

## Original Research Article

# Thymus size and its changes during treatment of children with severe acute malnutrition

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## ABSTRACT

**Background:** The study was conducted to radiologically demonstrate increase in thymus size with clinical recovery following nutritional rehabilitation in children with severe acute Malnutrition and to correlate the improvement with anthropometric and biochemical parameters.

**Methods:** Prospective observational study was conducted in 60 children in the age group of 6 months to 24 months with severe acute malnutrition. Children with severe systemic illnesses were excluded from study. After obtaining informed consent from parents, history focusing on demography, perinatal events, nutrition including breast feeding and immunization status were recorded. Anthropometric parameters were measured. All relevant blood investigations and ultra-sonogram of the chest for thymus size were done. All children were followed up during the course of hospital stay till discharge and were also followed up after 2 months. Relevant blood investigations and ultrasonogram of chest for thymus size were also done during follow up.

**Results:** The difference in means of thymic area by imaging at admission and at discharge ( $p$  and  $lt;0.0001$ ) and at admission and after 8 weeks ( $p$  and  $lt;0.0001$ ) were statistically significant. The increase in weight, length, weight for length, mid upper arm circumference, hemoglobin, total protein, serum albumin, serum globulin from admission to discharge and from discharge to 8 weeks after admission was statistically significant.

**Conclusions:** Thymus size can be used as a marker of immunological dysfunction in severe acute malnutrition and as a marker of severity of the illness. The thymus size was found to be increasing in size during nutritionally rehabilitation and recovery from the illness. Correlations between anthropometric parameters and thymic size are not robust in under-nourished state and during nutritional rehabilitation.

**Keywords:** Immunological dysfunction, Nutritional rehabilitation, Severe acute malnutrition, Thymic size

## INTRODUCTION

Severe acute malnutrition (SAM) is associated with 1 million to 2 million childhood mortality every year. It is one of the most important preventable causes of childhood mortality each year. The impairment of immune functions associated with malnutrition may be one reason for the high mortality in children with severe acute malnutrition, and thymic atrophy has been proposed as a marker of this immunodeficiency. The study done by

Rytter et al, found negative correlation of severity of malnutrition with thymic size and C-reactive protein level.<sup>1</sup> A study was conducted by Moore SE et al, concluded that thymic size in early infancy predicted later mortality.<sup>2</sup>

Again, after systematic review of 3402 related articles, Rytter et al, concluded that the immunological alterations associated with malnutrition in children may contribute to increased mortality.<sup>3</sup> Varg I et al, found positive

correlation with thymic size and neonatal anthropometric parameters.<sup>4</sup>

Though previous studies have documented that thymic atrophy is reversible when malnutrition is treated, little is known about the factors and causes that determine thymus growth with nutritional rehabilitation.<sup>5-8</sup>

This Institution being the largest Pediatric centre in South east Asia, catering to pediatric population across the state, probably, has the maximum number of nutritionally challenged in-patients. Hence, determining the anatomical status of the thymus in such children, before and after therapy, could well be used as an established objective marker for assessing the recovery in children with SAM.

## METHODS

Children aged 6 months to 24 months presenting with severe acute malnutrition admitted were included in the study. Children with Severe respiratory distress requiring intubation and inotropic support at admission, with low hemoglobin (<4gm%), with debilitating infections like HIV, Tuberculosis were excluded from study.

After obtaining informed consent from parents, demographic data regarding age, sex and locality was collected. History regarding the complaints for which the child was admitted to the hospital was noted. History regarding the neonatal period like birth weight of the child and hospitalization for any illness was noted. History regarding breast feeding practices whether exclusively breast fed or not, given any other type of milk (animal or commercial) apart from breast milk was also taken. History regarding developmental milestones was asked. Immunization status of the child whether completely or partially immunized was also asked.

Detailed clinical examination including anthropometry like weight, height/length, mid upper arm circumference, head circumference measured as per prerequisites was done. Systemic examination including cardiovascular system, respiratory system, abdominal system and neurological system was done. Presence of edema or wasting was noted. All relevant blood investigations done were noted down. Ultrasonogram of the chest for thymus size was done. In infants sonographic estimate of the thymic index, volume of the thymus seems to be easy, reliable and reproducible.<sup>9,10</sup>

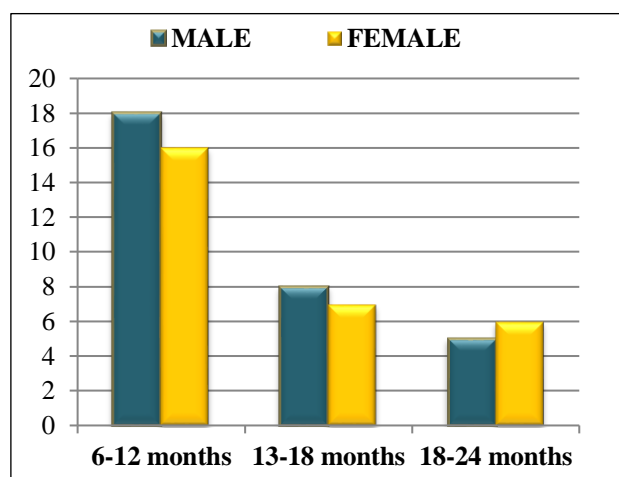
All children were followed up during the course of hospital stay till discharge and was also followed up after 2 months. Relevant blood investigations and ultrasonogram of chest for thymus size was also done during follow up. The size of the thymus was measured on day 1 or 2 of admission, at discharge and after 8 weeks after admission in follow up by qualified radiologist. Thymus size was measured using a ultrasound with a pediatric abdominal probe. The thymus

was identified as a poor homogenous echo structure in mediastinum anterior to and around the great vessels and the heart. The trace area of the largest lobe of thymus was measured with a transducer placed on the child's chest over the sternal bone in a sagittal projection through the chest.

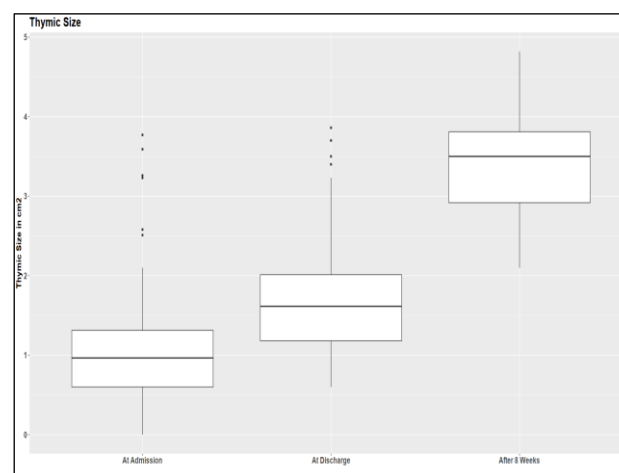
The statistical tests including parametric and non-parametric tests were done in R programming Language (R version 3.4.4 (2018-03-15) - "Someone to Lean On"). Bar charts and boxplots were created by GGPlot2 package (H. Wickham. Ggplot 2: Elegant Graphics for Data Analysis. Springer-Verlag New York, 2016). The computing platform was x86\_64-Arch-Linux-gnu (64-bit).

## RESULTS

Among 60 children, 34 children belonged to 6-12 months of age. 15 of them were between 13 and 18 months of age and 11 were between 19-24 months of age. 31 (51.67%) were male children and 29 (48.33%) were female children (Figure 1).



**Figure 1: Age and sex distribution in study group.**



**Figure 2: Boxplots of thymic sizes.**

Among 60 SAM children, 22 (36.67%) children were from urban area and 38 (63.33%) were from rural area. 19 (31.67%) were not exclusively breast fed for 6 months and 41 (68.33%) were exclusively breast fed for 6 months. All the children had appropriate development for age. 31 children were immunized to date. 29 children were partially immunized.

Fever, cough and breathlessness, diarrhoeal illness, anemia, apathy and organomegaly are major presenting

features. 8 (13.33%) had pus cells in urine and 3 (5%) had positive urine albumin. 42 (70%) had normal study in Chest X-ray and 18 (30%) had abnormal study in Chest X-ray. All the children were Mantoux negative and none was tested positive for HIV serology. Anthropometric and laboratory parameters are given in Table 1.

Thymic size increased from a mean level of 1.11 cm<sup>2</sup> at the time of admission to a level of 3.39 cm<sup>2</sup> at or after discharge (Figure 2).

**Table 1: Changes in anthropometric and laboratory values.**

Parameter	At admission (Mean±sd)	At discharge (Mean±sd)	p value	After 8 weeks (Mean±sd)	p value
Weight (gm)	6432±1121	7213±1132	<0.0001	8716±1150	<0.0001
Stature (cm)	72.07±6.4	72.58±6.3	<0.0001	74.9±5.9	<0.001
MUAC (cm)	10.9±1.17	11.3±1.1	<0.001	12.73±0.69	<0.001
Hemoglobin (gm)	8.25±2.16	-	-	10.72±0.80	<0.001
Sr. Albumin (gm/dl)	3.42±0.43	-	-	3.90±0.28	<0.001
Sr. Globulin (gm/dl)	2.65±0.44	-	-	3.0±0.29	<0.001
Sr. Calcium (mg/dl)	8.64±0.61	-	-	9.15±0.33	<0.001
Sr. Ionized Calcium (gm/dl)	4.0±2.8	-	-	4.12±0.13	<0.001
Sr. Phosphate(mg/dl)	3.9±0.58	-	-	4.27±0.84	0.01
Thymus Size (cm <sup>2</sup> )	1.11±0.87	1.18±0.79	<0.001	3.39±0.63	<0.001

At 8 weeks, the changes in size of thymus were correlated with changes in anthropometric and laboratory parameters. Results are summarized in Table 2.

**Table 2: Correlation of changes in thymic size with anthropometric and laboratory parameters.**

Parameter	Pearson correlation coefficient (r)	p Value
Weight	0.0451	0.7323
Stature	0.0192	0.8843
Weight for length	0.1301	0.3217
MUAC	0.1442	0.2695
Head circumference	-0.2904	0.0244
Hemoglobin	0.0304	0.8179
Sr. Calcium (total)	0.2013	0.1230
Sr. Phosphate	0.1670	0.2021
Sr. Albumin	0.1648	0.2084
Sr. Globulin	0.1047	0.4261
Sr. Ionized calcium	0.2605	0.0444

## DISCUSSION

In this study of 60 hospitalized SAM children, it was found that thymus size in severe acute malnutrition was initially small and in some sick cases it is invisible and the thymus size was found to be increasing in size with statistical significance on follow up scan after 8 weeks of

admission as the child is nutritionally rehabilitated and recover from the illness.

In this study mean age of presentation is 14.2 months. It is consistent with Rytter et al, study 1 (16.5 months). The average age of presentation in all the studies is less than 24 months. This could be explained because rapid growth occurs in first 2-3 years, requirement of nutrition for energy and body building increases.

Hence deficiency of protein and energy and other micro nutrients will lead to SAM in this age group. This age group is more vulnerable during the time of socioeconomic and political instability.

In this study, 63.33% children were from rural areas and 36.77% were from urban. It is because children from rural areas are most commonly affected in SAM due to poor income, lack of infrastructure, high prevalence of illiteracy, low immunization rates and inaccessibility to health care during illnesses.

The median thymus area increased from 1.10 cm<sup>2</sup> at admission to 1.76 cm<sup>2</sup> at discharge (p<0.001) and to 3.38 cm<sup>2</sup> after 8 weeks of admission (p<0.001).

This is consistent with study done by Rytter et al, were median thymus area increased from 1.3 cm<sup>2</sup> to 1.6 cm<sup>2</sup> (p=0.006) at discharge and to 2.5 cm<sup>2</sup> (p<0.001) at follow up.<sup>1</sup>

This is because most of the sick SAM children are immunodeficient at admission which is reflected as small thymus considering thymus as a marker of immunological dysfunction. In SAM children both humoral immunity and cell mediated immunity is depressed, there is defective skin barrier, defective mucosal defense mechanism, defective phagocytic and free radical scavenging function. Poor hygiene and handling of caretakers also makes SAM children susceptible to infection. Immune dysfunction is one of the reasons for life threatening infection in SAM children.

The change in thymus area was statistically significant and weakly correlating with anthropometric indicators such as weight ( $p=0.0023$ ,  $r=0.3867$ ), weight for stature ( $p=0.0434$ ,  $r=0.2617$ ) at the time of discharge. This is consistent with study done by Rytter et al.<sup>1</sup> Even this slight correlation was lost after 8 weeks. The 8-week period may be inadequate enough to cause a discernible change in most of the anthropometric measures. This may be a limitation of this study.

In this study, change in thymus area was not correlating with change in mid upper arm circumference ( $p=0.2695$ ,  $r=0.1445$ ). This is inconsistent with study done by Rytter et al, where in thymus area increased by  $0.20 \text{ cm}^2$  per cm increase in mid upper arm circumference at discharge.

Change in thymus area was statistically significant and positively correlated with ionised calcium ( $p=0.044$ ). This is inconsistent with study done by Rytter et al, where there is no significant change in thymus area with change in serum calcium.<sup>1</sup>

The change in thymus area was not statistically significant with change in serum phosphate. This is inconsistent with study done by Rytter et al, where there is significant and positive correlation of change in thymus area with change in serum phosphate.<sup>11</sup>

The change in thymus area was statistically significant and negatively correlated with head circumference ( $p=0.0244$ ). This is consistent with study done by Benn CS et al, where large head circumference is associated with a small thymus size.<sup>12</sup>

The association between change in thymus area with change in hemoglobin was statistically not significant ( $p=0.8179$ ) with correlation coefficient of 0.0304, this is inconsistent with study done by Rytter et al.<sup>1</sup>

## CONCLUSION

Thymus size in severe acute malnutrition was initially small and in some sick cases it is invisible and the thymus size was found to be increasing in size on follow up after 8 weeks of admission as the child is nutritionally rehabilitated and recover from the illness indicating that thymus size can be used as a marker of immunological

dysfunction in severe acute malnutrition and as a marker of severity of the illness.

There are poor correlations between thymic size and most of the anthropometric parameters which may enable thymic size to act as independent surrogate marker for undernourished and well-nourished states.

This observation may be proved by carrying out a study on a larger population with adequate control.

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