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Comparison of thymus size in normal versus malnourished children

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ABSTRACT

Background. Undernutrition has a detrimental effect on lymphoid organs like thymus that are responsible for production of T cells. Severe thymus gland atrophy has been observed in children with severe acute malnutrition. Hence, this study was aimed to measure thymus size in children with normal, moderate, and severe acute malnutrition who were hospitalized to the pediatric ward.

Methodology. A prospective observational study was conducted in pediatric ward with 60 children aged between 6 to 59 months. Based on the inclusion and exclusion criteria 20 children each were randomly selected as normal, moderate acute malnourished child and severe acute malnourished child. Anthropometric and thymic measurements were taken. Data was analyzed in SPSS v 29. ANOVA test and Post hoc Tukey HSD were done to find the difference.

Results. Thymic index was also high among normal children when compared to malnourished children. This infers statistically significant thymus atrophy among the malnourished when compared to healthy children. Pairwise comparison of means using post-hoc Tukey HSD revealed significant difference between normal children and those children with malnourishment ($p < 0.001$).

Conclusion. The present investigation concluded that malnourished patients have thymic atrophy and recurrent infections. Hence thymic measurement can be used as a tool to detect immunological modifications in children with malnourishment.

Keywords: malnutrition, thymic index, immunity, children, immunodeficiency, thymus

INTRODUCTION

A nutritional deficit brought on by an insufficient intake of calories or protein is known as malnutrition [1]. The American Society of Parenteral and Enteral Nutrition (ASPEN) defines pediatric malnutrition as "an imbalance between nutrient requirement and intake, resulting in cumulative deficits of energy, protein, or micronutrients that may negatively affect growth, development, and other relevant outcomes [2]."

In 2022, it was anticipated that 37 million children under the age of five were overweight or obese, 149 million were stunted and 45 million were wasted on a global scale [3]. According to NHFS-5 (India 2019–21), malnourishment (wasting, stunting and underweight) in children under the age of five has decreased from 21% to 19.3%, 38.4% to 35.5% and 35.8% to 32.1%, respectively, in comparison to NHFS-4 (India 2015-16) [4].

Undernutrition is a contributing factor in over half of fatalities in children under the age of five in low- and middle-income nations. Notably, India bears one-third of the worldwide burden of undernutrition [5].

Undernourished children are more susceptible to acute infections because undernutrition weakens the immune system and causes varying degrees of immunodeficiency. Undernutrition has a detrimental effect on the primary and secondary lymphoid organs that are responsible for responding to associated infections through immunosuppression. One such organ affected is the thymus, the main lymphoid organ that produces T cells [6].

The thymus is a retrosternal organ located in the superior mediastinum. It is bilobed with two com-

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ponents namely the cortex and medulla [7]. Thymopoiesis is a lifelong process that slows down with age as aging causes the thymus to shrink and lose some of its functions. However, the proliferation of intrathymic T cells is a continuous activity, the cessation of a particular harmful stimulation (malnourishment) leads way to restore the function back to normal steady state [8].

Amongst several mechanisms linking malnutrition to thymic atrophy, few proven mechanisms are that both acute and long-term protein deficiency can result in thymocyte depletion. As reported by Mitsumori et al., increased thymocyte death and decreased thymocyte proliferation appear to be the causes of malnutrition-related thymocyte depletion. Also, the imbalance between the synthesis of glucocorticoid hormones (which are elevated) and leptin (which is decreased) in malnutrition settings is at least largely to blame for the thymocyte depletion and subsequent organ shrinkage. [9]

Several studies have reported severe thymus gland atrophy in children with severe acute malnutrition [10]. According to studies by Garly et al patients with more severe atrophy may also have more severe immunological impairment [11]. This finding thus helps the clinicians to identify the underlying unidentified immunological impairment. Hence, this study was aimed to measure thymus size in children with normal, moderate, and severe acute malnutrition who were hospitalized to the pediatric ward at Chettinad Hospital and Research Institute.

MATERIALS AND METHODS

This is a cross-sectional study and was conducted between June 2023 and June 2024 in a tertiary care hospital, Chengalpattu. The Institutional Ethics Review Board authorized the study procedure, which was carried out in accordance with good clinical practice. The study population comprises of normal children and those children with moderate and severe acute malnutrition aged between 6 to 59 months admitted in pediatric ward. A total of 60 such children (20 normal children, 20 moderate acute malnourished and 20 severe acute malnourished children) were enrolled after obtaining informed written consent from their parents. Normal children were defined by weight-for-height between -2 and 2 z-scores and mid-upper arm circumference more than 12.5cm and without any acute or chronic illness. Moderate acute malnutrition (MAM), also known as wasting, is defined by a weight-for-height indicator between -3 and -2 z-scores (standard deviations) of the international standard or by a mid-upper arm circumference (MUAC) between 11.5 cm and 12.5 cm [12]. Severe Acute Malnutrition (SAM) was defined as mid-upper arm circumference (MUAC) <11.5 cm or weight for height Z score (WHZ) ≤ -3 SD or bipedal pitting edema [13]. We also include apparently healthy children but whose WHZ was between 2 to -2 z score were used as the reference thymus size for non-malnourished children in the same setting. Using convenient sampling method those fulfilling the eligibility criteria were included in the study.

Data of previous medical history, demographic profile was collected using a questionnaire. Anthropometric measurements like Length or height will be measured using an infant length board and MUAC using a measuring tape, both to the nearest 1 mm. Body weight was measured using a digital weighing scale to the nearest 0.1 kg. The WHZ were calculated using the Child Growth Standards of the World Health Organization (WHO) [14].

Thymus size was measured by the radiologist using ultrasonography. The procedure was done with the child lying on the back or in the mother's lap. Thymus sonography was performed on a real time scanner (Logiq P9 R3, GE Healthcare) using a single Linear (12 MHz) frequency transducer, to avoid variability. First the thymus was located and visualized in the anterior mediastinum, in longitudinal and axial planes by trans-sternal, supra-sternal and para-sternal approaches with the child in supine position.The thymus was identified as a homogenous well defined echo poor structure, with echogenicity close to the liver or spleen. Using the trans-sternal approach in axial plane, the maximum transverse diameter of the thymus was measured, followed by the maximum antero-posterior (AP) diameter on the right and left sides (average of right and left diameters was taken as the mean AP diameter). The transducer was then oriented longitudinally, and the largest sagittal area was measured according to the circumference drawn along the thymus on the monitor and a software built into the ultrasound scanner was used to assess the area.The thymic index which is an estimate of the thymic volume, was then ascertained using the method by Hasselbalch et al [15], by multiplying the largest transverse diameter and the largest sagittal area of the thymus (Figures 1, 2).

Statistical analysis

The data collected were entered in Microsoft Excel spreadsheet and analyzed using IBM SPSS v 29. The descriptive statistics of categorical variables were expressed in terms of frequency and percentages, for continuous variables it is expressed as mean and standard deviation. To find the significant difference in the multivariate analysis the one-way ANOVA with Tukey's Post-Hoc test was used and p value <0.05 was considered statistically significant.

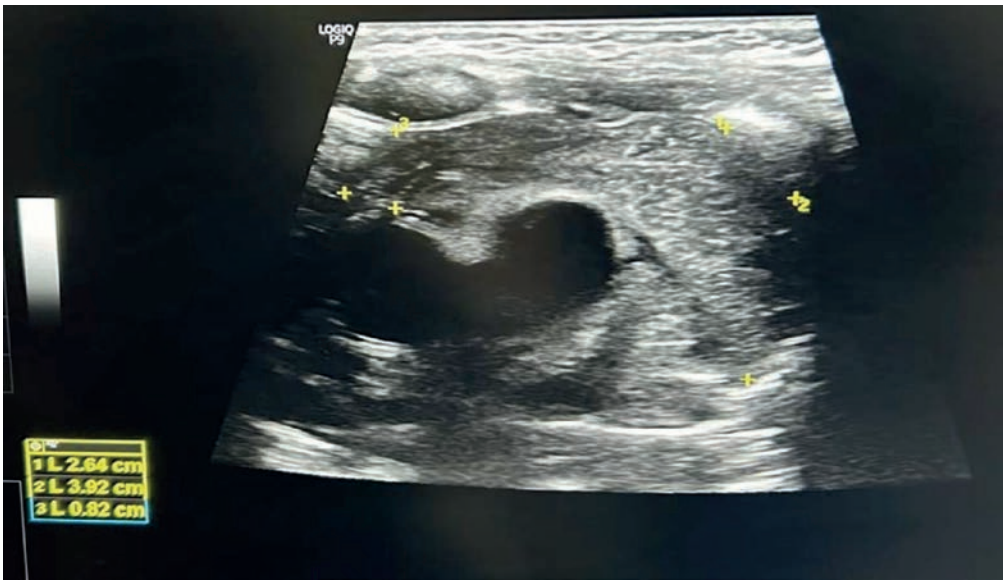

FIGURE 1. Thymus in an axial plane using the trans-sternal approach. The largest transverse diameter (labeled as numeral 2) is measured, along with the maximum anterior-posterior (AP) diameters on the left (numeral 1) and right (numeral 3) sides of the thymus.

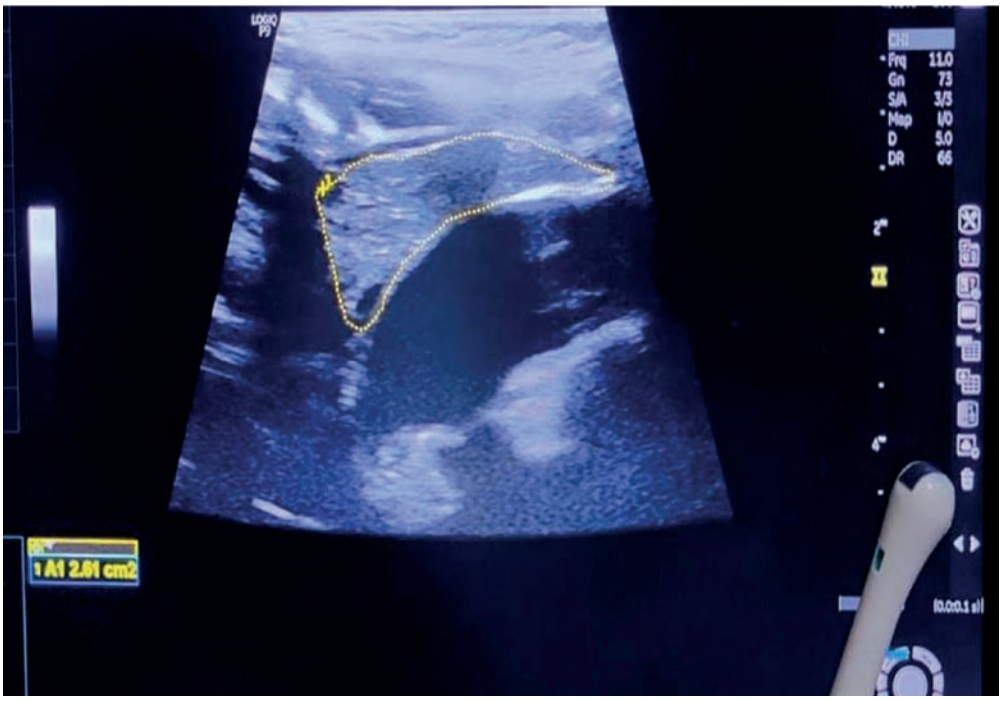

FIGURE 2. Thymus in its longitudinal plane. In this plane the largest sagittal area of the delineated thymus is calculated

RESULTS

The mean age of the study participants is 26.2 ± 15.9 months. Majority of those participated were between the age of 1 to 3 years. It was noted that children with malnourishment had increased history of recurrent infection. The mean MUAC was found to be 13.4 ± 1.5 cm (Tables 1, 2).

Table 3 depicts the thymic measurements recorded among the study participants. After adjusting for age, the mean thymus gland size was found to be 3.7 ± 1.3 cm^2. The mean thymic index was found to be 13.7 ± 7.1.

TABLE 1. Demographic characteristics of the participants

Characteristics	Number	Percentage
Age		
Up to 1 yr	18	30.0
1-3 yrs	24	40.0
3-5 yrs	18	30.0
Gender		
Male	31	51.7
Female	29	48.3
Recurrent infection		
No	45	75.0
Yes	15	25.0

TABLE 2. Anthropometric details of the participants

Characteristics	Mean ± SD
Weight	9.8 ± 2.9
Height	83.5 ± 13.4
Mid upper arm circumference	13.4 ± 1.5
Head circumference	45.6 ± 3

TABLE 3. Thymus measurements of the participants

Characteristics	Mean ± SD
Thymus length	2.9 ± 0.8
Width	1.9 ± 0.9
Area	3.7 ± 1.3
Thymic index	13.7 ± 7.1

The mean thymus gland size among the healthy children was 4.6 ± 0.73 cm^2 when compared to 3.37 ± 1.10 cm^2 in MAM and 3.17 ± 1.41 cm^2 in SAM children. Similarly, Thymic index was also high among normal children when compared to malnourished children. This infers statistically significant thymus atrophy among the malnourished when compared to healthy children (Table 4). This shows that the thymus is a sign of immunological failure, the SAM children's smaller thymus indicates immunodeficiency. Also, in children with SAM, immune failure constitutes one of the causes of potentially fatal infections. Recurrent infection rate was higher in children with decreased thymic index (Table 5).

TABLE 4. Association between malnutrition and thymus size

Characteristics	Normal	MAM	SAM	P value
Thymus length	3.76±0.36	2.55±0.69	2.53±0.60	0.0005
Width	2.69±0.69	1.8±0.78	1.33±0.79	0.0005
Area	4.6±0.73	3.37±1.10	3.17±1.41	0.0005
Thymic index	19.51±4.72	11.24±5.74	10.41±6.9	0.0005

*ANOVA test, $p < 0.05$ is significant

TABLE 5. Association between recurrent infection and thymus index

Characteristics	Recurrent infection		P value
	Yes	No	
Thymic index	40	20	0.0005

*Unpaired t-test, $p < 0.05$ is significant

Pairwise comparison of means using post-hoc Tukey HSD revealed significant difference between normal children and those children with malnourishment ($p < 0.001$)

DISCUSSION

Several postmortem studies and ultrasound findings have documented thymus atrophy in malnourished children [16]. The present study showed thymic index of 10.41 ± 6.9 cm^3 whereas it was 19.51 ± 4.72 cm^3 among the normal children. The mean thymus gland size among the healthy children was 4.6 ± 0.73 cm^2 when compared to 3.37 ± 1.10 cm^2 in MAM and 3.17 ± 1.41 cm^2 in SAM children. Also, history of recurrent infection was higher among the SAM children when compared to normal children. Similar results with decreased thymus size among malnourished were reported in studies by Nabukeera B et al [16], Nassar MF et al [18], Chevalier et al [19], Rytter MUH et al [20] and Parent G et al [21]. Similarity in the results amongst the compared studies may be owed to the similarity in methodology of the studies and similar age group of the study population.

It has been suggested that thymus atrophy in malnourished children may represent the immunological inadequacy brought on by malnutrition, making them more vulnerable to infections. Children with a small thymus had a greater mortality risk in community-based research [22]. This suggests that thymus size could be a marker of competent immune system, or simply an indicator of good health thereby validating the concept of the thymus as a "barometer of malnutrition" [23].

However, the process of thymus atrophy in malnutrition is unclear. Hormonal factors appear to have a role, according to animal research. A number of hormones, controlled by insulin-like growth factor 1 include prolactin, leptin and growth hormone. These hormones are known to control the growth and functioning of the thymus (hinder thymic regeneration and function) according to animal research [24]. Additionally, thymic atrophy may be exacerbated by zinc insufficiency, which is common in malnutrition. It affects thymocyte proliferation and differentiation, leading to reduced thymic output and thymic involution. [25]. Thymic atrophy has also been observed to be exacerbated by infections, albeit it is unclear if this is the result of an infection or its cause [26].

The limitation of the study are as followed: i) as it is a cross-sectional study the role of causality cannot be demonstrated. Hence a prospective study is recommended to know the causality; ii) small sample size makes it difficult to generalize the study results to community settings; iii) the inability to assess long-term impacts of thymic atrophy on immune function or recovery. Further clinical studies focusing on nutrient-based interventions and their impact on thymic regeneration are needed.

CONCLUSION

The present investigation concluded that malnourished patients have thymic atrophy. Malnourished child's immune systems will probably be im-

pacted by these alterations, which could be harmful given their early age. Though they could take longer to resolve than physical recovery, immunological modifications are fortunately reversible with nutritional therapy. Hence thymus size can serve as a gauge of the severity of the disease and an indicator of immune dysfunction in cases of severe acute malnutrition. As a conclusion, we advise a thorough evaluation of malnourished child's immune system through thymic parameters both during and after nutritional rehabilitation, until they completely recover.

To address the present's studies limitations, a longitudinal study with larger sample sizes can be considered to observe changes in thymus size over time and to explore the relationship between thymic atrophy and specific infections.

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