Original research

Artificial intelligence aneurysm measurement tool finds growth in all aneurysms that ruptured during conservative management

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ABSTRACT

Background Cerebral aneurysm rupture is associated with high rates of morbidity and mortality. Detecting aneurysms at high risk of rupture is critical in management decision making. Rupture risk has traditionally been associated with size—measured as a maximum dimension. However, aneurysms are morphologically dynamic, a characteristic ignored by large prospective aneurysm risk studies. Manual measurement is challenging and fraught with error. We used an artificial intelligence (AI) measurement tool to study aneurysms that ruptured during conservative management to detect changes in size not appreciated by manual linear measurement.

Methods A single practice database with >5000 aneurysms was queried. Patients followed conservatively for an unruptured aneurysm were identified using appropriate diagnosis codes. This cohort was screened for subsequent rupture using procedure codes. Only patients with two vascular imaging studies before rupture were included.

Results Five patients met the criteria. All patients had aneurysm enlargement, two of which were not detected from manual linear measurements, including adjudication and analysis, during a multidisciplinary neurovascular conference in a high volume practice. Maximum dimension increased at a minimum of 1.8% (range 1.8–63.3%) from the first scan to the last, and aneurysm volume increased at a minimum of 5.9% (5.9–385.5%), highlighting the importance of volumetric measurement.

Conclusions AI-enabled volumetric measurements are more sensitive to changes in size and detected enlargement in all aneurysms that ruptured during conservative management. This finding has major implications for clinical practice and methods used for interval aneurysm measurement in patients being conservatively followed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is well established that aneurysm morphology is dynamic. Aneurysms may change in size and shape with each cardiac cycle and may enlarge over longer periods of time. The largest prospective aneurysm rupture trials treat aneurysms as static; aneurysms are classified by maximum linear dimension during subject enrollment and kept in this category for the duration of the protocol—a deficiency which has major clinical implications. Another challenge in the aneurysm natural history and enlargement literature is the method of aneurysm size assessment, which is often performed by one or multiple linear measurements—a process fraught with inaccuracy and limitation.

WHAT THIS STUDY ADDS

⇒ This study uses artificial intelligence (AI)-rendered volumetric measurement of aneurysms and shows growth in all aneurysms that ruptured during conservative management. The result opens the possibility that all or the vast majority of aneurysms that rupture are in fact enlarging—a finding with profound implications. Additionally, this study raises the possibility that manual linear measurements are failing to detect a substantial percentage of enlarging aneurysms.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ For the community that treats aneurysms, employing an AI volumetric aneurysm tool for interval measurement is likely to dramatically increase sensitivity for detecting aneurysm enlargement. From a research standpoint, this study raises the possibility that risk factors previously thought to increase aneurysm rupture risk in fact increase risk for enlargement—and enlargement then increases risk for rupture. In this scenario, aneurysm rupture plays a role akin to that of a confounder, but as part of the causal pathway. It is telling that risk factors for enlargement are extremely similar to those for rupture and this relationship might account for substantial variability seen in the aneurysm rupture risk literature.

INTRODUCTION

Ruptured intracerebral aneurysms are associated with a high incidence of morbidity and mortality.[1] However, aneurysm treatment is not without risk and furthermore does not always reduce the natural history risk to zero.[2] At present, our best estimates of aneurysm rupture risk are dependent largely on aneurysm maximum diameter and to a lesser extent on location.[3 4] However, there are findings in highly cited prospective aneurysm rupture risk trials that are not consistent with observation from clinical

practice. For example, the majority of ruptured aneurysms in any ruptured aneurysm series are small[5] and yet these are purported to have the lowest natural history risk.[3 4] In addition, even carefully executed prospective trials yield contradictory results, most notably with respect to the critical issue of rupture risk for small anterior distribution aneurysms. Specifically, one major prospective trial found a 0% rupture risk for anterior distribution aneurysms <7 mm in maximum dimension in patients with no prior history of subarachnoid hemorrhage[4]; and another demonstrated risk that varied from 0.14–0.75% rupture risk per annum in this same cohort, significant risks, particularly in young patients.[3 4]

There are many reasons why aneurysm rupture risk as calculated by the most clinically utilized and academically referenced models may not accurately calculate risk for all aneurysms. One plausible factor is that these papers study aneurysm morphology as though it is static,[3 4] acting under the implicit assumption that aneurysm morphology does not change. Viewed this way, aneurysms of a certain size will remain so and are therefore categorized based on morphology at the time of subject trial enrollment, a categorization that is not modified over time in the context of the study. Yet, aneurysm architecture is profoundly dynamic.[6] Aneurysm morphologic dynamism can be broken down into two discrete categories. The first relates to hyperacute changes with each cardiac cycle—the study of which has only become possible in large scale with the advent of high resolution four dimensional CT angiography.[7] The second involves changes in the architecture of unruptured intracerebral aneurysms that typically occur over a subacute to chronic time course (days, weeks, months, years) related to the overall size and shape of the lesion. It is the latter form of dynamism that this research will focus on. This type of aneurysm dynamism has been shown to be clinically significant not only in papers looking at pre-ruptured aneurysm morphologic change,[8–26] but also in studies comparing pre- and post-rupture aneurysm morphology in which aneurysms often enlarge,[27–29] do not decrease in size,[28] and may form new daughter sacs[27 29] after rupturing.

There are major challenges associated with aneurysm measurement, not the least of which include variability in cross-sectional image slice angle and slice selection, edge definition, and digital caliper manipulation and usage—a tool which is likely to be far more precise than it is accurate. Physicians who diagnose these lesions in large numbers recognize that tiny movements with the caliper tool on digital imaging platforms can result in (fairly arbitrary) large relative changes in size. While a digital imaging platform caliper tool will give a measurement to 0.1 mm precision, this number is far more precise than it is accurate and vendors are aware of intrinsic measurement error.[15] On top of this intrinsic measurement error, lesions are often small (<10 mm), irregularly shaped, three-dimensional (3D) structures with superimposed complicating irregularities (figure 1)—that is, lobules, lobes, curvilinear forms, etc. In addition, the neck of the aneurysm is often a complex curviplanar shape (figure 1A); this further complicates measurement in that the precise location of the neck/artery interface changes as a function of radial position along the artery wall cross-sectional circumference, a feature that will be particularly challenging for any study using a maximum intensity projection (MIP) measurement system.[22] The inherent challenge born out of this complexity has resulted in different approaches to aneurysm measurement and, by extension, variability in techniques for monitoring growth.

However, there is reason to be skeptical of the accuracy of each of these aneurysm measurement approaches. Any single or even multiple linear measurements are limited in accuracy and may not truly capture the size of an aneurysm (figure 1). Indeed

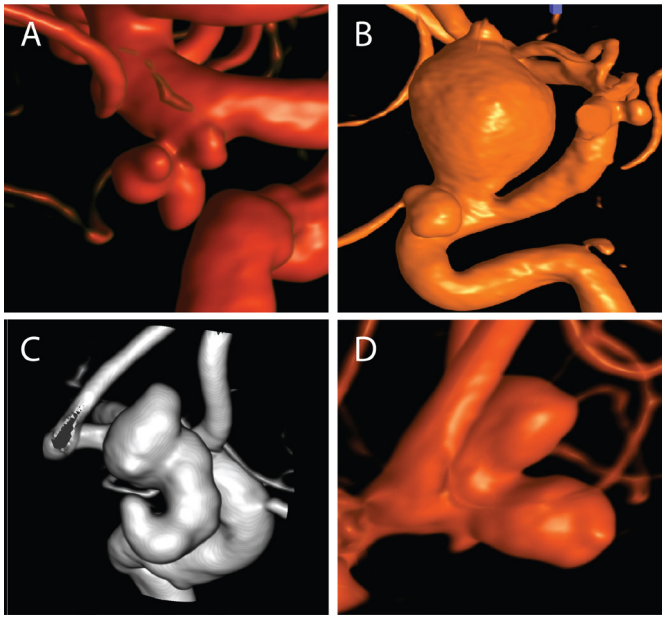

Figure 1 Angiographic volumetric acquisitions of (A) a right posterior communicating artery aneurysm. The multiple lobules create a complex curviplanar neck shape and render the aneurysm nearly impossible to characterize accurately with a single linear or even three linear measurements. (B) A right ophthalmic aneurysm with a dominant and non-dominant lobe. Single linear measurement is likely to exclude the smaller sac which could enlarge substantially without altering the maximum dimension. Measurements in three dimensions cannot accurately capture the size of this lesion. (C) A curvilinear anterior communicating artery aneurysm supplied from the left. Linear measurements will not capture the size of this lesion. (D) A true bilobed anterior communicating artery aneurysm. What craniocaudal dimension accurately captures the size of this lesion? Furthermore, a small focal lobule on the inferior aspect of the lesion at the base complicates measurement.

a much more accurate reflection of aneurysm size is in its volume or surface area. These, however, are difficult if not impossible to calculate manually.

A solution for these challenges exists, and the capability to calculate reproducible volumetric and surface area measurements might very well change our understanding of aneurysm dynamism and by extension rupture risk. With advancements in medical technology, artificial intelligence (AI) has been shown to be a useful tool for the diagnosis, monitoring, and treatment planning of diseases, including stroke and stroke imaging.[30] One study developed an AI neural network segmentation model to augment the clinician's diagnosis of unruptured intracerebral aneurysms (UIAs). Use of this model improved clinician sensitivity, accuracy, and inter-rater agreement when compared with analysis without the AI model.[31]

Rapid Aneurysm is a Food and Drug Administration-cleared imaging platform for cerebral aneurysm detection and management. Rapid Aneurysm aids in the management of UIAs through detection and quantitative monitoring of growth. The purpose of this study was to examine retrospectively aneurysms that had at least two cross-sectional neurovascular imaging studies before rupture, and to analyze these cases with the AI aneurysm measurement tool to assess for changes, some of which might not have been detected with manual linear measurements and/or the human eye.

METHODS

Institutional review board approval was obtained for this retrospective analysis. To identify patients for this study, an analysis of evaluation and management services was performed. Specifically, a prospectively maintained single-practice database of over 5000 aneurysm patients was queried to find patients who had an office visit with an unruptured cerebral aneurysm billing code followed by a ruptured aneurysm billing code. Patients who were being followed in office for an unruptured aneurysm were identified by searching for unruptured aneurysm diagnosis codes (437.3, 442.9, I67.1, I72.9). This cohort was screened for subsequent rupture by searching for an aneurysm procedure after the initial visit with a ruptured diagnosis code (430, I60-I60.9). Patients had to have at least two vascular imaging studies before the rupture to be included (thereby excluding two patients).

All computed tomography angiography (CTA) and magnetic resonance angiography (MRA) images from identified subjects were retrospectively processed by Rapid Aneurysm software for qualitative and quantitative UIA imaging. CTA and MRA image data were acquired for each case and uploaded to the Rapid Aneurysm web portal for vessel reconstruction and translation into a 3D surface model of the vessel network. The vessel reconstruction process was performed by trained Rapid personnel using a thresholding-based, semi-automated image-segmentation technique. Rapid Aneurysm uses a statistical shape model to automatically detect aneurysms in a 3D surface model of the vessel network. The 3D surface model is skeletonized by the software and a vessel network graph is generated. All terminal points-edges represented by the vessel graph are automatically classified by the software as either an intracranial circulation inflow, outflow, or potential aneurysm terminal edge. 3D ellipsoids are fitted to the vessel surface points of each potential aneurysm. Parameters that measure the shape, size, and parent vessel proximity are then automatically calculated for each potential aneurysm. The calculated parameters are compared with a set of fixed bounding parameters to filter false positives. The bounding parameters were determined from a training set of 110 segmented aneurysms with a representative number of normal and known aneurysm cases that have a size >3.0 mm. During the course of the original medical encounters, in the office and during follow-up, all patients as a matter of practice routine were presented at a multidisciplinary neurovascular conference. All imaging studies were reviewed by neurovascular neurosurgeons and neuroradiologists.

RESULTS

Through chart review, we were able to identify seven subjects who were being followed with UIAs before experiencing aneurysm rupture. Two of these subjects had only one cross-sectional imaging study before rupture and were therefore excluded. Five subjects had at least two imaging studies (CTA and MRA) preceding aneurysmal subarachnoid hemorrhage and were included from this study. Mean age was 62.2 years (range 51–75 years) with variable medical history and medications at the time of initial UIA imaging. Morphologically, four of the UIAs were saccular and one fusiform, and before Rapid Aneurysm software processing, three of the five UIAs had detected growth. These patients were recommended for treatment, which they had declined. Two of the five aneurysms were thought to be unchanged in size based on detailed measurements by neuroradiologists and assessment at neurovascular conference. Time between first and last pre-rupture imaging studies was an average of 3.71 years (range 0.98–13.46 years) (online supplemental table 1).

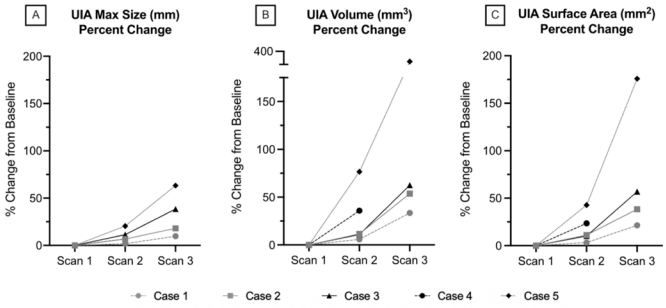

Figure 2 Aneurysm maximum dimension, volume, and surface area change over time. Five patients with an identified unruptured aneurysm received multiple scans to monitor the UIA over time using Rapid Aneurysm software. (A) Aneurysm maximum size (mm) showed a gradual increase of 1.82–63.3% between the first and last scans. (B) Aneurysm volume (mm^3) showed a gradual increase of 5.9–385.5% between the first and last scans. (C) Aneurysm surface area (mm^2) showed a gradual increase of 3.27–175.8% between the first and last scans. UIA, unruptured intracranial aneurysm.

Rapid Aneurysm software analysis demonstrated growth in all five UIAs in maximum size, volume, and surface area before rupture (figure 1A–C). The maximum size for UIAs at baseline was 4.8–16.8 mm, with an average baseline maximum size of 9.5 mm. Aneurysm maximum size increased for all five cases with a range of 1.82–63.3% increase from first scan to last (figure 2A). Aneurysm volume increased for all five cases with a range of 5.9–385.5% increase from the first scan to the last (figure 2B). Lastly, aneurysm surface area increased for all five cases with a range of 3.27–175.8% increase from the first scan to the last (figure 2C). Representative Rapid Aneurysm output images of UIA case 3, a saccular aneurysm, and UIA case 4, a fusiform aneurysm, visually demonstrate aneurysm growth when scans of the same UIA are overlaid (figure 3B,D). Along with the overlaid images, Rapid Aneurysm also presented side by side images of the UIAs with corresponding quantitative measurements (figure 3A,C). Case 1 CTA sagittal MIP (figure 4A,B) demonstrates the challenge in making manual linear measurements when following aneurysms. The Rapid Aneurysm 3D images (figure 4C,D) and overlay (figure 4E) demonstrate an enlarging aneurysm with an increase in volume of almost 6%.

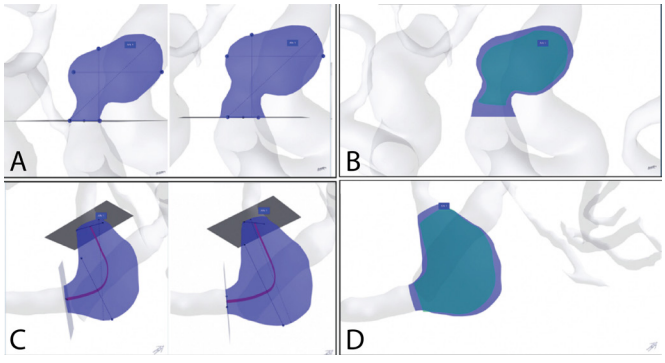

Figure 3 Comparison of Rapid Aneurysm output. Rapid Aneurysm outputs of case 3 (A/B) and case 4 (C/D). Panels A and C show side by side images of the first scan (left) versus the last scan (right) taken of the UIA. Panels B and D show the first and last scans overlaid, demonstrating aneurysm growth. UIA, unruptured intracranial aneurysm.

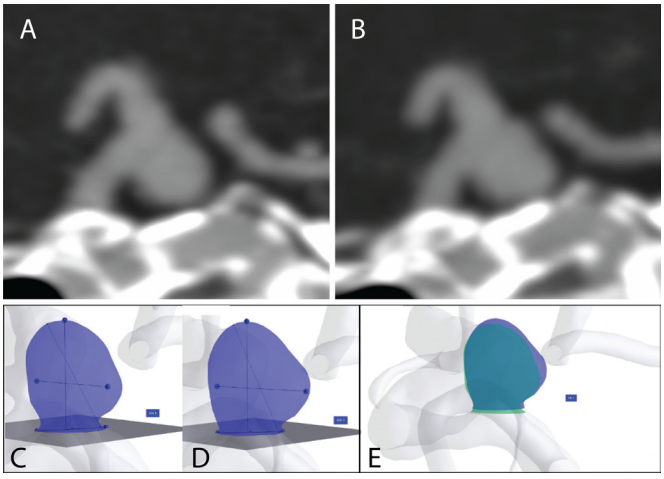

Figure 4 Case 1. Sagittal CTA maximum intensity projections from initial exam (A) and 1 year later (B). The images are in a nearly identical plane of section (which is both unusual and fortunate). Nevertheless, there is no discernable change in linear dimension despite a 5.9% change in volume. (C, D) Side by side images of the first scan (left) versus the last scan (right) taken of the unruptured intracranial aneurysm. (E) This panel shows the first and last scans overlaid, demonstrating aneurysm growth.

DISCUSSION

This study is significant in multiple respects. All aneurysms that ruptured during conservative management had enlarged—two of which (40%) had gone undetected in an experienced, high volume neurovascular practice. This raises the possibility that a larger percentage of aneurysms that rupture during conservative management are in fact enlarging. Furthermore, while the minimum relative enlargement in maximum dimension was only 1.8% at a minimum, the relative volumetric minimum enlargement in this series was almost 6%—a change in volume that is thought to be significant,[15] highlighting the limitations of linear maximum dimension in detecting/characterizing growth.

This point cannot be emphasized enough. Single linear maximum dimension might give a general sense of the overall size of an aneurysm and is likely to be the most reproducible approach in manual measurement because of its simplicity—both between practitioners and over time—but it is clearly limited in that an aneurysm could grow substantially in volume without a change in the maximum dimension (figure 1A,B). Additionally, there are many aneurysms for which linear measurements simply fail to capture the true size because of their curved morphology (figure 1C). Single linear measurement is therefore likely to be specific, but quite insensitive. Then there is the question of what change in maximum dimension to call 'significant'. While some studies use absolute cutoffs in length, these have two major drawbacks: (1) they vary substantially on a percentage basis based on the size of the aneurysm; and (2) they are fairly arbitrary and therefore vary significantly from paper to paper. Some studies use a cut-off of 1 mm,[8 16 17 32] others 0.5 mm,[9] 0.75 mm,[18] or 2 mm,[10 25 33] thereby limiting the generalizability of the literature as a whole and severely hampering meta-analyses from generating meaningful conclusions. Another approach is to adjust for aneurysm diameter, allowing that smaller changes in smaller lesions are larger on a relative basis—for example, a >1 mm increase for aneurysms <5 mm in size and ≥2 mm for aneurysms ≥5 mm.[11] Again, these cutoffs are somewhat arbitrary and are still limited by measurement error, the constraints of linearity, and the insensitivity of maximum dimension in detecting changes in size.

Recognizing the inherent limitations of following aneurysm size using maximum diameter, other studies have attempted to use measurements in each of the three dimensions. Notwithstanding aneurysm morphology that clearly precludes a three linear measurement system (figure 1), studies seem to use either a crude estimate of aneurysm volume—most commonly the ABC/2 approximation[15]—or criteria for growth in one, two, or three dimensions. This type of analysis can use an absolute cut-off for growth, that is, >2.0 mm in any dimension,[25] or can incorporate an understanding of known error associated with cross-sectional imaging measuring tools with criteria such as change in size to the nearest 10th of a millimeter greater than the measurement error per manufacturer software specifications (<2 mm±10%; 2–10 mm±5%; >10 mm±2%) for one or more aneurysm dimensions and change in aneurysm volume of ≥5%.[15] Because lobulations might be missed using any three-measurement system, other studies have used more complex growth criteria such as (1) growth ≥1 mm in ≥1 direction for identical or different imaging modalities; (2) growth ≥0.5 mm in two directions for identical imaging modalities (CTA or MRA); or (3) undisputable change in shape of the aneurysm, such as change from unilobar to multilobar shape.[21] Other studies use the criteria of at least 50% growth to accommodate significant change on a relative basis for small aneurysms,[19] while clearly excluding potential meaningful growth that does not cross this threshold. Some papers in the literature give no information on the threshold for defining growth.[12 32]

Yet even as growth criteria become more convoluted to accommodate clear gaps in sensitivity (with a likely cost of specificity and generalizability), none of these systems adjust for the simple possibility of an aneurysm enlarging minimally in all dimensions. This could be barely detectable by manual linear measurement, but result in a significant volumetric expansion, most particularly for a small aneurysm and on a relative basis—that is, a percentage of the total original volume. That two of the five aneurysms in this series evaded detection for this very reason is compelling.

All of this is to say that there is ample reason to be skeptical of the accuracy of the aneurysm growth literature for the simple fact of methodological challenges with manual aneurysm measurement. This is a potential issue with data quality that is not improved by data aggregation—that is, with larger sets of data such as those used in meta-analyses.[23 24]

The results of this study in which all ruptured aneurysms were detected to have grown raise the possibility that the mechanism of brain aneurysm rupture is in fact through growth. This hypothesis has often been conceived of and is suggested by much of the literature in that growth significantly increases the risk of hemorrhage.[14 15 22 24 33] However, our data also suggest that a reasonable percentage of enlarging aneurysms might have gone unnoticed when measured manually, raising the possibility that the strength of this association has been grossly underestimated.

While the number of subjects in this study makes it impossible to draw definitive conclusions, there is circumstantial or secondary evidence supporting this hypothesis as well. The risk factors for aneurysm growth in this body of literature are strikingly similar to the risk factors associated with rupture in prospective aneurysm rupture series (online supplemental table 2).

It may very well be that the distortion, thinning, and distension that occurs during growth is in fact mechanistically what leads to aneurysm rupture in the vast majority of cases. Risk factors such as aneurysm size,[9–11 21–24] female gender,[8 12 14 20 22–24] smoking,[8 12 15 16 21 23] and aneurysm posterior

distribution location[9 18 21 22] are associated with aneurysm growth, each of which is associated with rupture as well.[3 4 34 35]

The implication of this potential causal pathway and resultant dual association is quite profound. If these risk factors are truly associated with growth and it is growth that is associated with rupture, then aneurysm rupture is playing a role akin to that of a confounder, but as part of a causal pathway. This is a significantly different way of understanding aneurysm rupture risk. This subtle but truly important distinction could account for much of the inconsistency in the aneurysm rupture prediction literature[3 4]. For example, small anterior distribution aneurysms whose rupture risk is either 0%[4] or 1% per year,[3] depending on which prospective trial one chooses to follow, may be less likely to grow—but those that do are still at significant risk. These trials might have had large differences in the percentage of growing aneurysms, a variable that was not measured and therefore could not be accounted for. Significant variability between papers in the incidence of growth (range 3%[24] to 45%[8]) would support the potential for large variability between these studies, again unbeknown to investigators who did not gather aneurysm size data after the initial presentation. Understanding this mechanistic implication might enable the detection of high-risk aneurysms in cohorts traditionally thought of as lower risk, which would have extraordinary clinical significance.

If these hypotheses are correct, a second question arises—that of cadence or rate of growth. It may very well be that aneurysms fall into different categories of growth rate,[12] some of which are more likely to be caught on interval screening than others. These issues will be resolved by large prospective aneurysm trials using automated, accurate volume and surface area measurement tools.

One weakness of this study is clearly its size. However, the detailed data that this enabled—such as whether aneurysm size differences were found prospectively in a high-volume practice—add value to the analysis. The results here nevertheless are not meant to offer definitive answers, but to raise profound and critical questions, as well as to formulate important hypotheses for a neurovascular community that now has technology-enabled tools to perform studies that have not previously been possible.

Another potential limitation is variability in scan type and scanner technology from between and among subjects. The earliest scan that we used was from March 2006 and the latest from March 2018. All studies were CTAs with the exception of one study, which was an MRA. The MRA was the second of three scans (and therefore did not impact the final outcome for that patient) and showed the same trend that existed in its absence—specifically, there was enlargement from the first (CTA) to the second scan (MRA) of 12% and enlargement from the second (MRA) to the third scan (CTA) of 38% over 274 and 356 days, respectively, which was in line with the rates of growth observed from the other three-scan patients.

The CT technology used in scanning was somewhat limited to scanners available during this timeframe (2006–2018). Nevertheless, there is variability as patients were being followed clinically in multiple locations, each of which might have employed multiple scanners. While this is a negative in that there is variability in scan quality and resolution, we viewed this as a strength in two major ways: (1) this type of variability more closely matches the clinical setting in which patients are likely to be scanned on many types of scanners; and (2) scanner variability is likely to add noise to the data and make it more difficult to observe trends. Even in the context of this potential variability, we were able to see a consistent trend in that all aneurysms enlarged. In some respects, the scanner variability makes this finding both more generalizable and likely stronger as an effect.

Another potential limitation of this work is the absence of a control group of unruptured cerebral aneurysms. While the literature would suggest high risk of rupture in patients with known enlarging aneurysms, the increased sensitivity of a volume detection tool (the percentage change in volume was a minimum of 62% greater than the percentage change in maximum dimension in this series (range 62–607% greater)) raises the possibility of real growth going undetected in trials using manual linear measurement. The database used in this analysis was a treatment database and therefore long-term data on unruptured, untreated aneurysms were not available. It is likely to take large numbers of control patients to establish a reliable growth rate–rupture risk relationship, the type of analysis that is likely to require a multicenter collaboration.

CONCLUSION

The present study finds that aneurysms that ruptured during conservative management all demonstrated growth, only some of which was detectable by manual measurement in a high-volume neurovascular practice. The AI-enabled aneurysm volume and surface area tool represents a revolution in technique for measuring aneurysm size and therefore growth. There are strong reasons to believe that methodological challenges in the simple act of aneurysm measurement historically resulted in measurement inaccuracy (despite precision), lack of sensitivity to growth, and lack of specificity/generalizability. Future studies should use AI tools for aneurysm measurement and monitoring prospectively for large numbers of patients.

Contributors DHS: guarantor, designed the study, drafted the manuscript and interpreted the data, critically reviewed and edited the manuscript. DPG, JAS, AJD, KA, TDP, DRH and CGK drafted the manuscript and interpreted the data, critically reviewed and edited the manuscript.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ascension St. Vincent Health IRB# R20210059. This was an observational study. All participants agreed to their treatment(s) and consented to all items related to treatment, including collection of data for future studies.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data that support this study is available from the corresponding author upon reasonable request.

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