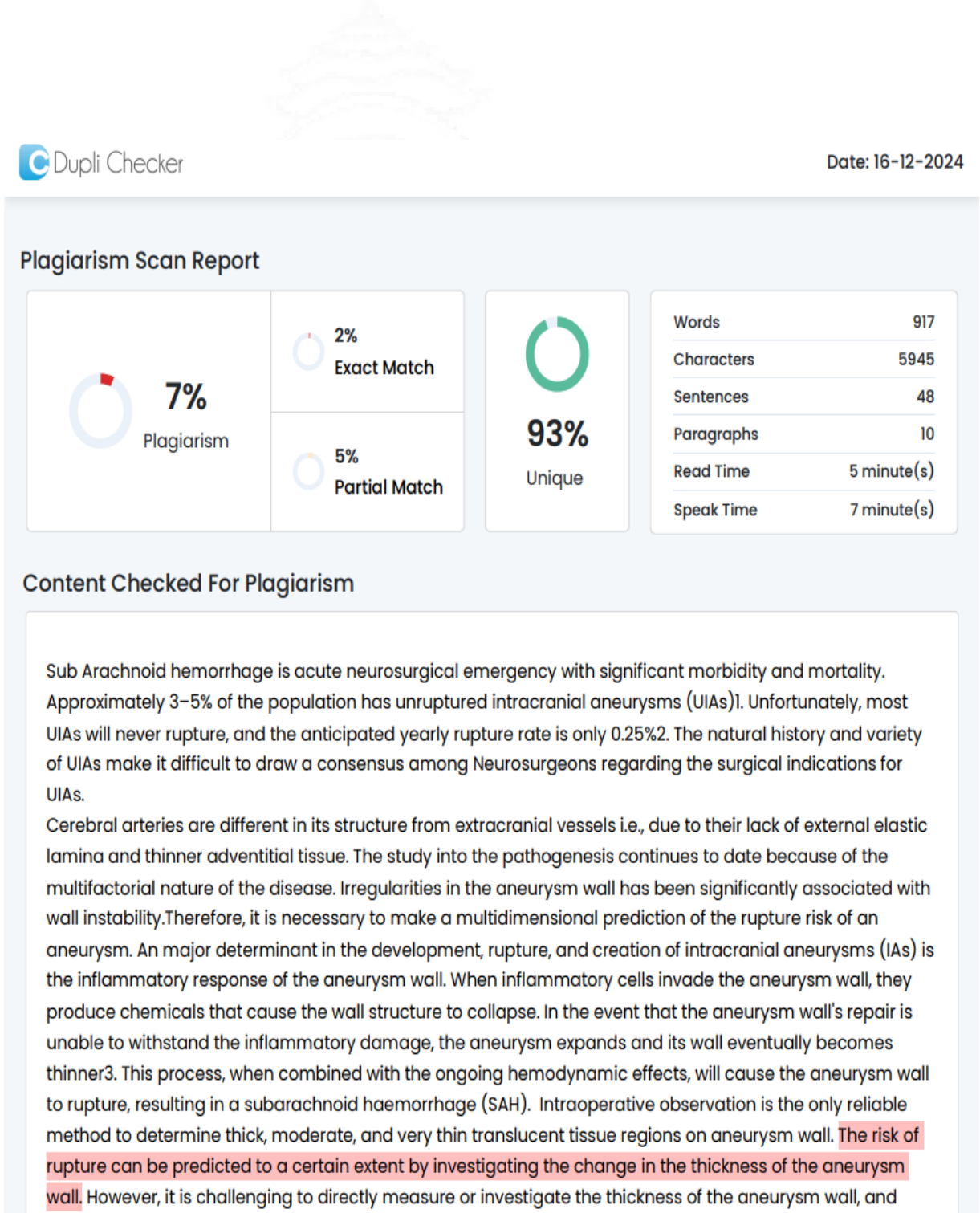
| Parameter         | Coarse(c) | Medium(m) | Fine(f) | GCI(f,m) | GCI(m,c)      |
|-------------------|-----------|-----------|---------|----------|---------------|
| $WSS_{max} @ t_1$ | 5.02      | 6.69      | 6.83    | 2.75%    | <b>0.225%</b> |
| $WSS_{max} @ t_2$ | 23.26     | 27.21     | 28.47   | 8.512%   | <b>2.587%</b> |
| $WSS_{max} @ t_3$ | 8.19      | 11.06     | 11.95   | 14.6%    | <b>4.187%</b> |
| $WSS_{max} @ t_4$ | 4.48      | 5.53      | 5.82    | 9.062%   | <b>2.375%</b> |

Table 3- Grid Convergence Index (GCI)

| Hemodynamic Results        | UWT          | PWT         |
|----------------------------|--------------|-------------|
| Maximum Wall Stresses      | 13.6 KPa     | 48.4 KPa    |
| Maximum Wall Displacements | 58.5 $\mu$ m | 162 $\mu$ m |

Table 4 - Quantified Hemodynamic Results - comparison between uniform and patient-specific models

APPENDIX D - PLAGIARISM CHECK REPORT



## **APPENDIX D: Patient Information Sheet And Consent Form**

**( English and Malyalam)**

### **Participant Information Sheet**

**Title of the study:**

**Computational Fluid Dynamics based tools to the aid of clinical decision-making in the management of intracranial aneurysms**

Principal Investigator: Dr. Jayanand Sudhir, Dept of Neuro-surgery, SCTIMST

Co-PI: Dr.Bhushan Sadashiv Akhade, Dept of Neuro-surgery, SCTIMST

IEC/841/August 2021

### **Introduction:**

You are being requested to participate in a research study on intracranial aneurysms. Intracranial aneurysms are out-pouchings of blood vessels in the brain. They pose a risk for rupture. They may also come to attention due to their pressure effects and stroke. They may also be incidentally diagnosed during scan for some other reason.

You have undergone evaluation and management of an intracranial aneurysm. We intend to conduct a study on the images of the angiography done in the institute to understand the blood flow pattern within the aneurysm. We hope to include 200 patients in this study.

You are being requested to give consent for your angiogram images to be used for this research study.

**If you take part, what you have to do?**

If you consent to participate in the study, a copy of your angiographic images will be processed to help understand the pattern of blood flow within the aneurysm. Enrolment into the study does not pose any risk to you. Data regarding the blood flow (blood flow velocity) and aneurysm characteristics (whether the aneurysm had ruptured or not), normally obtained during your management will be used for the study. No blood or other tissue/ biological samples will be collected for the study. No personal details will be collected. The identifier details in the scans will be masked to conceal identity.

**What will be done with the angiography images?**

A copy of the angiography images will be used for the study. The images will be processed using a computer in the institute hospital and transferred to Indian Institute of Technology, Madras, where further processing of the images will be done to yield the results.

**Will the study influence the outcome of my medical condition?**

No. The angiographic images are being requested for submission for research only after you have been subjected to the standard protocol of management in the institute hospital. The study will not affect the outcome of your management.

**Are there any side-effects or complications of the study?**

There are no side-effects or complications in this study. The study involves processing of the scan images only. No biological samples will be obtained from you for the study.

**Will I benefit from the study?**

No. There will be no personal benefit for you from the study. The results of the study may benefit the society by helping the medical fraternity in understanding intracranial aneurysms better and influence the management protocol for intracranial aneurysms in future.

**Will you have to pay for the study?**

No extra payment will have to be paid by you over the routine cost of management.

**Will your personal details be kept confidential?**

Upon enrolment, you will be identified in the study by a code. No personal details will be used for the study. Any detail relating to your identification in the angiography images will be masked. The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission.

If you have any further questions, please you can contact Dr. B Jayanand Sudhir (0471- 2524347) or email: [bjs@sctimst.ac.in](mailto:bjs@sctimst.ac.in).

In case you have any questions about the ethics approvals for this study, you can contact the Member Secretary of the SCTIMST-IEC. Phone: 0471 2524689 or email: [iec.mem.sec@sctimst.ac.in](mailto:iec.mem.sec@sctimst.ac.in)

## **Informed Consent form**

I, \_\_\_\_\_, aged \_\_\_\_\_, son/daughter of \_\_\_\_\_

- declare that I have read the above information provide to me regarding the study: *Haemodynamic imaging of 200 cases of intracranial aneurysms using computational fluid dynamics* and have clarified any doubts that I had. [ ]
- I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]
- I understand that my angiography images will be used for the study and that my participation in the study will not influence the usual course of my treatment in the hospital [ ]
- I also understand that my blood or other biological samples are not being used in the study. [ ]
- I permit the study staff and institutional ethics committee members to look at my health records and use the data including images for the study, maintaining confidentiality and not revealing the patient identity. I agree to this access
- I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]
- I understand that my identity will not be revealed in any information released to third parties or published [ ]
- I voluntarily agree to take part in this study [ ]
- I received a copy of this signed consent form [ ]

Name:

Signature:

Date:

Name of witness:

Relation to participant:

Date:

(Person Obtaining Consent) I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Name and Signature of Person Obtaining Consent:

**സമ്മതപത്രം**

പഠനത്തിന്റെ പേര്

ഫ്ലൂയിഡ് ഡൈനാമിക്സ് ഉപയോഗിച്ച് ഇൻട്രാക്രനിയൽ അന്യൂറിസമുള്ള 200 കേസുകളുടെ ഹീമോഡൈനാമിക് ചിത്രീകരണം

ആമുഖം

ഇൻട്രാക്രനിയൽ അന്യൂറിസത്തെപ്പറ്റിയുള്ള ഗവേഷണ പഠനത്തിൽ പങ്കെടുക്കുവാനായി താങ്കളോട് അപേക്ഷിക്കുന്നു. തലച്ചോറിലെ രക്തക്കുഴലുകളുടെ പുറത്തേക്ക് തള്ളുന്ന വീക്കമാണ് ഇൻട്രാക്രനിയൽ അന്യൂറിസങ്ങൾ. അവ പൊട്ടാനിടയുണ്ട്. അവയുടെ സമ്മർദ്ദത്തിന്റെ പ്രഭാവവും സ്ട്രോക്കും മൂലവും അവ ശ്രദ്ധയാകർഷിക്കുന്നു. മറ്റുകാരണങ്ങളാൽ സ്കാനർചെയ്യുമ്പോൾ സന്ദർഭശാലും രോഗം കണ്ടെത്താറുണ്ട്.

താങ്കൾ ഇൻട്രാക്രനിയൽ അന്യൂറിസത്തിന് ഈ ഇൻസ്റ്റിറ്റ്യൂട്ടിൽ വിലയിരുത്തപ്പെടുകയും ചികിത്സക്ക് വിധേയമാവുകയും ചെയ്തിട്ടുണ്ട്. അന്യൂറിസത്തിനുള്ളിലെ രക്തപ്രവാഹത്തെപ്പറ്റി ഇൻസ്റ്റിറ്റ്യൂട്ടിൽ നടത്തിയിട്ടുള്ള ആൻജിയോഗ്രാം ചിത്രങ്ങളുപയോഗിച്ച് ഒരു പഠനം നടത്താൻ ഞങ്ങളുദ്ദേശിക്കുന്നു.

ഈ പഠനത്തിൻ്റെ 20 രോഗികളെ ഉൾപ്പെടുത്തുവാൻ ഞങ്ങൾ ഉദ്ദേശിക്കുന്നു.

താങ്കളുടെ ആൻജിയോഗ്രാം ചിത്രങ്ങൾകൂടി ഈ പഠനത്തിൽ ഉൾപ്പെടുത്തുവാൻ സമ്മതം തരണമെന്ന് അപേക്ഷിക്കുന്നു.

ഇതിൽ പങ്കെടുക്കുവാൻ താങ്കൾ ചെയ്യേണ്ടത് എന്തെല്ലാം

താങ്കൾ ഈ പഠനത്തിൽ പങ്കെടുക്കുവാൻ സമ്മതിക്കുകയാണെങ്കിൽ താങ്കളുടെ ആൻജിയോഗ്രാം ചിത്രങ്ങളുടെ ഒരു പകർപ്പ് എടുത്ത് രക്തചംക്രമണരീതി മനസ്സിലാക്കുന്നതിനായി ഉപയോഗിക്കുന്നതാണ്. ഈ പഠനത്തിൽ പങ്കെടുക്കുകയാണെങ്കിൽ താങ്കൾക്ക് അപകടസാധ്യത ഒന്നും തന്നെയില്ല. താങ്കളുടെ രക്തചംക്രമണത്തിന്റെ (രക്തത്തിന്റെ ഒഴുക്കിന്റെ വേഗതയുടെ) സാധാരണ ചികിത്സയുടെ ഭാഗമായി ലഭ്യമാക്കപ്പെടുന്ന വിവരങ്ങളും അന്യൂറിസത്തിന്റെ സ്വഭാവവും ( അന്യൂറിസം പൊട്ടിയോ ഇല്ലയോ) ഈ പഠനത്തിൽ ഉൾപ്പെടുത്തുന്നതാണ്. രക്തത്തിന്റെയോ മറ്റ് ശരീര കോശങ്ങളുടെയോ സാമ്പിളുകൾ ഈ പഠനത്തിനായി എടുക്കുന്നതല്ല. വ്യക്തിപരമായ ഒരു വിവരങ്ങളും ഈ പഠനത്തിനായി എടുക്കുന്നതല്ല. തിരിച്ചറിയാതിരിക്കാനായി താങ്കളുടെ സ്കാനർ റിപ്പോർട്ടിലുള്ള താങ്കളുടെ തിരിച്ചറിയൽ വിവരങ്ങൾ മറയ്ക്കുന്നതാണ്.

ആൻജിയോഗ്രാഫി ചിത്രങ്ങൾ കൊണ്ട് എന്തെല്ലാം ചെയ്യും

ആൻജിയോഗ്രാഫി ചിത്രങ്ങളുടെ ഒരു പകർപ്പ് ഈ പഠനത്തിനായി ഉപയോഗിക്കും. വേണ്ട വിവരങ്ങൾ കിട്ടുന്നതിനായി ഈ ചിത്രങ്ങൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ആശുപത്രിയിലെ കമ്പ്യൂട്ടർ ഉപയോഗിച്ച് രൂപാന്തരപ്പെടുത്തുന്നതും, 'മറ്റൊരു കേന്ദ്രത്തിലേക്ക് (ഇൻഡ്യൻ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഓഫ് ടെക്നോളജി,

മദ്രാസ് നൽകുന്നതും അവിടെ ഫലം ലഭിക്കാനായി കൂടുതൽ പ്രക്രിയകൾക്ക് വിധേയമാക്കുന്നതുമാണ്

താങ്കളുടെ ആരോഗ്യപരമായ അവസ്ഥയെ ഈ പഠനം ബാധിക്കുമോ

ഇല്ല. ചികിത്സയ്ക്കായി ഇൻസ്റ്റിറ്റ്യൂട്ട് ആശുപത്രിയിൽ ക്രമീകരിച്ചിട്ടുള്ള സ്റ്റാൻഡേർഡ് ചികിത്സാക്രമങ്ങൾക്ക് താങ്കളെ വിധേയമാക്കിയശേഷമാണ് ഗവേഷണത്തിന് സമർപ്പിക്കുവാനായി ആൻജിയോഗ്രാം ചിത്രങ്ങൾ ചോദിക്കുന്നത്. ഈ പഠനം താങ്കളുടെ ചികിത്സാക്രമത്തെ ഒരുതരത്തിലും ബാധിക്കുന്നതല്ല.

ഈ പഠനത്തിന് എന്തെങ്കിലും പാർശ്വഫലങ്ങളോ ദുഷ്ഫലങ്ങളോ ഉണ്ടോ

മദ്രാസ്

ചിത്രങ്ങൾ പ്രോസസ് ചെയ്യുക മാത്രമേ ചെയ്യുന്നുള്ളൂ. പഠനത്തിനായി താങ്കളിൽ നിന്ന് ഒരു വിധ ശാരീരിക സാമ്പിളുകളും എടുക്കുന്നതല്ല.

ഈ പഠനം കൊണ്ട് താങ്കൾക്ക് എന്തെങ്കിലും ലാഭമുണ്ടോ.

ഒന്നും ഇല്ല. താങ്കൾക്ക് വ്യക്തിപരമായി ഒരു ലാഭവുമുണ്ടാകില്ല. ഇൻട്രാക്രനിയൽ അസ്സറിസത്തെപ്പറ്റി കൂടുതൽ അറിയുവാനും അതിന്റെ ചികിത്സാക്രമീകരണങ്ങൾ മെച്ചപ്പെടുത്തുവാനും ആരോഗ്യ ചികിത്സാരംഗത്തുള്ളവരെ ഈ പഠനഫലങ്ങൾ സഹായിച്ചേക്കാം.

ഈ പഠനത്തിനായി താങ്കൾ പണം മുടക്കേണ്ടതണ്ടോ

ഇല്ല. താങ്കളുടെ സാധാരണ ചികിത്സാ ചെലവുകളല്ലാതെ ഈ പഠനത്തിൽ ഉൾപ്പെടുന്നതിനാൽ താങ്കൾക്ക് ഒരു വിധ ചെലവുകളുമില്ല.

താങ്കളുടെ വ്യക്തിപരമായ വിവരങ്ങൾ രഹസ്യമായി സൂക്ഷിക്കുമോ

ഈ പഠനത്തിൽ ചേരുന്നതോടെ താങ്കൾക്ക് ഒരു പ്രത്യേക കോഡ് തന്ന് ആ കോഡ് മാത്രമായിരിക്കും ഈ പഠനത്തിൽ ഉപയോഗിക്കുക. വ്യക്തിപരമായ ഒരു വിവരങ്ങളും ഈ പഠനത്തിൽ ഉപയോഗിക്കുകയില്ല. ആൻജിയോഗ്രാഫി ചിത്രങ്ങളിൽ താങ്കളെ തിരിച്ചറിയുന്നതിനുള്ള എല്ലാ വിവരങ്ങളും മറച്ചിരിക്കും. ഈ പഠനത്തിലെ ഫലങ്ങൾ മെഡിക്കൽ ജേർണലിൽ പ്രസിദ്ധീകരിക്കുമെങ്കിലും താങ്കളുടെ പേര് ഒരു പ്രസിദ്ധീകരണത്തിലും ഫലപ്രകാശനങ്ങളിലും ഉണ്ടായിരിക്കുന്നതല്ല. എന്നാൽ താങ്കളെ സംബന്ധിക്കുന്ന മെഡിക്കൽ നോട്ടുകൾ ഈ പഠനവുമായി ബന്ധപ്പെട്ടിരിക്കുന്നവർ താങ്കളുടെ പ്രത്യേക അനുമതിയോടെ പുനപരിശോധിച്ചേക്കാം.

താങ്കൾക്ക് അധികമായി എന്തെങ്കിലും അറിയണമെന്നുണ്ടെങ്കിൽ ദയവായി ഡോ. ബി. ജയാനന്ദ് സുധീർ (0471-2524347) അല്ലെങ്കിൽ ഇമെയിൽ [bjs@sctimst.ac.in](mailto:bjs@sctimst.ac.in)

യഥാസ്ഥാനങ്ങളിൽ ( ) അടയാളപ്പെടുത്തുക

..... ന്റെ മകൻ/മകൾ/മാതാവ്/പിതാവായ  
.....വയസ്സുള്ള..... എന്ന ഞാൻ ഫ്ലൂയിഡ് ഡൈനാമിക്സ്  
ഉപയോഗിച്ച് ഇൻട്രാക്രനിയൽ അനുസമുള്ള 200 കേസുകളുടെ ഹീമോഡൈനാമിക് ചിത്രീക  
രണം എന്ന പഠനത്തെ സംബന്ധിച്ച് മേൽ വിവരിച്ചിരിക്കുന്ന കാര്യങ്ങൾ മുഴുവൻ വായിക്കുകയും  
സംശയനിവൃത്തി വരുത്തി കാര്യങ്ങൾ മുഴുവനായി മനസ്സിലാക്കിയതായും ഇതിനാൽ സാക്ഷ്യപ്പെടി  
ത്തിക്കൊള്ളുന്നു. [ ]

താഴെപ്പറയുന്ന കാര്യങ്ങൾകൂടി ഞാൻ മനസ്സിലാക്കുന്നു.

- ഈ പഠനത്തിൽ സ്വമനസ്സാലെയും സ്വമേധയായും ആണ് ഞാൻ പങ്കെടുക്കുന്നത്. എന്റെ സാധാരണ ചികിത്സയ്ക്കേറ്റ നിയമപരമായ പരിരക്ഷയ്ക്കേറ്റ ഭംഗം കൂടാതെതന്നെ എതുസമയത്തും ഇതിൽതുടരുവാനുള്ള അനുവാദം എനിക്ക് പിൻവലിക്കാവുന്നതാണ്. [ ]
- ഈ പഠനത്തിൽ എന്റെ ആൻജിയോഗ്രാഫി ചിത്രങ്ങൾ ഉപയോഗിക്കാം. [ ]
- ഞാൻ ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നത് ആശുപത്രിയിലെ എന്റെ സാധാരണ ചികിത്സാക്രമത്തെ ബാധിക്കുകയില്ല. [ ]
- എന്റെ രക്തത്തിന്റെയോ മറ്റ് ശരീരസാമ്പിളുകളോ ഈ പഠനത്തിൽ ഉപയോഗിക്കുകയില്ല. [ ]
- ഞാൻ ഈ പഠനത്തിൽനിന്ന് പിൻമാറിയാലും എന്റെ ആരോഗ്യരേഖകൾ നോക്കുന്നതിലേക്ക് പഠനം നടത്തുന്നവർക്കോ സ്ഥാപനത്തിലെ എത്തിക്സ് കമ്മിറ്റി അംഗങ്ങൾക്കോ എന്റെ അനുവാദം ആവശ്യമില്ലാത്തതാകുന്നു. [ ]
- ഏതെങ്കിലും തേർഡ് പാർട്ടിക്ക് കൊടുക്കുന്നതോ പ്രസിദ്ധീകരിക്കുന്നതോ ആയ വിവരങ്ങളിലൊന്നും എന്നെ തിരിച്ചറിയാനുതകുന്ന വിവരങ്ങൾ ഉണ്ടായിരിക്കുന്നതല്ല എന്നു ഞാൻ മനസ്സിലാക്കുന്നു. [ ]
- ഈ പഠനത്തിൽ സ്വമനസ്സാലെയാണ് പങ്കെടുക്കുന്നതെന്നും ഞാൻ സമ്മതിക്കുന്നു. [ ]
- സമ്മതപത്രത്തിന്റെ ഒപ്പിട്ട ഒരു കോപ്പി എനിക്ക് കിട്ടി. [ ]

പേര്

ഒപ്പ്

തീയതി

സാക്ഷിയുടെ പേര്  
മേൽപ്പറയുന്നയാളുമായുള്ള ബന്ധം

ഒപ്പ്

തീയതി

(സമ്മതം വാങ്ങുന്നയാൾ)

മെഡിക്കൽ റിസർച്ച് പ്രോജക്ടിനാവശ്യമായ സമ്മതപത്രത്തിനു വേണ്ടുന്ന എല്ലാ ഘടകങ്ങളും തൃപ്തികരമായി നിർവഹിച്ചിരിക്കുന്നുവെന്ന് ഞാൻ ബോധ്യപ്പെടുത്തുന്നു. പഠനപങ്കാളിയുമായി ഗവേഷണപദ്ധതിയെപ്പറ്റി സാങ്കേതികതര പദങ്ങളുപയോഗിച്ച് എല്ലാ വിവരങ്ങളെപ്പറ്റിയും ചർച്ച നടത്തുകയും പ്രതീക്ഷിക്കാവുന്ന അപകടസാധ്യതകളും പാർശ്വഫലങ്ങളും വിശദീകരിക്കുകയും

ചെയ്തു. പങ്കാളിയെ ചോദ്യങ്ങൾ ചോദിക്കാൻ പ്രേരിപ്പിക്കുകയും എല്ലാ ചോദ്യങ്ങൾക്കും ഉത്തരം നൽകുകയും ചെയ്തു എന്നും ഞാൻ സാക്ഷ്യപ്പെടുത്തുന്നു.

സമ്മതപത്രം വാങ്ങുന്ന ആളുടെ പേരും ഒപ്പും തീയതിയും