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Original Article

Paediatrics Section

Can Cardiothymic Thoracic Ratio be a Marker of Mortality in Preterm Neonates with Respiratory Distress Syndrome?

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ABSTRACT

Introduction: Thymic size is measured as Cardiothymic: Thoracic ratio (CT/T ratio) in chest X-ray. In a state of stress, the thymus tissue rapidly involutes, owing principally to the thymocytolytic effect of glucocorticosteroids. Different pre and postnatal factors affect thymic size in neonates.

Aim: To determine the thymic size in preterm neonates with Respiratory Distress Syndrome (RDF), its relation to survival to determine which antenatal and postnatal factors influence thymic size.

Materials and Methods: This prospective observational study was carried out in neonatal units of tertiary care hospital in North India from May 2018 to September 2019. Premature (<37 weeks gestation) neonates admitted in NICU with clinical and radiological evidence of RDS were included in the study. CT/T ratio was measured in chest X-ray. The quantitative data was presented as mean and standard deviation (SD) and were compared using student t-test, one-way ANOVA test and continuous non parametric data were compared using Pearson correlation coefficient test.

Results: Mean age of 110 studied neonates was 32.07±1.76 weeks. The mean±SD CT/T in the study was 0.361±0.043. Mean CT/T ratio (0.372±0.043) of non survivor (44) was higher (0.356±0.043) than survivor neonates (66). This difference was statistically not significant (p-value=0.058). Mean CT/T ratio >0.361 has sensitivity 59.09% and specificity 68.18% for non survivor group. Logical regression analysis for probability of survival showed that as CT/T ratio increases probability of survival decreases. Mean CT/T ratio was not affected by gestational age, sex, mode of delivery, use of antenatal steroid, pre-eclampsia, mother's parity, perinatal asphyxia and sepsis.

Conclusion: The mean CT/T ratio was higher in non surviving neonates with RDS as compared to those who survived. Mean CT/T ratio is a poor predictor for mortality in premature neonates with RDS.

Keywords: Newborns, Predictor, Prematurity, Thymic tissue

INTRODUCTION

Thymus is an important organ with immunologic functions and provides the environment for T lymphocyte differentiation and maturation [1]. The thymus is susceptible to involution in response to severe stress such as malnutrition, physical stress, graft-versus-host disease, acute RDS, trauma and sepsis [1]. This stress related involution appears to be mediated by the activation of Hypothalamic-Pituitary-Adrenal (HPA) axis [2].

After birth, HPA axis is important to maintain hemostasis and to respond to stress. The activation of HPA axis leads to a surge in serum corticosteroids which has been shown to have a thymocytolytic effect [2,3]. RDS causes stress and as a result thymic involution may be expected due to fetal inflammatory response syndrome [4].

Thymus size in premature infants can be measured by different methods, by ultrasonography or by chest radiograph expressed as CT/T ratio [5,6]. According to previous report, there are no significant relationships between CT/T ratio and birth route, sex, birth weight, or gestational age in term infants [6]. However, others demonstrated that small thymus is associated with low birth weight [7], histologic chorioamnionitis [1,8], bronco pulmonary dysplasia [7], intrauterine growth retardation [1,9] and decreased survival in RDS neonates compared with normal thymus [7,10].

The CT/T ratio had been reported to be higher in neonates with RDS than in those who did not have RDS [11], while one study reported a significant relationship between a small thymus and RDS [12]. Not all factors influencing the size of the thymus are known. Hence, the study was undertaken to determine whether thymic size in infants with RDS is related to survival or not.

Primary objective of present study was to assess the thymus size expressed as CT/T ratio radiographically in preterm neonates

with RDS and its role in prediction of mortality of newborns with RDS. Secondary objective of this study was to determine which antenatal and postnatal factors influence CT/T ratio.

MATERIALS AND METHODS

This prospective observational study was carried out in 110 preterm neonates with RDS at neonatal units of tertiary care hospital in Northern India during May 2018 to September 2019. The study was conducted according to the guidelines and approved by the Institutional Ethics Committee with the approval number 254/MC/EC/2020. Written informed consent was obtained from all parents or guardians before enrolment.

Inclusion criteria: Premature (<37 weeks gestation) neonates admitted in NICU with clinical (Silverman's score ≥3) [13] and radiological evidence (low lung volume, air bronchogram, bilateral symmetrical diffuse granular opacity) of RDS were included in study.

Exclusion criteria:

1. Congenital cardiac malformations.
2. Congenital anomalies like pulmonary hypoplasia, congenital emphysema, oesophageal atresia and diaphragmatic hernia.
3. Infants with a chest X-ray that is excessively rotated or the cardio-thymic shadow cannot be differentiated from that of the lungs owing to severe RDS.
4. Neonates who had already received surfactant prior to chest X-ray.
5. Refused consent.

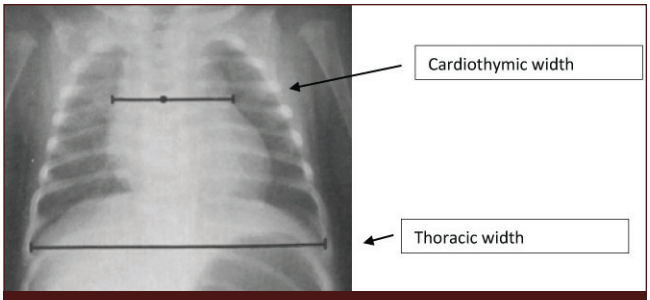
Sample size calculation: Sample size was calculated using the formula: $(n) = (Z_{1-\alpha/2})^2 (\sigma)^2/(d)^2$, where n= desired no of samples, $Z_{1\alpha/2}$=Standardised value for corresponding level of confidence (At 95% CI, it is 1.96 in two tailed and 1.64 in one tailed test), d= Margin of error or rate of precision, σ=SD which is based on previous study [14].

Sample size was calculated at 95% confidence interval and α-error of 0.05, assuming standard deviation of 0.026 in the mean CT/T ratio 0.367 as measured on chest X-ray among the preterm neonates with RDS as per the reference article [14]. At an absolute error/precision of 0.005 in the variation of CT/T ratio the required sample size was $n=(1.96)^2 (0.026)^2/(0.005)^2=104$ which was rounded off to 110 cases of preterm neonates with RDS.

Study Procedure

Predesigned structured proforma devised by investigators was used for history and data collection. Face validity was done by research review board and senior faculty among the researchers in department who had enough experience in neonatal care. After taking written consent from all parents/guardians and applying inclusion criteria and exclusion criteria, detailed antenatal and natal history was taken. Their mothers were analysed for mode of delivery, antenatal steroid administration, Pregnancy Induced Hypertension (PIH) and parity. Newborn examination included birth weight, assessment of gestational age by new Ballard score [15] and complete clinical examination including temperature recording, crown-rump length, mouth, eye, ear, umbilical cord, limbs, spine, heart, lung, abdomen and genitalia. Silverman WA and Andersen DH scoring was used for assessment of respiratory distress [13]. Preterm neonates with RDS were managed in NICU as per institutional protocol and neonatal outcome assessed by survival or death.

Thymus size was expressed as CT/T ratio by measuring the width of the cardio-thymic shadow at the level of carina and dividing it by the width of the thorax at the costo-phrenic angles by a single radiologist who was blinded to the identity and the clinical course of the patient [14]. For each X-ray chest, three readings were taken and their average was considered as the final CT/T ratio [Table/Fig-1].



[Table/Fig-1]: X-ray chest of a newborn with RDS. Cardiothymic: Thoracic ratio (CT/T) was calculated by measuring the width of the cardio-thymic shadow at the level of carina and dividing it by the width of the thorax at the costo-phrenic angles.

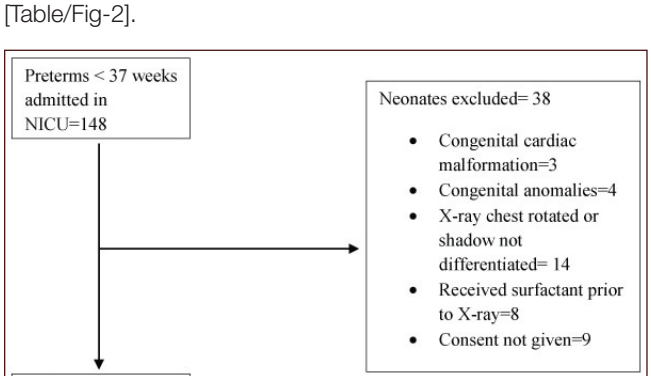
STATISTICAL ANALYSIS

Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). The categorical data was presented as numbers (per cent) and compared among groups using Chi-square test. The quantitative data was presented as mean and standard deviation and compared by student t-test, one-way ANOVA test whereas, continuous non parameteric data was compared using Pearson correlation coefficient test. Probability of survival graph was analysed by logical regression Cox and Snell R2 model. ROC curve analysis was done for non survival group. Probability was considered to be significant if less than 0.05.

RESULTS

Total 148 preterm neonates with RDS were admitted in NICU for management. Finally 110 newborn were included in the

study after exclusion of 38 neonates due to various reasons [Table/Fig-2].



[Table/Fig-2]: Shows how neonates were enrolled in the study.

Mean gestational age was 32.07±1.76 weeks and mean birth weight was 1496.18±364.18 grams. Demographic characteristics of study population are shown in [Table/Fig-3].

Parameters	No of patients (%)†
Birth weight (grams)	1496.18±364.18*
Gestational age (Weeks)	32.07±1.76*
Sex	
Male	59 (53.63%)
Female	51 (46.36%)
Mode of delivery	
Vaginal	76 (69.09%)
Caesarean	34 (30.91%)
Antenatal factors	
Pre-eclampsia	11 (10%)
Antenatal steroid (2 doses of Betamethasone)	17 (15.45%)
Postnatal factors	
Birth asphyxia	13 (11.81%)
Sepsis (Sepsis screen on 1st day, repeated after 3 days)	16 (14.54%)
Not survived	44 (40%)

[Table/Fig-3]: Demographic characteristics of the newborns.
*=mean±SD; †=Number of patients (%)

The mean±SD cardiothymic thoracic ratio (CT/T) in the study was 0.361±0.043. Mean CT/T ratio of birth weight <1000 g was statistically significant as compared to higher weight groups (p-value=0.034). The mean CT/T ratio of neonates requiring ventilation vs neonates not requiring ventilation was statistically significant (p-value=0.040). Requirement of surfactant was statistically significant in neonates with higher mean CT/T ratio. (p-value=0.017) [Table/Fig-4].

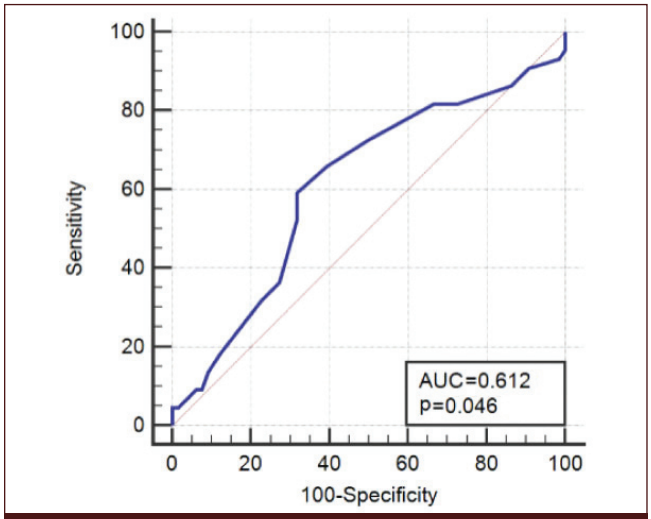
Mean CT/T ratio of non survivor (0.372±0.043) was higher than survivor (0.356±0.043). This difference was statistically not significant (p-value=0.058). There was no statistically significant difference in the mean CT/T ratio in relation to gestational age, sex, mode of delivery, use of antenatal steroid, pre-eclampsia, mother's parity, perinatal asphyxia and sepsis [Table/Fig-4].

Parameter		Mean CT/T ratio	p-value
Birth route	Vaginal delivery	0.365±0.043	0.145
	Caesarean section	0.352±0.044	
Birth weight (in grams)	<1000	0.401±0.047	0.034
	1000-1500	0.351±0.043	
	>1500	0.353±0.044	
Gestational age (in weeks)	<30	0.381±0.046	0.068
	30-34	0.351±0.043	
	34-36	0.352±0.046	
Sex	Male	0.36±0.043	0.231
	Female	0.35±0.044	
Antenatal steroid	Yes	0.364±0.044	0.792
	No	0.361±0.043	
Pre-eclampsia	Yes	0.360±0.044	0.884
	No	0.362±0.043	
Mother's parity	1	0.362±0.045	0.722
	2	0.361±0.044	
	≥3	0.352±0.045	
Ventilatory support required	Yes	0.376±0.047	0.040
	No	0.356±0.043	
Surfactant need	Yes	0.380±0.045	0.017
	No	0.358±0.043	
Sepsis Screen	Positive	0.344±0.046	0.091
	Negative	0.364±0.043	
Delayed cry	Yes	0.350±0.047	0.313
	No	0.363±0.043	
Outcome	Survived	0.356±0.043	0.058
	Not survived	0.372±0.043	

[Table/Fig-4]: Relationship of mean CT/T ratio with various demographic, antenatal and postnatal factors.
Student's t-test in birth weight, gestational age, mother's parity, survival outcome and in rest variables Chi-Square test were used; Level of significance was 0.05

There was poor negative correlation observed between birth weight and mean CT:T ratio, which was significant. (r=-0.247, p=0.009). Mean CT/T ratio >0.361 has specificity 68.18% and sensitivity 59.09% for non survivors (p-value=0.046), Area under the ROC curve (AUC)=0.612 [Table/Fig-5].

As mean CT/T ratio increases, probability of survival decreases. Odd ratio-0.0002, 95% confidence interval- 0.00 to 1.607 [Table/Fig-6].



[Table/Fig-5]: ROC curve analysis of non survived neonates with RDS.
Mean CT/T ratio >0.361 has specificity 68.18% and sensitivity 59.09% for non survival; (p-value=0.046), Area under the ROC curve (AUC)= 0.612

[Table/Fig-6]: Relation of mean CT/T ratio to probability of survival.
As mean CT/T ratio increases, probability of survival decreases; Odd ratio- 0.0002; 95% confidence interval- 0.0000 to 1.6071; Cox and Snell R^2 test used; Significance level was 0.05

DISCUSSION

In present study mean birth weight was 1496.18±364.18 grams in preterm with RDS and mean CT/T ratios were statistically significant in extremely low birth weight neonates than low birth weight (p-value=0.034). In accordance with present study, Wasim S et al., observed similarly trends [14].

In present study, mean gestational age was 32.07±1.76 weeks and mean CT/T ratio did not reach statistical significance for babies with gestational age <30 weeks (p=0.068). Similarly other studies conducted by Chen CM et al., Tooke LJ et al., and Wasim S et al., observed similar trend in mean gestational age and CT/T ratio of babies [6,8,14]. In study conducted by Hasselbalch H et al., there was no significant correlation between the thymic index and gestational age [16]. This difference could be due to use of ultrasonography for thymus measurement rather than CT/T ratio by chest X-ray.

In present study, mean CT/T ratio was not dependent on the sex of baby (p= 0.231). Other studies conducted by Tooke LJ et al., and Wasim et al., also observed similar trend [8,14]. In contrast to present study, Semercia SY et al., observed high mean CT/T ratio for female than male [17]. This could be due to high variability of sample size i.e., N=172.

In present study, investigators tried to find the relationship between mean CT/T ratio and mode of delivery of preterm neonates with RDS and observed high ratio in vaginally delivered neonates. Similar to present study, Tooke LJ et al., found higher ratio in vaginally delivered neonates [8] but other studies conducted by Chen CM et al., Wasim S et al., and Semerci SY et al., found higher ratio in neonates delivered by lower segment caesarean section [6,14,17]. This contrast observation could be due to difference in sample size and significantly high number of caesarean deliveries in other studies by Chen CM et al., (75%), Wasim S et al., (55%) and Semerci SY et al., (97.7%) as compared to present study (31%) [6,14,17].

Investigators in present study looked for effect of antenatal corticosteroids on CT/T ratio given to mothers of premature neonates with RDS. They found no difference in CT/T ratio of neonates irrespective antenatal use of corticosteroid in their mothers. In contrast to present study, other studies conducted by Tooke LJ et al., Wasim S et al., and Semerci SY et al., observed high CT/T ratio in neonates whose mothers did not receive antenatal corticosteroids [8,14,17]. This difference could be because of use of antenatal corticosteroids in small number of mothers 17 (15.46%) in present study.

Present study confirms high mean CT/T ratio observed by Tooke LJ et al., and Semerci SY et al., of neonates born to mothers who did not have PIH than whose mothers had PIH [8,17]. In present study, mean CT/T ratio was higher in neonates who did not require ventilator as compared to those required ventilator. Similar results were observed by study done by Wasim S et al [14].

In present study, mean CT/T ratio for those who required surfactant was statistically significantly higher than who did not require surfactant (p-value=0.017). In contrast to present study, a study conducted by Semerci SY et al., observed no difference in CT/T ratio on the basis of surfactant use [17]. This could be due to inclusion of preterm neonates between 30-34 weeks gestational age only for CT/T ratio comparison. Most of the neonates with RDS less than 30 weeks of gestation received surfactant therapy in their study; authors could not compare the CT/T ratio of this gestational age group.

Investigators in present study endorse the observations of study done by Wasim S et al., to see the effect of delayed cry after birth on CT/T ratio [14]. Both the studies agree upon high ratio in neonates who had history of delayed cry after birth.

In a study conducted by Hasselbalch H et al., there was no significant correlation between the thymic index and asphyxia [16]. This could be because of use of ultrasonography rather than chest X-ray for thymus size assessment.

In present study, mean CT/T ratio was more in without sepsis newborns than with sepsis newborn. Similar to our study, Wasim S et al., and Semerci SY et al., also reported high ratio in neonates without sepsis [14,17]. In a study conducted by Glavina Durdov M et al., on preterm neonates found that infection was more often associated with thymic involution than RDS [18].

The mean±SD CT/T in this study was 0.361±0.043 which was smaller than the mean of 0.40 found by Chen CM et al., [6]. Present study confirmed the observations reported by Tooke LJ et al., and Wasim S et al., [8,14]. Chen CM et al., reported that CT/T ratio was significantly greater in preterm with RDS than without RDS [6]. The underlying mechanisms remain unclear. Stress related thymus involution appears to be mediated by endogenous corticosteroids, which are released in stress. Corticosteroids can promote apoptotic cell death of cortical thymocyte. Preterm neonates had significantly lower cord blood cortisol levels compared to term neonates. Of the preterm neonates, serum cortisol concentrations were lower in those who developed RDS. Higher serum cortisol level may involute thymus in the preterm neonates without RDS [6].

Of the 110 neonate studied by us, 44 (40%) expired. In present study mean CT/T ratio of non survivor (0.372±0.043) was higher than survivor 0.356±0.043. This difference was statistically not significant (p=0.058). Present study confirmed the result of Wasim S et al., [14].

Higher CT/T ratio in non survivor neonates may be due to decrease in lung volume that is associated with severe RDS. Prolonged intrauterine stress has been shown to cause involution of the thymus.

Contrast to present study, Tooke LJ et al., reported statistically significant higher mean CT/T ratio of survivor than non survivor [8]. This could be due to difference in inclusion of cases <33 weeks gestation and high (53%) mortality in neonates was due to sepsis/necrotising enter colitis.

There was poor negative correlation observed between birth weight and mean CT:T ratio, which was significant. (r=-0.2473, p=0.009). Semercia SY et al., found that birth weight and CT/T ratio have positive correlation [17]. Varga I et al., found the highest correlation of thymus size with birth weight [19].

Mean CT/T ratio >0.361 has specificity 68.18% and sensitivity 59.09% for non survival. (p=0.046), Area under the ROC curve (AUC)=0.612. A paper published by Mandrekar JN states that an AUC of 0.5 suggests no discrimination (i.e., ability to diagnose patients with and without the disease or condition based on test, in this case mortality in patient with RDS), 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent and more than 0.9 is considered outstanding [20].

Limitation(s)

The measurements of CT/T ratio on chest radiograph is an indirect method for representing thymus size. Thymic size may differ according to the position of the infant. The authors did not evaluate serum cortisol levels which is secreted due to the stimulation of HPA axis and might be responsible for thymic involution. Measuring thymic index by USG may be an alternative and further studies can be done using USG to determine the correlation between CT/T and thymic index. In present study there are a very low number of neonates who received antenatal steroid.

CONCLUSION(S)

The mean CT/T ratio was more for non survived preterm neonates with RDS as compared to those who survived. Mean CT/T ratio is a poor predictor for mortality in premature neonates with RDS. Thymic size is not affected by sex, mode of delivery, antenatal use of steroid, gestational age, mother's parity, sepsis. Thymic size significantly affected by birth weight, use of surfactant and ventilator. The authors recommend that further studies can be done using USG to determine the correlation between CT/T and thymic index along with serum cortisol levels.

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