Is Aortic Z-score an Appropriate Index of Beneficial Drug Effect in Clinical Trials in Aortic Aneurysm Disease?

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Aortic Z-score (Z-score) is utilized in clinical trials to monitor the effect of medications on aortic dilation rate in Marfan (MFS) patients. Z-scores are reported in relation to body surface area and therefore are a function of height and weight. However, an information void exists regarding natural, non-pharmacological changes in Z-scores as children age. We had concerns that Z-score decrease attributed to "therapeutic" effects of investigational drugs for Marfan disease connective tissue diseases might simply reflect normal changes ("filling out" of body contour) as children age. This investigation studies natural changes with age in Z-score in normal and untreated MFS children, teasing out normal effects that might erroneously be attributed to drug benefit. (1) We first compared body mass index (BMI) and Z-scores (Boston Children's Hospital calculator) in 361 children with "normal" single echo exams in four age ranges (0 to 1, 5 to 7, 10 to 12, 15 to 18 years). Regression analysis revealed that aging itself decreases ascending Z-score, but not root Z-score, and that increase in BMI with aging underlies the decreased Z-scores. (2) Next, we examined Z-score findings in both "normal" and Marfan children (all pharmacologically untreated) as determined on sequential echo exams over time. Of 27 children without aortic disease with sequential echos, 19 (70%) showed a natural decrease in root Z-score and 24 (89%) showed a natural decrease in ascending Z- score, over time. Of 25 untreated MFS children with sequential echos, 12 (40%) showed a natural decrease in root Z-score and 10 (33%) showed a natural decrease in ascending Z-score. Thus, Z-score is over time affected by natural factors even in the absence of any aneurysmal pathology or medical intervention. Specifically, Z-score decreases spontaneously as a natural phenomenon as children age and with fill out their BMI. Untreated Marfan patients often showed a spontaneous decrease in Z-score. In clinical drug trials in aneurysm disease, decreasing Z-score has been interpreted as a sign of beneficial drug effect. These data put such conclusions into doubt. **(Am J Cardiol 2021;143:145−153)**

Percentiles and Z-scores provide a reproducible means to express how many standard deviations a single aortic measurement lies away from the mean respective to body surface area (BSA).[1,2] During the progression from childhood to adulthood the body experiences many changes in body size, shape, and leanness, affecting the BSA, which is an important component of aortic Z-score.[1,2] Z-score is often used to monitor aortic progression in children with Mafan disease, aiming to prevent devastating aortic pathologies[3-5] and to guide medical therapies (β-blockers and angiotensin receptor blockers [ARBs])[6,7] and timing of surgical repair.[6-12] This study aims to achieve insight into changes in the Z-score during normal childhood development in both normal children and those with Marfan syndrome. We hypothesize that the Z-score decreases naturally during advancing childhood, which may have implications on how we interpret studies which use the Z-score as an outcome measure for pharmacologic efficacy in this population.

Methods

We designed our study based on 2 main aims. (1) The first aim was to study the what happens to the aortic Z-score as a child ages. We did this by examining mean Z-scores in unrelated patients in 4 different age groups. Associated with this first goal, we examined body mass index (BMI) in these 4 age groups, suspecting to find increasing BMI as

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Table 1
Main study findings

POPULATION A				
NORMAL PATIENTS WITH SINGLE ECHO: COMPARISONS IN GROUPS OF INCREASING AGE: Age 0-1, Age 5-7, Age 10-12, Age 15-18				
Population	Number of patients	Aortic root diameter	Ascending diameter	BMI
"Normals"	361	↓ Z-score	↓ Z-score	↑

POPULATION B				
NORMAL AND MARFAN SYNDROME PATIENTS STUDIED OVER TIME (MULTIPLE ECHO EXAMS)				
Population	Number of patients	Changes over time as children aged (all with No Rx)		
		Aortic root diameter	Ascending diameter	BMI
"Normals"	27	70 % ↓ Z-score	89 % ↓ Z-score	↑
Untreated MFS	25	40% ↓ Z-score	33% ↓ Z-score	↑

MFS = Marfan disease.

Top Table. In four groups of increasing age, the mean Z-score decreases (both aortic root and ascending aorta), and the mean BMI increases. *Bottom Table.* In individual patients with multiple scans over time, for the "normal" population, the mean Z-score decreases as the child ages (both Root and Asc), and the BMI increases. For untreated MFS patients, Root mean Z-score decreases frequently, and Asc mean Z-score decreases occasionally.

Table 2
Population A patient characteristics

Age group	A (n=121)	B (n=72)	C (n=75)	D (n=93)
Mean Age (Min-Max)	77 Days (1-327)	5.8 Y (5-6.9)	11 Y (9.5-12.3)	16.3 Y (15-18)
No. of Males (%)	75 (62%)	45 (62.5%)	39 (52%)	54 (58%)
Mean BMI (Min-Max) (kg/m^2)	15.1 (7.6-26.9)	16.1 (9.1-24.6)	20.5 (14.4-37.8)	22.2 (14.9-34.2)

BMI = body-mass index; Y = years.

childhood leanness dissipates. (2) The second goal looked at changes of aortic Z-score over time in both normal children and in children with Marfan syndrome (Table 1).

All patients were identified by review of the Yale University pediatric echocardiography (echo) database; patients were included sequentially based on accessibility of exams. The echocardiograms were done using Philips IE33 (Philips Medical Systems, Andover, Massachusetts) and the GE Vivid 9 (General Electric, Milwaukee, Wisconsin) equipment. The echocardiograms were all re-read specifically for this study by a single trained investigator (SE) who was supervised by an experienced pediatric echocardiographer (CGW).

The first population referred to as Population A (Table 2) included individuals who had a single echo study between 2011 and 2015 for any of the indications listed in Table 3. Out of 513 echo studies, 152 were excluded due to suboptimal technical quality, lack of height and/or weight data, or the presence of a significant cardiac abnormality. The remaining 361 individuals, aged 1 day to 18 years, included 149 (41.2%) females. These children were further subdivided into 4 different groups based on age (A, B, C, and D) (0 to 1, 5 to 7,10 to 12, 15 to 18 years). The majority of the echos (n = 328) were reported as functionally and structurally normal. A minority had some findings that would not be expected to alter the aortic measurements, including patent foramen ovale (25 patients), small atrial septal defect (5 patients), small patent ductus arteriosus (2 patients) and small ventricular septal defect (1 patient).

Table 3
Indications for the echocardiography studies in Population A

Indication	Number of patients
Precordial Murmur	210 (58.5%)
Chest pain on exertion	58 (16%)
Syncope	39 (10.8%)
Family history of cardiomyopathy	16 (4.4%)
Abnormal electrocardiogram (EKG)	10 (2.7%)
Elevated Blood Pressure	4 (1.1%)
Follow up small atrial septal defect (ASD)	4 (1.1%)
Family history of sudden cardiac death	3 (0.8%)
Exertional dyspnea	2 (0.5%)
Family history of bicuspid aortic valve	2 (0.5%)
Other causes	13 (3.6%)

The second population, referred to as Population B, consisted of two sub-populations who had 2 sequential echo studies done at least 12 months apart between the years 2009 to 2016: Population B1 (Normals): including 27 normal (non-Marfanoid) children (16 [59%] females) aged 1 day to 20 years at the time of the initial echo study. The indications for the 54 echo studies are listed in Table 4. And, Population B2 (Marfan's disease [FS]) including 25 Marfan patients (12 [48%] females) aged 5 days to 18.5 years at the time of the initial echo study who were regularly followed in our pediatric cardiology clinic between the years 2001 to 2016. Five of these patients had 3 usable sequential echo studies, while 20 patients had only 2. Using each of the 2 sequential echocardiograms as a single observation, we reached a total of 30 observations for this population.

For the whole study, echo examinations from the Pediatric Cardiology department at our institution were reviewed and utilized. Data collected from our echocardiograms (including the actual aortic diameters, and patient height and weight) were entered into the Boston Children's

Table 4
Indications for the echocardiography studies in Population B (27 patients with 54 echo studies)

Indication	No. Of Echo studies (percentage)
Murmur	10 (18.5%)
Small ASD/PFO Follow-up	14 (26%)
S/P ASD/PFO Closure Follow-up	16 (29.5%)
Chest Pain	6 (11.2%)
Syncope	2 (3.7%)
Other indications (SOB on exertion, R/O Kawasaki, Evaluation of coronary origins, F/U PDA, Abnormal EKG, FH of Cardiomyopathy)	6 (11.2%)

ASD = atrial septal defect; FH = family history; F/U = follow-up; PFO = patent foramen ovale; R/O = rule out; SOB = shortness of breath.

Hospital Online Z-score calculator [https://zscore.chboston.org/] to generate a Z-score value for each measurement. The Boston Z-scores are based on the largest single center cohort of pediatric echocardiograms available.[13,14] The calculated Z-scores for both the ascending aorta and the aortic root where used for analysis.

For each individual, we measured the actual diameters for the ascending aorta and the aortic root. The measurements were taken according to the 2010 American Society of Echocardiography Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram.[15] Specifically, all measurements were the intraluminal dimensions taken in a parasternal long axis view during systole and perpendicular to the long axis of the vessel. The aorta was measured at 2 points—the aortic root and the ascending aorta at the level of the right pulmonary artery (Figure 1).

For the whole study, we reviewed the electronic charts of all patients in the three different populations to make sure no patient had received any of the following medications: beta blockers, ARBs, angiotensin converting enzyme inhibitors or calcium channel blockers.

Throughout the study, $p < 0.05$ was considered statistically significant.

Population A was used to analyze the *effect of age*. Linear regressions were performed to examine the correlation between Z-scores and age. The dependent variable is Z-score measured either in the ascending aorta or the aortic root. The explanatory variable is age at the time of the echocardiogram in years. We also compared the distribution of Z-scores between the 4 different age groups (A to D). Both mean difference test (*t* test) and median difference test (Wilcoxon test) were used for the comparison. Distribution plots and boxplots of Z-scores including both ascending and root Z-scores were generated for each group.

Population A was also used to analyze the *effect of BMI*. Linear regressions were performed to examine the correlation between Z-scores and BMI. The dependent variable is Z-score measured either in the ascending aorta or the aortic root. The explanatory variable is BMI.

Populations B1 and B2 were used to assess *changes in Z-score in the same individual over time*, for non-Marfan and Marfan patients, respectively. First, we looked at the percentages of observations that showed a natural decrease over time. Second, we determined if the initial and final

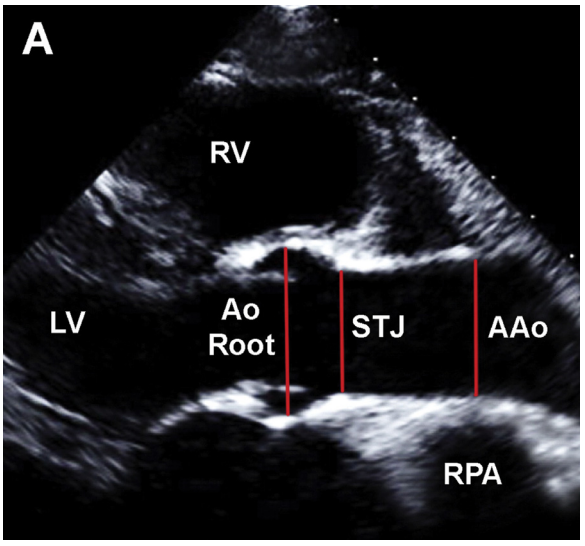


Figure 1. 2010 American Society of Echocardiography recommendations for quantification methods during the performance of a pediatric echocardiogram; all measurements were the intraluminal dimensions taken in parasternal long axis view during systole and perpendicular to the long axis of the vessel. In our study, we only measured the aortic root (Ao Root) and the ascending aorta (AAo). The ascending aorta was measured at the level of the right pulmonary artery (RPA). (Reprinted with permission from Lopez L, et al Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr. 2010;23:465-495.[15]).

Z-scores were different from each other among the normal or the non-treated Marfan patients. To release from the assumption of normality in distribution of Z-scores, the non-parametric procedure of Wilcoxon Signed rank test was performed and boxplots of Z-scores including the initial and final values were generated.

Results

Interobserver variability of echocardiographic measurements was assessed in 19 patients, showing high reliability, with the following intraclass correlation coefficients (ICC) for four aortic sites: Aortic valve annulus: ICC 0.936 (95% CI 0.833 to 0.975). Aortic root: ICC 0.963 (95% CI 0.905 to 0.986). Sinotubular junction: ICC 0.965 (95% CI 0.909 to 0.987). Ascending aorta: ICC 0.975 (95% CI 0.934 to 0.990).

Population A was used for the analysis of *the effect of age*. Linear regressions showed a significant negative correlation between age and ascending aorta Z-score ($p < 0.001$). That is to say, Z-score decreased among the groups of increasing child age. No significant correlation was found between age and aortic root Z-score (Figure 2).

Both Wilcoxon test and *t* test were performed for the 4 age groups (A to D) to test the differences in mean and median for the two groups.

For the ascending aorta, results showed that sub-group A (the youngest) had a significantly higher mean Z-score than group B ($p = 0.031$) and a significantly higher median Z-score than group B ($p = 0.019$) The tests also showed that

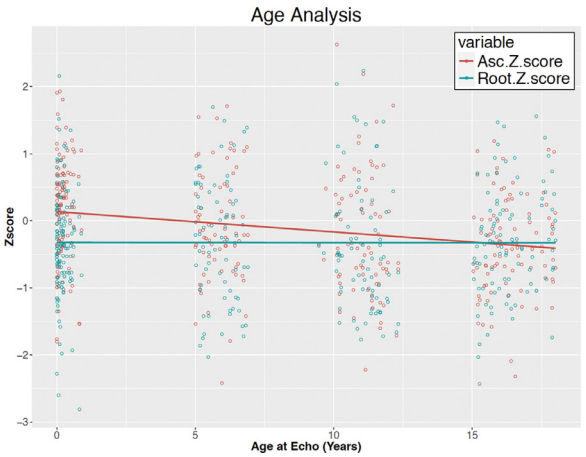


Figure 2. Linear regression analysis between the Age (X axis) and Z-score (Y axis) showing a significant negative correlation between the age and the ascending aorta Z-score ($p < 0.001$), but no significant correlation between the age and the aortic root Z-score. Population A was used for this analysis. Note that ascending aorta Z-score decreases naturally with aging in normal children. and Congenital Heart Disease Council. J Am Soc Echocardiogr. 2010;23:465-495.[15]).

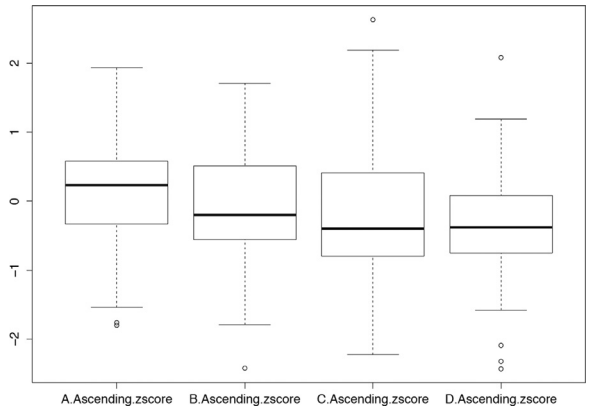


Figure 4. Boxplot of the ascending aorta Z-scores of the 4 age groups (*A*: mean age = 77 days, *B*: mean age = 5.8 years, *C*: mean age = 11 years, *D*: mean age = 16.3 years) of Population A (individuals who had a single echo study between 2011 and 2015 for any of the indications listed in Table 3). Note that ascending aorta Z-score decreases naturally with aging in normal children.

group B had a significantly higher mean Z-score than group D (the oldest) ($p = 0.013$). However, we could not reject the hypothesis that B and C groups and C and D groups are distributed identically. This pattern of ascending aortic mean and median Z-scores showing group A > B > D further confirms the decrease in ascending aorta Z-score with normal aging of children. The distribution plots and boxplot for the 4 different age groups are shown in Figures 3 and 4, respectively.

For the aortic root, results showed no significant differences between any of the 4 age groups. The distribution plots and boxplot for the 4 different age groups are shown in Figures 5 and 6, respectively.

The descriptive statistics including the mean, standard deviation, minimum, median, and maximum Z-scores of the ascending aorta and the aortic root for each age group are presented in Tables 5 and 6.

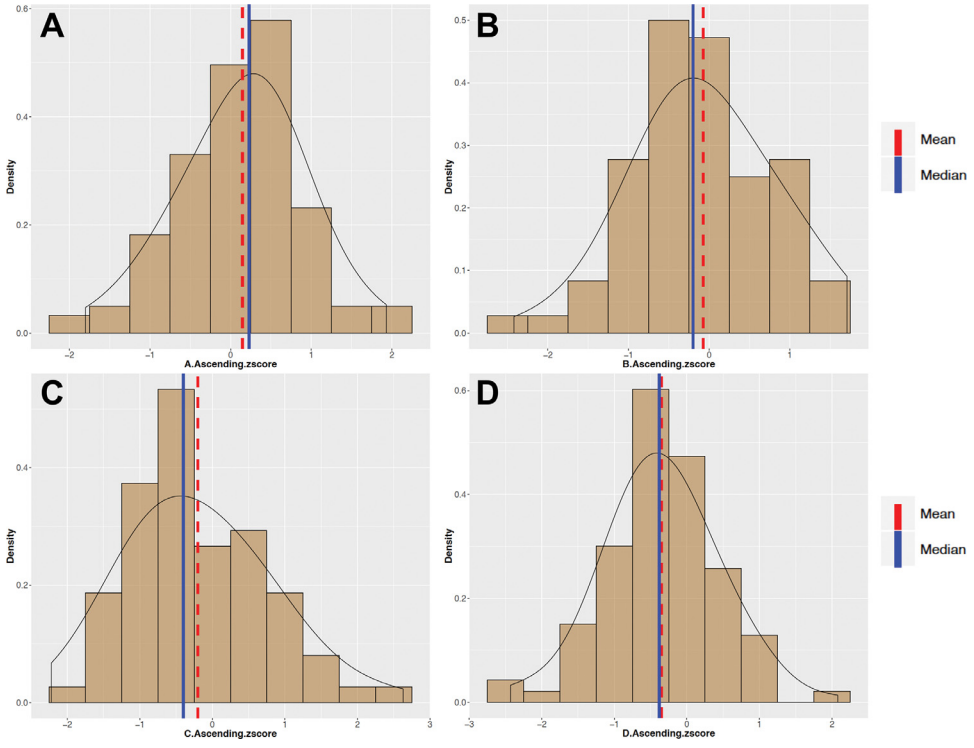


Figure 3. Distribution plots of the ascending aorta Z-scores of the 4 age groups (*A-D*) of Population A. Red lines represent the means, and blue lines represent the medians. Note that ascending aorta Z-score decreases naturally with aging in normal children.

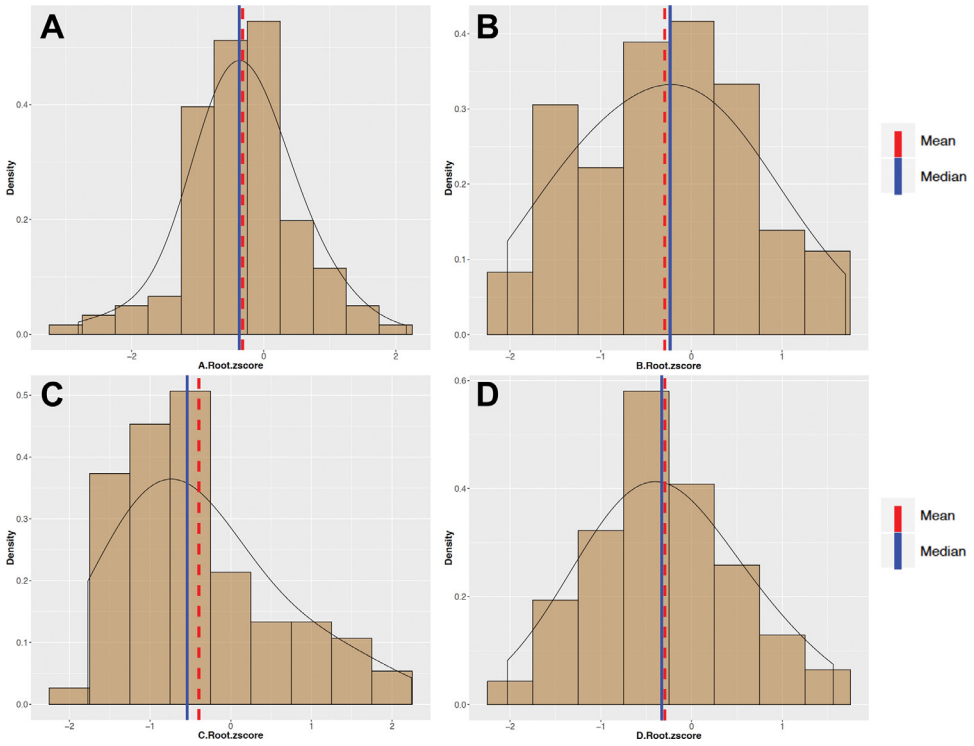


Figure 5. Distribution plots of the aortic root Z-scores of the 4 age groups (*A-D*) of Population A. Red lines represent the means, and blue lines represent the medians. Note that aortic root Z-score does not change significantly with aging in normal children.

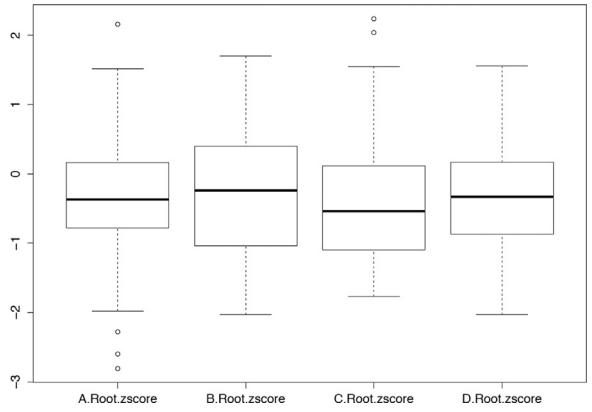


Figure 6. Boxplot of the aortic root Z-scores of the 4 age groups (*A-D*) of Population A showing no statistically significant differences between any of the median Z-scores of the 4 groups. Note that aortic root Z-score does not change significantly with aging in normal children.

Table 5
Descriptive statistics of the 4 age groups (A-D) of Population A showing the mean, standard deviation, minimum, median and maximum Z-scores for each age group both for the *ascending aorta*

Group	N	Mean	SD	MIN	Median	MAX
A.	121	0.147	0.741	-1.800	0.230	1.930
B.	72	-0.073	0.814	-2.420	-0.200	1.710
C.	75	-0.201	0.925	-2.220	-0.400	2.630
D.	93	-0.350	0.768	-2.430	-0.380	2.080

Population A was used for the analysis of the *effect of BMI variation*. Linear regression showed that BMI has a significant negative effect, in that increased BMI decreased

Table 6
Descriptive statistics of the 4 age groups (A-D) of Population A showing the mean, standard deviation, minimum, median and maximum Z-scores for each age group both for the *aortic root*

Group	N	Mean	SD	MIN	Median	MAX
A.	121	-0.320	0.798	-2.810	-0.370	2.160
B.	72	-0.295	0.907	-2.030	-0.235	1.700
C.	75	-0.394	0.953	-1.770	-0.540	2.240
D.	93	-0.295	0.786	-2.030	-0.330	1.560

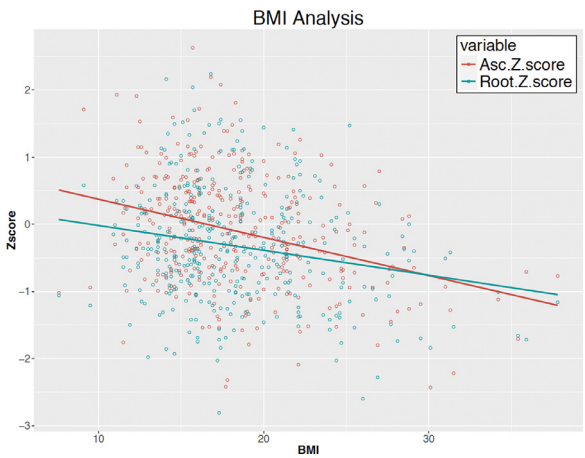


Figure 7. Linear regression analysis showing a negative correlation between the BMI and the Z- score for both the ascending aorta and the aortic root ($p < 0.001$) in normal children. Population A was used for this analysis.

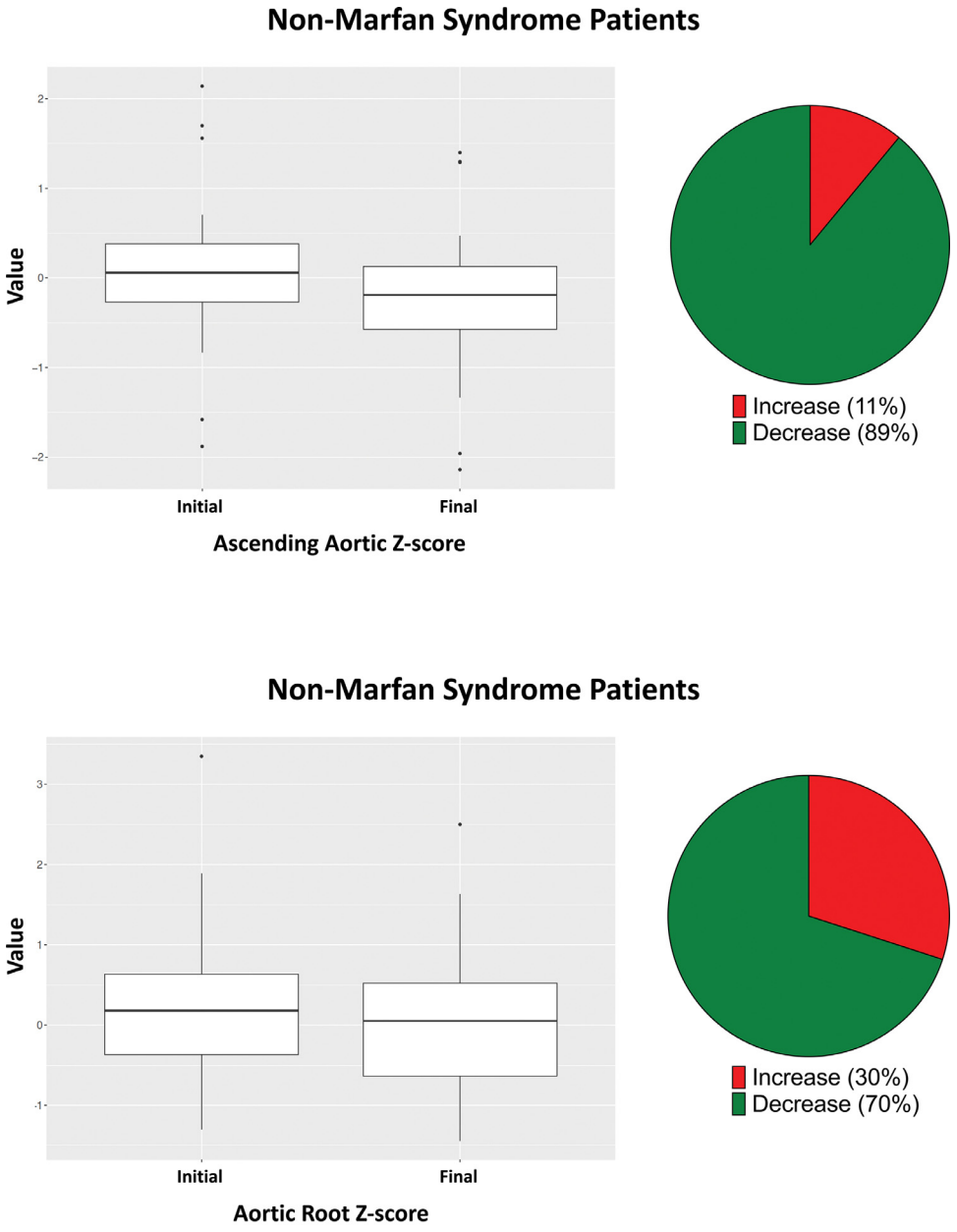


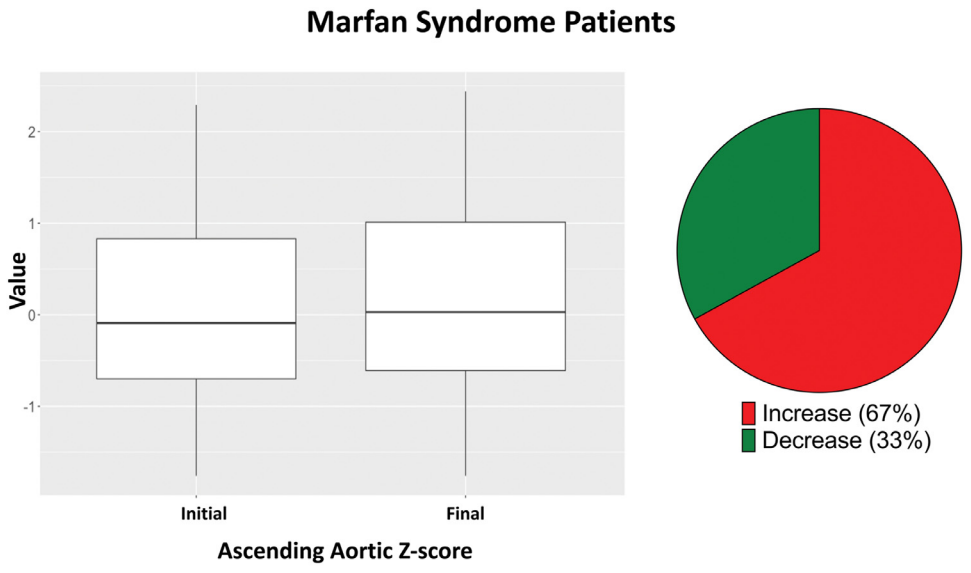
Figure 8. Changes of Z-score over time in non-treated non-Marfan individuals: (*A*) The boxplot (on the *left*) shows that the median of initial ascending aorta Z-scores is significantly greater than the median of final ascending aorta Z-scores ($p < 0.001$). The pie chart (on the *right*) shows the percentage of observations that showed a natural decrease of Z-score over time. (*B*) The boxplot (on the *left*) shows that the median of initial aortic root Z-scores is significantly greater than the median of final aortic root Z-scores ($p = 0.023$). The pie chart (on the *right*) shows the percentage of observations that showed a natural decrease of Z-score over time.

the Z-score of both the ascending aorta and the aortic root Z-score ($p < 0.001$) (Figure 7).

We now explore changes of Z-score in the same individual over time.

Normal (non-Marfan) group. Population B1 was used for *analysis of the normal (non-Marfan) group*. Over a mean follow-up period of 24.7 months (12 to 59 months), 19 out of 27 individuals (70%) showed a natural decrease of the aortic root Z-score, while 24 out of 27 individuals (89%) showed a natural decrease of the ascending aorta Z-score over time. For both the ascending aorta and the aortic root, the Wilcoxon signed rank test (with continuity correction) showed that the initial Z-scores are greater than the final Z-scores, and the results are statistically significant ($p < 0.001$). The boxplots for the initial and final Z-scores for both the ascending aorta and the aortic root are shown in Figure 8. We saw a natural decrease in Z-score over time (i.e., with aging of these children).

Population 2B was used for *analysis of the Marfan group*. Over a mean follow-up period of 27.8 months (12 to



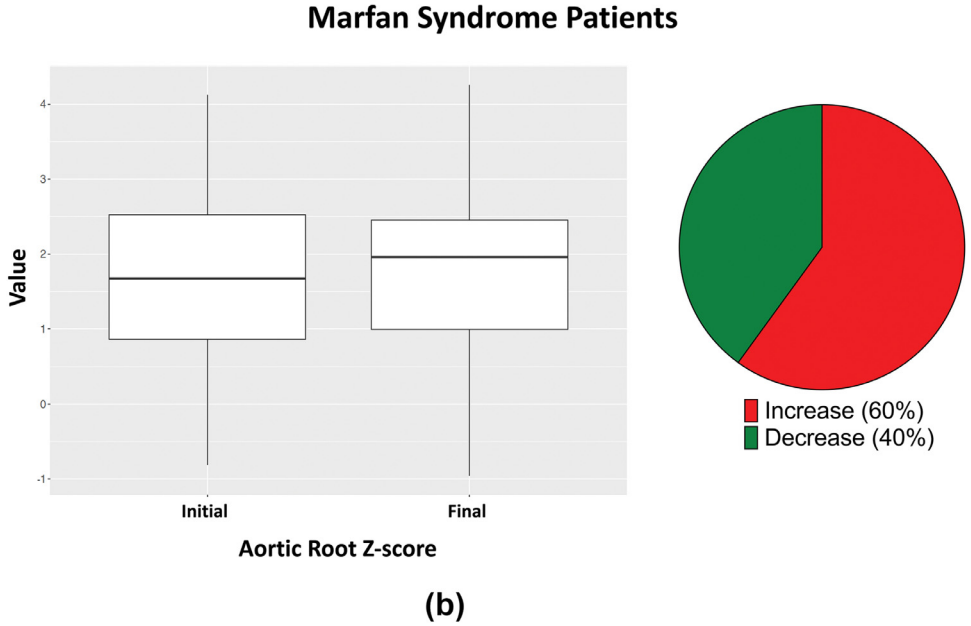


Figure 9. Changes of Z-score over time in non-treated Marfan patients: (*A*): The boxplot (on the *left*) shows that the median of initial ascending aorta Z-scores is significantly less than the median of final ascending aorta Z-scores (p = 0.013). The pie chart (on the *right*) shows the percentage of observations that showed a natural decrease of Z-score over time. (*B*): The boxplot (on the *left*) shows that the median of initial aortic root Z-scores and the median of final aortic root Z-scores are not significantly different (p = 0.249). The pie chart (on the *right*) shows the percentage of observations that showed a natural decrease of Z-score over time.

136), 12 out of 30 observations (40%) showed a decrease in the aortic root Z-score, while 10 out of 30 observations (33%) showed a decrease in the ascending aorta Z-score over time. The Wilcoxon signed rank test showed that the initial ascending aorta Z-scores are less than the final ascending aorta Z-scores, and the results are statistically significant (p= 0.013). However, there is no statistically significant evidence to show that the initial aortic root Z-scores are different from the final aortic root Z-scores (p = 0.249). The boxplots for the initial and final Z-scores for both the ascending aorta and the aortic root are shown in Figure 9.

Discussion

BSA based aortic Z-scores are commonly used to monitor aortic dilatation and to determine response to treatment in aortic diseases including Marfan Syndrome. In this paper, we show that the clinical applicability of BSA based

Z scores to determine bona fide aortic changes over time has inherent limitations.

Given that normal children do not commonly undergo echocardiograms, the groups of single echo exam patients (Population A), selected for no or minimal positive findings, represents a reasonable approximation to a "normal" population (as regards the aorta) among children receiving echo exams.

Our results show that as healthy children age, there is a significant decrease in ascending aorta Z-score values (Table 5). However, this is not true for all anatomical landmarks of the aorta, with the aortic root showing no significant change with increasing age (Table 6). Furthermore, our results show that there is a significant natural decrease in both the aortic root Z-score and ascending aorta Z-score as BMI increases ($p < 0.05$). This is entirely consistent with findings in a very recent study of the impact of BMI on aortic Z-score calculations in overweight groups.[16] The prevalence of childhood obesity (age 2-19 years) in the USA is substantial and increasing, from 13.9% in 1999 to 2000 to 17.2% in 2013 to 2014.[16,17] Height and weight both determine BMI as well BSA − the latter being the basis for aortic Z-score calculations.[18] Thus, the Z-score is extremely "BMI sensitive."

Furthermore, we have shown that both the aortic root Z-scores and ascending aorta Z-scores naturally reduce over time in sequential measures taken from physiologically normal children. More importantly, this is also the case for a substantial proportion of our Marfan Syndrome patients who were not treated with any form of medication.

Our study has limitations. It is a retrospective study. Our "normal" children had no significant lesions detected, but they were investigated for some reason.

Our findings with regards to Marfan Syndrome patients are particularly important. This is because previous studies, including the very important study by Lacro et al,[19] concluded that both atenolol and losartan decrease aortic Z-scores, warranting their use in this disease. However, this assumes that the decrease in aortic Z-score is attributable to the medication. Instead, we have found that in approximately 40% of individuals with Marfan Syndrome, the aortic Z-score naturally decreases over time. It is therefore unclear what proportion of the decrease in aortic Z-score measured by Lacro et al[19] can be attributed to the medication as opposed to a natural decrease over time associated with the aortic Z-score calculation. The conflict in results in previous meta-analyses that have investigated the efficacy of beta-blockers in Marfan Syndrome may be abetted by these natural decreases in Z-score.[20,21] In addition, to the best of our knowledge, no study has shown beta-blockers to reduce the hard end points of dissection and death. The thrust of our findings provides weight to the argument that beta-blockers and ARBs may not have efficacious properties with regards to aortic dilation and therefore aortic Z-score.

In agreement with our study, Van Kimmenade et al[22] also found that a high BMI in Marfan Syndrome is associated with a lower aortic Z-score value using two different equations. The first of these aortic Z-score equations was devised in 1989[23] when obesity was less prevalent; current calculations may be more susceptible to the effects of the current obesity epidemic. It is important to note that Van Kimmenade et al[22] also considered a third aortic Z-score equation which does not take account of weight in the formula and which therefore would avoid the artificial decrease in aortic Z-score with BMI. They, as well as Dallaire,[24] suggested that we use Z-scores which correlate with height rather than BSA and/or weight, which may be less misleading in evaluating aortic root measurements, at least in those with Marfan Syndrome. Even if children do not become frankly obese, with time they often lose the "leanness" of early childhood.

Our findings are consonant with a recent study by Braley et al, which demonstrates that an overweight condition in children can obscure significant aortic dilatation because the high BMI lowers the Z-score (and the converse may obtain as well).[16] Our study is also consonant with insights into the shortcomings of Z-scores in the pediatric age range insightfully articulated by Simpson and Chubb.[25] Echocardiographic expert Devereux et al have excluded body weight from calculations of normal aortic sizes in individuals 15 years old or greater, without loss of predictive ability.[26]

Our results highlight the complex nature of interpreting Z-scores as a diagnostic marker and a marker of disease progression or regression. Knowing this complexity, we are aware of limitations of our study that may affect the internal and external validity of our findings. The relatively small data set may limit our interpretation of these results. We had limited sequential echocardiographic images, which may introduce bias to our results. We calculated the Z-score of the aortic root and ascending aorta, however we did not assess the aortic annulus or sinotubular junction, which could have provided more anatomically inclusive information about the natural changes of Z-score values over time. Follow-up intervals for both the normal pediatric group and Marfan Syndrome group were about 25 and 28 months, respectively. Longer follow-up intervals may have enhanced and strengthened our analysis.

There are significant challenges in the generalizability of these results in light of the wide range of methods used to calculate the BSA in the current literature. In addition, there is an array of nomograms which were generated from specific populations/specific geographical locations which historical studies have utilized to calculate a Z-score. However, the majority of aortic Z-score calculators still incorporate BSA.[1]

In conclusion, the present study suggests that a decreasing aortic Z-score in clinical trials of medications should be "taken with a grain of salt," as natural forces decrease the Z-score as children age. We believe this retrospective cohort study provides evidence that Z-score analysis of the thoracic aorta is affected by other factors in the absence of aneurysmal disease or medical intervention. Our findings show that Z-score decreases spontaneously as children age and that obesity (or loss of leanness) produces a reduction in Z-score. This study suggests cautious interpretation of investigations which use Z-scores as a surrogate marker of disease progression.

Z-Score Authors' Contributions

Concept: Weismann, Elefteriades; Data Curation: Elkinany, Curtis, Smith, Zafar, Breen, Tranquilli, Rizzo,

Ziganshin; Formal Analysis: Elkinany, Weismann, Zafar, Breen, Rizzo, Elefteriades; Investigation: Elkinany, Weismann, Curtis, Smith, Zafar, Mukherjee, Elefteriades; Method: Elkinany, Weismann, Zafar, , Rizzo, Mukherjee, Ziganshin, Elefteriades; Writing Original: Elkinany, Weismann, Elefteriades; Writing Revision: Elkinany, Weismann, Curtis, Smith, Zafar, Breen, Tranquilli, Rizzo, Mukherjee, Ziganshin, Elefteriades.

Disclosures

The authors have no conflicts of interest to disclose.

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