Towards the Prediction of Successful Outcome of Transcatheter Aortic-Valve Replacement (TAVR)

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1 Personal Interest

Although I've always been interested in math, I didn't truly fall in love with the subject until the summer after my freshman year, when I attended the Program in Mathematics for Young Scientists (PROMYS). PROMYS was a competitive summer camp focused on teaching abstract number theory to high school students via daily lectures and challenging problem sets. Given this daunting description, I was more than a little surprised by the first equation that my professor scrawled on the board during the first lecture of the program:

$$1 + 1 = 2$$

Seemingly simple, but not necessarily so. The audience remained respectfully silent, but I imagine a few of them were wondering the same thing I was. Wasn't this an advanced mathematics program? Why were we focusing on something so simple?

Our questions were soon answered. The professor dove into explanations of the set of real numbers, changing bases, and modular forms, reminding the class with a wink that yes, we could do this without a calculator and no, Fermat's little theorem was certainly not the same as his last. A sea of abstruse formulas and symbols sprawled across the board, crowding around the now barely visible first equation. He ended with a short, but wise remark: "remember, it takes a lot of time and energy to produce such great simplicity."

Indeed, I began to appreciate such simplicity, and to re-define my understanding of mathematics. I came to see it as being much more than just its constituent symbols and equations, but a beautiful language capable of describing the logical foundations of all the natural sciences. Over time, that same beauty began to appear everywhere I looked. I used differential equations to analyze the spread of pandemic H1N1, formal logic to simulate human reasoning processes, and probability theory to complete my entry for the Intel Science Talent Search, "Towards the Prediction of Successful Outcome of Transcatheter Aortic-Valve Replacement (TAVR)." This project required that I learn Bayesian statistics, a field that I'd had no experience in. However, I managed to self-learn the necessary concepts by borrowing books, teaching myself to code in MATLAB, and taking an online course in statistics. Furthermore, I reached out to a biomedical engineering lab at Columbia University in the hopes of gaining guidance and access to more powerful computers. The lab head, Professor Laine, and his graduate students were extremely helpful, always offering me helpful advice/suggestions and putting me in contact with cardiologists at the nearby New York-Presbyterian Hospital. Without their endless help and encouragement, I could not have finished this project nor achieved Semifinalist status in the Intel Science Talent Search.

2 Research

2.1 Abstract

Aortic stenosis (AS) is a lethal disease that can lead to severe cardiac complications if left untreated. A new type of non-invasive treatment for AS, transcatheter aortic-valve replacement (TAVR), exhibits comparable success rates in comparison with conventional surgical aortic valve replacement. Nevertheless, it also demonstrates significantly greater rates of paravalvular regurgitation, a serious complication associated with increased rates of later mortality. In this study, we achieve three main objectives. First, we design a computer program for automatic 2-dimensional measurement of the aortic annulus that is statistically non-inferior to radiologists' manual measurements. Secondly, we use these measurements in addition to the Agatston calcium score to identify significant predictor variables of paravalvular regurgitation. At a significance level of 0.05, the predictor variables were identified to be aortic valve calcification and prosthesis mis-sizing. Lastly, we use these predictor variables to construct a multivariate Bayesian model that predicts the incidence of moderate post-TAVR paravalvular aortic regurgitation with 70% accuracy, highlighting its potential for clinical use in recommending patients to the appropriate AS treatment. In light of the fact that 50% of medically treated AS patients die within two years of onset of symptoms and as many as 30% of these patients cannot undergo surgery, TAVR is a life-saving procedure that has the potential to positively impact many patients' lives. Since TAVR cannot be conducted safely without prior assessment of risk, the proposed risk-stratification model reflects a significant advancement in AS patient care.

2.2 Introduction

Aortic stenosis (AS), a cardiovascular disease characterized by the narrowing of the heart's aortic valve and therefore obstruction to outflow of blood from the heart, affects up to 1.5 million people in the US alone and at least 5% of persons aged 75 and above [1]. It is one of a large class of cardiovascular diseases that makes up the number one cause of death, killing 600,000+ Americans each year [2]. The most common, calcific form of this disease is caused by the accumulation of calcium deposits on the cusps of the aortic valve, reducing the flexibility of the leaflets and the circumference of the aortic annulus (Fig. 1). The decreased functionality of the valve causes ventricular hypertrophy and reduced ejection fraction, which manifest in the patient as breathlessness, chest pain, faintness, palpitations, and various other physical symptoms. Left untreated, AS can lead to severe complications, including but not limited to, arrhythmias, heart failure, and cardiac arrest [3]. Thus, it is important for the condition to be treated in order to improve prognosis and prevent further cardiac complications. The primary treatment for AS is surgical aortic valve replacement

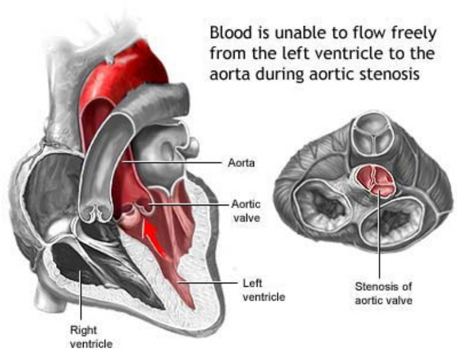

Figure 1: A diseased aortic valve

(SAVR). It has a high success rate and long life expectancy, averaging 11.3 years for patients 65 and older [4]. Nevertheless, SAVR is an invasive, open-chest procedure that may result in severe complications such as infection, stroke, or heart attack. As a result, not all patients are deemed suitable candidates for SAVR.

Due to advanced age, left ventricular dysfunction, frailty, and other high-risk factors, at least 30% of patients with aortic stenosis are poor candidates for aortic valve replacement surgery [1]. These patients are often recommended to alternative treatments involving less risk of mortality and surgical complications. One such treatment is aortic valvuloplasty, which uses a catheter to insert a balloon into the valve and inflate it, effectively expanding the opening of the valve and cracking the calcium deposits. Unfortunately, most patients who have undergone this procedure report symptom recurrence within six months and are eventually required to undergo surgical aortic valve replacement [5].

Another more recently developed treatment and the focus of this study is transcatheter aortic valve replacement (TAVR), a procedure which implants a bioprosthetic valve in the diseased native valve using a catheter with a balloon crimped on its end. The catheter is inserted either through the apex of the heart (transapical approach) or through the femoral vein (transfemoral approach), and guided towards the aortic valve (Figure 2). Once inside the valve, the balloon is inflated, expanding the prosthesis and displacing the native valve [6]. Owing to its non-invasive nature, TAVR offers a promising, less risky alternative to open-chest heart surgery for patients who cannot undergo surgery. In the recent Placement of Aortic Transcatheter Valves (PARTNER) trial, TAVR was shown to have comparable mortality rates and symptom improvements as surgical aortic-valve replacement and balloon aortic valvuloplasty [7]. Yet despite TAVR's apparent success, cardiologists were alarmed by the high rates of post-procedural paravalvular aortic regurgitation. In comparison with SAVR patients, TAVR patients were significantly more likely to develop paravalvular regurgitation, a severe complication associated with increased rate of later mortality [8]. Although this complication can be minimized by paying close attention to the sizing of the prosthesis, clinicians have been challenged with a medical conundrum: that is, whether to recommend patients to the TAVR procedure at the risk of exchanging one valvular disease (aortic stenosis) for another (aortic insufficiency, or paravalvular aortic regurgitation). Assuredly, most would agree that at the crux of the matter lies the need for a standard TAVR risk prediction model. Indeed, a number of risk stratification models already exist for assessing a

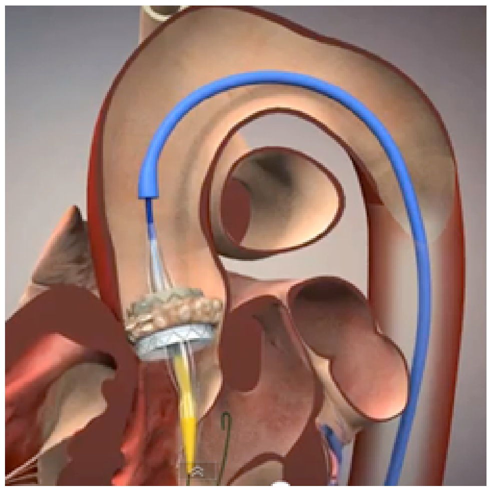

Figure 2: Transcatheter aortic-valve replacement.

patient's suitability for thoracic and/or cardiovascular surgery. The Society of Thoracic Surgeons (STS) risk model not only predicts operative mortality, but also severe nonfatal complications such as stroke, renal failure, and prolonged ventilation [9]. Similarly, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) model stratifies risk of in-hospital mortality for valvular surgery patients [10]. Both models are based upon large databases of patient data from five or more years, and have been verified for accuracy in various studies [11]. Nevertheless, neither of these prominent models, nor any other currently existing valve surgery risk stratification model, provides a custom prognosis for the TAVR procedure.

Due to TAVR's novelty[1], little progress has been made towards predicting its outcome. Ranucci *et al.* assessed the accuracy of the EuroSCORE and the age, serum, creatinine, and ejection fraction (ACEF) score in stratifying risk for TAVR and concluded that neither model was as adequate for TAVR as for SAVR [13]. Furthermore, Vahanian and Otto approached the problem from a different perspective and formulated a decision-making model for managing aortic stenosis that included TAVR as an option, but did not predict possible outcomes or stratify risks of the procedure [14]. The efforts to solve this puzzle are still ongoing, but

[1] TAVR was recently FDA-approved in the US, in November of 2011 [12].

more clinical causes and predictors of post-TAVR paravalvular aortic regurgitation must be identified before an adequate model can be formulated.

In view of the aforementioned rationale, this study focuses on efficiently elucidating the predictor variables of post-TAVR paravalvular aortic regurgitation and developing a clinical metric for recommending AS patients to the appropriate procedure. Therefore, we establish three main objectives. The first is to automate the process of aortic annular measurement, a manual procedure requiring 30-60 minutes per case for most radiologists. The measurements obtained from this automatic algorithm will be used to achieve the second objective, which is to identify significant predictors of post-TAVR paravalvular regurgitation. We hypothesize that greater calcification of the aortic valve, as well as undersizing of the prosthesis, are significant predictors of post-TAVR paravalvular regurgitation. Lastly, this study aims to formulate a mathematical model that succinctly consolidates the identified predictor variables into a single clinical metric that predicts the presence or non-presence of moderate post-procedural paravalvular aortic regurgitation.

2.3 Materials and Methods

2.3.1 Manual Data Collection

The data used for this study were obtained from 30 patients (24 women and 6 men; mean age $\pm$ SD, 83.3 $\pm$ 8.5 years) who underwent TAVR between November 2011 and April 2012. All patients underwent pre-procedure CT angiograms gated by electrocardiograms during breath-hold acquired with a Toshiba Aquilion ONE 320-slice scanner. Each volumetric dataset typically contained 640 image sections for each of 20 phases of the cardiac cycle. Image sections were 0.5 mm thick, spaced 0.25 mm apart, and reconstructed with a matrix of 512 by 512 pixels using a standard cardiac kernel. In-plane pixel spatial resolution was 0.5 mm by 0.5 mm. The aforementioned data were de-identified and collected in compliance with all privacy and HIPAA laws, and the affiliated Institutional Review Board (IRB) approved the study.

Initial measurements were quantified at end-diastole by cardiologists using a Vitrea 6.1 workstation. First, the clinicians manually identified the cardiac phase corresponding to end-diastole based on both the gated EKG and the resulting image volumes. The image series of the selected phase was subsequently used for a 3-dimensional multiplanar reconstruction, the starting point of their measurements. The cardiologists would then scroll through the images and center the axes of the axial plane on the aortic valve, after which they would shift the axes of the coronal and sagittal views to be aligned with the basal ring of the aortic valve, also known as the aortic annulus (Fig. 3). Once this double oblique transverse plane was selected, the cardiologists would take certain measurements, including a semi-automatic Agatston calcium score (Fig. 4), mean diameter, maximum diameter, minimum diameter, ellipticity index (ratio of the maximum diameter to the minimum diameter), sinotubular junction, area, and more such measurements of the aortic annulus.

Some of these measurements could not be acquired without first manually fitting an ellipse to the shape of the aortic annulus and then measuring the length of its major and minor axes, as well as its area. These manual measurements were used as a standard of comparison for the automatic algorithm developed in this paper. Other measurements, including the volume and categorical score of paravalvular leak, were obtained by live transesophageal echocardiogram (TEE) during the TAVR procedure.

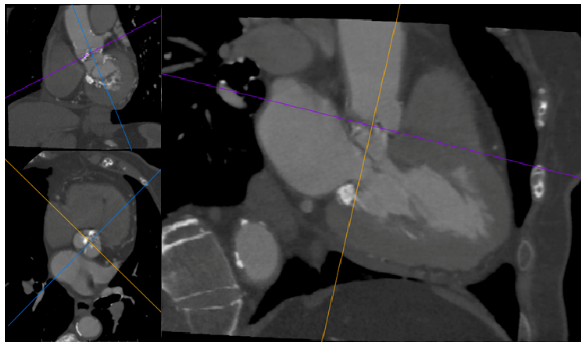

Figure 3: Three orthogonal double oblique views of multiplanar-reconstructed CT images of the aortic root

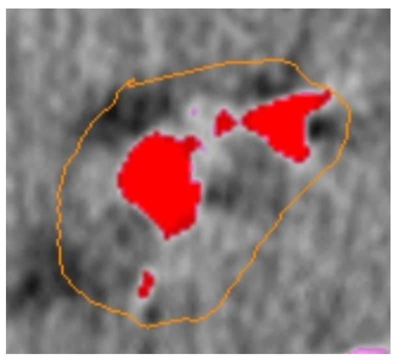

Figure 4: Semi-automatic Agatston calcium scoring. The cardiologist circles regions of high calcification, and Vitrea calculates the appropriate score for that region.

2.3.2 Automatic Algorithm for Aortic Annular Measurements

The algorithm proposed here does not attempt to address the tedious process of selecting the correct double oblique transverse plane. Rather, it aims to automatically locate and quantify the aortic annulus following the correct manual identification of the aforementioned plane.

Each image was first pre-processed using global histogram equalization and Canny edge detection, thus increasing the contrast and converting it to a binary edge image. To detect the elliptical shape of the aortic annulus, we applied a modified form of the Hough Transform to the binary edge image.

Given some ellipse with axes parallel to the coordinate axes, each of its points can be expressed as $(r\cos\theta, r\sin\theta)$. If the ellipse is rotated through angle α, then this point becomes $(r\cos(\theta+\alpha), r\sin(\theta+\alpha))$. By the sine and cosine sum trigonometric identities, these coordinates are equivalent to $(x\cos\alpha - y\sin\alpha, y\cos\alpha +$

$x \sin \alpha$). This transformation, once inserted into the standard equation of an ellipse, results in the following equation:

$$\frac{[(x-h)\cos\alpha + (y-k)\sin\alpha]^2}{a^2} + \frac{[(x-h)\sin\alpha - (y-k)\cos\alpha]^2}{b^2} = 1 \tag{1}$$

where (h, k) is the center of the ellipse, and a and b are the lengths of the major and minor axes, respectively.

The typical Hough Transform (used to detect lines or circles) makes use of an accumulator matrix, initialized as a zero matrix, to select the best-fit geometric figure. For a figure with n parameters in its equation, its corresponding accumulator matrix also has n dimensions. A range, with discrete intervals representing the acceptable degree of error, must be defined for each parameter and assigned to the appropriate dimension of the accumulator matrix. As such, the indices of each accumulator bin are mapped to possible sets of parameter values. The algorithm then computes every possible translation, dilation, and rotation of the figure that each foreground pixel in the binary edge image might lie on, extracts the dimensions of the aforementioned fitted figures, and increments the corresponding accumulator bins (with the same dimensions as the fitted figures) by 1. Thus, the dimensions of the bin with the greatest value are the set of parameter values of the best-fit figure [15].

In the case of our study, equation 1 has five parameters, and therefore requires the use of a five-dimensional accumulator matrix in computing the best-fit ellipse. If an acceptable degree of error for each parameter is arbitrarily selected to be 1 pixel or 1 degree, then approximately $n \times [\sqrt{(\frac{512}{2})^2 + (\frac{512}{2})^2}]^2 \times 512^2 \approx n \times 3.44 \times 10^{10}$ ellipses must be computed per 512 by 512 image, where n is the number of foreground pixels in the image. To reduce the computational load, we provided initial estimates of each parameter and then searched around this initial estimate for more accurate parameters, significantly decreasing the size of the accumulator matrix. We estimated (h, k) to be the center of mass of the image, α to be $0°$, a to be half the distance between the leftmost and rightmost foreground pixels, and b to be half the distance between the uppermost and lowermost foreground pixels. (The values of a and b were interchanged when $b > a$.) The lengths of these ranges were used to define the dimensions of the accumulator matrix.

For every foreground pixel in the image, the angle α was calculated for every possible combination of a, b, h, and k, after which the corresponding accumulator cell was increased in value by 1. After all the possible ellipses of each foreground pixel were computed, the indices of the maximum accumulator cell were extracted and designated as the dimensions of the best-fit ellipse. The lengths of the major and minor axis, the area, eccentricity, and circumference of the best-fit aortic annulus ellipse were then calculated (Fig. 5). All programming and computations were performed with Matlab software, version 2012a.

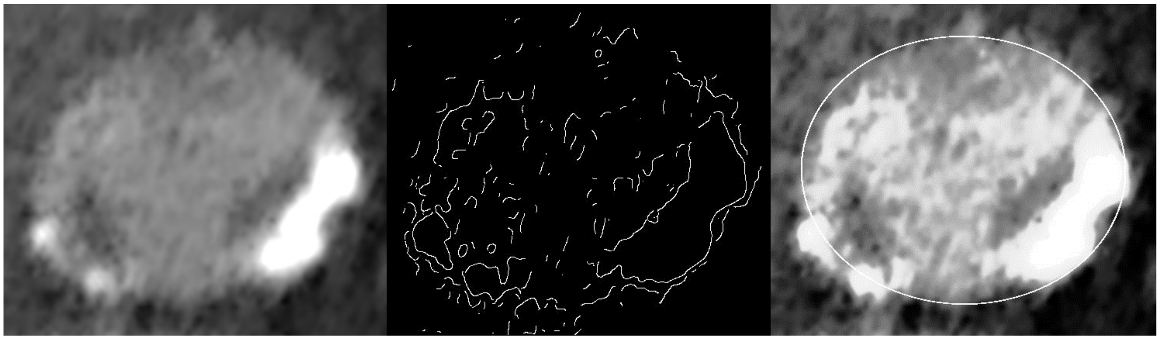

Figure 5: Stages of the algorithm. The original image is shown on the left, the binary edge image in the middle, and the best-fit ellipse overlaid over the contrast-adjusted image on the right.

2.3.3 Statistical Methods

To test the accuracy of this algorithm, the root mean square error (RMSE) values were calculated for the maximum and minimum annular diameter measurements of the automatic algorithm versus the cardiologists' manual measurements. It was not calculated for the other measurements, such as the ellipticity index, mean diameter, and area, since they were derived from the maximum and minimum annular diameter measurements. In addition, Bland-Altman plots were created to calculate the average difference between the measurements and to determine whether any points lay outside the acceptable region of error (two standard deviations from the mean difference).

2.3.4 Identification of Paravalvular Regurgitation Predictors

Once the aforementioned algorithm was derived and implemented with Matlab, the 30 patient data sets were split into those who experienced moderate or more severe post-procedural paravalvular regurgitation versus those who experienced trace or no post-procedural paravalvular regurgitation. Six independent, two-sample, one-tailed heteroscedastic Student's t-tests were employed on these data sets, comparing various clinical factors between the two groups. Five of these factors, difference in mean diameter, difference in maximum diameter, difference in minimum diameter, ellipticity index, and difference in area were measurements obtained from the automatic algorithm that accounted for mis-sizing of the prosthesis. The sixth factor, Agatston calcium score of the aortic valve, was measured by cardiologists on a Vitrea workstation. Level of significance was 0.05.

2.3.5 Multivariate Bayesian Prediction of Paravalvular Regurgitation

Using the predictor variables identified by the t-tests, we constructed a multivariate Bayesian model for predicting the presence of moderate post-procedural paravalvular regurgitation. Given a row x in an $m \times n$ matrix where each row represents a patient data set and each column represents a predictor variable, and binary classes ω_1 and ω_0 where ω_1 represents paravalvular regurgitation and ω_0 represents no paravalvular regurgitation, then the probability that patient x is of class ω_i (also known as the posterior probability) can be expressed by Bayes' theorem:

$$P(\omega_i|x) = \frac{P(x|\omega_i)P(\omega_i)}{P(x)} \tag{2}$$

In this equation, $P(x|\omega_i)$ is the likelihood, or conditional probability, of patient x being in class ω_i, and $P(\omega_i)$ is the prior probability. Since the conditional probability distribution was not sampled frequently enough to adequately approximate a continuous distribution, we used a multivariate normal probability distribution instead:

$$P(\vec{x}) = \frac{e^{-\frac{1}{2}(\vec{x}-\vec{\mu})^T \sum^{-1}(\vec{x}-\vec{\mu})}}{(2\pi)^{d/2}|\sum|^{1/2}} \tag{3}$$

where $\vec{x}$ is an n-component vector of patient parameters, $\vec{\mu}$ is the n-component vector of the means of each set of predictor variables, $\sum$ is the $n \times n$ covariance matrix, $|\sum|$ is the determinant of the covariance matrix, and $\sum^{-1}$ is the inverse of the covariance matrix. The mean vector and the covariance matrix can be expressed as follows:

$$\begin{aligned} \vec{\mu} &= \int \vec{x}P(\vec{x})\,\mathrm{d}\vec{x} \\ \sum &= \int (\vec{x}-\vec{\mu})(\vec{x}-\vec{\mu})^T P(\vec{x})\,\mathrm{d}\vec{x} \end{aligned} \tag{4}$$

The above equations can be used to calculate the posterior probabilities $P(\omega_0|x)$ and $P(\omega_1|x)$ for a patient data set x. When $P(\omega_0|x) > P(\omega_1|x)$, the patient is assigned to class ω_0, and vice versa [16].

2.3.6 Leave-One-Out Cross-Validation

The present study did not have enough data to create both a training set and an experimental set, so a leave-one-out technique was used to assess the accuracy of the model. We created an iterative program that re-trained the model 30 times, each time selecting a different point to be the experimental point, and using the other 29 as training data. In such a manner, the model was tested on all 30 patient data sets.

2.4 Discussion and Results

2.4.1 Algorithm Accuracy

The average computation time per image was 43.3 ± 7.3 seconds (Fig. 6). Mean manual measurements of the maximum and minimum annular diameter were 2.6 ± 0.2 cm and 2.1 ± 0.3 cm, respectively; and mean automatic measurements of the maximum and minimum annular diameter were 2.1 ± 0.3 cm and 1.6 ± 0.2 cm, respectively. The RMSE values for the maximum and minimum annular diameter measurements of the automatic algorithm versus the cardiologists' manual measurements were 0.415 and 0.351, respectively. In addition, the mean differences were -0.441 ± 0.415 cm and -0.441 ± 0.351 cm, indicating a relatively small degree of error in comparison with the measurements themselves. As indicated by Fig. 7 and Fig. 8, only

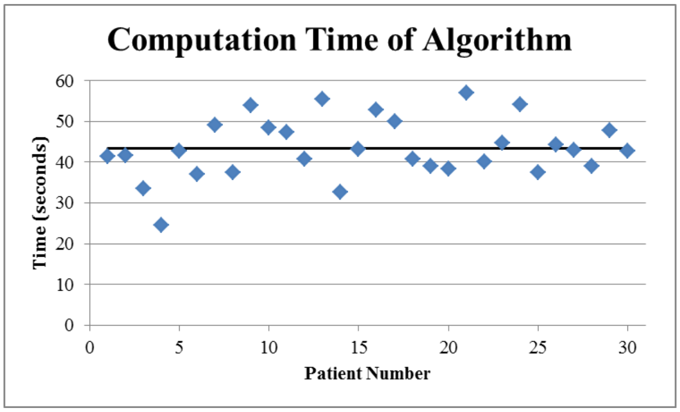

Figure 6: Computation time for 2-D aortic annulus assessment of 30 patients. The mean computation time per image, represented by the bold black line, was 42.8 seconds.

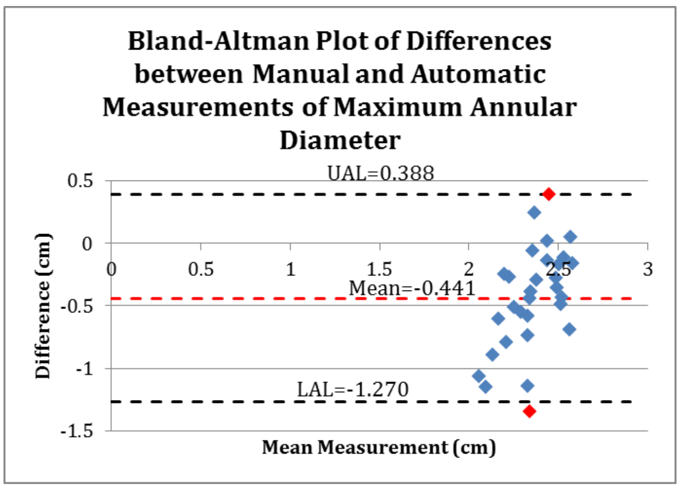

Figure 7: Bland-Altman plot of differences between manual and automatic measurements of maximum annular diameter. The mean difference, indicated by the dashed red line, is -0.441. The boundaries of the acceptable region of error, indicated by the dashed black lines, are -1.270 and 0.388. Only two points, filled in red, lie outside the acceptable region.

two points laid outside the acceptable region of error in the Bland-Altman plot for the maximum annular diameter and one point laid outside the acceptable region of error in the Bland-Altman plot for the minimum annular diameter. Therefore, the small RMSE values and scarcity of points outside the acceptable regions of error indicate that the algorithm's measurements are comparable with and statistically non-inferior to radiologists' manual measurements.

However, the algorithm demonstrates a slight tendency to underestimate aortic annular measurements, indicating a need for refinement of the fitted ellipse. For future clinical use, this can be achieved through a semi-automatic process, where the automatic algorithm performs initial detection of the best-fit ellipse, and a radiologist manually adjusts the ellipse. Although this process still requires manual intervention, it is faster than the current method and provides a reasonable starting point. Furthermore, accuracy can be improved

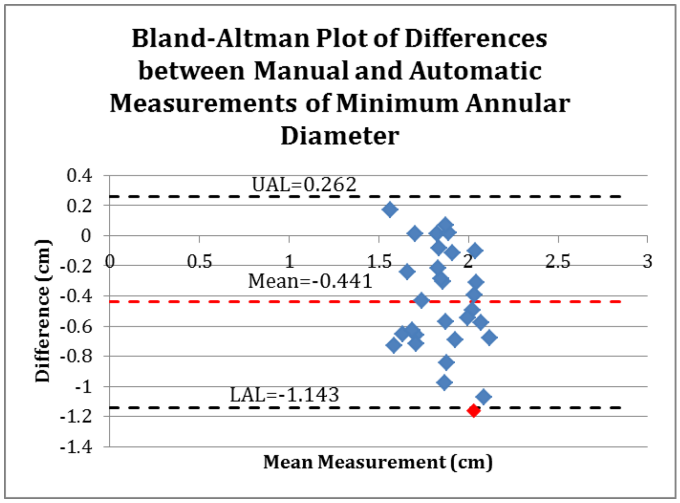

Figure 8: Bland-Altman plot of differences between manual and automatic measurements of minimum annular diameter. The mean difference, indicated by the dashed red line, is -0.441. The boundaries of the acceptable region of error, indicated by the dashed black lines, are -1.143 and 0.262. Only one point, filled in red, lies outside the acceptable region.

by decreasing the width of the accumulator bins and increasing the dimensions of the accumulator matrix, at the cost of computation time.

On the other hand, the errors in the algorithm's measurements may also be caused by physiological factors. For example, ridges of calcium can obstruct the edges of the aortic annulus in a CT image. A human eye would take note of this hindrance and attempt to extrapolate the line past the calcium, but a computer program might be fooled into detecting the edges of the calcium as the edges of the aortic annulus. In such a case, the error could be minimized by morphologically closing the edge image prior to applying the ellipse detection, thereby extrapolating missing edges in the gaps between existing edges.

2.4.2 Predictors of Paravalvular Regurgitation

The results of the t-tests conducted on difference in mean diameter, difference in maximum diameter, difference in minimum diameter, ellipticity index, difference in area, and Agatston calcium score of patients with moderate/severe paravalvular aortic regurgitation versus patients with no paravalvular aortic regurgitation, are shown in Table 1. Except for ellipticity index, all the clinical factors listed in Table 1 were significantly different in the group of patients who experienced moderate post-procedural paravalvular regurgitation versus those who experienced trace or no paravalvular regurgitation. This indicates that the first five factors may be effective predictors of post-TAVR paravalvular regurgitation.

The significant difference in Agatston calcium score between the two patient groups may be explained by the mechanical burden of calcification on the aortic valve. Accumulated calcium can obstruct stent expansion and create paravalvular gaps, allowing blood to flow past the valve even when it is closed. These results are consistent with those of Colli *et al.*, a study that found a significant association of transcatheter aortic

Clinical Factor	T-Test P-value
Agatston Calcium Score of Aortic Valve	0.041
Difference in Mean Diameter - Annulus vs. Prosthesis	0.008
Difference in Maximum Diameter - Annulus vs. Prosthesis	0.038
Difference in Minimum Diameter - Annulus vs. Prosthesis	0.010
Difference in Area - Annulus vs. Prosthesis	0.025
Ellipticity Index	0.394

Table 1: Results of the Student's t-test comparing various clinical factors between TAVR patients who experienced moderate or more severe post-procedural paravalvular regurgitation versus those who experienced trace or no post-procedural paravalvular regurgitation.

valve implantation echocardiographic calcification score with the presence of moderate paravalvular aortic regurgitation. In addition, that study used logistic regression analysis to screen patients undergoing TAVR [17]. Given that Colli *et al.*'s study was much larger than the present study (103 patients as opposed to 30), the results of this study are demonstrated to be reproducible.

Similar to the effects of calcification, an undersized prosthesis may increase transvalvular gradient and risk for post-procedural paravalvular regurgitation due to the lack of surgical sutures and possibility of paravalvular gaps. In contrast, ellipticity index does not exhibit a significant difference between the two groups, perhaps due to the tendency of the aortic annulus to mold to the shape of the new valve. In a study conducted by Willson *et al.*, manually-obtained 3-dimensional aortic annular measurements such as mean diameter, area, circumference, and eccentricity were analyzed in relation to the presence of post-procedural paravalvular aortic regurgitation. The results, which indicated that mean diameter, area, and circumference were predictive of paravalvular regurgitation but eccentricity was not, confirmed those of the present study [18]. Therefore, the support of results from other studies not only demonstrates the reproducibility of this study's results, but also highlights the significant predictive capacities of the identified predictor variables.

It is important to note here that the other aforementioned studies compared manual measurements, whereas the present study compared automatic measurements. Despite this difference in data collection methodology, the results indicated similar trends. This consistency is important because prior to this study, 2-dimensional measurements of the aortic annulus were always obtained manually by radiologists, a process that was both time-consuming and prone to intra-observer variability. Hence, our research reflects a significant improvement in efficiency that will allow cardiologists to screen TAVR candidates much faster without sacrificing accuracy.

2.4.3 Accuracy of Multivariate Bayesian Model

Of the five previously-identified predictor variables, Agatston calcium score of the aortic valve, and differences in maximum diameter, minimum diameter, and area of the aortic annulus from the corresponding measurements of the prosthesis, were compiled into a 30×4 matrix and used as the input for the model.

The fifth predictor, difference in mean diameter, was excluded from the model due to the fact that it was derived from the maximum and minimum diameters. As such, it would not increase the predictive power of the model. The leave-one-out cross-validation procedure revealed that the model was 70% accurate, correctly predicting the presence or non-presence of moderate post-procedural paravalvular aortic regurgitation in 21 out of 30 patients. In 77.8% (7 out of 9) of the cases where outcome was incorrectly predicted, the model predicted non-presence rather than presence of paravalvular regurgitation. This tendency to underestimate risk may perhaps be corrected by training with a larger sample size. In addition, using a larger sample size may provide enough information to approximate a custom-fitted probability distribution function, eliminating the need to force-fit the data to a multivariate normal distribution.

2.5 Conclusion

The present study proposes an automatic method of assessing the 2-dimensional characteristics of the aortic annulus for use in predicting risk of developing post-TAVR paravalvular aortic regurgitation. We show that the proposed algorithm is statistically comparable to manual assessment by a radiologist and can be used to facilitate screening of TAVR candidates. In addition, Agatston calcium score of the aortic valve, difference in maximum diameter of the aortic annulus and prosthesis, difference in mean diameter of the aortic annulus and prosthesis, difference in minimum diameter of the aortic annulus and prosthesis, and difference in area of the aortic annulus and prosthesis were identified to be significant predictors of post-TAVR paravalvular aortic regurgitation.

Despite these promising results, we must acknowledge the limitations of the data. The present study's data set was small, suggesting the possibility that certain statistically significant p-values were purely the result of chance. Although both biological explanations and other researchers' studies support these results, further studies comparing automatic measurements (rather than manual measurements, as with most studies) between different classes of TAVR outcomes must be conducted to further confirm this conclusion.

Moreover, the name "predictor variables" is not inappropriate. The model parameters we have identified here serve only as inputs of a predictive model and do not, by any means, elucidate the exact biological cause of paravalvular aortic regurgitation. Although cardiologists have presented some hypotheses, a few of which were mentioned in the previous section, no definite cause has been identified. Realistically speaking, this complication is likely caused by a combination of various clinical factors, rather than a single agent. Therefore, the present study cannot conclude that the identified predictor variables are causing the observed phenomenon, but future experimental studies for determining the biological progenitors of paravalvular regurgitation may provide greater insight into the matter.

The other major limitation of the data is the inconsistency of data collection methodology. (The Agatston calcium score was obtained semi-automatically, whereas the rest of the measurements were obtained automatically.) In order for this model to be useful in a clinical setting, measurements should be obtained in a consistent and efficient manner; therefore, another study worthy of pursuit would entail the extension of the automatic algorithm such that it can automatically select the double oblique transverse plane of the aortic annulus and calculate the Agatston calcium score for the region bound by the best-fit ellipse.

Given more time and data, the author of the present study would enhance the proposed outcome prediction model such that it predicts not only the presence of post-TAVR paravalvular aortic regurgitation, but also the probabilities of developing other complications, including bleeding, stroke, and death. Similar to the STS model, this model would account for pre-existing conditions, such as past cardiovascular surgery or respiratory ailments. In addition, the model's output would be a Boolean value indicating a patient's suitability for undergoing TAVR.

Despite the aforementioned limitations, our multivariate Bayesian model predicts post-TAVR incidence of moderate paravalvular aortic regurgitation with 70% accuracy and provides an easily-interpreted output value. This emphasizes its potential for aiding clinicians in assessing patient risk and recommending patients to the appropriate procedure. In light of the fact that 50% of medically treated AS patients die within two years of onset of symptoms and as many as 30% of these patients cannot undergo surgery [19], TAVR is a life-saving procedure that has the potential to positively impact many patients' lives. Since TAVR cannot be conducted safely without prior assessment of risk, such a risk-stratification model is crucial towards successful AS treatment. Much work remains to be done, but our research is the first step of many to come on the road to predicting successful outcome of transcatheter aortic-valve replacement.

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