Title: Vascular Deformation Mapping as a Method for 3D Growth Mapping During CT

Surveillance of Thoracic Aortic Aneurysm

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Summary Statement: Vascular Deformation mapping (VDM) is a deformable image registration-based technique for reliable, comprehensive assessment of the degree and extent of three-dimensional growth among patients with thoracic aortic aneurysm undergoing imaging surveillance.

Key Results:

- Inter-rater variability was low for VDM-derived measurements of aortic surface area change (bias= 0.0, limits of agreement: -0.03 to 0.03).

- VDM can depict distinct patterns/phenotypes of longitudinal 3D aortic growth.

- VDM derived peak Area Ratio values demonstrated excellent agreement with clinical diameter measurements (r=0.85, p<0.001), but VDM detected areas of growth outside of the maximally dilated segment in 6/14 (36%) in patients with growth, none of which were detected by clinical assessment.

Abstract:

Background: Aortic diameter measurements in patients with thoracic aortic aneurysm (TAA) suffer from significant measurement variability and are unable to quantify aortic growth in a comprehensive, three-dimensional manner.

Purpose: To develop and validate a technique for quantification of 3D growth based on deformable image registration in a cohort of patients with thoracic aortic aneurysm (TAA).

Materials & Methods: We retrospectively identified a cohort of 50 patients with ascending and descending TAA with ≥2 computed tomography angiography (CTA) studies between 2006-2020; 12 patients were excluded yielding 38 patients (68 surveillance intervals) for analysis. 3D aortic growth was quantified using Vascular Deformation Mapping (VDM), a technique that uses deformable image registration to warp an aortic mesh constructed from baseline anatomy, with growth quantified as the ratio of change in surface area at each triangular mesh element (Area

Ratio). Manual segmentations were performed by independent raters to assess inter-rater reproducibility. Registration error was assessed using manually placed landmarks. Agreement between VDM and diameter measurements was assess using Pearson's correlation and Cohen's kappa.

Results: Average age was 69.0 ± 9.3 years, and the majority were female (n=21, 55%) with aneurysm of the ascending aorta (n=26, 69%). VDM was technically successful in 35/38 (89%) patients and 58/68 intervals (85%). Median registration error was 0.77 mm (IQR: 0.54-1.10 mm). Inter-rater agreement was high for aortic segmentation (Dice= 0.97 ± 0.02) and VDM-derived Area Ratio (bias= 0.0, limits of agreement: -0.03 to 0.03). There was strong agreement (r=0.85, p<0.001) between peak Area Ratio values and diameter change. VDM detected areas of growth outside of the maximally dilated segment in 6/14 (36%) patients with growth, none of which were detected by diameter assessment.

Conclusion: VDM is a novel technique for reliable and comprehensive quantitative assessment of 3D aortic growth and growth patterns in TAA patients undergoing imaging surveillance.

Introduction

Thoracic aortic aneurysm (TAA) is a common disease that is increasing in prevalence worldwide, with approximately 3% of patients over the age of 50 having a dilated thoracic aorta (1-3) and recommended to undergo imaging surveillance (4). The majority of patients with TAA have an indolent disease course, with aortic growth occurring either slowly or not at all over a period of years to decades (5). However, life-threatening complications such as rapid growth, aortic dissection and rupture can occur in otherwise asymptomatic patients at pre-surgical aneurysm sizes (6, 7), emphasizing the need for better techniques to more accurately assess disease progression, inform surgical candidacy and predict complications. A fundamental limitation to improved management of TAA is the lack of imaging techniques to accurately assess aortic growth. Current medical imaging assessment techniques are based on measurements of maximal aortic diameter; however, the degree of variability associated with aortic diameter measurements – on the order of ± 1-5 mm despite optimal measurement technique – frequently prevent confident assessment of disease progression at average TAA growth rates (<1 mm/year)(8-11). Furthermore, diameter measurements are inherently 2-dimensional and are performed in fixed anatomic locations and are thus unable to capture the 3-dimensional (3D) nature of TAA growth. Lastly, accurate and comprehensive aortic diameter measurements require significant time and effort, often performed by dedicated 3D laboratories at larger centers; algorithms that allow for semi- or full-automated TAA analysis could significantly improve the efficiency of current workflows.

To overcome these limitations, prior research has described the feasibility of a medical image analysis technique, termed Vascular Deformation Mapping (VDM), for three-dimensional (3D) assessment of aortic growth using deformable image registration techniques (12, 13). This approach utilizes high-resolution, volumetric computed tomography angiography (CTA) data, and allows for comprehensive quantification of aortic growth at any point on the aortic wall, avoiding the limitations of manual definition of analysis planes and caliper measurements.

Despite these advantages, image analysis techniques based on deformable image registration are not without potential errors and pitfalls, and thus an evaluation of the VDM in a clinical population with TAA is needed to understand the reliability and clinical utility of this technique.

A clinical cohort of TAA patients undergoing imaging surveillance was used to undertake this study focused on two primary objectives: 1) determine performance of the VDM algorithms in a clinical cohort of TAA patients undergoing imaging surveillance including assessment of reproducibility and identification of sources of error in the analysis workflow; 2) characterize unique patterns of 3D aortic growth observed in TAA patients and assess the agreement of VDM analysis with standard diameter measurements.

Methods

Patient Identification and Clinical Data Abstraction

All procedures were approved by the local institutional review board (HUM00133798) and informed consent was waived given the retrospective design. Using electronic medical records search software, we identified 50 patients at our institution undergoing imaging surveillance of TAA in either the pre- or post-operative setting with serial (n≥2) CTA examinations covering the thoracic aorta between 2006-2020. Patients were excluded from analysis for: non-ECG gated acquisition (n=5), lack of thin slice (≤3mm) reconstructions (n=1), poor aortic opacification (<200 HU at ascending aorta, n=2), interval surgical aortic repair (n=2) or severe motion artifact (n=3) (**Figure 1**). Patients with mild motion-related blurring affecting only the aortic root were included as long as the proximal coronary arteries could be clearly visualized. A total of 38 unique patients encompassing 105 CTA examinations and 68 surveillance intervals were selected for analysis. Clinical and demographic information was collected by chat review. Maximal diameter measurements of the thoracic aorta were recorded from clinical CT reports for comparison with VDM assessment. Of note, all aortic measurements

at our center are performed in a dedicated 3D lab by trained technologists using standardized

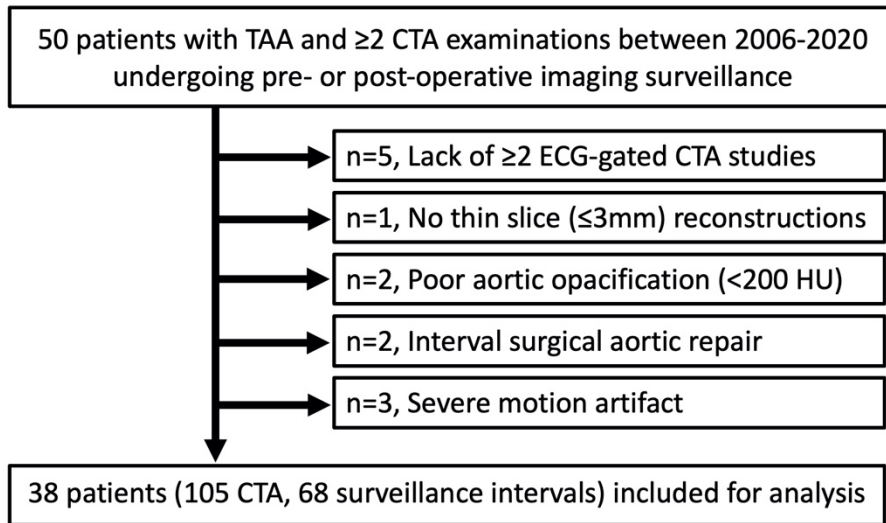measurement protocols and locations and centerline-based measurement technique (4).

Figure 1: Flow diagram depicting inclusion and exclusion criteria.

Vascular Deformation Mapping

The VDM analysis pipeline for measurement of three-dimensional aortic growth uses

deformable image registration to quantify the local deformation of the aortic wall between two

CTA examinations and results are visualized by superimposing a colorized scale of deformation

values on the three-dimensional surface of the aortic geometry. The steps involved in VDM

analysis include: 1) segmentation of the thoracic aorta on CTA images from scans acquired at

two different time points with the first time point considered the fixed image and the second time

point considered the moving image; 2) image pre-processing steps including cropping and

clamping voxels with negative Hounsfield values at 0 to avoid adjacent lung influencing the

registration and dilation of aortic masks by 3 voxels to ensure inclusion of the wall; 3) rigid

registration (Euler) to approximately align the two CTA images (Elastix, Utrecht,

Netherlands)(14); 4) alignment of the aortic centerline using a highly regularized multi-image,

multi-metric deformable registration which applies a penalty term to enforce rigid movement of

voxels within the aortic segmentation but allows deformation of the peri-aortic voxels optimized

rigid aortic registration (15); 5) multi-resolution, multi-metric b-spline deformable image

registration using mutual information with 10 mm grid spacing and a bending energy penalty of 100 (16); 6) generate a polygonal mesh of the aortic surface (approximately 100,000 - 400,00 unique surface elements) at baseline (fixed) geometry; 7) translate mesh vertices of baseline model using the deformation field calculated in Step 5; 8) quantify deformation as the ratio of surface area change at each triangular mesh element (termed Area Ratio) with colorized visualized in Paraview (Kitware Inc., Clifton Park, NY, USA). Registration and generation of VDM results take approximately 20 mins on a standard high-performance PC (Intel Xenon W-2235 CPU @ 3.8 Ghz with 6 Cores) with MPI parallelization. A simplified schematic overview of the VDM analysis pipeline is presented in **Figure 2**.
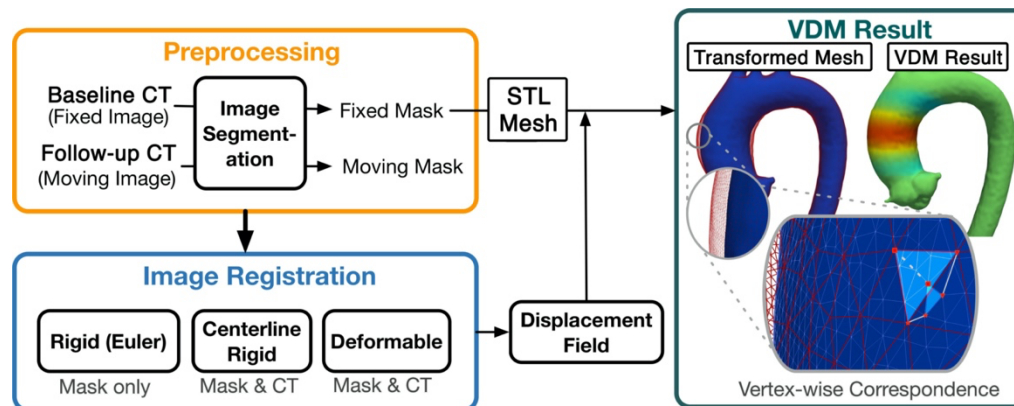

Figure 2: Simplified schematic overview of the steps involved in the VDM analysis pipeline. ECG-gated aortic CTA DICOM data is retrieved for baseline and follow-up examinations and CTA data undergoes aortic segmentation (orange box), followed by rigid and deformable registration (blue box). The displacement field calculated from registration steps is used to translate the mesh vertices of the baseline model, and the ratio of change in the surface area of each mesh element (Area Ratio) is plotted on the aortic surface using a colorized scale.

Image Segmentation Technique, Inter-Rater Reproducibility Analysis

Manual aortic segmentation is used in the VDM workflow to create aortic masks and is thus a potential source of variability. While all CTAs were segmented by a rater with 4 years of experience with aortic image analysis (I.H.), we had an additional rater with 5 years of experience (T.V.B.) perform segmentations on 45 randomly selected CTA intervals to investigate the influence of manual segmentation variability on VDM output. Raters segmented the thoracic aortic from the root to just beyond the celiac axis, including the proximal arch vessels, using state-of-the-art segmentation tools (Mimics v22.0, Materialise, Leuven, Belgium).

Quality Assurance Process and Registration Accuracy Assessment

Considering the potential for accumulated error in the VDM output due to the multistep nature of the analytic pipeline, we adopted a multistep quality assurance (QA) protocol to evaluate the validity of each VDM output, with QA steps performed by a senior researcher with 15 years of experience with cardiovascular imaging (N.B.). The QA protocol involved visual confirmation of segmentation and registration accuracy using dual color/channel plots to ensure overlap of the aortic luminal boundary after the final deformable registration step; specific steps in the QA protocol are described in the **Supplementary Material**. The identified case of registration failures/errors was recorded.

To assess registration accuracy, landmarks were manually placed along the aortic wall by a senior researcher with 15 years cardiovascular image analysis experience (N.B), and landmark registration error was determined by calculating the Euclidean distance between homologous points after the final deformable transformation. Conserved anatomic landmarks such as branch points (coronary, arch vessels and intercostal arteries) and discrete intimal calcifications were used to place landmarks on the aortic surfaces across serial CTAs within each patient. Deformable registration was performed using VDM parameters, in both the forward and reverse directions, and using all possible combinations of CT intervals for each patient.

Statistics

Patient characteristics were reported as mean ± SD for normally distributed continuous variables, median and interquartile range (IQR) for non-normal continuous variables, and frequencies for categorical variables. Normality was assessed using the Shapiro-Wilk test. Pearson's correlation coefficient was used to assess correlation between continuous variables. Binary categories were created based on published data on reducibility of clinical diameter

measurements (8-10) with "growth" defined as diameter change in the aneurysmal segment of ≥3 mm based on clinical measurements and ≥1.2 Area Ratio change by VDM (i.e., 20% increase in surface area). Agreement of growth assessment (binary yes/no) between clinical measurements and VDM was determined using Cohen's kappa statistic (κ). Inter-rater agreement of aortic segmentations was assessed using Dice Similarity Coefficient (DSC) to determine the overall degree of segmentation overlap, and Average Hausdorff Distance (AVD) to assess the average distance between segmentations at the aortic boundry. To assess inter-rater agreement of surface Area Ratio, the mesh values from each rater's VDM analysis (unique segmentations) were mapped to a common aortic geometry to allow point-to-point correspondence for direct comparison. A p-value of <0.05 was considered significant for all statistical tests. Statistical analyses were performed using Stata 14.0 (StataCorp LP, College Station, TX).

Results

Patient Characteristics and VDM Analysis Failures

Among the 38 patients who were included for analysis, the 3D growth mapping with VDM was completed without error in 35 (89%). VDM analysis was deemed successful after QA steps in 58 of 68 intervals (85%). The reasons for registration failure we identified included: irregular slice intervals in source DICOM images (n=3), excessive motion/stair-step artifact (n=2), streak artifact from dense superior vena cava (SVC) contrast (n=2), and streak artifact related to SVC cardiac implantable electronic device (CIED) leads (n=3). Examples of error cases are shown in **Supplemental Figure 1**.

The average patient age was 69.0 ± 9.3 years (range: 46-85 years) and the majority were female (n=21, 55%). The majority of TAAs involved the ascending aorta (n=26, 69%) and were considered degenerative in etiology by clinical notes (n=23, 60%). Approximately one-third of patients (11/38) had a history of prior aortic repair and were undergoing post-surgical imaging

surveillance. Complete patient characteristics are shown in **Table 1**. CTA examinations were performed between November 2006 and January 2020, with the median number of CTAs per patient of 2 (IQR: 2, 3; range: 2-7) with median surveillance interval of 1.1 years (IQR: 1.0, 2.0; range: 0.4-11.8).

Characteristics (n=38)	Mean ± SD (range)
Age (years)	69.0 ± 9.3 (range: 46-85)
Sex (male/female), n	17/21
Hypertension, n (%)	27 (73%)
Hyperlipidemia, n (%)	19 (50%)
Smoking history, n (%)	22 (58%)
History of connective tissue disease, n (%)	2 (5%)
Body mass index (kg/m^2)	28.2 ± 5.5 (range: 14.2-40.5)
Aneurysm Location	
Ascending, n (%)	26 (69%)
Descending, n (%)	10 (26%)
Both, n (%)	2 (5%)
Aneurysm Etiology	---
Degenerative, n (%)	23 (60%)
Atherosclerotic, n (%)	9 (24%)
Genetic, n (%)	2 (5%)
Inflammatory, n (%)	1 (3%)
Bicuspid aortic valve, n (%)	3 (8%)
Baseline Maximal Aortic Diameter (mm)	45.8 ± 5.6 (range: 33-58)
Prior Aortic Surgery, n (%)	11 (29%)

Table 1: Patient characteristics and demographics.

Registration Accuracy and Inter-rater Reproducibility Analysis

A total of 199 unique landmarks were manually placed at discrete anatomic locations along the aortic wall in 79 CTAs with an average of 7.2 landmarks per patient. Considering all registration combinations, a total of 1,021 point-pairs were used to assess landmark registration error. The median registration error was 0.77 mm (IQR: 0.54-1.10 mm, range: 0.07-4.57 mm; **Supplemental Figure 2**).

Inter-rater agreement for aortic segmentation was high with average Dice similarity coefficient of 0.97 ± 0.02 (range: 0.93-0.99) and an Average Hausdorff Distance of 0.12 ± 0.20 mm (range: 0.01-1.20 mm). When comparing the inter-rater agreement of Area Ratio values between approximately 5.4 million homologous surface elements, we found no bias (bias= 0.0) narrow limits of agreement (-0.03 to 0.03 Area Ratio; Bland-Altman plot in **Figure 3A**), and excellent inter-rater correlation of Area Ratio values (r=0.95, **Figure 3B**).
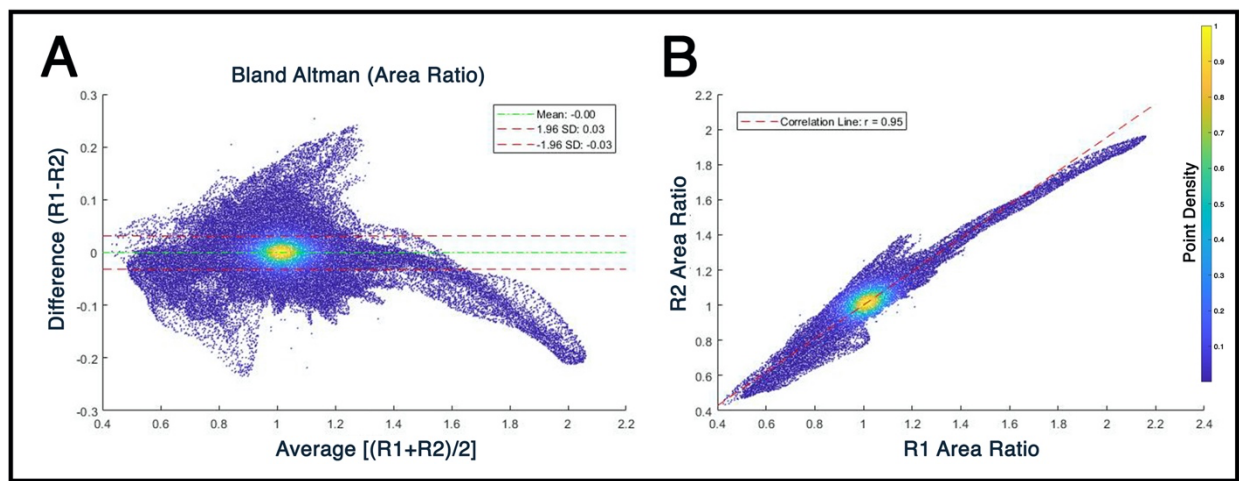

Figure 3: Bland-Altman plot with bias (dashed green line) limits of agreement (dashed red lines) depicting interrater agreement of Area Ratio values at homologous surface mesh elements (~5.4 million) generated from VDM analysis.

Three-Dimensional Growth Assessment

Overall, the median Area Ratio by VDM was 1.13 (IQR: 1.10, 1.19, range: 1.05 - 1.78), and growth was detected by VDM in 14/58 (24%) intervals (defined as peak Area Ratio ≥1.2).

VDM analysis was able to clearly depict aortic growth in common TAA locations including ascending (**Figure 4A**), descending (**Figure 4B**), aortic root (**Figure 4C**) and perianastomotic (**Figure 4E**). The location of growth by peak Area Ratio was localized to segment of maximal aortic dilation in 9/14 intervals (64%); however, in 6/14 (36%) intervals VDM depicted growth outside of the segment of maximal dilation (n=4 arch, n=2 descending). None of these 6 areas of sub-maximal growth were detected by clinical diameter measurements. Furthermore, changes in 3D aortic growth during imaging surveillance were also able to be clearly visualized by VDM (**Figure 5**). Among the 14 patients that had more than one surveillance interval, 11/14 (78%) patients demonstrated stable aortic dimensions by VDM at all surveillance intervals (**Figure 5A**), 2/14 (15%) demonstrated progressive growth at every interval, and 1 (7%) patient demonstrated stability at the initial surveillance interval and growth at subsequent intervals (**Figure 5B**).
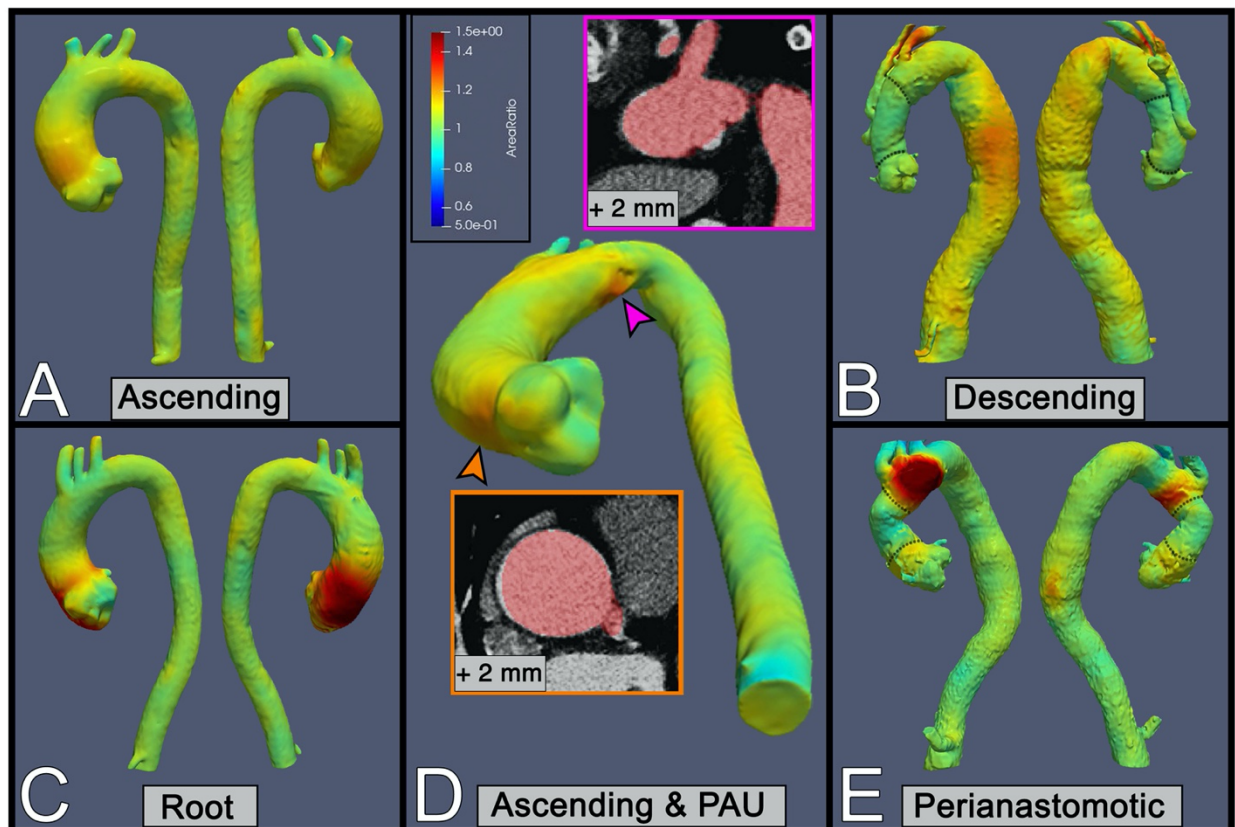
Figure 4: Examples of TAA growth patterns identified by VDM in a clinical cohort of patients undergoing CTA imaging surveillance. Representative examples of ascending aortic growth involving the tubular segment (A) and root (B), as well as post-surgical growth involving the descending aorta (B) and perianastomotic region in the arch (E); black dotted lines depict surgical graft anastomoses. Six intervals demonstrated growth in locations other than the primary aneurysmal segment, for example an enlarging penetrating ulcer was noted in the arch of a patient with a growing ascending aneurysm (D). Red masks depicting the baseline anatomy are overlaid on follow-up CT scans after rigid registration to allow for visual depiction of growth.
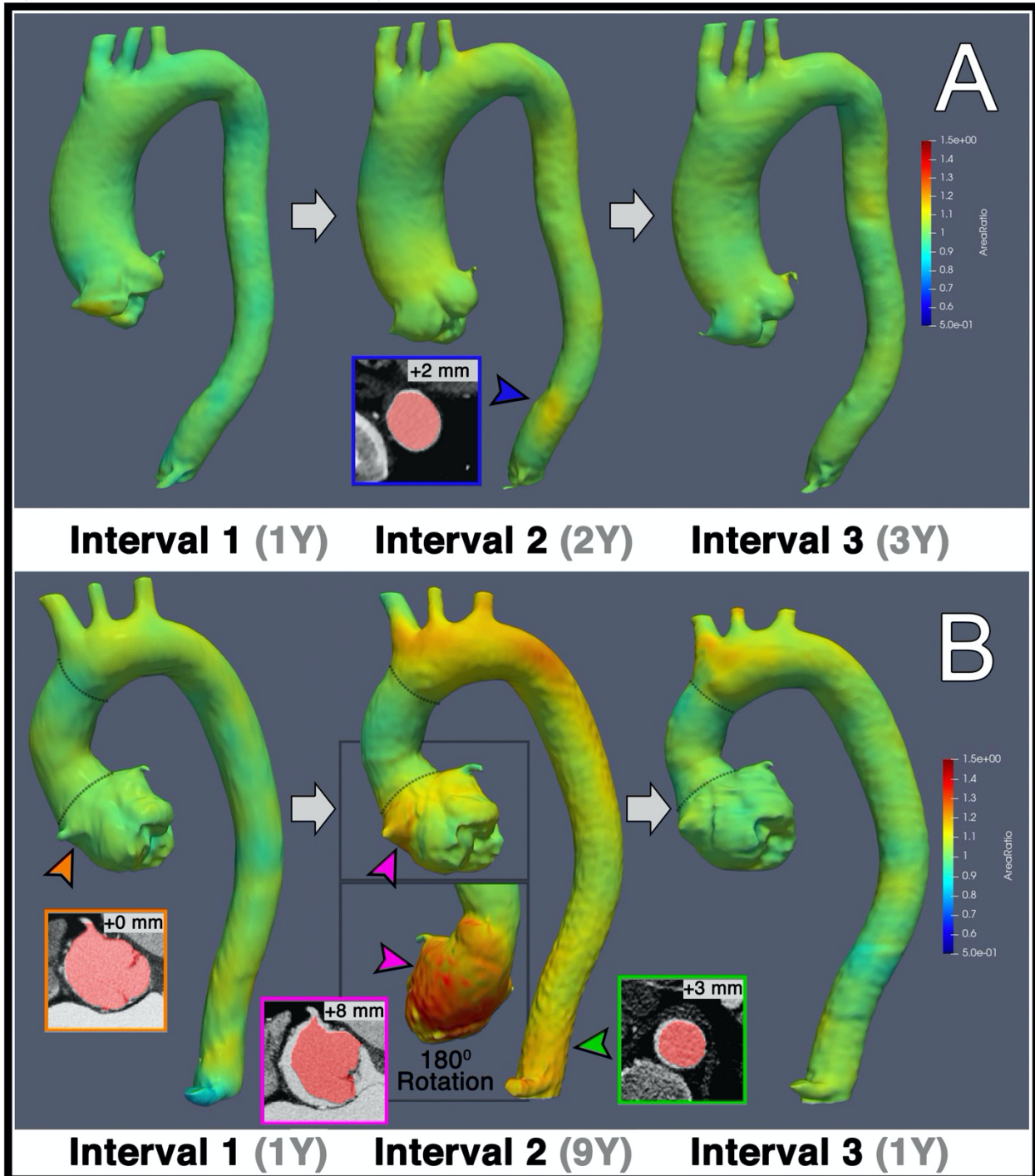

Figure 5: Representative cases depicting changes in 3D growth by VDM over serial surveillance intervals. Panel A depicts a patient with a stable ascending TAA over multiple surveillance intervals, but a small focal region of growth

was detected at the distal descending level in Interval 2. Panel B shows a patient with Marfan syndrome who underwent valve-spring root and ascending repair, who demonstrated stability of the root (orange arrowhead) at Interval 1 (first interval after surgery, and at Interval 2 demonstrated progressive growth of the root (purple arrowhead), arch, and distal descending aorta (green arrowhead), with growth in the arch persisting on Interval 3. Dotted lines indicate graft anastomoses.

Agreement with Clinical

There was strong agreement (r=0.85, p<0.001) between peak Area Ratio values and the change in maximal aortic diameter as measured by clinical CT (**Figure 6**). When analyzing growth as a binary outcome, there was agreement between VDM and clinical diameter growth categorizations in 89% (49/55) of surveillance intervals (kappa= 0.70, 95% CI: 0.42-0.86). Of note, clinical diameter change was not able to be determined in 3 surveillance intervals as baseline diameter was not clinically reported. Among the 6 cases where growth assessments were discordant between VDM and clinical diameter measurements, there were 4 cases where VDM detected growth while diameter measurements did not, and 2 cases where diameter measurements detected growth but VDM did not. In 3 of the 4 discrepant cases with growth by VDM the location of peak Area Ratio was at the sinotubular junction, while the location of the clinically reported maximal diameter was at the mid-ascending level. In 6 surveillance intervals VDM analysis detected an additional region of growth (≥1.2 Area Ratio) outside of the maximally dilated segment, of which 5/6 were located in the arch (3 arch penetrating atherosclerotic ulcers, 1 proximal left subclavian artery, and 1 fusiform dilation of mid arch) and 1 was at the location of a small descending TAA PAU (**Figure 5A, Interval 2**).
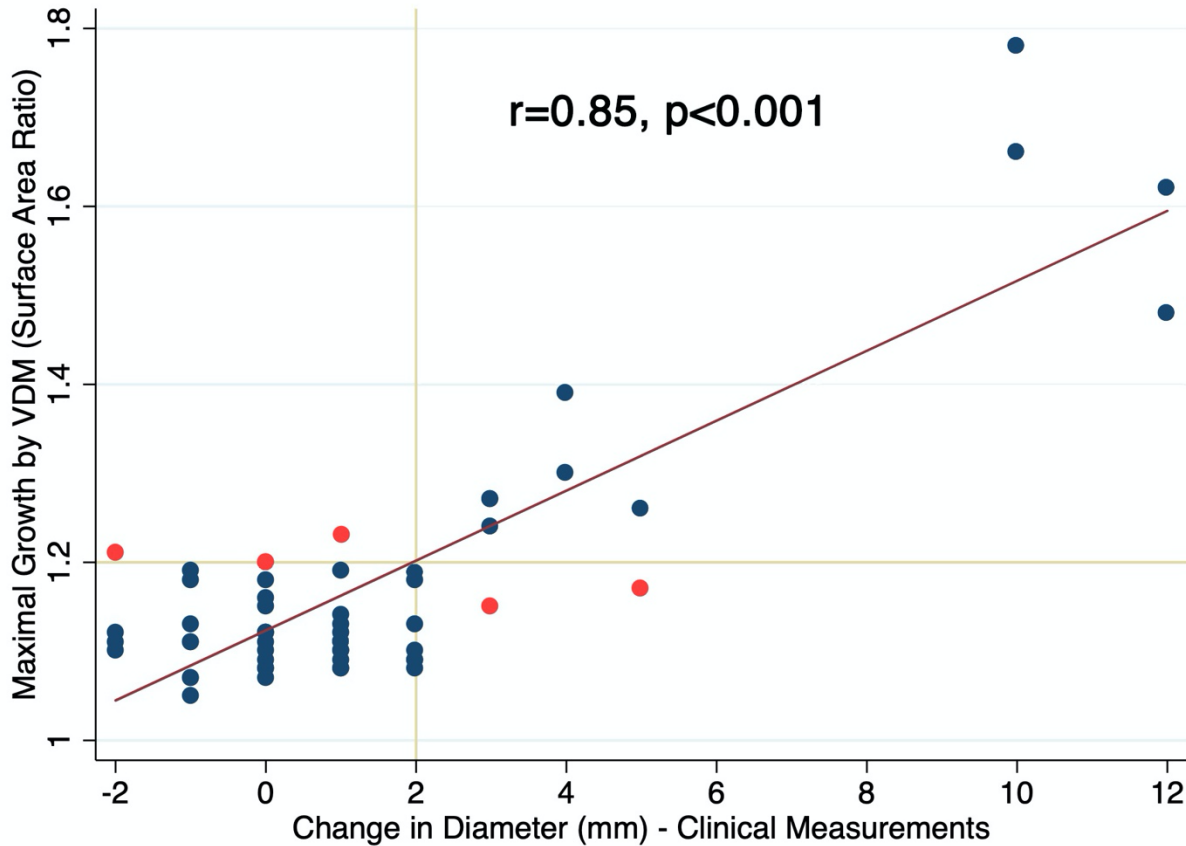
Figure 6: Scatterplot depicting the agreement between maximal aortic growth quantification by clinical diameter measurements and VDM (Area Ratio) at the aneurysmal segment. Green shaded regions depict regions of concordant growth assessments, while red points depict cases with discrepant growth assessments.

Discussion:

In this work we present results to support validation of a novel method for three-dimensional thoracic aortic aneurysm growth quantification using Vascular Deformation Mapping (VDM) in a clinical cohort of patients with various manifestations of thoracic aortic aneurysm (e.g., ascending, descending and postsurgical) commonly encountered in clinical practice. In summary, we found that VDM analysis was technically successful in 85% of the evaluated intervals, and that the most common reasons for failure of the VDM analysis included artifacts related to streak and motion (i.e., stairstep) at the ascending aorta. Despite small degrees of inter-rater variability in aortic segmentations, the final surface Area Ratio from VDM analysis demonstrated excellent interrater agreement. In addition to demonstrating the feasibility

for quantifying 3D aortic growth in the maximally dilated segment, VDM identified additional areas of growth outside of the primary aneurysmal segment in approximately one third of patients. Lastly, while VDM demonstrated agreement with clinical growth assessments in the majority of cases, the 3D nature of VDM allows for a more comprehensive depiction of the extend and distribution of growth along the aortic surface than is possible with diameter measurements.

Aortic diameter is the current metric used to assess growth and determine candidacy for surgical repair. However, diameter measurements suffer from significant measurement variability and are limited in their ability to predict rapid growth and risk acute complications such as aortic dissection (6, 11). Assessment of aortic growth is a primary objective of imaging surveillance, providing an indirect assessment of aortic wall integrity and useful information about the trajectory of disease progression and likelihood of need for future surgical intervention (4, 17). However, confident assessment of disease progression by aortic diameter is often difficult, and measurement variability alone can occasionally result in growth rates that erroneously suggest the need for surgical repair (5). The Vascular Deformation Mapping technique represents an attempt to overcome such limitations by harnessing the high-resolution and volumetric (plane-independent) nature of CTA data in combination with deformable image registration techniques which are capable of registering medical images with submillimeter accuracy (16). While we observed small degrees of inter-rater variability in VDM derived Area Ratio values, the degree of measurement variability relative the range of observed growth (± 0.03 limits of agreement compared to range of 1.05 – 1.78) was proportionally smaller than the typical degree of diameter measurement variability relative to the range of diameter growth we observed (± 2 mm with range of diameter change of -2 – 12 mm), suggesting higher measurement precision with VDM. While aortic diameter has a clear relationship with tensile wall stress (e.g., law of Laplace), this relationship assumes a circular shape, uniformly distributed and unidirectional stresses, and homogenous composition of the aortic wall,

assumptions which are not accurate in TAA. Thus, a kinematic assessment of aortic surface area changes by VDM may more accurately reflect underlying wall stresses due to the localized and multi-directional nature of the assessment.

Beyond simply providing a reproducible assessment of aortic growth assessment, the 3D nature of VDM allows for a more comprehensive evaluation of aortic growth than is possible with 2D aortic diameter measurements. Quantitative mapping of TAA growth allows for investigation of unique patterns/features of growth (e.g., eccentricity, longitudinal extent, multifocality) that are not able be easily captured using conventional approaches. While VDM represents one of the first techniques for quantitative mapping of disease progression in TAA, similar image analysis techniques using deformable image registration have been employed to yield quantitative imaging biomarkers for more comprehensive disease assessment and phenotyping in the lungs (e.g., COPD, pulmonary fibrosis)(18, 19), brain (e.g., glioma)(20-22), and bones (23, 24). The development of such quantitative methods to assess TAA disease progression have potential to improve risk stratification by better delineating surveillance intervals with slow growth versus no growth and may serve as a quantitative metric to better assess the effects of pharmacologic and surgical interventions. Preliminary investigations have suggested that VDM analysis may be able to help with surgical planning by better depicting the full extent of aortic growth (13), and in combination with computational modeling techniques may be a useful for investigating the mechanisms underlying development acute complications such as rupture and aortic dissection (25, 26).

Our study has several limitations. First, we did not systematically investigate patient outcomes in this study given that our objectives were focused on evaluating the technical performance, reproducibility and clinical validity of VDM. As such, the localized changes in aortic surface area measured by VDM require further investigation to define their prognostic significance, although such studies will require significantly larger patient cohorts with long-term follow-up given the slow nature of TAA growth and low rates of complications. Secondly, while

VDM analysis was technically successful in the vast majority of cases, the technique is susceptible to errors in the presence of streak and motion artifact, and thus the performance of VDM may be suboptimal at centers that do not routinely utilize ECG-gating and/or have older generation CT scanners with narrower detector arrays, limiting generalizability. Modern CT scanners that use high-pitch acquisition (e.g., FLASH) to generate motion free aortic images without the need for ECG gating may help overcome this limitation, however, we have nonetheless developed QA procedures to easily identify regions of registration failure indicating an erroneous VDM outputs. Thirdly, given the need for aortic segmentation and registration, VDM analysis does currently require more analysis time than diameter measurement, however, with the addition of deep learning techniques for automated aortic segmentation (27), the burden of analysis time can significantly shortened and shifted from human analysts to computational time with only minimal human interaction for registration QA. Lastly, given that we analyzed clinical CTA data, there is no available ground truth by which to adjudicate discrepant growth assessments between VDM and clinical diameter assessments. However, given the well-known variability of diameter measurements, the well-validated nature of b-spline deformable registration algorithms, VDM's high degree of inter-rater reproducibility and our rigorous QA procedures, we believe that VDM analyses included in our analysis accurately depict changes in aortic wall morphology.

Conclusion:

Vascular Deformation Mapping (VDM) is an emerging and robust method for three-dimensional quantification of longitudinal aortic growth in a heterogeneous clinical population of patients with thoracic aortic aneurysm. VDM analysis yielded reliable growth assessments in the vast majority of surveillance intervals with excellent inter-rater reproducibility, with failure events arising from the presence to streak and motion image artifacts. Accurate, quantitative 3D assessments of aortic growth may provide a more nuanced assessment of patient risk to better

inform surveillance intervals and treatment decisions. Data provided by VDM provides a unique

opportunity to identify unique disease phenotypes to significantly advance our understanding of

the growth trajectories and outcomes for patients with TAA.

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Disclosures:

NSB- Entitled to royalties related to licensure of intellectual property related to the VDM

technique.

CRH- Employee of Imbio LLC, a company which has financial interests in VDM technology.

BDR- Entitled to royalties related to licensure of intellectual property related to the VDM

technique to Imbio, a company in which he has a financial interest.

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Supplementary Material:

Quality Assurance (QA) Protocol

The steps included in our QA protocol included: 1) visual inspection of the fixed and moving image masks to confirm absence of segmentation errors, 2) inspection of the warped moving image after each sequential registration step using open-source transformix/elastix software (Utretch, Netherlands) to ensure appropriate transformation of the moving image towards to the fixed image target, 3) inspection of a dual-channel image created using a gradient magnitude filter to enhance the aortic boundary, with fixed and warped moving images colored red and blue respectively (i.e., area of image overlap display as purple), and lastly 4) confirmation that areas deformation on the colorized VDM surface plot correspond to areas of offset between the fixed image and warped moving image after rigid transformations before deformable transformation. All QA issues were resolved when possible (e.g., segmentation/copping errors), but if remediation was not possible then the analysis interval was considered failed, and the cause of failure was recorded.
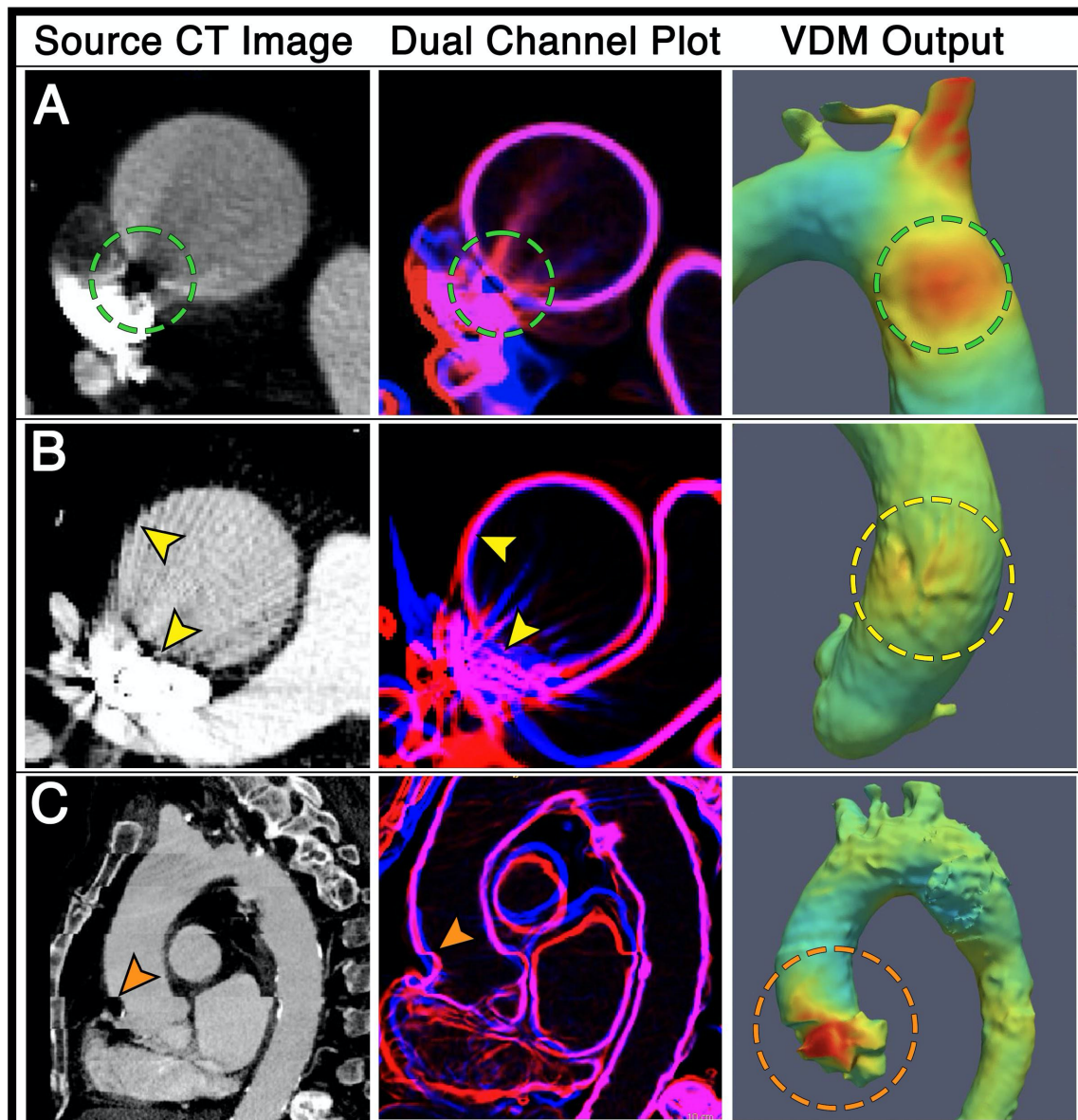
Supplemental Figure 1: Representative examples of error cases identified by our quality assurance steps. Streak artifacts related to dense contrast material in the superior vena cava (SVC) results in distortion of the luminal boundary, misregistration on dual channel image and artifactual growth along the posterolateral ascending aorta on VDM (A). Similarly, streak artifact from metallic lead in the SVC results in mild but more diffuse distortion of the aortic boundary, with corresponding misregistration on dual channel images and mild intensity artifactual deformation on VDM (B). Stair-step artifact can be visualized on source CT image (orange arrowhead), which results in misregistration and erroneous deformation on VDM analysis (C).
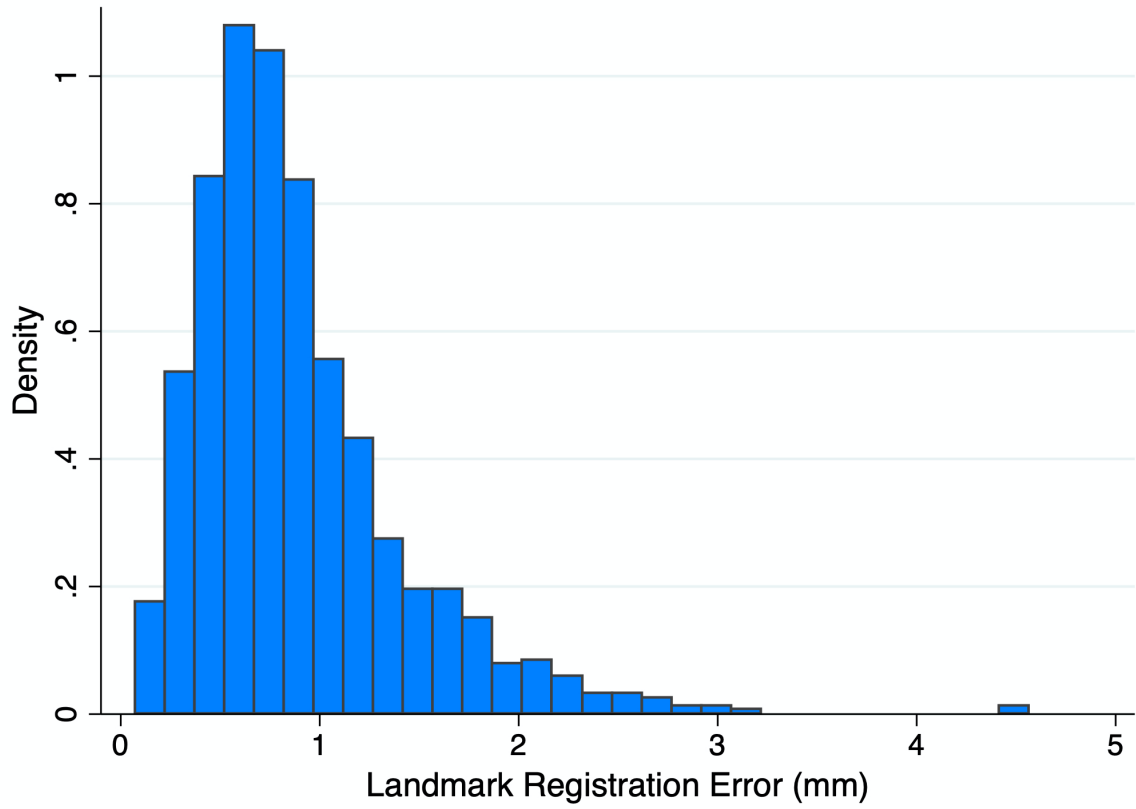
Supplemental Figure 2: Histogram displaying the distribution of registration errors measured by manual placement of 199 unique landmarks (1,021 point-pairs). Median registration error was 0.77 mm (IQR: 0.54-1.10 mm, range: 0.07-4.57 mm).