

# Normal reference ranges for aortic diameters in preterm infants



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**Objective:** To establish normal reference ranges and Z-scores for aortic diameters in preterm infants according to the body surface area and assess their correlation with body weight, body surface area, and gestational age.

**Patients and methods:** In a prospective study, 268 preterm infants who fulfilled the criteria for inclusion were examined. Echocardiograms were performed to measure the ascending aorta, transverse aorta, and aortic isthmus diameters on 0 days to 6 days of life and at weekly intervals until the babies reached 36 weeks. Body surface area was divided into 13 groups from 0.07 m<sup>2</sup> to 0.19 m<sup>2</sup>.

**Results:** The mean gestational age was 29.8 [p 2.38 standard deviation (SD)] weeks, ranging from 24 weeks to 35 weeks. The mean body weight was 1479 (p 413 SD) g, ranging from 588 g to 3380 g, and the mean body surface area was 0.13 m<sup>2</sup>, ranging from 0.07 m<sup>2</sup> to 0.19 m<sup>2</sup>. All the aortic diameters correlated well with both body weight and body surface area. Reference ranges with the mean p SD, range, and Z-scores were calculated for aortic diameters according to the body surface area. A significant gradual increase was observed in ascending aorta, transverse aorta, and aortic isthmus diameters with increasing body surface area. Overall, a progressive and significant increase in ascending aorta, transverse aorta, and aortic isthmus diameters was observed during the first 9 weeks of life.

**Conclusion:** The ascending aorta, transverse aorta, and aortic isthmus diameters exhibited a significant correlation with the body surface area and body weight. This study provides reference data with Z-scores that can be used as a normal reference tool for the ascending aorta, transverse aorta, and aortic isthmus diameters for preterm infants based on the body surface area.

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**Keywords:** Aortic diameters, Body surface area, Preterm infants, Reference ranges, Z-scores

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## Introduction

For the past 60 years, echocardiography has been practiced as the primary mode of investigation to evaluate the anatomy and function of the heart [1,2], yet there are few studies that describe a normal premature neonate’s heart. Pre-term hearts differ significantly from a term neonate’s heart, and there is a gradual transition to a mature neonate heart. This study aimed to evaluate the anatomic and physiologic characteristics of the premature infant’s heart, and the changes that occur during the early postnatal period. As more preterm infants survive because of improved critical care services, an increasing number of preterm infants require at least one echocardiogram during the 1st month of life. Thus, it is vital to have adequate reference values. Unfortunately, there are currently no universally accepted normal values. Few studies in the literature involve the hearts of premature infants [3,4]. Our aim was to establish these normal values by studying a large number of healthy premature babies. The main objective of the study was to establish these normal reference values with Z-scores during the first 9 weeks of life and also to determine whether these diameters correlate with other variables, such as body surface area, body weight, and chronological age.

## Materials and methods

### Patients

In this prospective study, 400 premature infants under 36 weeks of gestation, admitted to the neonatal units between January 2008 and December 2010, were consecutively recruited and studied. The babies were from mixed populations; the majority were Arabs, and the remainder were from other Asian nations. Of the 400 premature infants, 268 (Table 1) fulfilled the following inclusion criteria:

- Infants with normal hearts (infants with small patent foramen ovale or small patent ductus arteriosus were not excluded).
- Healthy preterm infant with no evidence of sepsis, renal failure, etc.
- Absence of other major congenital anomalies or syndromes.
- Absence of gestational diabetes in the maternal history.
- Preterm infants on low ventilator settings (low ventilator settings when infant did not require high-frequency ventilation nor unusually high rates and pressures) or nonventilated preterm infants.

### Abbreviations

GA	Gestational Age
BSA	Body Surface Area
SD	standard deviation
IQ	Inter Quartile

We excluded sick preterm infants and those with major congenital anomalies, either cardiac or noncardiac.

Ethical approval was obtained from the ethical committees of both the Kuwait Ministry of Health and the Faculty of Medicine of Kuwait University. The study was funded by a grant from the Kuwait Foundation for the Advancement of Sciences. The parents were informed that the infants would be enrolled in an observational study and not in any therapeutic trial. Prior written consent was also obtained from the parents.

### Methods

Before the study was undertaken, the pediatric cardiologist responsible for conducting the echocardiograms was trained and observed by two senior pediatric cardiologists through the pretest echocardiograms for external validity and generalization. Interpersonal variability was evaluated, and once no significant variability in the readings was found, that doctor was assigned to conduct the study. Two different senior pediatric cardiologists also supervised these interpretations for generalization. The assigned cardiologist was not directly involved in the patient’s care. Echocardiographic studies were obtained with a

Table 1. General characteristics of the preterm babies.

Characteristics	Result
Male:Female (N)	126:142
Gestational age (wk)	
Mean ± SD	29.8 ± 2.38
Median (range) IQ	30 (24–35) 28–32
Weight (g)	
Mean ± SD	1479 ± 413
Median (range) IQ	1460 (588–3380) 1164–1730
Length (cm)	
Mean ± SD	40.1 ± 3.56
Median (range) IQ	40 (25–50) 38–42
Body surface area (m <sup>2</sup> ), mean (range)	0.123 (0.07–0.19)
Echocardiograms per baby (min–max)	1–5
Age (wk) at study (min–max)	1 day–9 weeks

IQ = interquartile; SD = standard deviation.

Table 2. Correlation of aortic diameters with gestational age and body weight.

Cardiac dimension (cm)	Gestational age (wk) <i>r</i> ( <i>p</i> )	Weight (g) <i>r</i> ( <i>p</i> )
Ascending aorta diameter (cm)	0.185 (<0.001)*	0.509 (<0.001)*
Transverse aorta diameter (cm)	0.236 (<0.001)*	0.484 (<0.001)*
Aortic isthmus diameter (cm)	0.123 (0.012)**	0.357 (<0.001)*

\* Correlation significant at the 0.01 probability level.

\*\* Correlation significant at the 0.05 probability level.

Siemens Cypress scanner, using a 7.5-MHz probe. The equipment used was standardized and certified by the Ministry of Health's biomedical engineer.

Each infant was examined as follows: In the supine position, the aortic diameters were measured from the following views: (1) the ascending aorta was measured in the parasternal long axis view at the maximal diameter between the sinotubular junction and arch vessels during midsystole. (2) The proximal transverse aorta diameter was measured between the first and second arch branch in the suprasternal long axis view during midsystole. (3) The aortic isthmus diameter was measured 1.0 mm distal to the left subclavian artery from the suprasternal long axis view during midsystole. All measurements were performed according to the American Society of Echocardiography recommendations [5], as adapted by Silverman [6], for premature infants, and according to the recently published guidelines for performance of a pediatric echocardiogram by the Pediatric Council of the American Society of Echocardiography [7]. According to the latest American Society of Echocardiography recommendations, great artery diameters should be measured from one intraluminal inner edge to the opposite inner intraluminal edge, perpendicular to the long axis of the vessel at the moment of maximal expansion (i.e., in midsystole) [7] because vessel dimensions in systole are larger than in diastole [8]. Infants were examined within the first 6 days of life and at weekly intervals until they reached term (36 weeks). The examinations were recorded on video, and all the data were stored in Digital Imaging and Communications in Medicine (DICOM) format. Before the study was undertaken, the pediatric cardiologist responsible for conducting the echocardiograms was trained and observed by the two senior pediatric cardiologists through the pretest echocardiograms for external validity and generalization. Inter-observer and intra-observer variability was evaluated using repeated-measures analysis of variance in 50 patients and once no significant variability in the readings was found, that doctor was assigned

to conduct the study. All the interpretations were made by an assigned pediatric cardiologist who recorded the images and were observed by two different senior pediatric cardiologists. The interpreter was blinded to the age, sex, and patient's previous/succeeding data at the time of image analysis. Standard parameters were measured by the interpreter and the calculated parameters were evaluated by the computer software, which was part of the echo machine. In rare situations, when the readings recorded by the computer were found to be inconsistent, the readings were repeated on the same day to recheck for accuracy. Two pediatric cardiologists who were blinded to the serial values of that particular infant validated the measurement. Adequate time was spent by the three pediatric cardiologists to obtain accurate values and to avoid errors.

Some premature infants became unfit after one or two echocardiograms and had to be excluded from the study. A few infants were re-included as they recovered rapidly after a brief period of illness.

### Statistical analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 21.0 software (IBM Corp., Armonk, NY, USA). The normal distribution assumptions for ascending aorta, transverse aorta, and aortic isthmus diameter variables, and for weight and gestational age were ascertained with the Kolmogorov–Smirnov test. Body surface area was used as the independent variable in different regression analyses to predict the mean values of each aortic diameter. The DuBois and DuBois formula [9] was used to calculate body surface area. The descriptive statistics are presented as mean and standard deviation (SD), range, and Z-score, as some of the variables failed to meet the assumption of normality of data.

The number of SDs from the mean is termed the Z-score, also known as the normal deviate or standard score. A measurement that is two SDs above the mean (the 97.7th percentile) has a Z-score of +2, whereas a measurement that is two SDs below

Table 3. Mean ± SD (range), Z-score values of great artery diameters against BSA.

BSA (m <sup>2</sup> )	N	Ascending aorta	Transverse aorta	Aortic isthmus
0.07	3	0.56 ± 0.017 <sup>a</sup> (0.55–0.58) <sup>b</sup> –0.63 to –0.05 <sup>c</sup>	0.46 ± 0.03 (0.44–0.50) –1.47 to –0.63	0.33 ± 0.03 (0.31–0.37) –1.60 to –0.52
0.08	9	0.61 ± 0.04 (0.55–0.66) –1.40 to +0.60	0.49 ± 0.04 (0.44–0.57) –1.69 to +0.02	0.38 ± 0.02 (0.33–0.40) –1.39 to –0.22
0.09	30	0.63 ± 0.05 (0.55–0.73) –1.87 to +1.23	0.50 ± 0.04 (0.45–0.59) –1.69 to +0.10	0.38 ± 0.03 (0.33–0.49) –1.51 to +0.90
0.10	45	0.67 ± 0.05 (0.59–0.89) –1.87 to +2.60	0.55 ± 0.05 (0.46–0.66) –1.69 to +0.70	0.41 ± 0.04 (0.30–0.47) –2.20 to +0.90
0.11	64	0.69 ± 0.04 (0.63–0.79) –1.23 to +1.26	0.54 ± 0.05 (0.46–0.66) –1.84 to +0.54	0.42 ± 0.04 (0.31–0.50) –2.13 to +0.78
0.12	80	0.72 ± 0.04 (0.64–0.85) –1.61 to +1.50	0.59 ± 0.04 (0.51–0.67) –1.38 to +0.42	0.45 ± 0.03 (0.39–0.54) –0.91 to +1.07
0.13	71	0.75 ± 0.05 (0.66–0.88) –1.79 to +1.37	0.60 ± 0.05 (0.50–0.75) –1.74 to +0.94	0.46 ± 0.04 (0.34–0.56) –1.93 to +1.10
0.14	54	0.78 ± 0.06 (0.59–0.93) –3.30 to +1.62	0.62 ± 0.06 (0.50–0.73) –1.90 to +0.59	0.47 ± 0.05 (0.36–0.59) –1.72 to +1.29
0.15	36	0.81 ± 0.04 (0.71–0.89) –1.46 to +1.02	0.66 ± 0.04 (0.56–0.75) –1.22 to +0.71	0.50 ± 0.04 (0.42–0.61) –0.83 to +1.44
0.16	19	0.81 ± 0.05 (0.73–0.96) –1.56 to +1.45	0.66 ± 0.06 (0.54–0.76) –1.66 to +0.60	0.52 ± 0.05 (0.39–0.60) –1.45 to +1.17
0.17	4	0.85 ± 0.04 (0.79–0.89) –1.02 to +0.29	0.69 ± 0.02 (0.65–0.70) –0.61 to –0.12	0.53 ± 0.05 (0.50–0.60) –0.08 to +1.03
0.18	2	0.96 ± 0.05 (0.92–0.99) –0.49 to +1.29	0.81 ± 0.01 (0.80–0.81) +0.66 to +0.75	0.58 ± 0.00 (0.58–0.58) +0.74 to +0.74
0.19	1	0.99 <sup>a</sup> +0.97 <sup>c</sup>	0.81 +0.56	0.66 +1.37

BSA = body surface area; SD = standard deviation.

<sup>a</sup> Mean ± standard deviation (cm).

<sup>b</sup> Range (cm).

<sup>c</sup> Z-score.

the mean (the 2–3rd percentile) has a Z-score of –2. A Z-score of 3 corresponds to the 99.865th percentile, whereas a Z-score of 4 corresponds to the 99.997th percentile. For practical purposes and ease of understanding, the infants were grouped as follows. Based on body surface area, infants were divided into 13 groups, ranging from 0.07 m<sup>2</sup> to 0.19 m<sup>2</sup>. The Spearman rho was applied to determine whether there was any correlation between the two variables. The two-tailed probability value  $p < 0.05$  was considered statistically significant (Table 2). The Z-scores were calculated for ascending aorta, transverse aorta, and aortic isthmus diameters against body surface area using the standard formula [10]. Ranges for the Z-scores were calculated for each measured

parameter against the body surface area. Normal expected Z-scores for ascending aorta, transverse aorta, and aortic isthmus diameters were calculated against each body surface area and plotted in a graph to represent –2, –1, 0, +1, and +2. Measured values were plotted as a scatter plot.

## Results

Among the 400 infants, 268 preterm infants who fulfilled the inclusion criteria were studied at weekly intervals until they reached 36 weeks of age. A total of 418 echocardiograms were assessed during the study period. The general characteristics of the infants are presented in Table 1. A slight female predominance was noted (Male:Female =

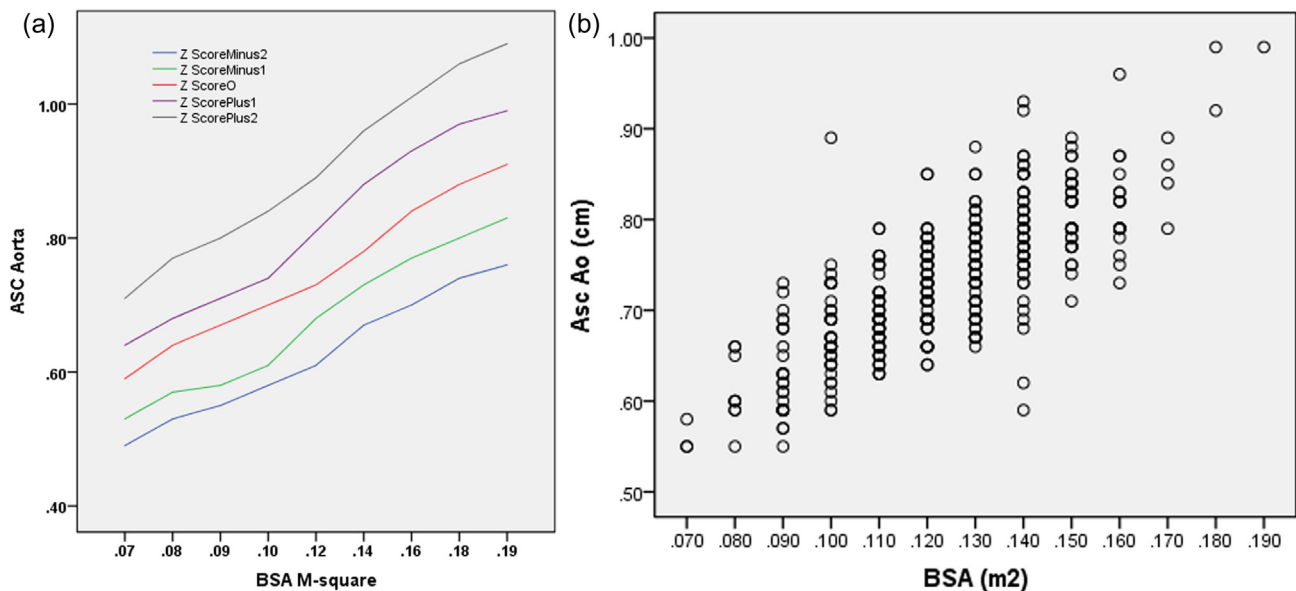


Fig. 1. (A) Expected normal Z-scores for ascending aorta diameter (cm) according to BSA. (B) Scatter plots for ascending aorta diameter (cm) according to BSA. BSA = body surface area.

1:1.13). The mean gestational age was 29.8 ( $\pm 2.38$  SD) weeks, ranging from 24 weeks to 35 weeks. The mean body weight was 1479 ( $\pm 413$  SD) g, ranging from 588 g to 3380 g, and the mean body surface area was 0.123 m<sup>2</sup>, ranging from 0.07 m<sup>2</sup> to 0.19 m<sup>2</sup>.

In view of the overall spectrum relating to aortic diameters in preterm infants, three different reference ranges have been presented. Reference ranges, with mean  $\pm$  SD, range, and Z-score, values for ascending aorta, transverse aorta, and aortic isthmus diameters according to body surface area are presented in Table 3. Our ranges of normal values against body surface area are similar to the expected values.

Overall, a progressive and significant increase for ascending aorta, transverse aorta, and aortic isthmus diameters was observed during the first 9 weeks of life. The “growing velocities” for the ascending aorta and aortic isthmus were faster in body surface areas between 0.07 m<sup>2</sup> and 0.10 m<sup>2</sup> and thereafter showed approximately a 0.02 cm/0.01 m<sup>2</sup> increase in body surface area. For example, if one wants to see the reference range for an infant with a particular body surface area, refer to Table 3 and, for Z-scores, refer the graphs. Measured Z-scores in our group of preterm infants correlated with the expected Z-scores for the particular body surface area. If one wishes to calculate the accurate Z-score for a particular aortic diameter, we have plotted the value against the body surface area in the graphs (Figs. 1–3A). Scatter plot graphs (Figs. 1–3B) show the measured

values of ascending aorta, transverse aorta, and aortic isthmus diameters in preterm infants against the body surface area.

Attempts were made to reduce the number of tables and graphs. To obtain more accurate values and create an easy ready reference for the pediatric cardiologists, who routinely conduct echocardiograms, it was decided to consolidate our findings into one self-explanatory table and three scatter plot graphs.

#### Strengths and limitations

Our study has several strengths. First, we evaluated important echocardiographic parameters in a large group of preterm infants for whom the available normal reference values were limited or even absent. Second, we prospectively enrolled the largest population of healthy preterm infants studied so far. Third, efforts were made to build new and robust Z-score reference. Fourth, all reported measurements in the database represent only those performed with excellent visualization and no ambiguity. A minor limitation of our study is that we used the DuBois and DuBois formula to calculate the body surface area, which occasionally underestimates body surface area [11–14]. The difference is negligible in very low body weight and length.

#### Discussion

We present reference ranges and Z-scores of ascending aorta, transverse aorta, and aortic isthmus



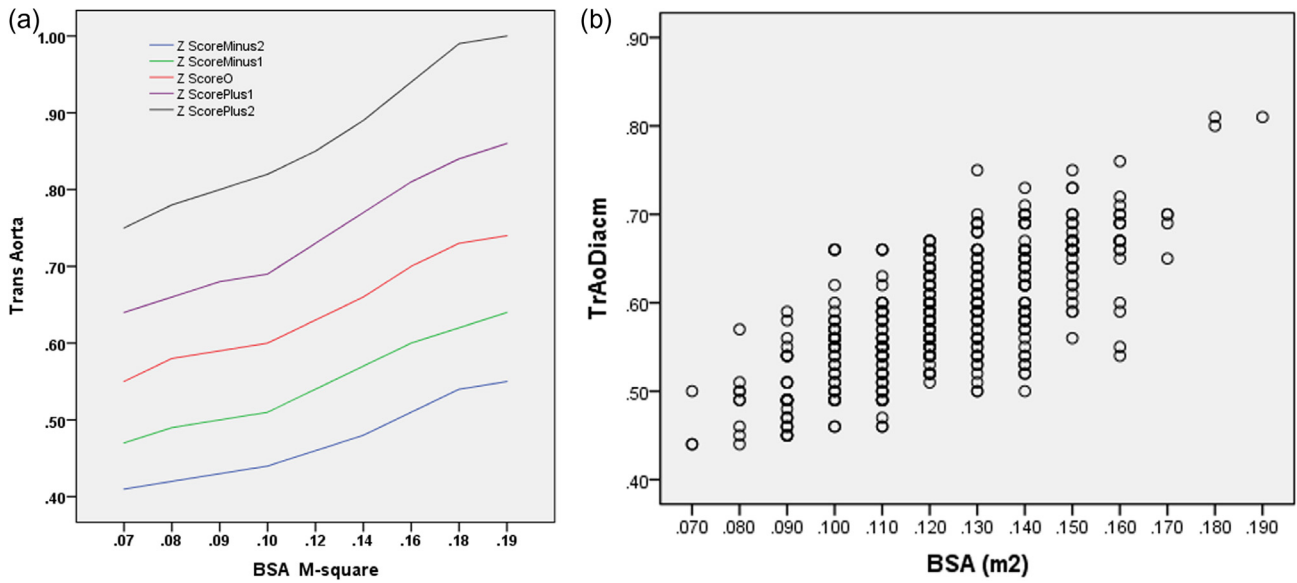


Fig. 2. (A) Expected normal Z-scores for transverse aorta diameter (cm) according to BSA. (B) Scatter plots for transverse aorta diameter (cm) according to BSA. BSA = body surface area; dia = diameter.

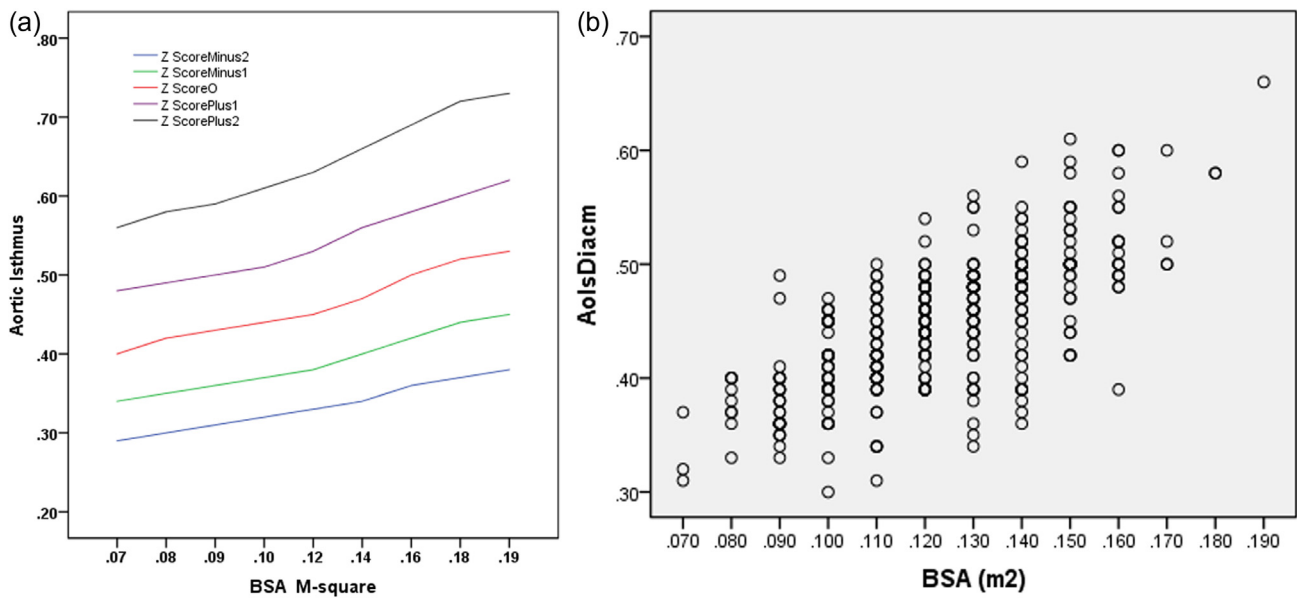


Fig. 3. (A) Expected normal Z-scores for aortic isthmus diameter (cm) according to BSA. (B) Scatter plots for aortic isthmus diameter (cm) according to BSA. BSA = body surface area.

mus diameters for a complete population of preterm infants. There is a close correlation between the body weight and all the aortic diameters. Normal reference ranges are available for adults and children, but few references have been produced for evaluating preterm infants in modern neonatal units. Available studies include small numbers of preterm infants and measurements performed over a wide age range.

Body surface area is the expression of body size with the highest correlation to cardiac dimensions [15]. Normalization to body surface area is currently the standard approach [7,11,16–19]. However, various formulas to calculate body surface area exist [12,20–22] and there is no agreement as to which formula should be used in preterm neonates and infants [13,23]. Nomograms were then developed, from which the Z-score of a

cardiac structure could be estimated from a knowledge of the body surface area and the echocardiographically derived measurement.

The concept of Z-scores is often unfamiliar to echocardiographers. Normalization of the dimensions of cardiac structures to the size of the body, using so-called Z-scores, is becoming increasingly common in the management of infants and children with congenital heart disease. As a normalized variable, Z-scores eliminate many sources of variance in raw values. However, the nonlinearity of both the mean and the variance of growth of cardiovascular structures in conjunction with change in body size is a predictable source of variance that is eliminated using Z-scores. In its recent recommendations, the American Society of Echocardiography advocated that when pediatric normalization is performed, reference values should be expressed as Z-scores [7]. Z-scores are superior to dichotomous “normal values” because they allow clinicians to appreciate the “magnitude of abnormality.” Z-score estimates are now part of the decision making in clinical and surgical management in pediatric cardiology [24,25].

In 1995, Imai et al. [26] measured 19 parameters for the heart and great artery (four valves, pulmonary tree, aortic arch, ascending and descending aorta, ventricular septum, and left ventricular internal and posterior wall dimensions) using cross-sectional echocardiography in 55 premature and full-term infants (ranging in gestational age from 23 weeks to 41 weeks, and in body weight from 543 g to 3966 g). The increase in each dimension correlated closely with body weight and was found to follow a linear regression. In a 2013 study by de Waal et al. [27], the diameter measurements of pulmonary valve annulus, ascending aorta, and superior vena cava using standardized methodology were collected retrospectively from nine prospective studies on transitional hemodynamics in preterm infants. Data were analyzed to calculate weight-corrected percentiles of diameters used for blood flow measurements. They analyzed 2870 measurements in 694 preterm infants weighing less than 1750 g. The median gestational age was 27 weeks (range, 23 weeks to 34 weeks), and the median time of measurement was 22 hours after birth (range, 0.5 hours to 70 days). Seventy-six percent of measurements were performed while the infant received mechanical ventilation, and 20% were collected while the infant received cardiovascular support. Mean diameters increased with weight, and SDs were comparable over the weight range. The Z-scores were not calculated in these studies.

Our study involved 268 premature infants (the largest in number in any such study to date). All infants were healthy, and any infant who became sick during the study was excluded. This study reports serial measurements of ascending aorta, transverse aorta, and aortic isthmus diameters during the first 9 weeks of life in a selected population of preterm infants with a body weight of 588 g to 3380 g and between 24 weeks and 35 weeks of gestational age. Measurements of ascending aorta, transverse aorta, and aortic isthmus diameters showed a significant correlation with body weight and body surface area. There was a progressive and significant increase in aortic diameters over time. This has been shown in normal children and adults for aortic root and ascending aorta by Roman et al. [28] and Gautier et al. [29]. Trowitzsch et al. [30] found that the “growing velocities” of the large vessels in premature infants at 23 weeks’ to 36 weeks’ gestation were much greater than that of term babies during the first 3 years of life. In 2014, Cantinotti et al. [31] established reliable echocardiographic Z-scores for 22 cardiovascular structures against body surface area in neonates, infants, and toddlers. More recently, an increasing number of commercial software vendors have incorporated Z-scores into pediatric echocardiographic reporting features.

Our study provides accurate reference ranges with Z-scores, as the data were collected from a large number of preterm infants. The results established according to the body surface area in this study contribute to the determination of the lower and upper limits of the aortic diameters obtained by echocardiography in normal preterm infants.

Our ranges of normal values against body surface area are similar to the values reported by Cantinotti et al. [14]. We hope that these data with Z-scores and graphs will be accepted by neonatal units as normal reference ranges of preterm aortic diameters. These data will be useful as a ready reference for the pediatric cardiologists who routinely perform echocardiograms in preterm infants. These self-explanatory tables will provide normal reference ranges of ascending aorta, transverse aorta, and aortic isthmus diameters based on the body surface area presented as the mean  $\pm$  SD, range, and Z-scores as multiple options for reference values.

## Conclusion

Significant correlations are noted between the body weight and body surface area and the aortic

diameters. A progressive and significant increase in ascending aorta, transverse aorta, and aortic isthmus diameters was observed during the first 9 weeks of life. The values with Z-scores and graphs presented can be used as a normal reference tool for ascending aorta, transverse aorta, and aortic isthmus diameters for preterm infants based on the body surface area.

### Authors' contributions

Study concept/design, securing funding, and critical revision and approval of the article: L.A.; data collection and analysis, and drafting of article: M.T.V.; revisions of the article: J.R.; statistical analysis: P.N.S.

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