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Ascending Aortic Length and Risk of Aortic Adverse Events

The Neglected Dimension

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ABSTRACT

BACKGROUND Little information is available regarding the longitudinal changes of the aneurysmal ascending aorta.

OBJECTIVES This study sought to outline the natural history of ascending thoracic aortic aneurysm (ATAA) based on ascending aortic length (AAL) and develop novel predictive tools to better aid risk stratification.

METHODS The ascending aortic diameters and lengths, and long-term aortic adverse events (AAEs) (rupture, dissection, and death) of 522 ATAA patients were evaluated using comprehensive statistical approaches.

RESULTS An AAL of ≥13 cm was associated with an almost 5-fold higher average yearly rate of AAEs compared with an AAL of <9 cm. Two AAL "hinge points" with a sharp increase in the estimated probability of AAEs were detected between 11.5 and 12.0 cm, and between 12.5 and 13.0 cm. The mean estimated annual aortic elongation rate was 0.18 cm/year, and aortic elongation was age dependent. Aortic diameter increased 18% due to dissection while AAL only increased by 2.7%. There was a noticeable improvement in the discrimination of the logistic regression model (area under the receiver-operating characteristic curve: 0.810) due to the introduction of aortic height index (AHI) (diameter height index + length height index). The AHIs <9.33, 9.38 to 10.81, 10.86 to 12.50, and ≥12.57 cm/m were associated with a ~4%, ~7%, ~12%, and ~18% average yearly risk of AAEs, respectively.

CONCLUSIONS An aortic elongation of 11 cm serves as a potential intervention criterion for ATAA, which is even more reliable than diameter due to its relative immunity to dissection. AHI (including both length and diameter) is more powerful than any single parameter in this study. (J Am Coll Cardiol 2019;■:■–■) © 2019 by the American College of Cardiology Foundation.

Two decades ago, we first reported the natural history of ascending thoracic aortic aneurysm (ATAA) and found a sudden increase in the risk of dissection and rupture at a critical ascending aortic diameter of 6 cm (1). On the basis of this, we recommended an aortic diameter of 5.5 cm as the threshold for pre-emptive operative repair, which became widely accepted (2,3). However, diameter alone is insufficient for precise risk stratification. An International Registry of Acute Aortic Dissections study showed that nearly 60% of patients with type A aortic dissection had a diameter <5.5 cm (4). This phenomenon is partially explained by population statistics (bell curve of aortic diameter

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ABBREVIATIONS AND ACRONYMS

AAEs = aortic adverse events

AAL = ascending aortic length

AHI = aortic height index

ATAA = ascending thoracic aortic aneurysm

AUC = area under the curve

CT = computed tomography

DHI = diameter height index

LHI = length height index

MRI = magnetic resonance imaging

distribution) (5). Our recent study revealed an earlier hinge point of 5.25 cm at which the risk of aortic adverse events (AAEs) (dissection, rupture, or death) increases significantly (6), suggesting that "leftward shift" of the surgical threshold is needed, but caution must be exercised because a slight alteration in the surgical criteria based on diameter would increase the number of surgery candidates exponentially. Therefore, it is of paramount importance to supplement diameter-based intervention criteria. Currently, the most practical, reliable, and easily accessible indicator is still aortic morphology derived from radiographic imaging, especially widely available computed tomography (CT) and magnetic resonance imaging (MRI).

The aorta as a 3-dimensional organ manifests both diameter and length. It has been noticed that the aorta elongates with aging, illustrated by prevalent tortuosity in the elderly (7). We wondered whether aortic elongation was related to or could predict AAEs. Owing to technical limitations, there has been no ideal automated tool to evaluate ascending aortic length (AAL) until recently. With the popularity of imaging reconstruction techniques, some studies have suggested that aortic elongation may be related to aortic dissection (8,9). However, the precise quantitative relationship between AAL and AAEs needs further elucidation.

Accordingly, we aim to outline the natural history of ATAA based on AAL, and develop novel predictive models to further refine the management of patients with ATAA, utilizing in-depth statistical analysis and a much larger database compared with previous reports.

METHODS

PATIENTS AND DATA COLLECTION. This study was approved by the Institutional Review Board of the Yale University School of Medicine with written informed consent waived.

As part of our ongoing investigations into the natural history of thoracic aortic aneurysm, our database at the Aortic Institute of Yale-New Haven Hospital currently includes a total of 3,861 patients with thoracic aortic disease. Exclusion criteria for this study were as follows: 1) patients with a maximal ascending aortic diameter <3.5 cm; 2) patients without available CT scans or with poor-quality scans; 3) iatrogenic or traumatic dissection, type B aortic dissection, and chronic aortic dissection; 4) patients <18 years of age; 5) patients lacking demographic data, especially height; 6) patients with congenital aortic malformations; and 7) patients with penetrating aortic ulcer or intramural hematoma. A total of 522 ATAA patients (with a total of 851 aortic diameter measurements and 645 AAL measurements) form a subset in whom available and suitable radiologic studies have been re-read and reanalyzed in a standardized manner for the purposes of this study.

We collected demographic and clinical variables retrospectively from medical charts and electronic medical records. Diameter height index (DHI) was defined as aortic diameter (cm) divided by patient height (m) (DHI = Diameter/Height).

To ascertain the precise outcomes for each patient, follow-up was achieved first via exhaustive efforts with the clinical encounter records. We further validated the information by obtaining death certificates. For living patients who did not follow up with our center, efforts were made to obtain recent medical records from their referring physicians. Aortic deaths included "definite" and "possible" aortic deaths, per the classification proposed by Lederle et al. (10). Definite aortic deaths included deaths attributed to aortic dissection or aortic rupture. Dissection and rupture were confirmed by at least 1 of the following: autopsy, operation, death certificate, or radiologic imaging. Possible aortic deaths included: 1) patients presenting with symptoms of impending rupture but without objective confirmation of rupture; 2) sudden deaths not attributable to other causes; 3) "cardiac" deaths not attributable to any specific "cardiac" cause such as coronary artery disease or heart arrhythmia (i.e., without ruling out of dissection or rupture).

IMAGING ANALYSIS. The aortic size was measured in diastole for gated CT scans. We used Visage version 7.1.12 (Visage Imaging, San Diego, California) to process the images further. The measurement of diameter consisted of 2 parts. First, we measured diameters at different planes perpendicular to the centerline from the sinotubular junction to the origin of the innominate artery. We then measured the aortic root in the coronal view. The maximal measurement was taken as the ascending aortic diameter. When measuring AAL, the aortic annulus and origin of the innominate artery were marked manually at the appropriate level and plane (**Figure 1**). The imaging system could then trace the aorta along the centerline automatically and perform curved multiplanar reformatting. The anatomic landmarks were confirmed again on the reconstructed flattened aorta. AAL was then measured as the direct distance along the centerline between the annulus and the origin of the innominate artery. All diameter measurements were doubly confirmed by the senior author (J.A.E.)

and 2 senior team members (J.W. and M.A.Z.). CT reports by the radiologists from the department of radiology at Yale-New Haven Hospital were also reviewed as a reference to ascertain that there was no obvious disagreement. Follow-up measurements were performed at the same plane and level in a standard manner. In case of any discrepancy, scans were re-evaluated in a core meeting.

STATISTICAL ANALYSIS. Details of statistical analytic methods are provided in the Online Appendix.

The maximal ATAA size was taken as the "aortic size" for all AAE calculations, whereas the first and last aortic size measurements were used for growth rate estimation. The average yearly rate of AAEs was calculated by the number of occurrences over the average duration of observations within a specified aortic size range. Growth rate estimates of AAL were calculated using the instrumental variables approach (11). Patients were divided into 4 categories of yearly risk of AAEs. The nomogram was calculated through the average of the predicted 5-year risk from the Cox proportional hazards model using "coxph" function from "survival" package in R. Kaplan-Meir survival analyses were visualized by "survminer" and "ggplot2" packages in R.

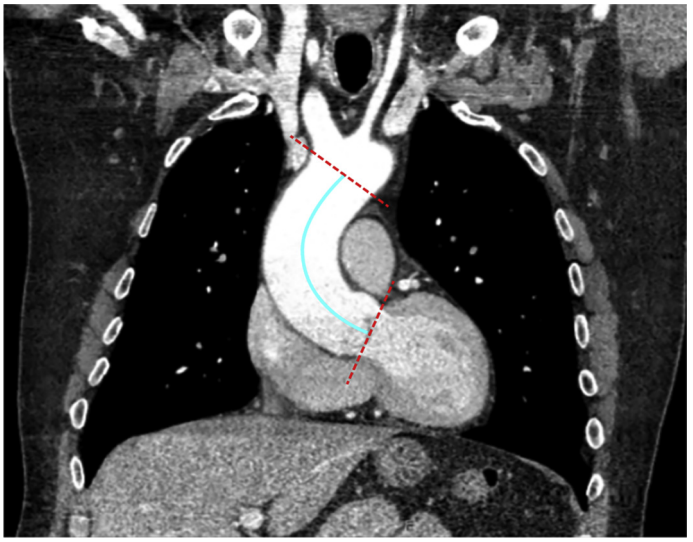
Variables showing $p < 0.05$ in the univariable regression were entered into the multivariable model. The area under the receiver-operating characteristic curve (AUC) was used to assess the discriminative performance of the logistic regression model and compared with DeLong test. AAE-free survival was estimated using Kaplan-Meier analytical method and compared with the log-rank test.

R software version 3.5.1 (R Foundation for Statistical Computing), Excel (Windows Excel 2016, Microsoft, Redmond, Washington), and GraphPad Prism version 7.00 for Windows (GraphPad Software, San Diego, California) were used for data analysis and visualization. A 2-tailed $p < 0.05$ was considered statistically significant.

RESULTS

RELATIONSHIP BETWEEN ASCENDING AORTIC LENGTH AND AAEs. The clinical characteristics of the 522 patients are shown in Table 1. The mean age was 65.8 ± 13.6 years and male sex was predominant (72.4%). Overall, the average aortic diameter was 4.8 ± 0.7 (range 3.5 to 9) cm and AAL was 11.2 ± 1.3 (range 7.3 to 15.4) cm. During a mean follow-up of 42.0 months (range, 5 days to 336 months), 424 (81.2%) patients were AAE-free and 98 (18.8%) patients developed AAEs. Specifically, 64 (12.2%) patients suffered type A aortic dissection, 5 (0.9%) patients suffered rupture, and 31 (5.9%) died of ATAA (i.e., aortic deaths). A total of 21 (4.0%) mortalities could be attributed to causes other than aortic aneurysm (i.e., nonaortic deaths), for which the detailed cause of death breakdown is provided in Online Table 1. As illustrated in Figures 2A and 2B, a significant "rightward shift" of the aortic diameter and AAL distribution was observed in the AAE group compared with the AAE-free group ($p < 0.001$).

FIGURE 1 Ascending Aortic Length



Ascending aortic length is measured as distance **(blue)** from the aortic annulus **(red)** to the origin of innominate artery **(red)**.

Based on previous work by our group (6), we indexed AAL to patient height (length height index [LHI] = AAL/height). Pearson's correlation coefficient was 0.338 between height and AAL ($p < 0.001$), which also braced the indexation. According to spline regression results, the nonlinearity was not significant ($p > 0.1$), thus proving linearity of all key variables (diameter, DHI, AAL, LHI). The average yearly rates of AAEs are presented in Figure 3. An AAL of ≥13 cm was associated with an almost 5-fold higher average yearly rate of AAEs compared with an AAL of <9 cm (Figure 3C). An LHI of ≥7.5 cm/m was associated with a >5-fold higher average yearly rate of AAEs compared with an LHI of <5.5 cm/m (Figure 3D).

As expected, absolute AAL increased gradually from 10.81 (95% confidence interval: 10.45 to 11.16) cm to 11.48 (95% confidence interval: 11.20 to 11.74) cm as age increased from <50 to ≥80 years (Figure 4). The mean estimated aortic elongation rate was 0.18 cm/year.

TABLE 1 Patient Characteristics

Age, yrs	65.8 ± 13.6
Height, m	1.74 ± 0.11
Weight, kg	76.9 ± 37.8
Male	378 (72.4)
Bicuspid	103 (19.7)
Bovine arch	91 (17.4)
MFS	14 (2.7)
Family history*	
None	238 (45.6)
Proven	113 (21.6)
Likely	19 (3.6)
Possible	41 (7.9)
Unknown	111 (21.3)
History of heart surgeries	59 (11.3)
AAA	20 (3.8)
Hypertension	181 (34.7)
Smoking	
Nonsmoker	297 (56.9)
Current smoker	107 (20.5)
Former smoker	118 (22.6)
Dyslipidemia	142 (27.2)
COPD	22 (4.2)
DM	24 (4.6)
Autoimmune disease	7 (1.3)
CAD	65 (12.5)
Stroke	13 (2.5)
CKD	
None	502 (96.2)
Stage 1	2 (0.4)
Stage 2	2 (0.4)
Stage 3	10 (1.9)
Stage 4	3 (0.6)
Stage 5	3 (0.6)
Steroid use	8 (1.5)
Active malignancy	27 (5.2)

Values are mean ± SD or n (%). *A likely family history indicated that relative(s) of a patient expired suddenly and at a young age (≤50 years for men and ≤60 years for women); there was the presence of an abnormal chest x-ray (widened mediastinum); or the death was attributed to a possible aortic or aneurysm cause by a medical professional. A possible family history indicated that relative(s) of a patient expired suddenly at any age, except those included in the "Likely" category, and there is no clear medical indication of a possible cause of death (e.g., myocardial infarction).

AAA = abdominal aortic aneurysm; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; MFS = Marfan syndrome.

Multivariable logistic regression showed that the odds of AAEs were 12.4-fold greater in patients with AAL ≥13 cm compared with AAL <9 cm ($p < 0.001$) adjusted for age, bicuspid aortic valve, family history, smoking, dyslipidemia, and chronic kidney disease. The AAE-free survival estimated by Kaplan-Meier analysis as a function of the AAL is shown in **Figure 5A**. The predicted 5- and 10-year AAE-free survival rates for patients with an AAL of <9, 9 to 9.9, 10 to 10.9, 11 to 11.9, 12 to 12.9, and ≥13 cm were 91.6%, 82.6%, 88.6%, 82.0%, 70.1%, and 63.6%, respectively ($p < 0.001$), and 91.6%, 73.4%, 77.2%, 52.4%, 70.1%, and 47.7%, respectively ($p < 0.001$). Similarly, multivariable logistic regression revealed that the adjusted odds of AAEs were 9.5-fold greater in patients with LHI ≥7.5 cm/m compared with LHI <5.5 cm ($p < 0.001$). The AAE-free survival curve stratified by LHI is shown in **Figure 5B**.

To assess the impact of dissection on aortic length, we identified 10 patients with fortuitous CT scans before type A aortic dissection from within our study cohort, with a mean time interval of 1.5 years. As shown in Online Figure 1, the diameters were 4.4 ± 0.9 cm and 5.2 ± 0.9 cm, before and after aortic dissection, respectively, with an increase of 0.8 cm (18%). The AALs were 11.1 ± 1.5 cm and 11.4 ± 1.4 cm before and after aortic dissection, respectively, with an increase of 0.3 cm (2.7%). To control for prior aortic size, time between aortic measurements, age, and sex, we used the equation proposed in our previous work (12) to recalculate the impact of aortic dissection on aortic diameter and length, with an estimated increase of 0.63 cm ($p < 0.001$) and 0.05 cm ($p = 0.727$), respectively.

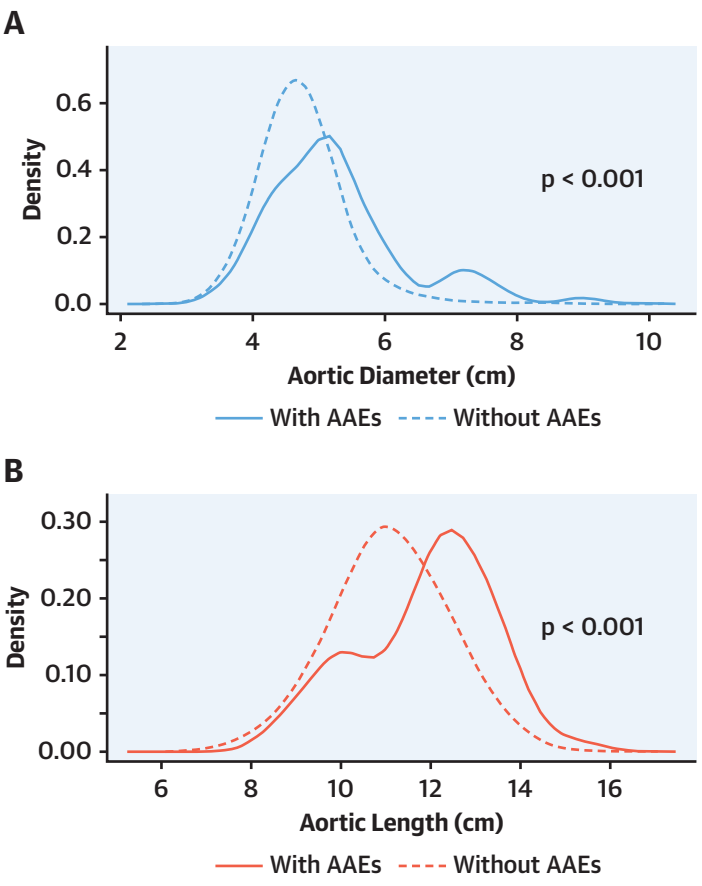
RISK STRATIFICATION BASED ON AAL. To confirm an appropriate cutoff value of the AAL for risk prediction, we divided the continuous data into smaller intervals of 0.5 cm instead of 1 cm. Two "hinge points" were observed at which a sharp increase in the estimated probability of AAEs occurred: between 11.5 to 12.0 cm and 12.5 to 13.0 cm (**Figure 6**). Remarkably, an AAL of ≥13 cm was associated with a 32-percentage-point increase in the probability of AAEs compared with an AAL of <7 cm. Accordingly, we recommend 11 cm as a conservative (not overly aggressive) intervention criterion for ATAA. Among the cohort of patients with aortic dissection, 44 had a diameter <5.5 cm. Intriguingly, among those 44 patients, 31 (70.4%) had an AAL of ≥11 cm, showing the importance of supplementing aortic diameter with aortic length for risk stratification.

Given the positive correlation between AAL and height, it may not be "fair" to classify patients of the same AAL but different height into the same risk zone. Therefore, we provide an easy-to-use risk stratification nomogram based on both the patients' AAL and height. Aortic lengths are provided on the horizontal axis and height on the vertical axis, whereas the LHI values are displayed within the cells (Online Figure 2). LHIs <6.56, 6.57 to 7.67, 7.69 to 8.93, and >8.97 cm/m were associated with a ~4%, ~7%, ~12%, and ~18% average yearly risk of AAEs, respectively.

COMPARATIVE EFFECTIVENESS OF DHI VERSUS AORTIC HEIGHT INDEX. Next, we took the arithmetic sum of DHI and LHI as a new indicator called aortic height index (AHI), for the purpose of reflecting the aortic morphology comprehensively (i.e., with respect to both diameter and length). We classified the cohort into 2 groups based on the AHI (high-AHI group: AHI ≥10 cm/m [n = 112]; low-AHI group: AHI <10 cm/m [n = 410]). There were more AAEs in the high-AHI group (35.7%, n = 40 of 112) than in the low-AHI group (14.1%, n = 58 of 410) ($p < 0.001$). We then performed a propensity score-matching analysis with 379 patients matched. After matching, there were no persisting differences in baseline characteristics between the high- and low-AHI groups (Online Figure 3). Matched samples still revealed more AAEs in the high-AHI group (35.8%, n = 38 of 106) than in the low-AHI group (17.5%, n = 48 of 273) ($p = 0.003$), lending further credence to the previous results. Spline regression proved the linearity of AHI. As is shown in Online Figure 4, yearly rates of AAEs increase along with aortic diameter in general. However, predictions and expectations do not match for moderately dilated aortas (4.5 to 5 cm), which is currently an important gray area for diameter-based guidelines. On the contrary, the yearly rates of AAEs increase with the increasing AHI without any exceptions. Also, the AAEs yearly rate for an aortic diameter of >6 cm is 3.1-fold higher than that for diameters <4 cm, while the AAEs yearly rate for an AHI of >12 cm/m is 27.8-fold higher than that for aortas <8 cm/m. This indicates that the AHI-based model has better discrimination than the diameter-based model in distinguishing the AAEs risk. This assessment is supported statistically by the AUC to evaluate the discriminative capability of the logistic model with diameter and AHI as the key variables: AUC for the diameter- and AHI-based models are 0.783 and 0.810, respectively ($p = 0.08$). In addition, AUCs for DHI-, AAL-, and LHI-based logistic models are 0.782, 0.781, and 0.783, respectively.

CONVENIENT PREDICTION TOOLS BASED ON AHI. We further calculated another nomogram combining the DHI and LHI for clinical convenience, with AHI values displayed within the cells (**Figure 7**). The AHIs <9.33, 9.38 to 10.81, 10.86 to 12.50, and ≥12.57 cm/m were associated with a ~4%, ~7%, ~12%, and ~18% average yearly risk of AAEs, respectively. An easy-to-use Excel (Microsoft Corp., Redmond, Washington) calculator is provided to facilitate all the calculations regarding DHI, LHI, and AHI (Online Figure 5). The 3-dimensional plot (**Figure 8**) allows accurate estimation of the yearly risk of AAEs based on the DHI and LHI. We can weigh the predicted yearly risk of complications for a specific patient against the anticipated elective operation mortality of the corresponding center for better clinical decision making.

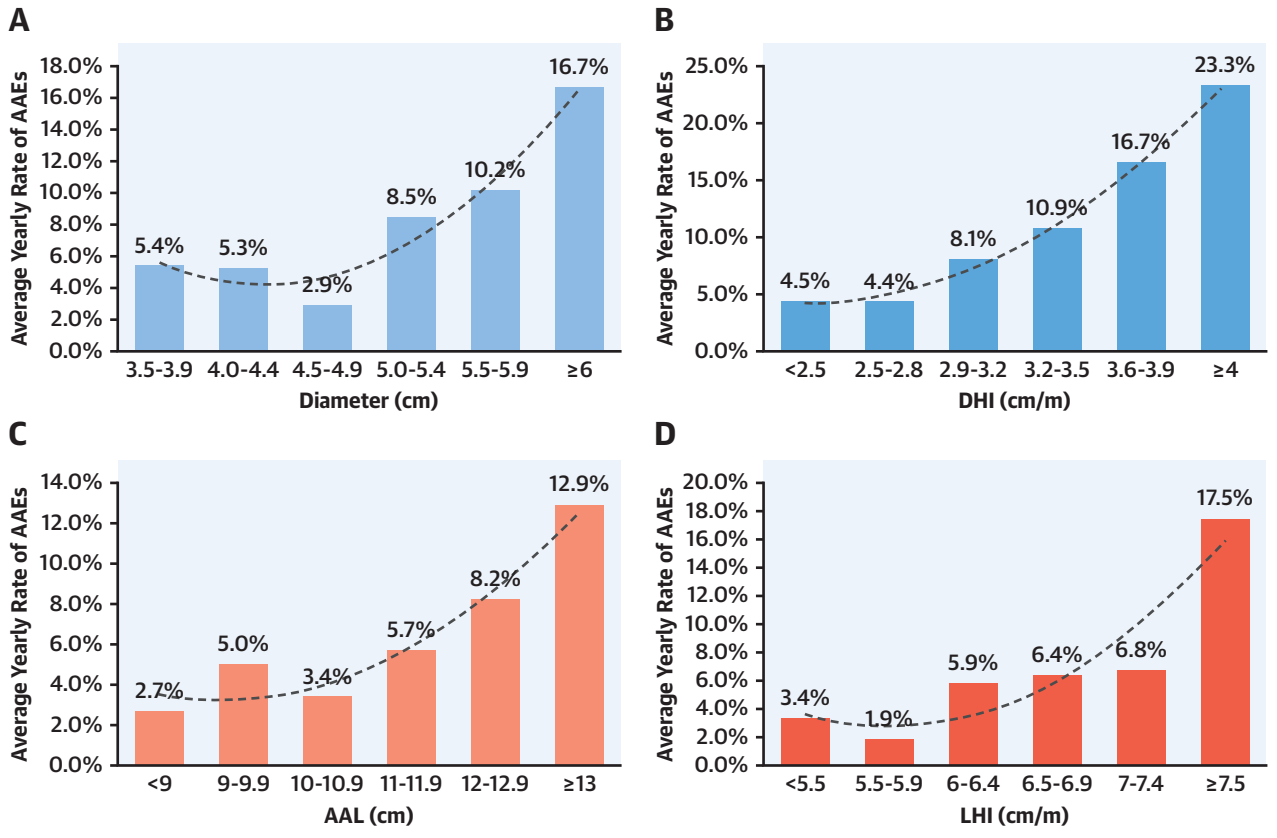
FIGURE 2 Aortic Size Distribution



Kernel density plots showing the distribution of **(A)** aortic diameter and **(B)** ascending aortic length. The peaks of a density plot help display where values are concentrated over the interval. AAEs = aortic adverse events.

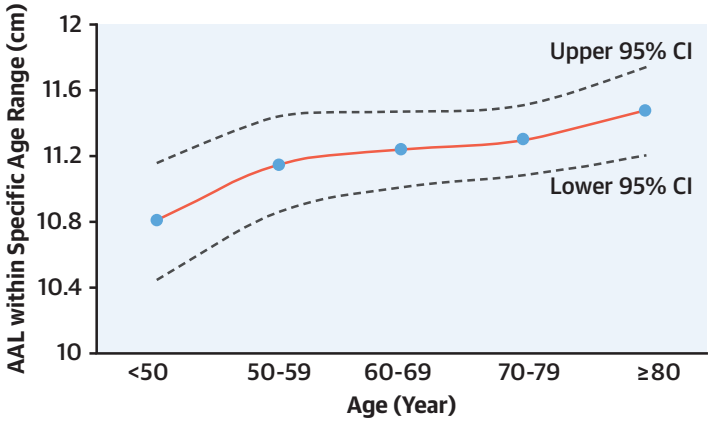
RECALCULATIONS WITH AORTIC DEATHS. Based on prior investigations of the natural history of TAA (from our group and other groups), all-cause death has been used as a reliable endpoint (6,13), and is also adopted in this study. However, to further consolidate our findings, we also recalculated the key results above with aortic deaths as an endpoint (Online Figures 6 to 8), and found that our main results and conclusions remained quite stable.

FIGURE 3 Yearly Rates of AAEs



Yearly rates of aortic adverse events (AAEs) at various **(A)** diameters, **(B)** diameter height indices (DHIs), **(C)** ascending aortic lengths (AALs), and **(D)** length height indices (LHIs). An overall upward trend is observed concerning different parameters related to aortic morphology.

FIGURE 4 Ascending Aortic Elongation

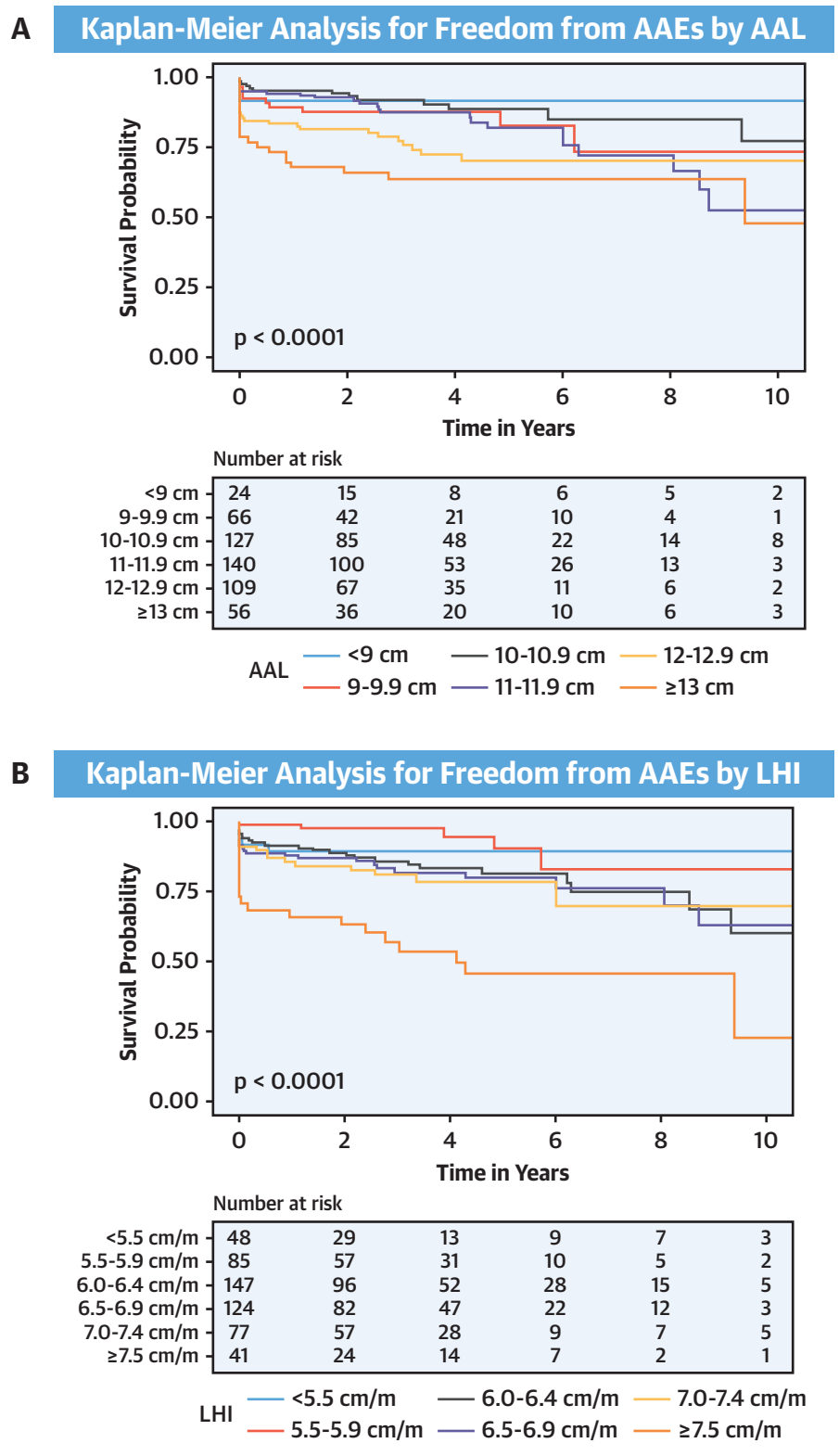


Ascending aortic elongation is age dependent. AAL = ascending aortic length; CI = confidence interval.

DISCUSSION

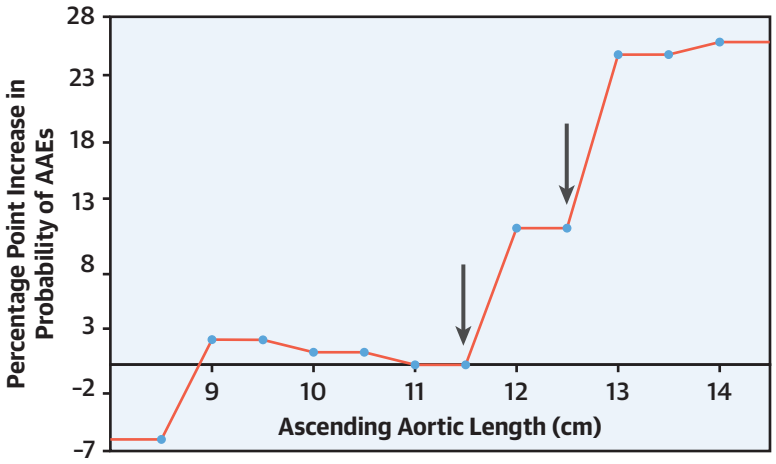
In this study, we demonstrate that aortic elongation is associated with an increased risk of AAEs, using multiple statistical approaches as cross-validations. An AAL of ≥13 cm was associated with an almost 5-fold higher average yearly rate of AAEs compared with an AAL of <9 cm (Figure 3C). Multivariable logistic regression showed that the odds of AAEs were 12.4-fold greater in patients with AAL ≥13 cm compared with patients with AAL <9 cm ($p < 0.001$). Importantly, we detected 2 AAL hinge points with a sharp increase in the estimated probability of AAEs (11.5 to 12.0 cm and 12.5 to 13.0 cm) (Figure 6). Therefore, an AAL of 11 cm may be taken as an intervention threshold for elective ATAA repair. This cutoff appears to be a valuable complement to aortic diameter. Among 44 patients with aortic dissection <5.5 cm, 31 (70.4%) had an AAL of ≥11 cm. Krüger et al. (14) reported an AAL of 9.2 cm in the normal

FIGURE 5 Survival Free From AAEs



Kaplan-Meier analysis for freedom from AAEs stratified by **(A)** AAL and **(B)** LHI. Abbreviations as in Figure 3.

FIGURE 6 Hinge Plot



Two "hinge points" **(black arrows)** were observed at which a sharp increase in the estimated probability of aortic adverse events (AAEs) occurred: 11.5 to 12.0 cm and 12.5 to 13.0 cm, respectively.

population, which is well below the 11 cm we proposed as a cutoff. They also pointed out that a value of 12 cm was exceeded in 2% of the healthy patients and in 45% of patients with type A aortic dissection (14). Their findings are consonant with our results and recommendations.

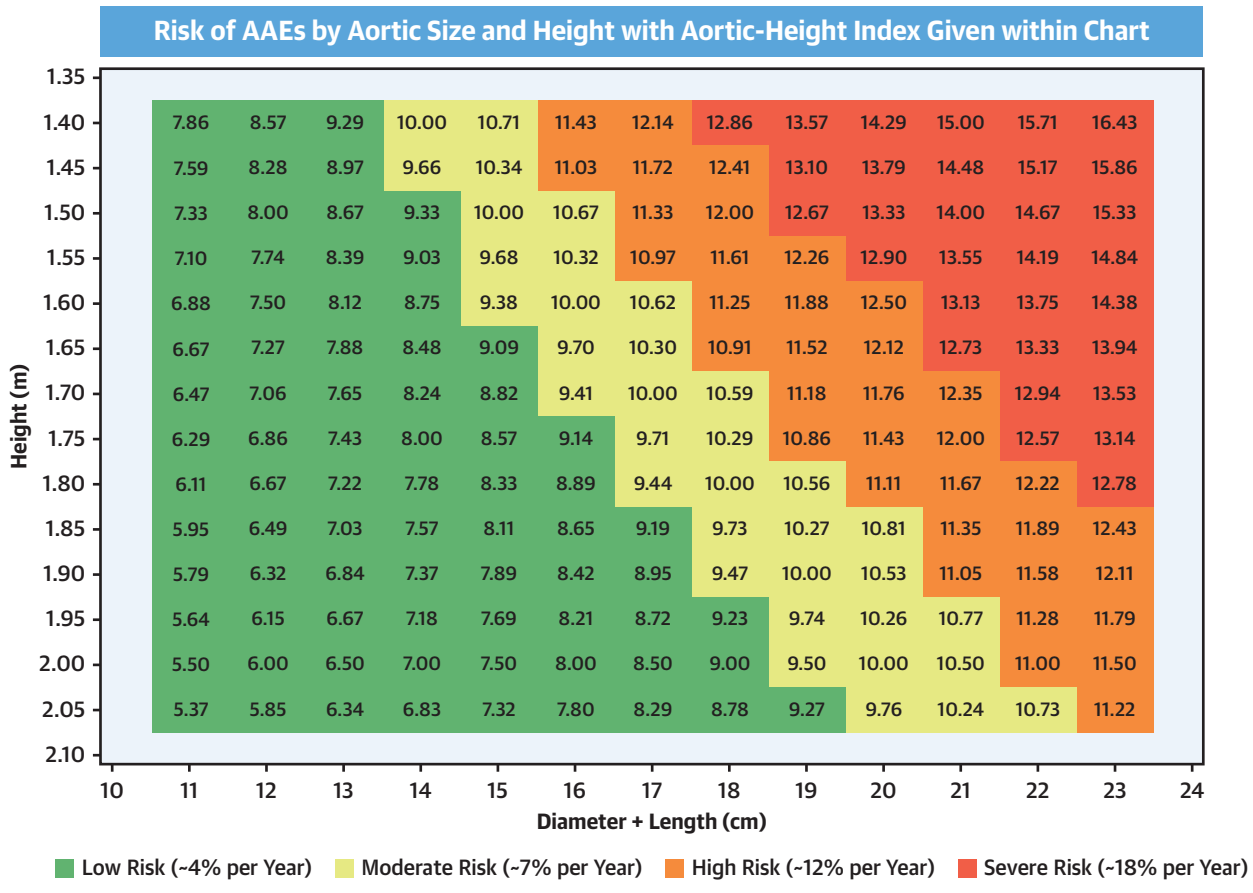
Height and aortic size are both genetically influenced, so they are highly likely to be correlated, a fact confirmed by the Pearson correlation coefficient ($r = 0.338$, $p < 0.001$). Thus, we indexed AAL to patient height and proposed the concept of the LHI, which was shown to be a good predictor of AAEs (**Figure 3D, Figure 5B**). We did not index AAL with body surface area or body mass index because weight is prone to significant fluctuation throughout adulthood, while height remains fairly constant. In addition, as aortic elongation is age dependent, it might be of value for future studies to investigate age-adjusting intervention cutoffs (7).

In view of the fact that both aortic length and diameter are embodiments of aortic morphology, we took the sum of LHI and DHI as a new parameter called AHI, hoping to better reflect aortic morphology in 2 dimensions. Surprisingly, this simple arithmetic addition resulted in a significant improvement in discrimination. Receiver-operating characteristic analysis revealed an AUC of 0.810 for the AHI-based logistic regression model (Online Figure 4C), greater than any single indicator, including diameter, DHI, AAL, and LHI. We demonstrated that no matter how good a single parameter may be, integrating multiple indicators organically can improve AAE prediction in ATAA greatly. We present a risk stratification nomogram (**Figure 7**), an excel calculator (Online Figure 5), and a 3-dimensional yearly risk estimation plot (**Figure 8**) featuring AHI, which are easy to use, with different colors indicating the risk of AAEs.

Uniquely, we measured AAL from the aortic annulus to the origin of the innominate artery (**Figure 1**), instead of from the sinotubular junction. Traditionally, the ascending aorta is defined as the portion between the sinotubular junction and the origin of the innominate artery. However, it is hard to discern the exact location of the sinotubular junction in patients with an aneurysm involving both the root and mid-ascending aorta, which is frequently the case. In contrast, the aortic annulus and innominate artery are easy-to-identify anatomic landmarks, permitting easy and standardized measurement.

Why is aortic elongation related to AAEs? We found that aortic elongation is age dependent (**Figure 4**), consistent with other studies (15). It has been well established that aortic aging is accompanied by elastin fiber fracture and breakdown, leading to a reduction of vessel compliance (16). Elongation itself may indicate the thinning of the aortic wall and fragmentation of elastin fibers. Sugawara et al. (15) confirmed that aortic elongation was associated with a significant increase in aortic pulse wave velocity (beta = 0.5) and brachial/aortic pulse pressure ratio (beta = 0.24), which denote an elevation in central arterial stiffness. Stiffness would lead to a reduced

FIGURE 7 AHI Nomogram

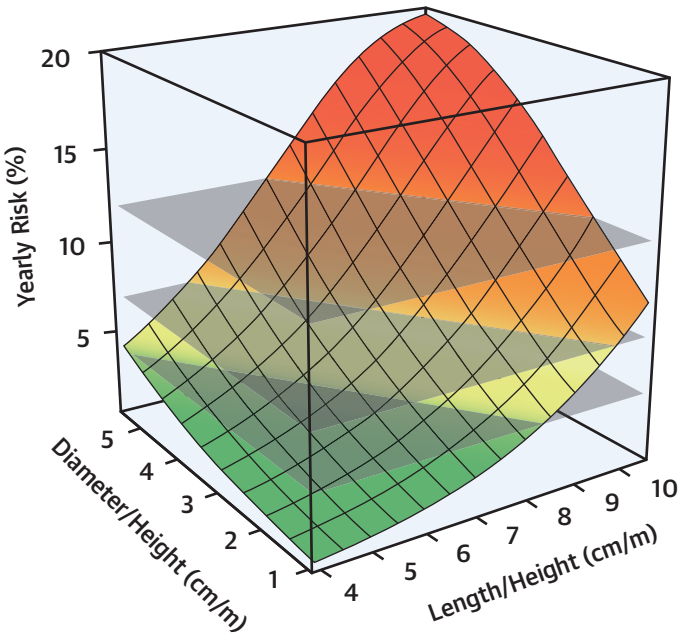


Aortic height index (AHI) nomogram as a function of aortic size (diameter + length) (x-axis) and height (y-axis), with the AHI given within cells. The table has a 4-tier, color-coded warning system, with **red** representing the most severe, followed by **orange**, **yellow**, and **green**. AAEs = aortic adverse events.

elastic recoil capacity and increase the wall stress (15). Tortuosity resulting from elongation is also likely to create an asymmetrical flow profile resulting in abnormal wall shear stress, thus predisposing the vessel to hemodynamic damage. The increased wall stress could activate mechanotransduction pathways, which have a direct effect on structure and function of cells in the aortic wall. Della Corte et al. (17) have shown a regional pattern of vascular smooth muscle cell apoptosis in the ascending aorta resulting from local mechanical stresses.

The Achilles heel of previous natural history studies is the significant and instantaneous change in aortic diameter induced by the dissection (6). Therefore, considering the measurement after dissection as the aortic size before dissection is an inevitable limitation because of the rarity of acquiring measurements pre- and post-dissection. It has been shown that aortic diameter increases by 16.9% to 31.9% when dissection occurs (12,18). We also found an 18% increase in aortic diameter after acute type A dissection. Therefore, the diameter cutoff obtained in previous studies may be overestimated, which suggests a "leftward shift" of the intervention standard. Surprisingly, the increase in AAL after dissection is only 2.7%, which is similar to another study (5.4%; $p = 0.09$) by Rylski et al. (18). Considering prior aortic size, time interval, age, and sex, the sudden increase caused by dissection per se is even closer to zero ($p > 0.05$). The relative stability of AAL to aortic dissection is beneficial for identifying an appropriate intervention threshold "uncontaminated" by the acute post-dissection enlargement. Admittedly, the pre- to-post-dissection aortic length

FIGURE 8 3-Dimensional AAE Prediction Plot



Prediction plot as a function of DHI (x-axis) and LHI (y-axis), with the yearly risk of AAEs presented on the z-axis. AHI, aortic height index; other abbreviations as in Figure 3.

sample size is only 10 cases, and needs further validation.

Although many of our investigations have focused on aortic size, we feel strongly that it is important to develop and validate nonsize parameters and criteria. Increased vessel wall stress and decreased tissue compliance were analyzed by Martin et al. (19) and were found to be risk factors for aortic complications. Positron emission tomography scanning gives useful information regarding physiological and functional aspects of the diseased aortic wall. Pioneering work has been undertaken by Nchimi et al. (20) to ascertain if positron emission tomography can differentiate between stable and unstable aneurysms. However, their work has been focused predominantly on abdominal aortic aneurysms. Three-dimensional reconstruction volume measurements have been documented as a reliable method for tracking abdominal aortic aneurysmal growth, avoiding the potential confounders of diameter measurements, such as plane angulation (21). In their recent analysis, Trinh et al. (22) suggested that thoracic aortic volume measurement may be more sensitive and reliable to detect growth than just diameter alone. In our study, we used diameter and length as our measurements. Geometrically, we have similar data to volumetry, as volume of a tube is length multiplied by cross-sectional area. It should be noted cautiously that both diameter and volume are greatly subjected to geometry change resulting from dissection, limiting their role as a reliable intervention standard. According to Rylski et al. (18), ascending aortic volume after dissection increases by 37.9% ($p < 0.001$) compared with pre-dissection volume. Yet only post-dissection images are generally available, so both diameter and volume measurements are not representative of the dimensions of the aorta just before the occurrence of dissection. Aortic length is less severely affected by the dissection itself.

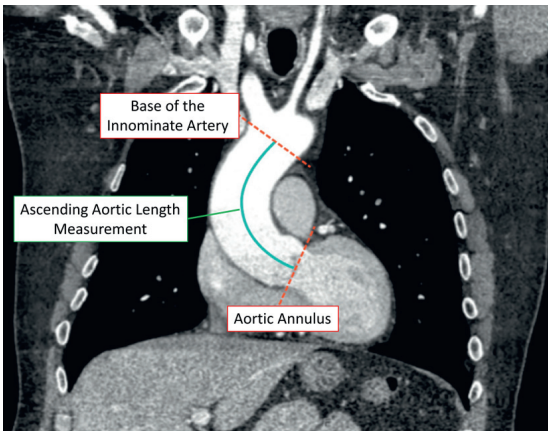
Although we used only CT and MRI as our measurement modalities in the current study, we feel that optimal imaging of the thoracic aorta should include both transthoracic echocardiography and CT or MRI scanning. These are complementary, not competitive, modalities (23). Echocardiography "sees" the aortic valve, aortic root, and lower ascending aorta ideally. However, interval CT or MRI imaging is required to visualize the upper ascending, arch, and descending aorta. Thus, the length data on which our calculations are based should be readily available as part of complete aortic imaging.

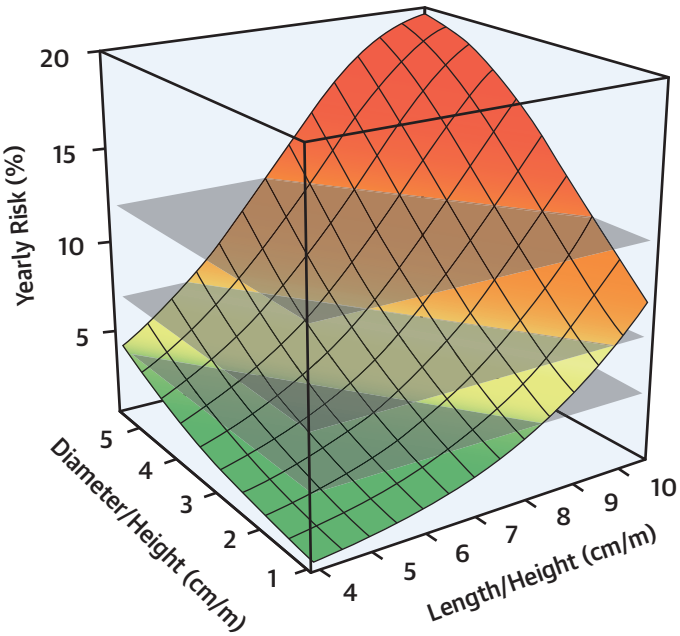
STUDY LIMITATIONS. First, the retrospective and observational nature of the investigation may bring about bias. By design, we were not able to include patients who died before hospital admission. To form a homogeneous cohort, we also excluded patients with penetrating aortic ulcer or intramural hematoma, who are at a high risk of AAEs. Also, as a tertiary aortic referral center, we likely see a "filtrate" of patients deemed too sick or complex for purely local care. Although prospective trials are advantageous, we are not aware that any prospective trial has ever been done on ATAA withholding surgical intervention until an aortic dimensional criterion is met. The catastrophic nature of thoracic aortic rupture or dissection would make such a study difficult to justify. Second, although large for this disease, the sample size could be even larger.

CONCLUSIONS

This study supports the following recommendations or conclusions: 1) an aortic elongation of 11 cm serves as a potential intervention criterion for ATAA; 2) aortic length demonstrates a mean growth rate of 0.18 cm annually; 3) aortic elongation is age dependent and relatively immune to dissection; and 4) AHI (including both length and diameter; easily discernible via modern imaging modalities) is more powerful than diameter alone in predicting AAEs, with an increased

CENTRAL ILLUSTRATION Ascending Aortic Length Can Predict Aortic Complications





Wu, J. et al. J Am Coll Cardiol. 2019;■(■):■-■.

The measurement of ascending aortic length from the aortic annulus to the origin of the innominate artery along the center line **(left)** and yearly risk of aortic adverse events based on aortic morphology (diameter and length) and height **(right)**. In the CT image **(left), red lines** demarcate landmarks at the aortic annulus and at the base of the innominate artery; the **blue line** indicates aortic length.

AUC. The easy-to-use nomogram and 3-dimensional plot provided, incorporating both aortic diameter and length, allow clinical application of this more advanced decision-making tool.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Inclusion of the length of the ascending aorta as well as its diameter (the ratio of aortic diameter + length to body height) is a more reliable indicator of the risk of AAEs than diameter alone.

TRANSLATIONAL OUTLOOK: More work is required to validate the predictive value of this morphometric index as a guide to timing therapeutic interventions in larger, heterogeneous populations with ascending aortic aneurysms and to explore the pathophysiological processes involved in aortic elongation and their relationship to clinical outcomes.

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KEY WORDS aortic adverse events, aortic aneurysm, aortic dimensions, aortic elongation, natural history, thoracic aortic aneurysm

APPENDIX For an expanded Methods section and supplemental figures and a table, please see the online version of this paper.