HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2024.88155
Haydarpasa Numune Med J 2025;65(1):38–43

hnhtipdergisi.com

ORIGINAL ARTICLE

Does the Cardiothymic-Thoracic Ratio in Very Low Birth Weight Infants Indicate the Risk of Developing Bronchopulmonary Dysplasia?

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Abstract

Introduction: Fetal systemic inflammatory response triggered by infection and inflammation in preterm infants contributes to bronchopulmonary dysplasia (BPD) and preterm delivery. This study aims to determine whether there is a relationship between small thymus size and the risk of developing BPD.

Methods: The cardiothymic/thoracic (CT/T) ratio was measured on AP chest X-ray obtained within the first 6 hours of life in very low birth weight (VLBW) infants weighing less than 1500 g between 2018 and 2023. Clinical information was collected independently from electronic medical records by two neonatologists. The demographic data of the infants included gestational age, mode of delivery, gender, birth weight, and Apgar scores at 5 and 10 minutes.

Results: A total of 195 VLBW newborns (102 boys, 93 girls) were included in the study. The mean gestational age was 28.5 weeks, and the mean birth weight was 1074 grams. There was a statistically significant difference in the incidence rates of BPD by gestational age. The risk of BPD was 6.702 times higher in babies born weighing less than 1000 grams. The CT/T ratio was significantly lower in infants who developed BPD compared to those who did not.

Discussion and Conclusion: The thymus is an essential organ for the immune system. In our study, the finding that lower birth weight and gestational age were associated with a smaller CT/T ratio suggests a higher rate of inflammation, leading to increased morbidity and mortality. Identifying preterm infants with a small thymus may help clinicians recognize those at high risk for developing BPD.

Keywords: BPD; CT/T ratio; thymus size.

The thymus is a vital organ that plays a significant role in T-cell development in the fetal immune system. Morphological maturation of the thymus occurs between the 16th and 20th weeks of gestation.[1]

Infections and inflammation are associated with mortality and morbidity in preterm infants. In cases of infection/inflammation, maternal prostaglandin production induces the proliferation of proinflammatory T cells. This process is also linked to preterm birth and affects the developing fetüs.[2,3] These mechanisms contribute to the development of bronchopulmonary dysplasia (BPD) and cerebral palsy (CP) through the fetal systemic inflammatory response.[4,5]

Additionally, intrauterine infections can alter thymus size, and smaller thymus size has been associated with increased infant mortality in various fetal and neonatal diseases.[6]

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Submitted Date: 23.05.2024 **Revised Date:** 01.10.2024 **Accepted Date:** 10.10.2024
Haydarpaşa Numune Medical Journal

The aim of this study is to determine whether there is a relationship between small thymus size and the risk of developing BPD.

Materials and Methods

This was a single-center, retrospective, observational cohort study. Participants were preterm infants with a birth weight <1500 grams who received care at the hospital between January 2018 and January 2023 and had chest radiographs. The study was conducted according to the principles of the Declaration of Helsinki. Ethics committee approval was obtained on February 22, 2023, with the reference number 2023/0123. All clinical data from the electronic health record were extracted and used for this study.

Infants who survived less than four weeks, had confirmed severe congenital anomalies, or did not have a portable anteroposterior (AP) X-ray within the first six hours of life were excluded.

Bronchopulmonary dysplasia (BPD) was defined as the requirement for supplemental oxygen at 36 weeks corrected gestational age. Chest radiographs were performed according to widely accepted technical standards, including appropriate X-ray dose, symmetrical appearance, and visualization of at least six anterior ribs above the diaphragm.

On the routine AP supine chest X-ray, the transverse thymic width at the level of the carina and the transverse thoracic width, passing through the bilateral cardiophrenic sinuses, were measured. The cardiothymic/thoracic (CT/T) ratio was calculated as the ratio between the width of the cardiothymic image at the level of the carina and the transverse diameter of the thorax at the level of the costophrenic angles (Fig. 1). Based on previous literature, a CT/T ratio <0.28 was considered small.[7]

Clinical information was collected independently from electronic medical records by two neonatologists who were unaware of the radiological findings. Maternal characteristics included gestational hypertension, prolonged premature rupture of membranes (PPROM) for more than 18 hours, and antenatal corticosteroid administration (number of betamethasone doses). Demographic data of the infants included gestational age, mode of delivery, gender, birth weight, and Apgar scores at 5 and 10 minutes.

Statistical Analysis

Statistical analyses were performed using SPSS 22 for Windows (IBM Corp., NY, USA). Conformity of the parameters to normal distribution was evaluated using the Kolmogorov-Smirnov test. Student's t-test was used to compare normally distributed parameters between two groups, while the Mann-Whitney U test was used to compare non-normally distributed parameters.

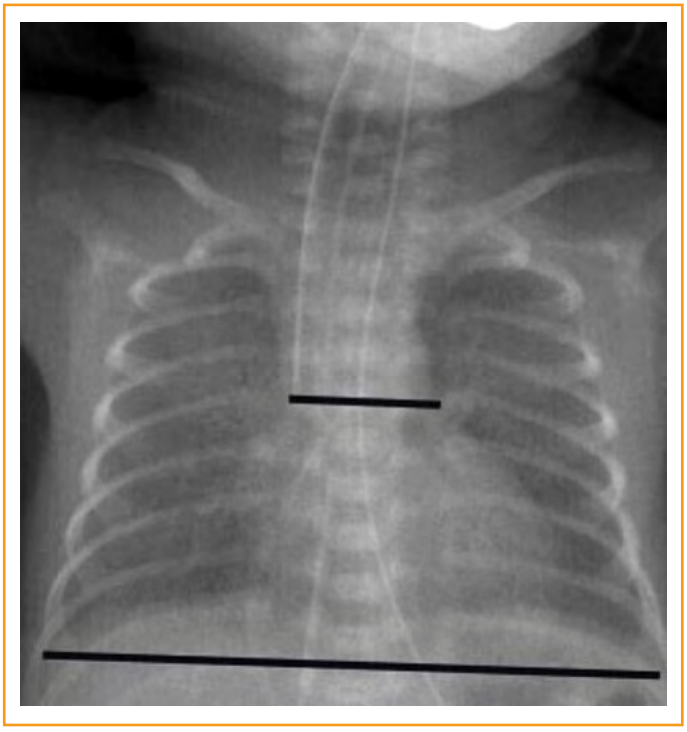

Figure 1. CT/T in VLBW preterm infants is measured on portable anteroposterior chest radiographs by dividing the width of the cardiothymic image at the level of the carina by the transverse diameter of the thorax at the level of the costophrenic angles.

For qualitative data, the Chi-square test and Continuity (Yates) correction were used. Odds ratios were calculated using risk assessment. Pearson correlation analysis was applied to examine relationships between normally distributed parameters. Logistic regression analysis was used for multivariate analysis. Statistical significance was set at $p<0.05$.

Results

A total of 195 newborns with very low birth weight (VLBW) (102 boys, 93 girls) were included in the study. The gestational age of the infants ranged between 22.3 and 34 weeks, with a mean value of 28.59±2.63 weeks. Of these, 31 (15.9%) infants were born between 22-26 weeks, 95 (48.7%) between 26-30 weeks, and 69 (35.4%) between 30-34 weeks. Their birth weights ranged between 480 g and 1500 g, with a mean value of 1074.24±281.65 grams. The birth weight of 79 (40.5%) infants was less than 1000 g, while 116 (59.5%) infants weighed 1000 grams or more. The clinical characteristics of the two groups are presented in Table 1.

Table 1. Descriptive findings on study parameters

	Mean±SD	Min.	Max.
Gestational age (wk)	28.59±2.63	22.3	34
Birth weight (g)	1074.24±281.6	480	1500
Apgar1 (median)	4.93±2.08 (5)	0	9
Apgar 5 (median)	7.24±1.71 (8)	1	10
Antenatal steroid dose (median)	2.44±1.05 (2)	1	4
CT/T ratio	0.29±0.05	0.17	0.47
		n	**%**
Gestational age (wks)			
22-26		31	15.9
26-30		95	48.7
30-34		69	35.4
Birth weight (g)			
<1000 g		79	40.5
≥1000 g		116	59.5
Gender			
Male		102	52.3
Female		93	47.7
Mode of delivery			
C/S		179	91.8
SVD		16	8.2
PROM			
(+)		44	22.6
(-)		151	77.4
Gestational hypertension			
(+)		69	35.4
(-)		126	64.6
BPD			
(+)		116	59.5
(-)		79	40.5

PROM: premature rupture of membranes; C/S: cesarean section; SVD: Spontaneous vaginal delivery.

The incidence of BPD in infants born with a birth weight of less than 1000 g (83.5%) was statistically significantly higher than in those with a birth weight of 1000 grams or more (43.1%) (p=0.001; p<0.05). The risk of BPD was 6.702 times higher in infants born with a birth weight of less than 1000 grams (OR=6.702; 95% CI=3.331-13.483).

The incidence of BPD was 59.8% in boys and 59.1% in girls, with no statistically significant difference. The BPD rate was 58.1% in infants born by cesarean section and 75% in those born by normal delivery, with no statistically significant difference. Similarly, the incidence of BPD was 61.4% in patients with PPROM and 58.9% in those without PPROM, showing no statistically significant difference. The incidence of BPD was 62.3% in infants of mothers with hypertension during pregnancy and 57.9% in infants of mothers without hypertension, with no statistically significant difference.

Table 2. Correlation of thymus size with the week of birth, birth weight, and number of antenatal steroid doses

	Thymus /Thoracic Ratio
Gestational age(wks)	
r	0.243
p	0.001*
Birth weight (g)	
r	0.279
p	0.001*
Number of antenatal steroid doses	
r	0.061
p	0.446

Pearson correlation analysis; *p<0.05

Table 3. Factors associated with BPD

	BPD, n (%)		p
	(+)	(-)	
Gestational age (wks)			
22-26	27 (87.1)	4 (12.9)	[1]0.001*
26-30	71 (74.7)	24 (25.3)	
30-34	18 (26.1)	51 (73.9)	
Birth weight (g)			
<1000 g	66 (83.5)	13 (16.5)	[2]0.001*
≥1000 g	50 (43.1)	66 (56.9)	
Sex			
Male	61 (59.8)	41 (40.2)	[1]0.925
Female	55 (59.1)	38 (40.9)	
Mode of delivery			
C/S	104 (58.1)	75 (41.9)	[2]0.292
SVD	12 (75)	4 (25)	
PROM			
(+)	27 (61.4)	17 (38.6)	[2]0.910
(-)	89 (58.9)	62 (41.1)	
Pregnancy Hypertension			
(+)	43 (62.3)	26 (37.7)	[1]0.551
(-)	73 (57.9)	53 (42.1)	
CT/T ratio (meant±SD)	0.28±0.05	0.30±0.05	[3]0.019*
Antenatal steroid doses (Mean±SD (median))	2.45±1.08 (2)	2.44±0.1 (2)	[4]0.907

Chi-square test [1]Continuity (yates) correction; [3]Student t test; [4]Mann Whitney U test; *p<0.05.

There was no statistically significant difference in the doses of antenatal steroids administered between infants who developed BPD and those who did not (Table 2).

There was a statistically significant difference in BPD incidence rates by gestational age (p=0.001; p<0.05). The risk of BPD in infants born between 22-26 weeks was 19.125 times higher than in those born between 30-34 weeks (OR=19.125; 95% CI=5.879-62.213). The risk of BPD

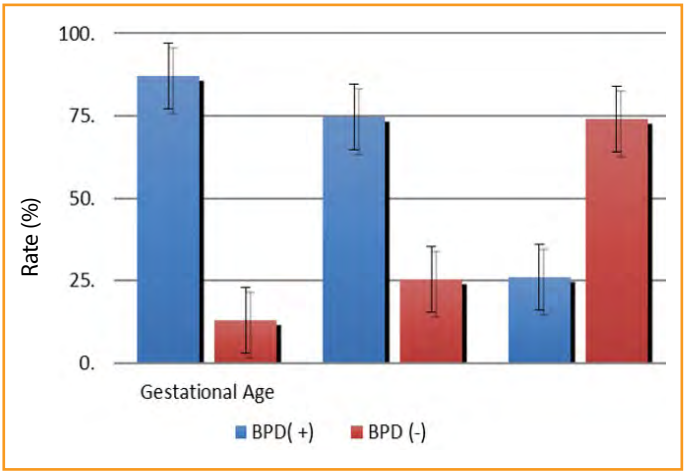

Figure 2. The graph of BPD incidence rates by gestational week shows that the risk of BPD increases as the gestational week decreases.

in infants born between 26-30 weeks was 8.382 times higher than in those born between 30-34 weeks (OR=8.382; 95% CI=4.124-17.034) (Table 3). BPD incidence rates by gestational week are shown in Figure 2.

There was a weak positive correlation (24.3%) between gestational age and thymus size, which was statistically significant (p=0.003; p<0.05) (Table 4). The correlation graph between gestational age and CT/T ratio is shown in Figure 3A. Similarly, there was a weak positive correlation (27.9%) between birth weight and thymus size, which was also statistically significant (p=0.001; p<0.05). The correlation graph between birth weight and CT/T ratio is shown in Figure 3B.

Table 4. Evaluation of thymus size according to birth week with and without BPD

	CT/Tratio	
Gestational Age(wks)	**BPD (+)**	**BPD (-)**
22-26	0.27±0.04	0.28±0.03
26-30	0.29±0.05	0.30±0.06
30-34	0.28±0.06	0.30±0.05
p	0.374	0.825

Table 5. Factors associated with the development of BPD

		95% C.I. for OR		
Step 2	**OR**	**Lower**	**Upper**	**p**
Birth weight (<1000 g)	3.056	1.281	7.291	0.012*
22-26 w	8.156	1.815	36.655	0.006*
26-30 w	5.152	2.378	11.159	0.001*

[a]Variable(s) entered on step 1: Birth weight (g), Gestational age(w), CT/T ratio.

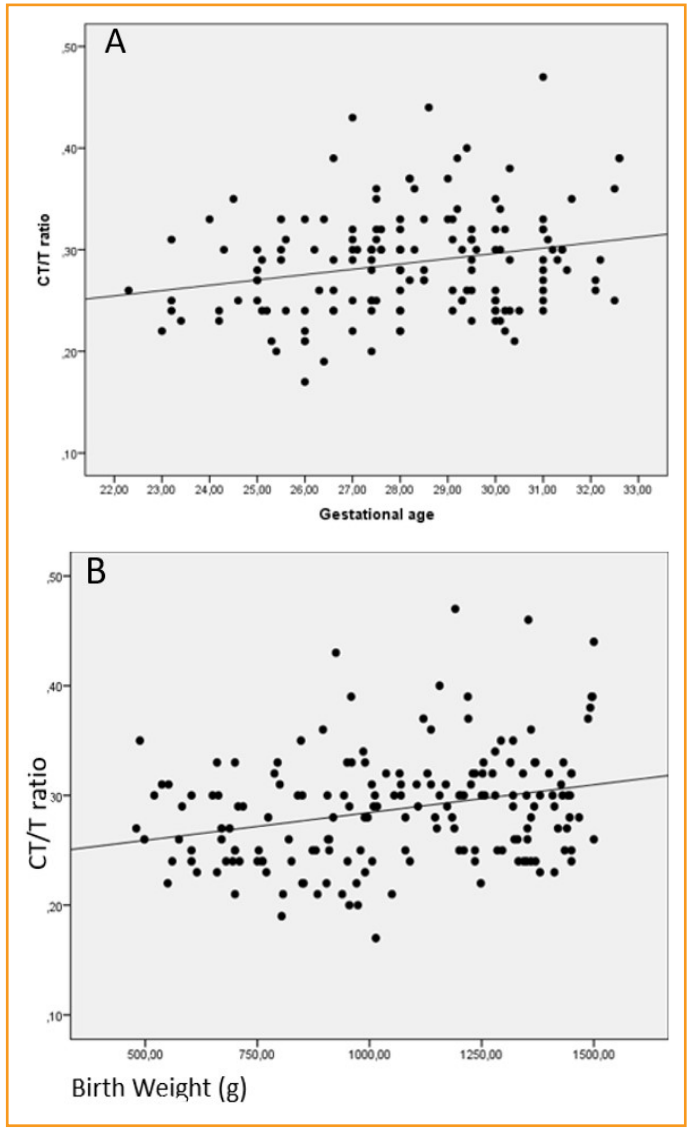

Figure 3. Correlation of thymus size with gestational age **(a)** and birth weight **(b)**. Thymus size increases with increasing gestational age and birth weight.

When we evaluated the effects of birth weight, gestational age, and thymus size on the presence of BPD using backward stepwise logistic regression analysis, the model was found to be statistically significant (p=0.001; p<0.05). The Nagelkerke R-square value was 0.335, and the explanatory coefficient of the model (75.6%) was at a reasonable level. The effects of birth weight and gestational age on the model were statistically significant. It was observed that:

- A birth weight below 1000 g was associated with a 3056-fold increased risk of BPD.
- Being born between 22-26 weeks was associated with a 8156-fold increased risk of BPD.
- Being born between 26-30 weeks was associated with a 5152-fold increased risk of BPD (Table 5).

Discussion

According to National Institute of Child Health and Human Development data, the BPD rate is 23% in babies born with a birth weight between 501-1500 g, 57% in those between 501-750 g, 32% in those between 751-1000 g, 14% in those between 1001-1250 g, and 6% in those between 1251-1500 g. The rate of BPD in infants under 1000 g has been reported as 89%. In our study, this rate was found to be 83.5%, which is comparable to current studies and statistically significantly higher compared to infants over 1000 g (43%).

As mentioned in the methods section, a small thymus (CT/T ratio ≤0.26) in VLBW infants has been associated with BPD and chorioamnionitis.[8,9] De Felice et al.[9] evaluated thymus size in 400 VLBW infants, whereas 51 patients with BPD were assessed in their study. They reported that a small thymus (CT/T<0.28) was observed in 94.1% of infants who had BPD and in 2.9% of infants who did not have BPD. On the other hand, our study included 195 patients with VLBW and 116 patients with BPD and, to the best of our knowledge, is the most extensive study on this topic. In our study, the mean CT/T ratio was found to be 0.28 in infants who had BPD and 0.30 in those who did not have BPD.

In contrast, Chen et al.[10] showed that the CT/T ratio was higher in premature newborns with respiratory distress syndrome (RDS) compared to preterm neonates without RDS.[10] This suggests that thymus involution during the perinatal period is a complex process influenced by blood cortisol levels. Higher serum cortisol levels may involute the thymus in preterm neonates without RDS, while serum cortisol concentrations were significantly lower in those who developed RDS. The CT/T ratio was found to be higher in preterm infants born by cesarean section, which was attributed to higher serum cortisol levels during vaginal delivery.

Additionally, Jeppesen et al.[11] demonstrated a relationship between postpartum infection and thymus size. Thymic involution has been suggested as a stress-related condition resulting from the activation of the hypothalamic-pituitary-adrenal (HPA) axis during pregnancy.[12] In VLBW infants, a small thymus at birth has been associated with high cortisol levels.[13]

Compared to ultrasound, chest radiography is more commonly used to estimate thymus size in preterm infants. Our study demonstrated a positive, weak, statistically significant correlation between birth weight and thymus size (p=0.001). These results suggest that VLBW infants with a small thymus on chest radiographs at birth may have a higher risk of developing BPD.

Fetal thymus size is sensitive to pregnancy complications.[14] Aspiration of amniotic fluid may cause congenital pneumonia in the immature fetus. It has been shown that an inflamed lung in neonates may be more susceptible to injury caused by barotrauma or oxygen toxicity compared to a normal lung.

The inflammatory source should be considered multidimensionally in the development of BPD. Inflammatory cell formation may start with chorioamnionitis in the intrauterine period.[15] Di Naro et al.[12] concluded that a small thymus was found in cases of intraamniotic infection/inflammation. This study demonstrates that a strong relationship exists between the presence of laboratory and histologic signs of intrauterine infection and fetal thymic involution in preterm labor patients. Antenatal infection and inflammation render the premature infant's lungs more vulnerable to injury, which can be the main factor causing BPD.[16]

The main weakness of our study was the limited number of patients and, thus, the lack of statistical power, though we found statistically significant results. The most important limitation of our study was that we did not have the opportunity to examine antenatal infection and chorioamnionitis, which might have affected thymus size. Another limitation of the study was its retrospective design.

Conclusion

The thymus is an essential organ for the immune system. In our study, the finding that the smaller the birth weight and gestational week of the preterm, the smaller the CT/T ratio suggested a higher rate of inflammation and, hence, a higher rate of morbidity and mortality. Identifying premature babies with a small thymus can help clinicians identify infants who carry a high risk of developing BPD, and interventions like the initiation of dexamethasone therapy after the first week of life may be appropriate.[17]

Ethics Committee Approval: The study was approved by Istanbul Medeniyet University Ethics Committee (No: 2023/0123, Date: 22/02/2023).

Peer-review: Externally peer-reviewed.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept – S.G.B., H.F.O., D.S.; Design – S.G.B., D.S.; Supervision – H.F.O.; Data collection &/or processing – S.G.B., D.S.; Analysis and/or interpretation – S.G.B., H.F.O., D.S.; Literature search – S.G.B., H.F.O., D.S.; Writing – S.G.B., D.S., H.F.O.; Critical review – S.G.B., H.F.O., D.S.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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