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Original Article

Defining ascending aorta dilatation in pediatric bicuspid aortic valve: Comparison of known classical and new z-score nomograms, and anthropometric parameters indexing for its assessment

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ABSTRACT

Background: Ascending aorta (AscAo) dilatation assessment and definition in pediatric bicuspid aortic valve (BAV) is challenging. We compared the Pediatric Heart Network (PHN) nomogram against the Halifax (HZ) one and analyzed their association with body surface area indexing (BSA—I).
Methods: Echocardiographies from a national BAV registry were analyzed. AscAo and sinus of Valsalva, standardized using nomograms and BSA—I, were compared by correlation and Bland-Altman tests. Nomogram +2 and + 3 z-scores thresholds contrasted against >21 mm/BSA-m2 by logistic regression and kappa agreement index. Age subgroup analysis was between adult-size (≥10 years and BSA ≥1.5 m^2) and small children.
Results: A total 3858 reports were analyzed. The PHN nomogram resulted in higher AscAo z-scores (median 1.516 versus 1.413). Nomogram correlation was $Rho_{Spearman} = 0.979$ and Bland-Altman agreement bias was 0.302, with higher divergence in extreme z-scores. Patients ≥10 years and BSA ≥1.5 m^2 showed better concordance (bias −0.212 versus 0.440) despite similar correlation to the younger group. There was moderate but significant correlation amongst AscAo BSA-indexed diameters and PHN ($Rho_{Spearman} = 0.514$, $p < 0.001$) and HZ nomograms ($Rho_{Spearman} = 0.366$, $p < 0.001$), being higher in the older cohort than the younger, both by PHN ($Rho_{Spearmam}$ 0.961 versus 0.424) and HZ ($Rho_{Spearman}$ 0.952 versus 0.540). Higher area under the curve was obtained by PHN. A lower percentage was classified as dilated with PHN than by BSA-I in the adult-size cohort, but not in younger patients.
Discussion: There was good correlation and concordance between HZ and PHN nomograms, the latter resulting in higher z-scores. PHN has better agreement with BSA-I than HZ, with the PHN > +3 z-score threshold being the highest predictor for BSA-I dilatation definition, also showing higher specificity and sensitivity. BSA-I classified fewer patients as dilated than nomograms in adult-sized children but not in the younger cohort. Clinicians should be aware of this effect of BSA when normalizing diameters.

Introduction

Progressive ascending aorta (AscAo) dilatation, one of the complications of bicuspid aortic valve (BAV), is associated with 10–12-fold higher dissection risk in adulthood [1]. One of the main challenges in the pediatric population is distinguishing disease from normality in growing bodies. Despite nomograms being the most widely used tool, no consensus has been reached in the scientific community as to which is the best assessment approach. Compared to centiles, z-scores offer more sensitivity in detecting changes at the extremes and are easier to interpret [2,3]. On the other hand, z-scores face some limitations: heterogeneity and small sample size in the published literature [4–6], lack of consensus on which body surface area (BSA) formula to apply or which indexing variable should be used [7], such as height, as it has been theorized that lean body mass correlates better with organ size and is potentially more suitable for extreme body mass index (BMI) [8–10]. Additionally, for older children with adult-like size (≥10 years of age with BSA ≥1.5 m^2), BSA-indexing (BSA—I) has been described as a better method in previous literature [11].

This study aimed to assess the nomogram by the Pediatric Heart Network (PHN) [12] in pediatric BAV, as well as to compare with the classically used Halifax z-score (HZ), published by Warren et al. [13] and to contrast them against BSA-indexing.

Materials and methods

This was an observational study, including data from the Spanish multicenter prospective and retrospective national registry for pediatric patients with BAV [14]. Patients with aortic root or AscAo surgery and affected by concomitant connective tissue disease were excluded from the analysis.

Registered echocardiographic measurements were performed at sinus of Valsalva (SoV) and AscAo at the level of the right pulmonary artery crossing. They were measured at mid-systole and inner edge-to-inner edge as per pediatric echocardiographic guidelines [15].

For standardization, these results were entered into the published HZ and PHN equation and indexed by Haycock-formula derived BSA (dividing diameters by BSA). The PHN z-score regression equation was derived from a 3215 subjects sample, aged ≤18 years, including a varied ethnicity although there were fewer numbers in some African-American groups (girls age < 1 month, 3–6 years, and 16–18 years, boys age < 1 month), and other girls age 16–18 years due to the retrospective nature of the study. The measurements were done on DICOM by only two Core Lab observers [12]. On the other hand, the HZ nomogram was built both from retrospective and prospective data, included 317 subjects aged ≤18 years, and the measurements were done with a tape. The BSA used at PHN was obtained calculating the Haycock formula [BSA (m^2) 0.024265 x height (cm) 0.3964 x weight (kg) 0.5378] [12], whereas Warren et al. used Boyd [BSA (m^2) = weight (kg) 0.4838 × height (cm) 0.3 × 0.017827] [13].

Data were reported as median and interquartile range (IQR) for continuous variables and as proportion (%) for categorical variables. Age was calculated as a truncated value. Normality distribution was previously examined by Saphiro-Wilk test. Leven test was used for equality of variances. Chi-squared test was used for proportions and qualitative variable comparison and Student T or Wilcoxon tests for quantitative data accordingly. Nomograms were compared against themselves and with BSA-indexed values. Correlation (strength of association between variables) was analyzed using Spearman coefficient. Concordance (assumes that variables measure the same construct) was studied with Bland-Altman plots analysis. Agreement for ordinal and nominal variables was calculated with the Cohen's kappa index (classification: mild: 0.2–0.4; moderate: 0.41–0.6; substantial: 0.61–0.8, and almost perfect: >0.8) [16,17]. The dilatation definition of AscAo or SoV >21 mm/m2 was contrasted against two pre-settled thresholds of z-scores >2 and > 3 with chi-square, logistic regression, and kappa index. Confidence intervals (CI) were two-sided and set at 95 %. Two-tailed p-value <0.05 was considered statistically significant.

All data registered were anonymized and ethical committee approval allowed a waiver for consent forms. The research was performed in line with the Declaration of Helsinki.

Results

Demographics

A total of 4013 echocardiography scans were included, after elimination due to incomplete data, 3858 scans were eventually analyzed, corresponding to 1649 patients. Males represented 69.10 % of the sample.

Median (IQR) age at time of the examination was 9 (4–13) years, height was 132 (105–145) cm, and weight 29 (17–48) kg.

Males had statistically significant higher z-scores at AscAo and SoV regardless of the nomogram used and lower BSA-indexed diameters (Online Fig. 1).

The PHN and HZ nomograms comparison

Correlation

There was statistically significant high correlation between HZ and PHN at AscAo (rho = 0.979, $p < 0.001$) and at SoV (rho = 0.980; $p < 0.001$), although with significantly higher z-scores using PHN, both at AscAo [median (IQR) PHN 1.52 (0.16; 3.09) versus HZ 1.41 (0.03;2.85), $p < 0.001$] and SoV [median (IQR) PHN 0.25 (−0.84; 1.47) versus HZ 0.25 (−0.67; 1.25), $p < 0.001$].

Concordance

The Bland-Altman concordance analysis between the two nomograms at AscAo resulted in a bias of 0.302 (upper limit of agreement of 1.354, lower −0.750), while at SoV the bias estimate was 0.122 (upper agreement limit of −0.848, lower 1.091). A trend towards higher divergences was observed at the extremes, particularly in the more positive z-scores (Fig. 1).

Modifiers

Differences between AscAo nomograms correlated negatively with age ($r = -0.040$; $p < 0.001$) and BSA ($r = -0.431$, $p < 0.00$) but not at SoV (age $r = -004$; $p = 0.110$; BSA $r = -0.004$; $p = 0.066$). Gender did not modify the nomogram differences, either at AscAo (0.007, $p = 0.518$) or at SoV (−0.001, $p = 0.853$).

Comparison of nomograms and body surface area indexed measurements

BSA-indexed values correlated better with PHN than HZ both at AscAo (PHN vs BSA-I Spearman rho = 0.514; $p < 0.001$; HZ vs BSA-I Spearman rho = 0.366; $p < 0.001$) and at SoV (PHN vs BSA-I Spearman rho = 0.481; $p < 0.001$; HZ vs BSA-I Spearman rho = 0.356; $p < 0.001$).

Comparison of +2 and + 3 z-score thresholds against >21 mm/m2 indexed diameters showed that the odds ratio (OR) of diameters being classified in the same category by BSA-I and a nomogram was higher when using PHN than HZ, regardless of which z-score threshold was used.

Of the patients classified as dilated by the BSA-indexing method, the PHN nomogram classified a lower percentage as dilated, both by z-score > +2 and > + 3 and equally at AscAo and at SoV (Table 1).

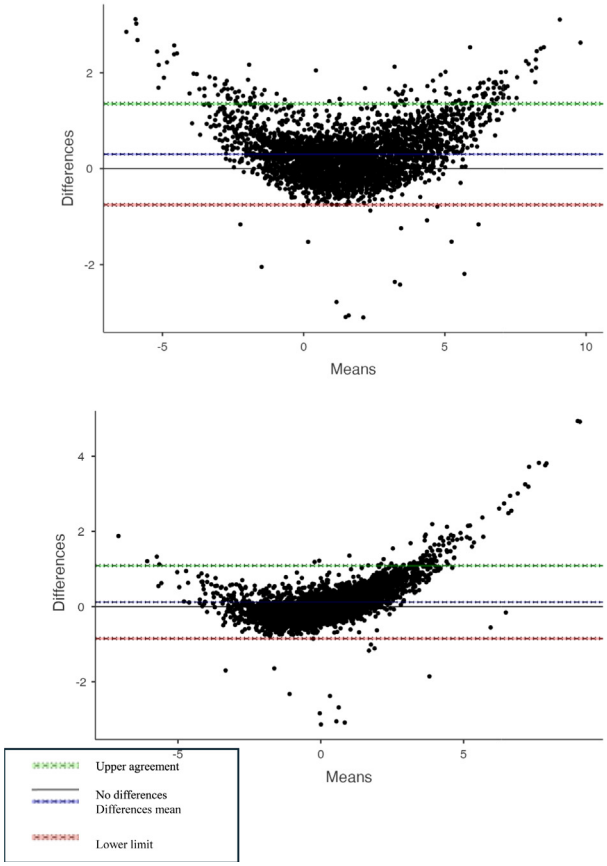
PHN nomogram resulted in a higher agreement index with BSA-I than HZ (Table 2), also obtaining a larger area under the receiving operating curve than HZ when contrasted against BSA-indexing of >21 mm/m2, with higher sensitivity and specificity (Fig. 2).

Study on age groups

Patients were divided according to age and BSA criteria as stated by Siurana et al. [18]. There were 755 investigations from the older group (≥ 10 years old and ≥1.5 m^2 of BSA) and 3029 in the younger population. Data from a total 74 patients were discarded at this stage due to missing BSA or age information.

Nomograms comparison

At AscAo, the older group showed a correlation between PHN and HZ nomograms of $Rho_{Spearman} = 0.996$ ($p < 0.001$). PHN median and



Ascending aorta PHN vs HZ

		95% Confidence Interval	
	Estimate	Lower	Upper
Bias	0.302	0.284	0.319
Lower limit of agreement	-0.750	-0.780	-0.720
Upper limit of agreement	1.354	1.324	1.383
	PHN		Halifax
Variance	4.46		4.71

Sinus of Valsalva PHN vs HZ

		95% Confidence Interval	
	Estimate	Lower	Upper
Bias	0.122	0.105	0.138
Lower limit of agreement	-0.848	-0.876	-0.821
Upper limit of agreement	1.091	1.064	1.119
	PHN		Halifax
Variance	3.36		2.34

HZ= Halifax z-score; PHN=Pediatric Heart Network z-score

Fig. 1. Bland Altman analysis. Concordance study between Halifax and Lopez nomograms.

Table 1
Study of nomograms thresholds and BSA-indexed dilatation definition.

Nomograms thresholds		Diameter AoAsc indexed by BSA		OR [CI95%] (same classification by both methods)	Proportion difference of non-classified by z-score and yes by BSA-I (chi square)
		</=21 mm/m^2	>21 mm/m^2		
AscAo HZ z-score > 2	z-score ≤ 2	1386 (62.7)	825(37.3)	2.86 (2.49–3.29, $p < 0.001$)	$P < 0.001$
	z-score > 2	520 (37.0)	886 (63.0)		
AscAo PHN z-score > 2	z-score ≤ 2	1446 (67.3)	701 (32.7)	4.53 (3.93–5.23, p < 0.001)	
	z-score > 2	460 (31.3)	1010 (68.7)		
AscAo_HZ z-score > 3	z-score ≤ 3	184 (60.1)	1117 (39.9)	4.00 (3.45–4.76, p < 0.001)	P < 0.001
	z-score > 3	222 (27.2)	594 (72.8)		
AscAo PHN z-score > 3	z-score ≤ 3	1702 (63.5))	978 (36.5)	6.25 (5.26–7.69, p < 0.001)	
	z-score > 3	204 (21.8)	733 (78.2)		
Nomograms thresholds		Diameter SoV indexed by BSA		OR [CI95%] (same classification by both methods)	Proportion difference of non-classified by z-score and yes by BSA-I (Chi square)
		</=21 mm/m^2	>21 mm/m^2		
SoV_HZ z-score > 2	z-score ≤ 2	1722 (53.8)	1478 (46.2)	4.43 (3.48–5.70, p < 0.001)	P < 0.001
	z-score > 2	86 (20.8)	327 (79.2)		
SoV_PHN z-score > 2_	z-score ≤ 2	1698 (57.0)	1283 (43.0)	6.28 (5.07–7.84, p < 0.001)	
	z-score > 2	110 (17.4)	522 (82.6)		
SoV_HZ z-score > 3	z-score ≤ 3	1798 (51.3)	1704 (48.7)	10.66 (5.83–21.85, p < 0.001)	
	z-score > 3	10 (9.0)	101 (91.0)		P < 0.001
SoV_PHN z-score > 3	z-score ≤ 3	1785 (53.3)	1563 (46.7)	12.02 (7.97–19.03, p < 0.001)	
	z-score > 3	23 (8.7)	242 (91.3)		

Number of patients in each category, Absolute number and (%).
AscAo, ascending aorta; BSA-I, body surface area indexing; HZ, Halifax z-score; OR, odds ratio; PHN, Pediatric Heart Network z-score; SoV, sinuses of Valsalva.

mean z-score were lower than HZ [1.667 (SD 2.030) vs 1.879 (SD 1.909), $p = 0.037$], with a Bland-Altman plot bias of −0.212.

In the younger age group, $Rho_{Spearman}$ was 0.984 ($p < 0.001$) and Bland-Altman bias was 0.440, with higher PHN mean and median z-scores than HZ [1.718 (SD 2.252) versus 1.278 (SD 2.208), $p < 0.001$].

At SoV PHN and HZ correlation resulted in $Rho_{Spearman} = 0.993$ ($p < 0.001$) in the older cohort, with a Bland-Altman bias of −0.217, with mean and median PHN z-score lower than HZ [0.215 (SD 1.791) vs 0.432 (SD 1.485), $p = 0.005$]. Those aged <10 years old or with BSA <1.5 m^2 showed nomogram correlation of $Rho_{Spearman} = 0.985$ ($p < 0.001$) and a Bland-Altman bias 0.210 with higher PHN mean and median z-scores than HZ [0.444 (SD 2.129) versus 0.219 (SD 1.642), $p < 0.0001$] (Fig. 3).

Table 2
Agreement study between nomograms and body surface area indexed diameters on the age-grouped analysis: Kappa Cohen Analysis.

Kappa Cohen analysis for agreement study between nomogram thresholds and BSA-indexed diameters >21 mm/m^2						
	All patients		Patients ≥ 10 years and BSA ≥ 1.5 m^2		Patients < 10 years or BSA < 1.5 m^2	
KAPPA INDEX	SOV	ASC AO	SOV	ASC AO	SOV	ASC AO
HZ Z-SCORE > 2	0.134	0.247	0.386	0.132	0.129	0.309
PHN Z-SCORE > 2	0.228	0.351	0.344	0.169	0.213	0.392
HZ Z-SCORE > 3	0.050	0.237	0.664	0.276	0.036	0.255
PHN Z-SCORE > 3	0.121	0.329	0.666	0.311	0.096	0.329

Interpretation: 0.8–1 = perfect; 0.6- < 0.8 = substantial; 0.4- < 0.6 = moderate; 0.2- < 0.4 = mild; <0.2 = no.
AscAo, ascending aorta; BSA, body surface area; HZ, Halifax z-score; OR, odds ratio; PHN, Pediatric Heart Network z-score; SoV, sinuses of Valsalva.

Comparison of nomograms against body surface area indexed measurements

At AscAo, the correlation amongst BSA-I values and HZ showed a $Rho_{Spearman} = 0.952$ ($p < 0.001$); and by PHN $Rho_{Spearman} = 0.961$ ($p < 0.001$) in the older group. Whereas for the younger patients, $Rho_{Spearman}$ was 0.424 ($p < 0.001$) using HZ; and $Rho_{Spearman}$ of 0.540 ($p < 0.001$) with PHN nomogram.

At SoV, correlation against BSA-I for the older patients by HZ was $Rho_{Spearman} = 0.942$ ($p < 0.001$), and $rho_{Spearman} = 0.945$ ($p < 0.001$) by PHN. In the younger group, the correlation obtained at SoV when applying HZ was $rho_{Spearman} = 0.383$ ($p < 0.001$); and $rho_{Spearman} = 0.478$ ($p < 0.001$) by PHN.

In Table 3 the logistic regression analysis to associate the dichotomization of the nomograms at > +2 and > +3 z-scores against diameters >21 mm per square-meter of BSA is shown. In the younger cohort, at AscAo, the PHN nomogram categorized significantly more patients in line with BSA-indexing than by HZ, which did not happen at the SoV level.

In the older cohort, there was no patient that had a diameter indexed >21 mm/m2 which did not surpass the > +2 z-score threshold. No significant differences at SoV were observed between the two nomograms.

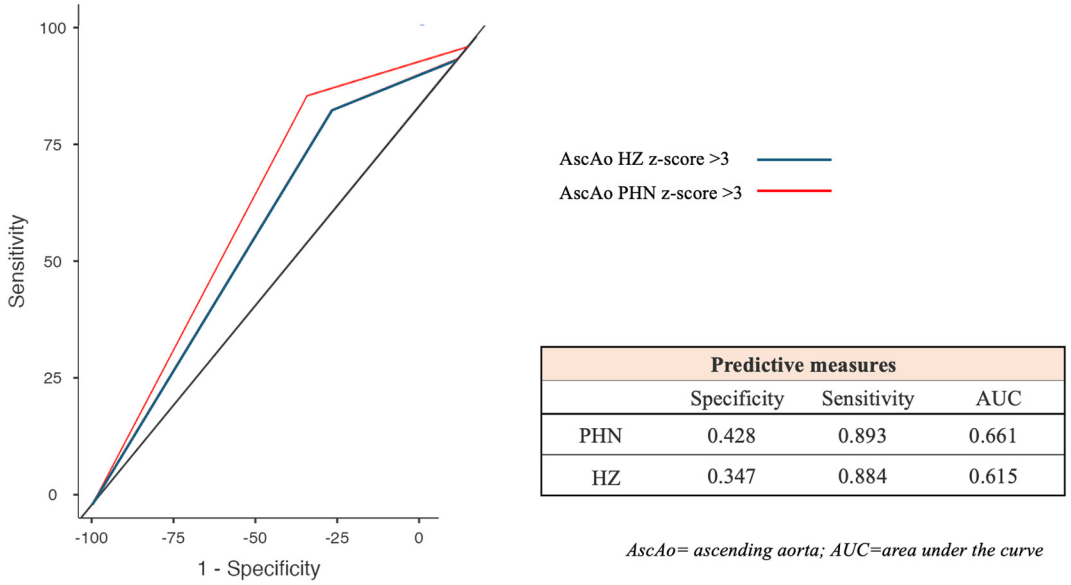
Compared to HZ, for those patients with a BSA-I > 21 mm/m2, the PHN classified less patients as non-dilated in the younger cohort. The opposite phenomenon happened with the older cohort.

In the agreement analysis amongst the previously mentioned > + 2 and > +3 z-score thresholds with >21 mm BSA-indexed values we obtained the higher kappa index at PHN > +2 for AscAo and SoV in the younger group, and PHN > +3 resulted with the best kappa index in the teenager group at both sites (Table 2).

Discussion

To our knowledge, this is the first study comparing PHN and HZ nomograms for aorta dilatation definition in real-life pediatric patients affected by BAV, on the basis that PHN z-score is a newer and wider population-built nomogram, and the correspondence with BSA-indexed diameters.

Precise identification of aortic dilatation is essential, as the diagnosis of an enlarged aorta means lifestyle modifications will be needed,



Predictive measures			
	Specificity	Sensitivity	AUC
PHN	0.428	0.893	0.661
HZ	0.347	0.884	0.615

AscAo= ascending aorta; AUC=area under the curve

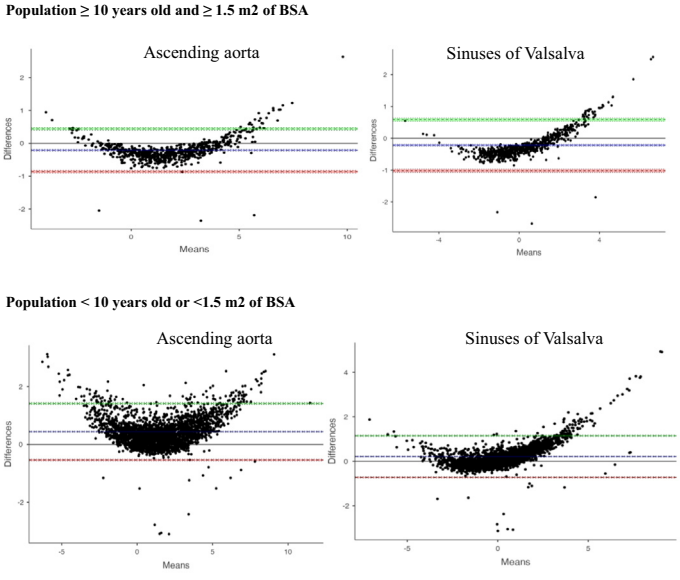
Fig. 2. Receiver-operating characteristic curve on compliance of the >21 mm diameter per m2 of body surface area criterion. Comparison of both nomograms at >3 z-score threshold.

including limitations on physical activity or participation in sports, and may influence the timing or necessity of pharmacological chemoprophylaxis treatment.

These management strategies can have a significant impact on long-term morbidity. On one hand, they may contribute to lower dissection risk; however, overly restrictive recommendations, such as limiting exercise from an early age and hampering social relationships, may increase the likelihood of developing cardiovascular risk-related diseases and contribute to psychological disorders during adolescence or adulthood.

In the demographics analysis, we observed that males had statistically higher z-scores, both by PHN and HZ, in concordance with reported higher values on valve size and left ventricle mass in males [19,20]. On the other hand, when applying the BSA-indexing, females showed higher median values. Seemingly, in a multicentric adult healthy cohort, it was observed that women had higher BSA-indexed aortic measurements, which is in line with having lower BSA [21].

Our study showed that PHN nomogram resulted in statistically higher normalized measurements at AscA and SoV albeit by only 0.1 points. We also reported high correlation between HZ and PHN z-scores, both at SoV and at AscAo levels and demonstrated good concordance, with greater differences between the nomograms at the extremes. Similar results have been reported in several studies, including comparisons against Cantinotti and Pettersen nomograms. This could be explained as being due to the different population analyzed by Lopez et al., who included a higher number of neonates when creating the formula, some authors considered the PHN nomogram was preferable because the referral measurements were made inner edge-to-inner edge in systole, as per pediatric guidelines [22–25]. As in our work, it has been reported that highest differences occur at extreme values, a



	ASCENDING AORTA			SINUSES OF VALSALVA		
≥10 years old and BSA ≥ 1.5m2	Estimate	95% CI Lower	Upper	Estimate	95% CI Lower	Upper
Bias	-0.212	-0.236	-0.189	-0.217	-0.247	-0.188
Lower limit of agreement	-0.863	-0.904	-0.822	-1.021	-1.071	-0.970
Upper limit of agreement	0.438	0.398	0.479	1.145	1.115	1.175
Variance	PHN		HALIFAX	PHN		HALIFAX
	4.12		3.65	3.21		2.20
< 10 years old or BSA<1.5 m2	Estimate	95% CI Lower	Upper	Estimate	95% CI Lower	Upper
Bias	0.436	0.418	0.455	0.210	0.192	0.227
Lower limit of agreement	-0.540	-0.571	-0.509	-0.725	-0.755	-0.695
Upper limit of agreement	1.412	1.381	1.444	1.145	1.115	1.175
Variance	PHN		HALIFAX	PHN		HALIFAX
	4.92		4.65	3.43		2.40

Fig. 3. Bland Altman analysis. Concordance study between HZ and PHN nomograms.

Table 3
Agreement study between nomograms and body surface area indexed diameters on the age-grouped analysis: analysis of best nomogram threshold.

Group < 10 years or < 1.5 m2 BSA					
Nomograms thresholds		Diameter AoAsc indexed by BSA		OR [CI95%] (same classification by both methods)	Proportion difference of non-classified by z-score and yes by BSA-I (Chi square)
		</=21 mm/m^2	>21 mm/m^2		
AscAo HZ z-score > 2	z-score ≤ 2	990 (54.5)	825 (45.5)	4.76 (4.00–5.88, p < 0.001)	P < 0.001
	z-score > 2	209 (19.8)	844 (80.2)		
AscAo PHN z-score > 2	z-score ≤ 2	1001 (58.8)	701 (41.2)	7.14 (5.88–8.33, p < 0.001)	
	z-score > 2	198 (17.0)	968 (83.0)		
AscAo_HZ z-score > 3	z-score ≤ 3	1146 (50.6)	1117 (49.4)	11.11 (8.33–14.26, p < 0.001)	P < 0.001
	z-score > 3	53 (8.8)	552 (91.2)		
AscAo PHN z-score > 3	z-score ≤ 3	1139 (53.8)	977 (46.2)	14.26 (10.-16.67, $p < 0.001$)	
	z-score > 3	60 (8.0)	692 (92.0)		
SoV_HZ z-score > 2	z-score ≤ 2	1083 (42.3)	1477 (57.7)	33 (16.67–100.00, p < 0.001)	P < 0.001
	z-score > 2	6 (2.0)	300 (98.0)		
SoV_PHN z-score > 2	z-score ≤ 2	1069 (45.5)	1281 (54.5)	20.70 (14.29–33.33, <0.001)	
	z-score > 2	20 (3.9)	496 (96.1)		
SoV_HZ z-score > 3	z-score ≤ 3	1089 (39.1)	1694 (60.9)	0.00 (0.00–0.00, $p = 0.951$)	P < 0.001
	z-score > 3	0 (0.0)	83 (100.0)		
SoV_PHN z-score > 3	z-score ≤ 3	1089 (41.1)	1560 (58.9)	0.00 (0.00–0.00, $p = 0.949$)	
	z-score > 3	0 (0.0)	217 (100.0)		

Group ≥ 10 years old and ≥1.5 m^2 of BSA				
Nomograms thresholds		Diameter AoAsc indexed by BSA[a]		OR [CI95%] (same classification by both methods)
		<o = 21 mm/m^2	>21 mm/m^2	
AscAo HZ z-score > 2	z-score ≤ 2	396 (100.0)	0 (0.0)	123,646,605.53 (0.00–1.76·10^37, $p = 0.983$)
	z-score > 2	311 (87.4)	45 (12.6)	
AscAo PHN z-score > 2	z-score ≤ 2	445 (100.0)	0 (0.0)	146,771,352.36 (0.00–2.75·10^75, $p = 0.982$) -
	z-score > 2	262 (85.3)	45 (14.7)	
AscAo_HZ z-score > 3	z-score ≤ 3	538 (100.0)	0 (0.0)	227,539,019.65 (0.00–2.27·10^70, $p = 0.980$)
	z-score > 3	169 (79.0)	45 (21.0)	
AscAo PHN z-score > 3	z-score ≤ 3	563 (99.8)	1 (0.2)	172.03 (37.08–3061.52, p < 0.001)
	z-score > 3	144 (76.6)	44 (23.4)	

Nomograms thresholds		Diameter SoV indexed by BSA (number (%))		OR [CI95%] (same classification by both methods)	Chi square proportion difference of non-classified by z-score and yes by BSA-i
		<o = 21 mm/m^2	>21 mm/m^2		
SoV_HZ z-score > 2	z-score ≤ 2	639 (99.8)	1 (0.2)	239.62 (50.31–4296.34, p < 0.001)	$p = 0.563$
	z-score > 2	80 (72.7)	30 (27.3)		
SoV_PHN z-score > 2	z-score ≤ 2	629 (99.7)	2 (0.3)	101.34 (29.86–633.75, p < 0.001)	
	z-score > 2	90 (75.6)	29 (24.4)		
SoV_HZ z-score > 3	z-score ≤ 3	709 (98.6)	10 (1.4)	148.89 (58.23–417.15, p < 0.001)	$P = 0.051$
	z-score > 3	10 (32.3)	21 (67.7)		
SoV_PHN z-score > 3	z-score ≤ 3	696 (99.6)	3 (0.4)	282.43 (91.97–1243.12, p < 0.001)	
	z-score > 3	23 (45.1)	28 (54.9)		

Number of patients in each category, absolute number and (%).
AscAo, ascending aorta; BSA-I, body surface area indexing; HZ, Halifax z-score; OR, odds ratio; PHN, Pediatric Heart Network z-score; SoV, sinuses of Valsalva.
[a] Chi-square not possible due to 0 in some groups.

phenomenon called heteroscedasticity, with higher heterogeneity of variances at the edge boundaries [12,26–28].

As a novelty, in the present work we report differences between both nomograms significantly decreased with older age and higher BSA at AscAo, but not at SoV. Colan et al. [28] and Lopez et al. [12], while creating the nomograms, analyzed the effects of race, gender, and age and found them to be non-relevant. Dallaire et al. did observe that weight influences the size in younger children, but height becomes more relevant when they reach teenage years [29]. On the other hand, other works have shown that BSA is not inferior to the use of height indexing [30], but further studies are required to determine if gender or age should be addressed differently.

One explanation for the lack of relevant differences at SoV between the nomograms could be the lesser extent of BAV-aortopathy disease at the root level.

We observed both nomograms had statistically significant but moderate correlation with BSA-indexed diameters, although PHN nomogram performed better than HZ.

One of the accepted definitions in the scientific community of dilatation is an indexed diameter above 21 mm per BSA square meter, hence in this project we consistently reported that, for AscAo, PHN nomogram threshold set at values above 2 and 3 z-score resulted in higher OR and area under the curve than HZ to meet the mentioned dilatation definition. These results, which are in line with previous reports that define PHN as resulting in higher z-scores for AscAo [22]. Similar results were obtained for SoV; the PHN > +3 z-score cut-off showed the best association, followed by the HZ > +3 threshold. Despite that, globally we found poor *agreement* between BSA-indexed values and the nomograms, only reaching mild agreement at AscAo, performing slightly better when using the PHN.

On the basis that normalization tends to overestimate in the teenage group compared to BSA-indexing, and using the limit of 10 years of age and BSA ≥1.5 m^2 [11], we performed an age-divided analysis [31]. We found high significant correlation between the two nomograms in both age groups. In the older cohort the concordance bias was smaller than in the younger one at the AscAo, whereas it was similar in the SoV. The teenage subjects had average lower PHN z-score both at AscAo and SoV, although not clinically relevant, as it only differed from 0.2 z-score points, in contrast to the younger cohort [18]. We observed good correlation between the nomogram

and BSA-indexed values for the older group at both AscAo and SoV, unlike the observation in the young subjects group in which the correlation was low at all levels studied. This again, is in line with what was previously described that the BSA- indexed scale is more appropriate for teenagers [18].

Interestingly, in the older group, we found that at AscAo most of the patients classified as dilated by the nomograms were not dilated by the BSA-indexed criteria, unlike in the young group in which they also complied with the BSA-indexed criteria.

The older group showed mild agreement between the BSA-I criteria >21 mm/m2 and the > + 3 thresholds, PHN performing better than HZ. In the young cohort, although correlation was lower and agreement analysis was less powerful, the PHN nomogram also resulted in higher agreement indexes. These results are also in line with another recent publication on pediatric BAV comparing z-score against a Q-score, based on machine-learning, which obtained similar results to ours, observing that classical nomograms tend to overestimate diameters, mostly in teenagers with young adult anthropometric dimensions, as we reported in the present work [32].

Limitations

Limitations for the present work include no comparison between z-scores using BSA or height as children have lower rates of obesity. However, it would be an interesting comparison because some publications such as one by van Kimmenade et al. found that in adults height-indexing correlated better with dilatation [33]. Further studies comparing a higher number of patients and other nomograms would be interesting to increase evidence.

Conclusions

The PHN nomogram results in higher z-scores compared to the HZ nomogram in the global sample, significantly classifying more patients as dilated. However, the opposite phenomenon is observed for children older than 10 years and with a BSA over 1.5 m^2.

The PHN correlates better with BSA-I than HZ in all age groups, although a tendency to better agreement was found in the teenage population.

Globally, the PHN nomogram appears to be at least non-inferior to HZ, and shows better agreement, specificity and sensitivity with BSA—I, which can be explained by the newer, wider, and larger cohort from which the data were obtained. Of note, the nomograms classify more patients as dilated than BSA-I in children but for the teenager adult-size population, in whom the BSA-indexing diagnosis was much less than by using the nomograms. This is important, as clinicians should be aware of the impact of age and size on the interpretation of z-scores, which determine sport restrictions and the initiation of prophylactic medicines and strategies. Also, our work should prompt more studies on long-term evolution of morbimortality and diameter progression.

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CRediT authorship contribution statement

Andrea FB did the analysis, manuscript writing and review. Anna SR designed the idea and mentored the process. The rest of the authors included patients and reviewed the final manuscript.

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Declaration of competing interest

The authors declare no conflicts of interest.

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All authors introduced data, read the final manuscript and are responsible for its content and integrity. Andrea Freixa-Benavente had full access to all the data in the study and takes responsibility for the data analysis.

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