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Thymus assessments at birth in echocardiography: a preliminary cohort study

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Abstract

Background Echocardiography is a tool used in neonatal period to screen for congenital heart defects and to assess the function of the cardiovascular system. It enables obtaining a three-vessel view (3VV) to show how the superior vena cava, the aorta and the pulmonary trunk relate to each other. A 3VV also provides a view of the thymus gland.

Methods It is a preliminary study. Using the thymus measurements obtained in echocardiography of neonates delivered in one healthcare centre, a total of 1,331 thymus records were collected and statistically analysed. The study was conducted on group of 321 preterm neonates and 1,010 full-term neonates. The superior mediastinal view (three-vessel view, 3VV) was chosen for thymus measurements, with the parallel vascular system, including the superior vena cava, the aorta and the pulmonary trunk, with visible branching to the right and left pulmonary artery. Thymus width, depth and thymic 3VV index were measured. Thymic 3VV index (TI 3VV) is defined as a product of multipling the width and the depth of the thymus in three-vessel view projection.

Results Based on a statistical analysis, a correlation was found of 3VV thymus dimensions and thymic 3VV index with body weight, gestational age and body surface area (BSA). These measurements led to the important finding that the TI 3VV value depends on thymus width and depth, more prominently the latter. The 3VV measurement of thymus depth alone can serve as a screening tool to assess the size of the gland.

Conclusions Inclusion of thymic measurements in neonatal echocardiography protocol can be used as a screening tool to assess the size of thymus gland.

Keywords Thymus, Thymic index, Three vessel view, Neonate, Echocardiography

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Background

Echocardiography is now a standard procedure in Neonatal Units, serving not only as a tool to screen for congenital heart defects, but also to assess the function of the cardiovascular system [1]. Complementing the echocardiography findings with an assessment of thymus dimensions may provide a better understanding of a patient's condition, especially when congenital heart disease or dysmorphic features are diagnosed.

The prenatal three vessel-view (3VV) standard ultrasound scan shows how the superior vena cava, the aorta and the pulmonary trunk relate to each other. The 3VV provides an excellent view of the thymus gland from the second trimester of pregnancy [2].

The thymus is a primary lymphoid organ. The thymus size in relation to body weight is the largest in neonates and infants [3, 4]. Ultrasound is the best method for preliminary or screening tests of the thymus size in everyday clinical practice [5].

Thymic hypoplasia or aplasia is associated with impaired cell-type immunity. Immune system dysfunctions may occur with an incidence rate of 1:2,000–1:3,000 live births, but the actual incidence is higher as some cases remain undiagnosed due to mild clinical presentation [6–8].

Vaccines containing live pathogens are contraindicated in the deficiencies in which the specific immune response does not exist or is ineffective because they constitute a direct threat to a child's life [9–12].

The aim of the study was to analyse the thymus parameters in 3VV projection obtained from echocardiography scans performed in full-term and preterm neonates, and their correlation with birth weight, body surface area (BSA) and gestational age.

The second objective of the study was to find a screening method of thymus size assessment in examinations performed by an echocardiographer.

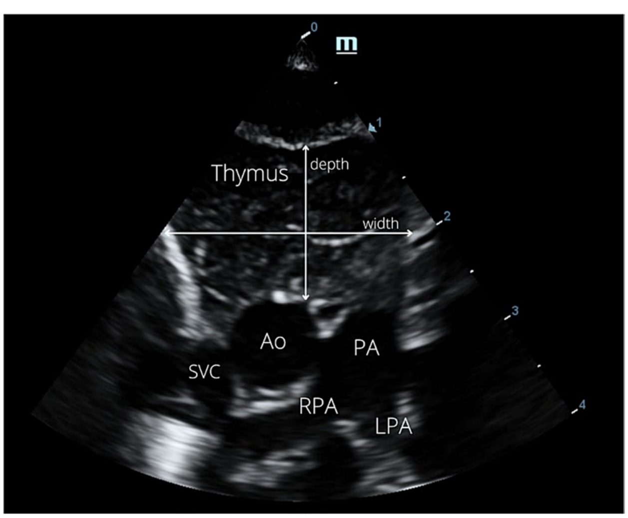

Fig. 1 Echocardiography three vessel view (3VV). Thymus width is the widest dimension of the thymus in the 3VV, with a line drawn parallel to the image. Thymus depth is the dimension along the ultrasound beam axis, perpendicular to the width dimension drawn from the point between the aorta and the pulmonary trunk. SVC – superior vena cava (short axis), Ao – aorta (short axis), PA – pulmonary artery (oblique axis), RPA – right pulmonary artery, LPA – left pulmonary artery

Methods

Thymus size measurements were obtained through echocardiographic scans in 1,331 neonates delivered at the Department of Obstetrics and Pathology of Pregnancy of the Medical University of Lublin between 2018 and 2021. Informed consent was obtained from a parent or legal guardian.

The study covered female and male neonates, including 321 preterm infants (590 - 4,340 g) and 1,010 full-term infants (1,830 - 4,900 g), whose gestational age ranged from 23 to 42 weeks. Body weight and length were assessed using Fenton's growth charts [13], and BSA was determined using the Haycock formula [14]. The analysis involved 1,331 neonates, among whom 5,5% were neonates with a birth weight below the 10th centile (hypotrophy, small gestational age - SGA) and 10% with a body weight above the 90th centile (hipertrophy, large gestational age - LGA). The birth weight of the remaining neonates was appropriate for gestational age (AGA). Thymus measurements were taken on days 1-7 during echocardiography performed as a standard screening test in neonates.

At the time of the study, the children were either breast-fed or given breast milk from the Breast Milk Bank. Those preterm infants in whom nutritional oral feeding was impossible received parenteral nutrition and trophic nutritional support including breast milk at the time of the study.

Echocardiography results which did not include thymus measurements or which provided an unclear image of the organ contours were excluded from the analysis, and so were neonates with cyanotic heart defects, aorta, pulmonary trunk or vena cava defects, mediastinal vascular abnormalities, genetic syndromes diagnosed or dysmorphic features potentially indicative of a genetic syndrome.

To perform the examination, a Mindray DC-70 X-Insight ultrasound machine was used, and measurements were conducted with a P10-4E sectoral probe (scanning angle: 90°), with the focus situated at the depth of the thymic parenchyma. The optimal gain setting was used to yield normal echogenic thymic parenchyma with a hyperechoic thymus capsule and clear hypoechogenic vessels. The 3VV provides a view of the pulmonary trunk (oblique axis), the aorta (short axis), and the superior vena cava (short axis) (Fig. 1).

The width and depth of the thymus glands were evaluated in the 3VV projection, and the corresponding thymic 3VV index (TI 3VV) was calculated. In the study, thymic 3VV index (TI 3VV) is defined as a product of multiplying the width and the depth of the thymus in three-vessel view projection. Correlations between the above-listed parameters and birth weight, gestational age and BSA were statistically analysed.

Bias during the clinical trial

The sectoral-probe examination is burdened with measurement error, especially for the thymus width, due to the distortion of the sectoral probe image as a "pie-shaped" image. The measurement of thymus width using the sectoral probe is burdened with measurement error due to the deviation of the ultrasound beam from the transducer axis. The depth measurement better reflects the real dimensions because the ultrasound beam propagates perpendicularly to the transducer surface. The ultrasound scan of the thymus may yield varying measurements due to the child feeling anxious and the child's respiratory phase. Certain clinical conditions such as mechanical ventilation, pneumothorax or emphysema, make the measurement of thymus width difficult due to excessive lung distension. 3VV ultrasonography cannot be used to detect thymus shape anomalies, the ectopic thymus, or to estimate thymic volume. The results of statistical analysis in the group of extremely preterm infants are subject to population bias because of the small size of the study group, due to the low number of such cases in the neonatal population.

Patient involvement

The study protocol was approved by the Bioethics Committee at the Medical University of Lublin (Consent No. KE-0254/279/2018). Informed consent was obtained from a parent or legal guardian.

Between 2018 and 2021, a total of 2,443 echocardiographic scans were performed. From among those scan records, the ones which were selected included 3VV thymus imaging with a good view of the whole organ. A flow chart of the patient selection process is shown in Fig. 2. The characteristics (descriptive statistics) of study participants are shown in Table 1.

Statistical analysis

The study included quantitative variables which were subjected to statistical analysis. Two quantitative variables, i.e., pregnancy duration and body weight of neonates, were treated as independent variables in the statistical analyses. In terms of pregnancy duration, two groups were distinguished: full-term and preterm neonates (Table 2).

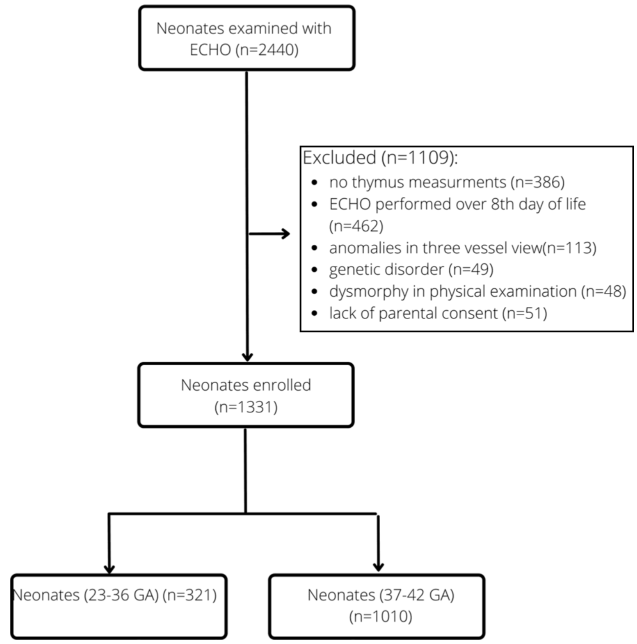

Fig. 2 A flow chart of the patient selection process

Table 1 Baseline characteristics of the cohort including foetal gender, gestational age and weight

Variable		*N*		%	
Gender	Female	585		43.95	
	Male	746		56.048	
	N	M	Me	SD	SEM
Age	1,331	37.613	38.00	2.667	0.073
Birth weight	1,331	3,145.793	3,240.00	737.102	20.204

N – number tested, M – mean, Me – median, SD – standard deviation, SEM – standard error of mean

Table 2 Descriptive statistics of thymus parameters in preterm and full-term neonates

Variables	**Preterm neonates**				
	N	**M**	**Me**	**SD**	**SEM**
Thymus width [mm]	321	23.26	23.60	5.789	0.323
Thymus depth [mm]	321	12.58	12.70	3.284	0.183
Thymic 3VV index [mm2]	321	3.03	3.024	1.241	0.069
Variables	**Full-term neonates**				
	N	M	Me	SD	SEM
Thymus width [mm]	1,010	28.58	28.50	4.540	0.142
Thymus depth [mm]	1,010	15.03	15.00	3.132	0.098
Thymic 3VV index [mm2]	1,010	4.33	4.23	1.268	0.039

N – number tested, M – mean, Me – median, SD – standard deviation, SEM – standard error of mean

Five birth weight categories were distinguished: ≤999 g, 1,000–1,499 g, 1,500–1,999 g, 2,000–2,499 g, ≥2,500 g, in order to investigate possible differences in thymus width and depth and in the thymic 3VV index for preterm neonates of different body weights (five categories) (Table 3).

The following statistical methods were used in the study: histograms, data distribution with the

Table 3 Descriptive statistics of thymus parameters in the group of preterm neonates in five birth weight categories: ≤999 g, 1,000–1,499 g, 1,500–1,999 g, 2,000–2,499 g, and ≥2,500 g

Variables	**Birth weight of ≤999 g**				
	N	**M**	**Me**	**SD**	**SEM**
Thymus width [mm]	15	12.75	11.90	3.739	0.965
Thymus depth [mm]	15	6.95	6.30	2.290	0.591
Thymic 3VV index [mm2]	15	0.92	0.80	0.509	0.131
Variables	**Birth weight of 1,000–1,499 g**				
	N	M	Me	SD	SEM
Thymus width [mm]	34	17.61	17.40	3.568	0.611
Thymus depth [mm]	34	8.69	8.85	1.955	0.335
Thymic 3VV index [mm2]	34	1.56	1.55	0.572	0.098
Variables	**Birth weight of 1,500–1,999 g**				
	N	M	Me	SD	SEM
Thymus width [mm]	54	20.65	21.00	3.931	0.535
Thymus depth [mm]	54	11.45	11.55	2.652	0.361
Thymic 3VV index [mm2]	54	2.39	2.38	0.775	0.105
Variables	**Birth weight of 2,000–2,499 g**				
	N	M	Me	SD	SEM
Thymus width [mm]	90	23.32	23.35	4.361	0.459
Thymus depth [mm]	90	13.17	12.80	2.655	0.279
Thymic 3VV index [mm2]	90	3.09	2.97	0.892	0.094
Variables	**Birth weight of ≥2,500 g**				
	N	M	Me	SD	SEM
Thymus width [mm]	128	27.05	26.80	4.566	0.403
Thymus depth [mm]	128	14.34	14.60	2.452	0.216
Thymic 3VV index [mm2]	128	3.88	3.69	0.975	0.086

N – number tested, M – mean, Me – median, SD – standard deviation, SEM – standard error of mean

Table 4 The results of the analysis of the correlation between thymus parameters and birth weight, body surface area (BSA) determined using the Hancock formula (in square metres), and duration of pregnancy (in weeks), in the studied groups of neonates

Thymus parameters	**Spearman's rank correlation**		
	Birth weight [g]	**BSA (Haycock formula) [m2]**	**Gestational age (weeks)**
Thymus width [mm]	0.548*	0.529*	0.353*
Thymus depth [mm]	0.359*	0.318*	0.249*
Thymic 3VV index [mm2]	0.529*	0.492*	0.344*

* statistical significance

Shapiro-Wilk test, descriptive statistics: M (mean), Me (median), SD (standard deviation), SEM (standard error of mean), the Mann-Whitney U test, the Kruskal-Wallis H test with multiple comparisons, Spearman's rank correlation coefficient and multiple regression analysis.

Results

This study concerns the analysis of the size of the thymus, in particular the width and depth of the organ, and the analysis of thymic 3VV index values in relation to a child's parameters at birth (body weight, BSA) and gestational age. Thymus width and depth, and the thymic 3VV index were shown to significantly correlate with a child's birth weight, BSA and gestational age (Table 4). The strongest correlations were found between birth weight and thymus width and the TI 3VV, and between thymus width and BSA (Figs. 3, 4, 5, 6, 7, 8, 9, 10 and 11).

The second element of the statistical analysis was to verify what effect thymus depth and width had on the thymic 3VV index value. Multiple regression analysis indicated that the TI 3VV value was influenced by both thymus depth and width, and of these two, the former had a greater impact on thymic 3VV index value (Table 5).

The next step was to verify whether the values of thymus width, thymus depth and the thymic 3VV index differed between the groups of full-term and preterm neonates. The analysis conducted using the Mann-Whithey U test revealed statistically significant differences in the values of the analysed parameters in the groups of full-term and preterm neonates (Table 6; Figs. 12, 13 and 14).

Additionally, a significance analysis was performed of the differences in thymus width, thymus depth and the thymic 3VV index in the group of pre-term neonates, divided into five body weight categories.

The analysis revealed that there were no statistically significant differences in thymus width in preterm neonates with a body weight of ≤999 g compared to neonates with a body weight of 1,000–1,499 g, in neonates with a body weight of 1,000–1,499 g compared to neonates with a body weight of 1,500-1,999 g, and in neonates with a body weight of 1,500-1,999 g compared to neonates with a body weight of 2,000–2,499 g. The remaining differences in thymus width in neonates representing various body weight categories were statistically significant (details in supplementary files).

The analysis showed that there was no statistically significant difference only for thymus depth in neonates with a body weight of ≤999 g compared to neonates with a body weight of 1,000−1,499 g. The remaining differences in thymus depth in neonates representing various body weight categories were statistically significant (details in supplementary files).

No statistically significant differences were found for thymus width and the TI 3VV in the group of the smallest preterm neonates with a body weight of ≤999 g, and partially in the group of neonates with a body weight of 1,000–1,499 g, due to the small cohort involved in the study (details in supplementary files).

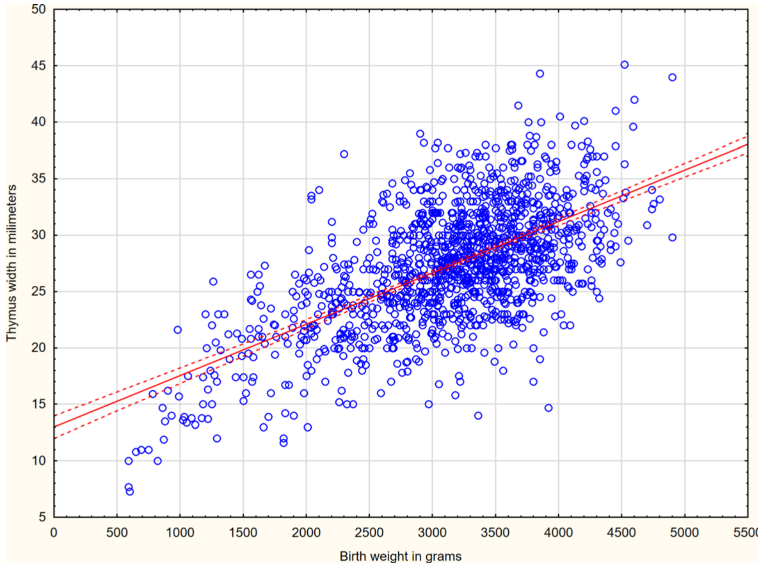

Fig. 3 Graph correlation between thymus width in millimetres and birth weight in grams

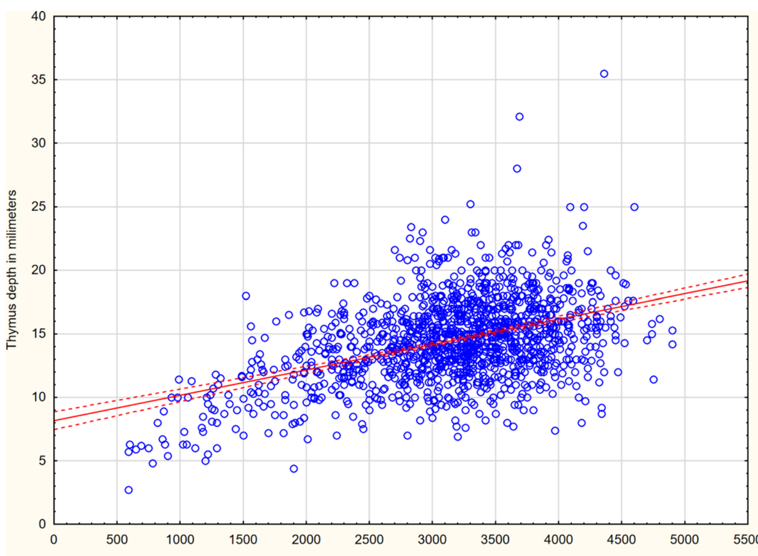

Fig. 4 Graph correlation between thymus depth in millimetres and birth weight in grams

Discussion

The PubMed database was searched, on January 2018, for manuscripts concerning thymic measurements in newborns. Following keywords were used: infant, newborn, premature, thymus gland; ultrasonography, thymic size, thymic index. Keywords were searched together after being set as "or" and "and" and were freely combined. Manuscripts published between 1996 and January 2018 concerning thymic measurements in were analyzed. All searches were without language restriction.

In the literature on this subject matter, researchers have undertaken similar analyses of the thymus size in both preterm and full-term neonates. Studies have focused on analysing the thymus size in relation to the following variables: birth weight, body length, gestational age, gender and feeding type. Notably, each of these studies was based on a small group of patients [4, 15–22] (Table 7). So far, there have been few descriptions of the thymus parameters in pre-term neonates [4, 15, 16].

The study was conducted on a group of 1,331 children, including 321 preterm neonates and 1,010 full-term neonates. After reviewing the available literature, This is the first paper to describe in detail the thymus size in preterm neonates and it appears to be the most comprehensive study of the thymus gland in full-term and preterm neonates.

Based on thymus measurements performed in full-term neonates, it was found that the average width of

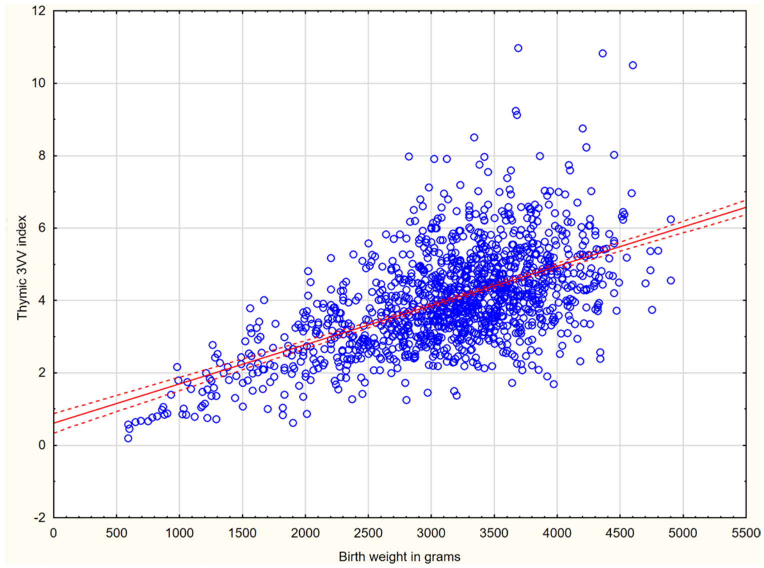

Fig. 5 Graph correlation between the TI 3VV and birth weight in grams

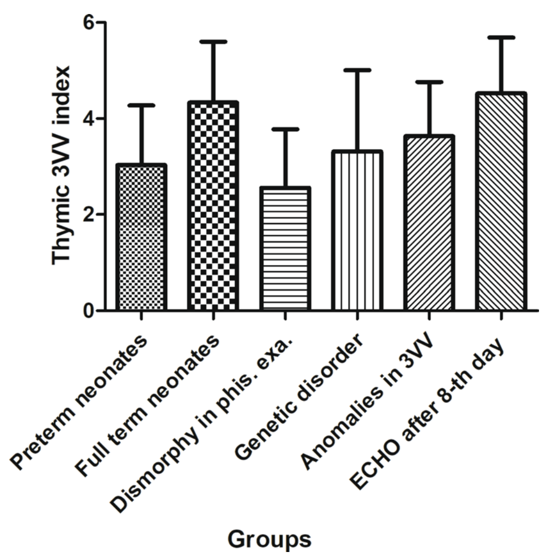

Fig. 6 Graph correlation between thymus width and body surface area (BSA) determined using the Haycock formula

the thymus in neonates is 28.58 mm SD±4.54 mm, the average depth of the organ is 15.03 mm SD±3.13 mm, and the average thymic 3VV index is 4.33, SD±1.26 mm (Table 2). The thymic 3VV index value differs from thymic index described by others authors (Table 7).

The difference results from a different method of assessing the size of the thymus. Available literature shows ultrasound scans of the thymus in neonates as a separate procedure. The thymic index is the product of multiplying the largest value of thymus width, depth and length. Due to thymic individual asymmetry, the researchers performed measurements without defined projection. In our study, we propose a new tool for assessing the size of the thymus, not yet described.

We have established a precise reference point for measuring the thymus. Thymus Dimensions are taken during echocardiography in one precise standard projection. It allows to repeat and compare studies between centers and observe the organ size over time. In the three-vessel view projection, the thymic 3VV index is calculated (3VV indicates that the value reffers to three vessel view projection and it is the product of two dimensions of the thymus: width and depth). The value is in mm2, therefore it is lower compared to other authors. We propose to use thymic 3VV index as a screening tool to assess size of the organ/thymus.

This study also includes data on the thymus dimensions of 321 preterm children. Given the diversity of this patient group, i.e., gestational age of 23–36 weeks and body weight of 590 – 4,340 g, the averaged values of thymus dimensions and TI 3VV do not reflect the real size of this organ. Therefore that group was divided into five subgroups based on body weight recorded at birth. For each of these subgroups, the mean values of thymus width, thymus depth and the thymic 3VV index were calculated separately (Table 3). In the available literature, measurements of the thymus size in preterm neonates were based on small study groups. Moreover, there are no data on the thymus size for various subgroups of preterm neonates, with only summary analyses being available (Table 7). This is the first paper to describe in detail the thymus size in preterm neonates.

Statistically significant differences in thymus depth and the thymic 3VV index were found for each group of preterm neonates except for the group with a birth weight of ≤999 g and 1,000 –1,499 g. This is presumably attributable to the small size of the group (Table 6).

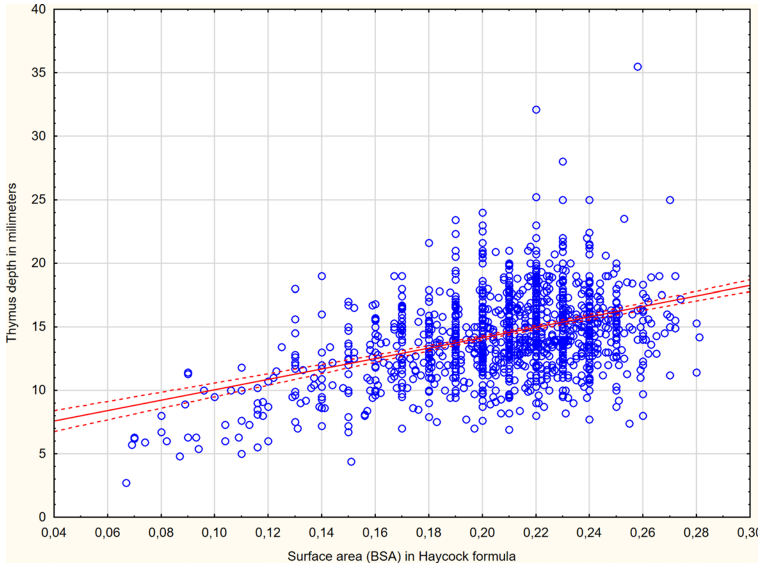

Fig. 7 Graph correlation between thymus depth and body surface area (BSA) determined using the Haycock formula

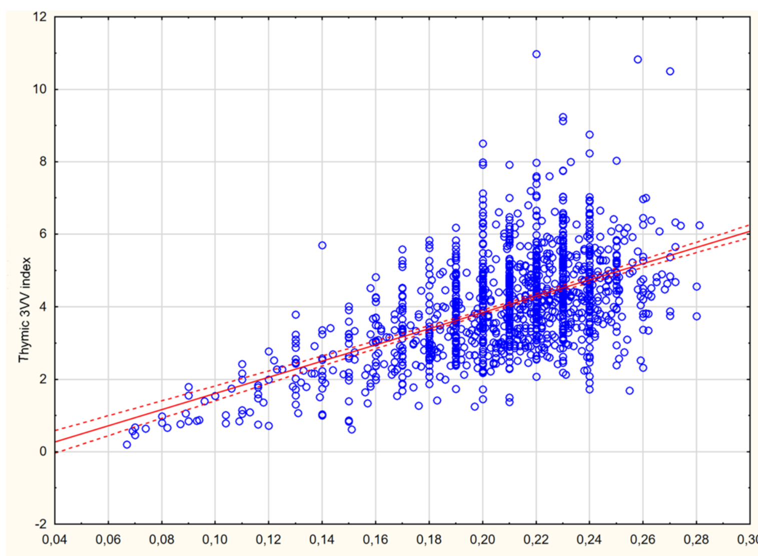

Fig. 8 Graph correlation between the TI 3VV and body surface area (BSA) determined using the Haycock formula in square metres

The differences in thymus width between the individual weight groups are not pronounced, which may be due to the fact that the thymus is situated between the right and left lung, and the aerated lung tissue renders it impossible to accurately measure the width of the gland. This can be particularly visible in preterm neonates who are mechanically ventilated or provided with non-invasive respiratory support.

Limitations

Potential risk of bias of the study was limitedThe examination was performed on the first days after birth. Therefore, potential impact of the timing of examination on the size of the thymus gland in neonates was excluded. At the time of the study, the children were either breast-fed or given breast milk from the Breast Milk Bank. Infants with mixed breast and formula feeding were excluded from analysis. The potential impact of the feeding type on the size of the thymus gland in neonates was excluded [4, 23, 24].

In the literature, there are two methods of the thymus size assessment using ultrasonography, i.e., the thymic index (TI) and the estimated volume of the thymus gland. The TI is calculated by multiplying the largest transversal width of the thymus and the sagittal area of the major thymus lobe, assessed in a longitudinal image [18]. Estimated volume of the thymus gland (is based on multiplying three diameters of each lobe). In the literature on the

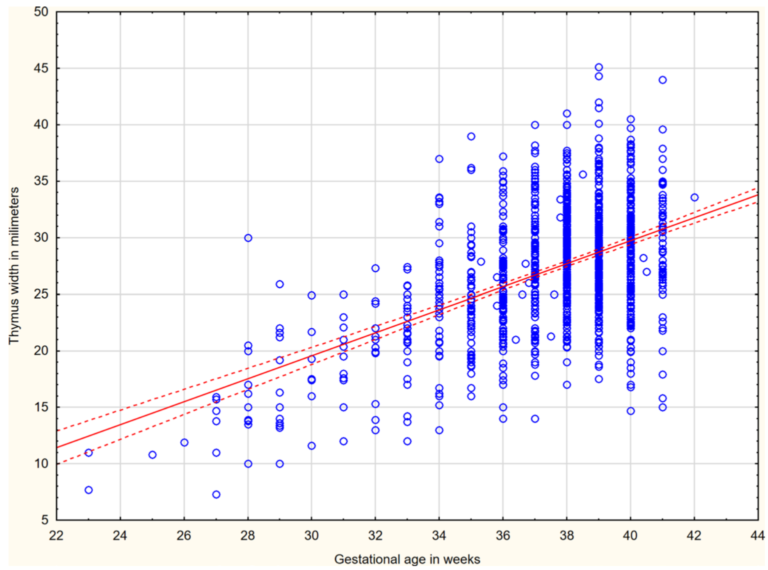

Fig. 9 Graph correlation between thymus width in millimetres and gestational age in weeks

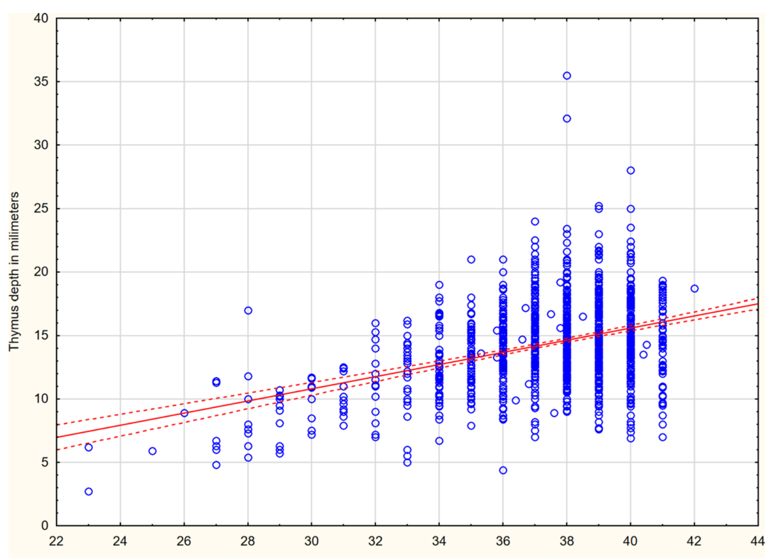

Fig. 10 Graph correlation between thymus depth in millimetres and gestational age in weeks

subject matter, researchers have based their observations on the thymus size assessment based on the TI defined above [4, 15–19, 21, 22]. Despite the fact that the TI does not reflect the actual weight and size of the thymus, it has been found to correlate well with the estimated volume of the thymus gland [21] and its volume in post-mortem examinations [18].

Of course, due to the asymmetry of the thymus gland – the right lobe being bigger than the left lobe – and because of numerous variations in the shape of the organ, the proposed method for determining the TI 3VV is not ideal. But neither was the TI calculated by previous researchers [4, 15–19, 21, 22].

Conclusions

Thymus size screening tests can facilitate therapeutic and diagnostic decisions. We propose three vessel view as a standard measuring scan in neonatal echocardiography protocol. The TI 3VV assessment is best done by referring to a child's weight or BSA at birth.

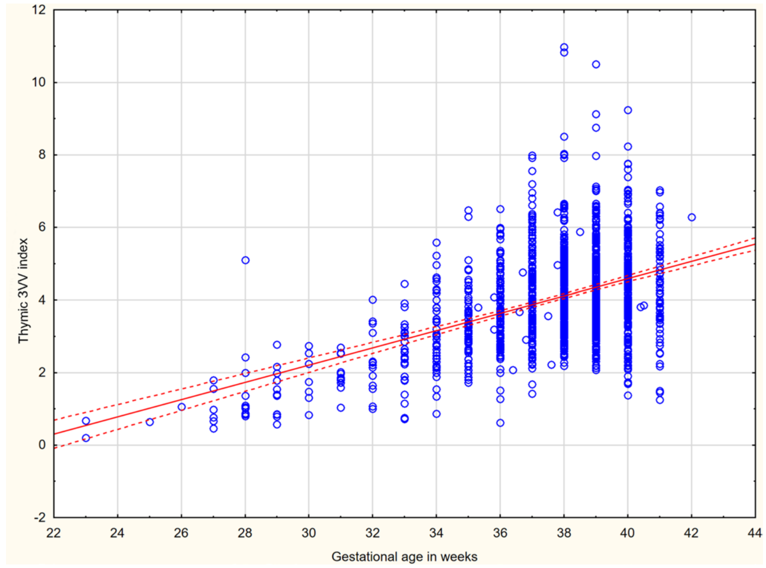

Fig. 11 Graph correlation between the TI 3VV and gestational age in weeks

Table 5 A summary of multiple regression analysis

	B	SD (B)	β	t	Sig. (*p*)
Constants			-3.4974	-98.725	0.00
Thymus width [mm]	0.5161	0.004	0.1324	104.639	0.00
Thymus depth [mm]	0.6534	0.004	0.27001	132.478	0.00

Note $R^2=0.9732$. $F(2.1328)=24{,}155$. $p<0.00001$

Table 6 Results of the significance analysis of the differences in thymus parameters in the groups of full-term and preterm neonates

Thymus parameters	Mann-Whitney U test				
	Sum.rank preterm	Sum.rank full-term	U	Z	*p*
Thymus width [mm]	126,495.0	759,951.0	74,814.00	-14.551	< 0.001
Thymus depth [mm]	149,454.5	736,991.5	97,773.50	-10.723	< 0.001
Thymic 3VV index [mm2]	126,188.5	760,257.5	74,507.50	-14.602	< 0.001

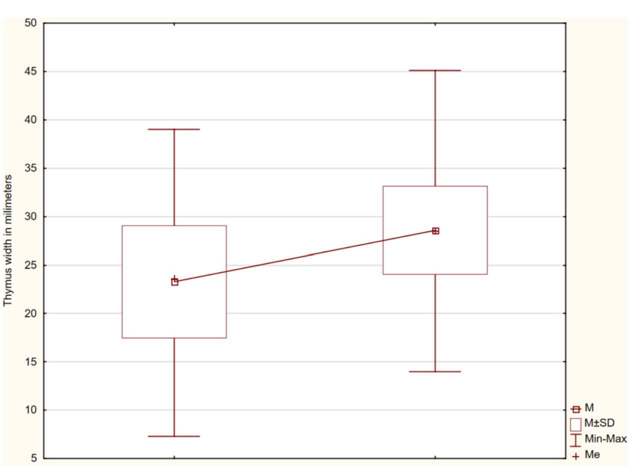

Fig. 12 Descriptive statistics of thymus width in the group of pre-term and full-term neonates

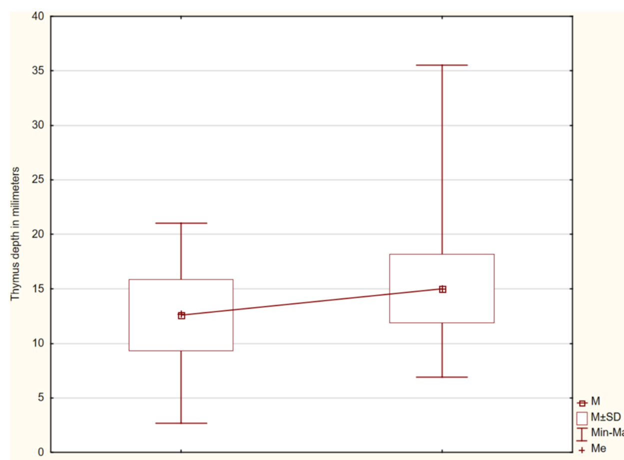

Fig. 13 Descriptive statistics of thymus depth in the group of pre-term and full-term neonates

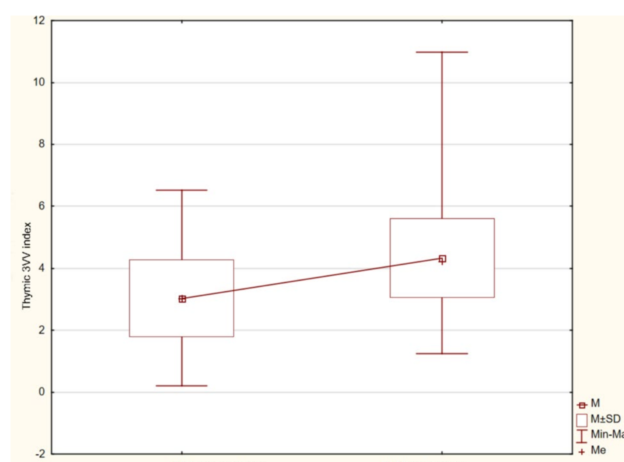

Fig. 14 Descriptive statistics of the TI 3VV in the group of pre-term and term neonates

Table 7 Mean values of thymus index according to several authors

	Author	*N*	Description of the study group	Average TI	Test duration	Ultrasound transducer	Test purpose:	Excluded group:
1.	Magu [15]	200	Preterm infants (26– 36 GA). India	4.7	day 0– 7	linear 5– 10 MHz	• Relationship of the thymic size in vivo in preterm neonates with gestational age (GA) birth weight (BW) and length of the body	Babies delivered by mothers with medical complications (pregnancy-induced hypertension, eclampsia, antepartum haemorrhage) and infants with heart defects
2.	Jeppensen [16]	80	Preterm infants (24– 36 GA). Denmark	5.2	day 0– 19	7.5 MHz (sector 60°)	• Assessment of the thymic size in vivo in preterm neonates • Relationship of the thymic size and gestational age (GA), birth weight, the occurrence of postnatal infections, and maternal alcohol and tobacco intake during pregnancy	• congenital malformations • congenital infections of children
3.	Yekeler [4]	151	Full-term – 131 + preterm-20. Istanbul	18.0 + 11.9	0– 2 years	7- MHz linear and 5– MHz sector probes (sector probe used in older infants)	• Assessment of thymic size changes with age and its relationship with gender, breast vs. formula feeding, and full-term or preterm status	Infants with: • mixed breast and formula feeding • thymic disease. • Severe infection/chronic illness • receiving steroids/chemotherapy
5.	Mehta [17]	250	Full-term. India	2.98	-	-	• Assessment of the thymic size in full-term healthy neonates • Assessment of the thymic size, shape, location, echogenicity and echotexture for both male and female reference populations	-
6.	Hasselbalch [18]	149	Full-term. Denmark	12	day 0–7	7 MHz sector probe (sector 112”)	• Assessment of the thymic size in full-term healthy neonates • Assessment of the correlation of the thymic size with weight, length, gender, gestational age, the level of perinatal asphyxia. and the distribution of mature T-lymphocytes	-
7.	Iscan [19]	65	Full-term. Turkey	13.6	-	7.5 MHz linear probe.	• Assessment of thymus volume	Neonates with: • congenital abnormality • birth trauma • neonatal infection • metabolic disorders
8.	Varga [21]	212	Full-term. Slovakia	9.08	day 3	10 MHz linear probe	• Comparison of the two ways of expressing the size of the neonates thymus: the Thymus index and estimated volume of thymus.	Neonates: • Born prematurely • with congenital infection • with chromosomal anomaly/malformation
9.	Ozkan [22]	220	Full-term. Turkey	9.12	day 1–2	10-MHz linear probe	• Relationship between the shape. size. diameter and thymic index values and gestational age, height and weight values	Excluded: • Septic neonates • cesarean section
10.	Our results	1,331	Full-term 1,010 + preterm (23–36 GA)-321	4.33 (full-term).	day 0–7	10 MHz sector probe (sector 60”)	• Thymus size analysis sTI 3VV • Assessment of the TI 3VV correlation with the child’s birth weight, gestational age and body surface area (BSA).	Neonates with: • cyanotic heart defects • aorta, pulmonary trunk or vena cava defects, mediastinal vascular abnormalities, • genetic syndrome, • dysmorphic features

Abbreviations

3VV	Three-vessel view of superior vena cava aorta and pulmonary trunk
TI	Thymic index
BSA	Body surface area
TI 3VV	Thymic index at the level of three vessel view
SGA	Small for gestational age
LGA	Large for gestational age
AGA	Appropriate for gestational age

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

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Author contributions

Dr Monika Wójtowicz-Marzec- conceptualization, data curation, methodology, investigation, project administration, resources, supervision, validation, visualization, writing original draft, review and editing. Dr Agnieszka Berendt-resources, writing original draft, formal analysis, review and editing. Dr Jacek Bogucki- formal analysis, software, writing review and editing All authors reviewed the manuscript.

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Data availability

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Declarations

Ethical approval

The study protocol was approved by the Bioethics Committee at the Medical University of Lublin (Consent No. KE-0254/279/2018).

Consent to participate

Informed consent was obtained from a parent or legal guardian for participation in the study.

Informed consent was obtained from a parent or legal guardian for publication of identifying information/images in an online open-access publication.

All methods were carried out in accordance with guidelines and regulations in the Declaration of Helsinki.

Consent for publication

Informed consent was obtained from parents or legal guardians for study publication in an online open-access publication.

Competing interests

The authors declare no competing interests.

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