RESEARCH ARTICLE

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# Nutritional Status and Body Composition at Diagnosis, of South Indian Children with Acute Lymphoblastic Leukaemia (ALL)

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## Abstract

**Background:** Accurate estimation of body composition, particularly, Body Cell Mass (BCM), which is independent of hydration status is important in children with cancer. This study aimed to accurately measure the anthropometry and body composition of children with Acute Lymphoblastic Leukaemia (ALL) at diagnosis and compare them with healthy children from South India. **Methods:** This was a cross-sectional study in children aged 2 to 8 y with ALL from St. John's Medical College Hospital, Bengaluru, and age and sex-matched, normal-weight children recruited as controls from communities. Anthropometry (weight, height, circumferences), skinfolds and body composition measurements using a whole-body potassium counter were performed. Body mass index-for-age, weight and height for age z-scores were calculated using WHO child growth standards. Biochemical markers, dietary intake and physical activity details were recorded. Categorical and continuous variables were analyzed by chi-square and independent t-tests respectively. **Results:** The mean age of the children with ALL (n = 39) was 4.6±1.9 y and control group (n=39) was 4.7±1.9 y; 61.5% were boys. The prevalence of underweight, overweight/obesity and stunting were 17.9%, 7.7%, and 10.3% respectively. The mean weight and height, of children with ALL and children in the control group were 16.8±6.2 kg and 16.4±4.1 kg, 104.3±14.9 cm and 105.1±12.2 cm, respectively with no statistical difference. Children with ALL showed lower body cell mass index kg/m$^2$ (4.6± 0.8), compared to children in the control group (4.7±0.9) p=0.527, but higher fat mass index kg/m$^2$ (3.6±1.1 vs. 3.4±0.8) p=0.276. **Conclusion:** At diagnosis, anthropometric and body composition measurements were similar between children with ALL and children in the control group. The BCM showed a non-significant trend of being lower in children with ALL, which requires close monitoring during treatment. Evaluating early-stage nutritional status and body composition can help in planning appropriate interventions during treatment to prevent long term non-communicable diseases.

**Keywords:** Leukemia- children- nutritional status- body composition- body fat- body cell mass

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## Introduction

Cancer is one of the leading causes of death related to non-communicable diseases in children and adolescents from both high and low-middle income countries [1]. The most common types of cancers observed in Indian children are leukemias, lymphomas and tumors in the central nervous system [2], with lymphoid leukemia being the most common; 27.9% of boys and 16.1% of girls having lymphoid leukemia compared to other types of cancer [3]. Acute lymphoblastic leukemia (ALL), which is caused by the production and buildup of malignant, immature lymphatic blasts mainly in the bone marrow and peripheral blood [4] is the most common type of lymphoid leukemia. Improvement in treatment and healthcare systems in recent years have resulted in increased survival rate of children with cancer; 85% of children with cancer currently survive ≥ 5 y, while in mid-1970, the 5 y survival rate was ~58% [5].

Nutritional status plays a critical role in cancer. Poor nutritional status leads to poor health by disrupting cellular integrity and altering physiological processes which affects

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growth, increases susceptibility to infections and tolerance to treatment [6]. Anthropometric measurements have been widely used to evaluate the nutritional status of children with cancer, but they may not accurately identify children who are malnourished [7]. Body mass index (BMI, kg/m$^2$), commonly used to evaluate nutritional status, is dependent on weight, which in patients with cancer may be affected by changes in hydration, especially during the treatment phase, and hence may not be an accurate index of nutritional status [7]. Accurate measurements of body composition, independent of hydration status, are needed to evaluate the "true" nutritional status of children with cancer. Body cell mass (BCM), the metabolically active component of fat free mass (FFM), is not affected by hydration status [8] and measuring BCM may provide a better assessment of the nutritional status in children with cancer. BCM can be accurately measured using a whole-body potassium counter (WBKC), which measures the gamma ray radiation emitted from the naturally occurring radioactive isotope of potassium $^{40}$K, present in the BCM [9].

Nutritional status of children at the time of diagnosis of cancer has been observed to be predictive of the clinical outcome [10], with both undernutrition and overweight/ obesity having adverse effects on the prognosis [11,12]. Undernutrition at diagnosis, has shown to be a poor prognostic factor in children, leading to a lower event-free survival (EFS), poor tolerance to chemotherapy, increased risk of infections, poor bone marrow reserve and greater treatment-related mortality [13,14]. Conversely, being overweight/ obese at diagnosis increased the risk of death and relapse rate by 30–50% in children with leukemia [15]. Obesity may increase insulin resistance, altering the adipokine concentrations [11,16], resulting in metabolic changes that subsequently increase the risk of disease resistance and progression [17]. Measuring and correcting the nutritional status at diagnosis in children with cancer will help in better tolerance of the treatment and play a critical role in improving the short and long-term outcomes along with quality of life. This is particularly relevant in Indian children who are postulated to be of the "thin fat phenotype", having normal body weight, but higher body fat [18,19]. Currently, there is no data available on the nutritional status and body composition, particularly BCM of Indian children with ALL at diagnosis. Thus, the aim of the present study was to assess the nutritional status by accurately measuring the anthropometry and body composition (BCM and fat mass (FM)) of children with ALL at diagnosis and compare it with normal healthy control children from South India.

## Materials and Methods

The present cross-sectional analysis is part of a longitudinal multicentric project funded by the International Atomic Energy Agency (IAEA), Vienna, Austria to understand the body compositional changes in children with ALL at diagnosis and during the treatment phase. The children with ALL were recruited from the pediatric oncology ward of St. John's Medical College and Hospital, Bengaluru, India. Newly detected cases of children with ALL, classified as either standard, intermediate or high-risk category for the treatment protocol, aged 2 to 8 y and in whom measurements could be performed ≤14 days post diagnosis, were included in the study. The age limit of <9 y was set to avoid any puberty related confounding effects on body composition. Children with diabetes, hormonal problems, sepsis, down's syndrome, neurological, developmental, and genetic disorders, severely ill and relapse patients were excluded. Healthy age and sex matched, normal weight (BMI z scores between -2 to +1 SD) children, were recruited as controls from the community. Ethical approval was obtained from the Institutional Ethical Committee, St. John's Medical College and Hospital, Bengaluru. The study was registered in the clinical trial registry of India (CTRI), (CTRI/2019/11/022181). Parents provided written informed consent, and children > 5 y gave their assent.

*Questionnaires*

Socio demographic details were collected using a questionnaire administered by a trained researcher. Socioeconomic status was classified using the modified Kuppuswamy scale 2019 [20]. Medical history was recorded by the clinician. In children with ALL, a validated nutrition screening tool (SCAN) was used to assess the risk of malnutrition [21]. Three-day, 24 hr food recalls (2 non-consecutive weekdays and 1 weekend) were used to record the dietary intake. Nutrient intake was computed using a nutrient database for Indian foods [22] and from the United States Department of Agriculture (USDA) [23]. Details on physical activity were recorded using a questionnaire.

*Anthropometric measurements*

Body weight of the children was recorded using a digital weight scale (Salter, Germany) to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm using a mobile stadiometer (Seca 213, USA), following standard protocols [24]. BMI was calculated as weight (kg)/height (m$^2$). Height-for-age z-scores (HAZ), weight for age z-scores (WAZ) and BMI-for-age z-scores (BAZ) were computed using the child growth standards from the World Health Organization (WHO) [25]. Circumferences of mid upper arm (MUAC), waist, abdomen and hip were measured using non-stretchable tape (ADC 396, USA) using standard procedures [24]. Skinfold measurements of triceps (TSF), biceps, subscapular and suprailiac were measured using Holtain calipers to the nearest 0.2 mm [24]. Arm muscle area (AMA) cm$^2$ was calculated by the formula: AMA = (MUAC $-\pi$TSF)$^2$/4$\pi$. All the anthropometric measurements were measured by the same researcher and intra-individual variability was <1%. Parental height and weight were measured using standard protocols for anthropometry [24].

*Biochemical markers*

Biochemical parameters such as serum total protein, albumin, urea, creatinine, and potassium were recorded from the medical records of the children with ALL when available, at the time of admission. Fasting venous blood

samples were collected from both children with ALL and in the control group for the assessment of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and complete blood count (CBC). TG and TC levels were determined in serum samples using enzymatic colorimetric assay and cholesterol oxidase phenol 4-amino antipyrine peroxidase (CHOD-PAP) methods respectively. Serum HDL-C and LDL-C levels were measured using direct enzymatic colorimetric assay (Cobas 6000, Roche Diagnostics, Switzerland) [26]. Biorad lyphochek assayed chemistry controls were used as quality controls and the inter and intra-assay precision were <5.0% and <2.5% respectively. CBC was estimated in EDTA whole blood samples using an automated hematology analyzer (Sysmex XN 350, Sysmex Corporation, Kobe, Japan) based on fluorescence flow cytometry, hydrodynamic focusing and cyanide-free sodium lauryl sulphate (SLS) method for determining haemoglobin [27]. Instrument specific trilevel controls were used for quality check with an inter and intra-assay precision <1.5% for all the three levels.

*Estimation of Body Cell Mass (BCM)*

The total body potassium (TBK) was estimated by measuring the naturally occurring radioactive isotope ($^{40}$K) gamma-ray emittance from the children, using a WBKC with a shadow shield design, built at St John's Research Institute [9]. Plastic bottles filled with deionized water and potassium chloride were used to create anthropomorphic phantoms to calibrate the WBKC. Additionally, a virtual phantom algorithm was developed to derive calibration equations for human subjects. The error of the WBKC measurement for the measurement of TBK in children was 2.6%. Since ~ 98% of the body's potassium is present in the BCM, by measuring the TBK, BCM can be estimated accurately.

Children were positioned in a supine posture, under the detectors on the adjustable bed of the WBKC, which was moved in two to three sweeps, based on the height of the child. This allowed for the measurement of TBK content from the superior to inferior segments of the body, with counting intervals of 20 to 30 minutes for each segment, based on the children's height. From the captured gamma spectrum (radioactive isotope emittance), the data was obtained as counts per second (CPS), using the multichannel analyzer and computer driver software. A Monte Carlo approach was employed, incorporating diverse body shapes and sizes to account for variations in human body dimensions, to calculate TBK from CPS [9]. TBK was calculated using the fixed proportion of $^{40}$K to other stable potassium isotopes. BCM was derived from TBK using the formula: BCM (kg) = 0.0092*TBK (mmol) [28]. FFM was calculated as the sum of BCM, extracellular fluid (ECF), and extracellular solid (ECS). The calculation of ECF assumed that extracellular water (ECW) constituted 98% of ECF. ECW was determined by subtracting the total body water (TBW) from the intracellular water (ICW), which was assumed to constitute 70% of BCM, under the presumption that BCM hydration is rigorously regulated [29]. TBW was obtained from an age, gender and ethnicity specific prediction equation [30]. The ECS was calculated as 7% of TBW [31]. By utilizing the ratio of TBW (derived as the sum of ECW and ICW) and FFM (sum of BCM, ECF and ECS), the hydration factor of FFM was computed. The FM (kg) was then calculated as the difference between total body weight (kg) and FFM (kg). The FFM index (FFMI) and FM index (FMI) were calculated to normalize for height, by dividing the FFM (kg) and FM (kg) by the square of height (m) and the BCM index (BCMI) was derived by dividing BCM (kg) by the square of height (m) raised to the power of 2.15. The value of 2.15 was derived through regression analysis in South Indian children normalizing for height.

*Statistical analyses*

The outliers were detected using box plots and generalized extreme studentized deviate test. The assumption of normality for the primary measurements (body weight, BCM, and FM) was evaluated through the examination of Q-Q plots. Children with WAZ/BAZ <-2 SD were classified as underweight, >1 SD as overweight and >2 SD as obese and HAZ <-2 SD as stunted. Categorical variables were reported as numbers and percentages and a Chi-square t-test was used to test the association between the children with ALL and children in the control group. Anthropometric measurements and body composition estimates were represented as mean ± SD and compared using an independent t-test between children with ALL and children in the control group. The 5$^{th}$, 10$^{th}$, 25$^{th}$, 50$^{th}$, 75$^{th}$, 85$^{th}$, 90$^{th}$ and 95$^{th}$ percentiles were reported for %BCM for children with ALL and children in the control group. Spearman's correlation test was used to test the correlation between AMA and BCM. The significance level was set at 0.05. The statistical analyses were performed using SPSS version 25.

## Results

One hundred and twelve patients were screened, among which 45 children were eligible based on the inclusion/exclusion criteria. Out of the 45 children who were enrolled, 6 children did not cooperate for the body composition measurements; 39 children completed all the study measurements. Thirty-nine age and sex matched children were recruited as controls. The children with ALL were assessed 8 ± 5 days post diagnosis. The comparison of the parental and children characteristics in both the study groups is presented in Table 1. The children were predominately from middle socio-economic status and the parental characteristics were comparable between children of both groups. The ratio of boys to girls was ~60:40 in both groups, and the mean age of the children was similar.

While children in the control group were of normal weight, the children with ALL had prevalence of underweight, overweight/obesity and stunting as 17.9%, 7.7% and 10.3% respectively. The majority of the children were diagnosed with B-cell ALL and categorized as intermediate risk category. Five of the children with ALL had a history of weight loss in the preceding month; with a mean weight loss of 1.5 ± 0.4 kg. According to the SCAN

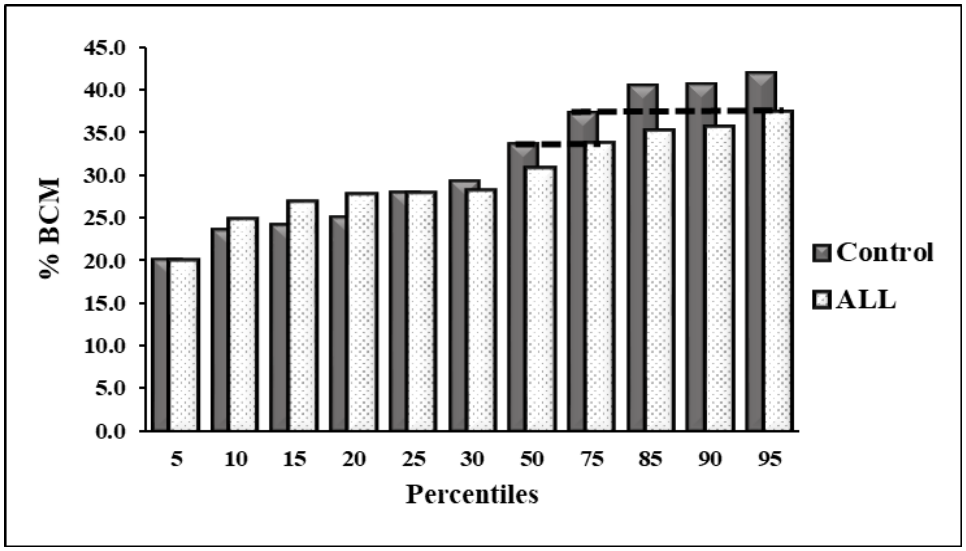


Figure 1. Comparison of %BCM Percentiles between Children with ALL and Children in the Control Group. BCM, Body Cell Mass; Control, Children in the control group; ALL, Children with ALL.

Table 1. Comparison of the Parental and Children Characteristics of Children with ALL and Children in the Control Group

| Variable | Children with ALL (n= 39) | Children in control group (n= 39) | p value |
|---|---|---|---|
| Parental characteristics | | | |
| Maternal age (y) | 30.4 ± 5.1 | 29.7 ± 4.6 | 0.503 |
| Maternal weight (kg) | 57.9 ± 9.1 | 62.1 ± 11.4 | 0.115 |
| Maternal BMI (kg/m$^2$) | 23.6 ± 4.0 | 24.7 ± 4.5 | 0.370 |
| Paternal age (y) | 35.7 ± 5.3 | 35.2 ± 4.5 | 0.683 |
| Paternal weight (kg) | 71.4 ± 8.3 | 72.8 ± 11.3 | 0.640 |
| Paternal BMI (kg/m$^2$) | 25.7 ± 2.9 | 26.1 ± 5.0 | 0.783 |
| Socio Economic Status | | | |
| Upper | 2 (5.1) | 3 (7.7) | 0.758 |
| Upper Middle | 14 (35.9) | 15 (38.5) | |
| Lower Middle | 14 (35.9) | 10 (25.6) | |
| Upper Lower | 8 (20.5) | 11 (28.2) | |
| Lower | 1 (2.6) | | |
| Parity | | | |
| One | 7 (17.9) | 10 (25.6) | 0.269 |
| Two | 25 (64.2) | 26 (66.7) | |
| Three | 7 (17.9) | 3 (7.7) | |
| Characteristics of children | | | |
| Age (y) | 4.6 ± 1.9 | 4.7 ± 1.9 | 0.801 |
| Sex | | | |
| Boys | 24 (61.5) | 24 (61.5) | 1.000 |
| Girls | 15 (38.5) | 15 (38.5) | |
| Diagnosis | | | |
| B Cell ALL | 34 (87.2) | - | - |
| T Cell ALL | 5 (12.8) | | |
| Risk Category | | | |
| Standard risk | 3 (7.7) | - | - |
| Intermediate risk | 27 (69.2) | | |
| High risk | 9 (23.1) | | |

Values are Mean ± SD and n (%); *p value < 0.05 analyzed by independent t test and chi-square t-test; BMI, Body Mass Index; B Cell ALL, B Cell Acute Lymphoblastic Leukemia; T Cell ALL, T Cell Acute Lymphoblastic Leukemia.

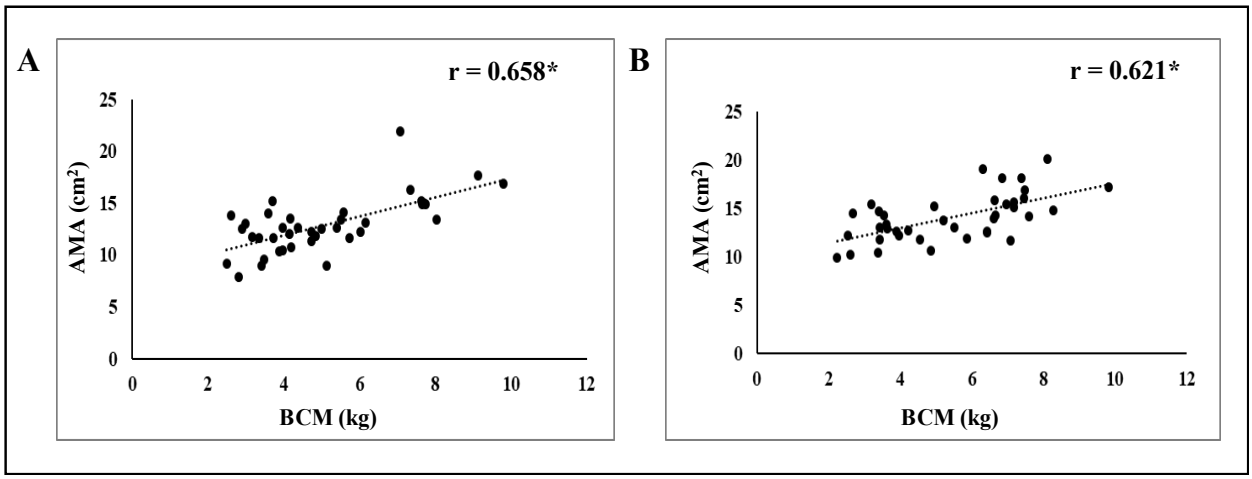


Figure 2. Correlation between Arm Muscle Area (AMA) and Body Cell Mass (BCM) in Children with ALL and Children in the Control Group. Panel A: Correlation between AMA ($cm^2$) and BCM (kg) in children with ALL; Panel B: Correlation between AMA ($cm^2$) and BCM (kg) in children in the control group assessed by Spearman's correlation.

tool for nutritional assessment, 41% of children with ALL were identified as being at risk of malnutrition. There were no statistically significant differences observed at diagnosis, in any of the anthropometric parameters and body composition estimates between the children who were at risk vs those who were not at risk for malnutrition as assessed by the SCAN tool.

The anthropometric characteristics of children of both groups are presented in Table 2. There were statistically no significant differences observed between the children with ALL and children in the control group in any of the anthropometric parameters at diagnosis, except for the waist circumference (WC), being significantly higher (p=0.002), in children with ALL.

Table 3 depicts the comparison of body composition estimates between the two groups. Although there were no significant differences in any of the body composition estimates between the groups, estimates of TBK (g), BCM (kg), %BCM and BCMI showed trends of being lower in the children with ALL, while FM (kg), %FM and FMI showed higher trend. The comparison of the 5$^{th}$, 10$^{th}$, 25$^{th}$, 50$^{th}$, 75$^{th}$, 85$^{th}$, 90$^{th}$ and 95$^{th}$ percentiles of %BCM between children with ALL and children in the control group is presented in Figure 1. It was observed that the 50$^{th}$ percentile value of %BCM (33.6%) of children in the control group was equivalent to the 75$^{th}$ percentile value of %BCM (33.7%) of children with ALL, similarly the 75$^{th}$ percentile value of %BCM (37.4) of children in the control group was equivalent to the 95$^{th}$ percentile value of %BCM (37.5) of children with ALL indicating that

Table 2. Comparison of Anthropometric Characteristics of Children with ALL and Children in the Control Group

| Variable | Children with ALL (n= 39) | Children in control group (n= 39) | p value |
|---|---|---|---|
| Height (cm) | 104.3 ± 14.9 | 105.1 ± 12.2 | 0.786 |
| Weight (kg) | 16.8 ± 6.2 | 16.4 ± 4.1 | 0.740 |
| BMI (kg/m$^2$) | 15.1 ± 2.0 | 14.7 ± 1.1 | 0.196 |
| WAZ | -0.6 ± 1.4 | -0.7 ± 0.7 | 0.790 |
| HAZ | -0.8 ± 1.2 | -0.5 ± 0.7 | 0.213 |
| BAZ | -0.4 ± 1.3 | -0.7 ± 0.8 | 0.227 |
| MUAC (cm) | 14.9 ± 2.4 | 15.5 ± 1.3 | 0.179 |
| Waist Circumference (cm) | 53.0 ± 6.7 | 49.2 ± 3.4 | 0.002* |
| Waist to Height Ratio | 0.5 ± 0.1 | 0.5 ± 0.0 | 0.594 |
| Abdominal circumference (cm) | 52.9 ± 7.8 | 49.9 ± 6.7 | 0.078 |
| Hip circumference (cm) | 52.4 ± 7.9 | 53.4 ± 5.1 | 0.521 |
| AMA (cm2) | 12.8 ± 0.4 | 14.0 ± 0.4 | 0.953 |
| Triceps skinfolds (mm) | 6.9 ± 2.2 | 7.3 ± 1.3 | 0.292 |
| Biceps skinfolds (mm) | 4.6 ± 2.0 | 4.6 ± 0.8 | 0.986 |
| Subscapular skinfolds (mm) | 5.6 ± 2.0 | 5.6 ± 1.3 | 0.957 |
| Suprailiac skinfolds (mm) | 5.0 ± 2.4 | 5.2 ± 1.4 | 0.663 |

Values are Mean ± SD; *p value < 0.05 analyzed by independent t test; BMI, Body mass index; WAZ, Weight for age Z score; HAZ, Height for age Z score; BAZ, BMI for age Z score; MUAC, Mid upper arm circumference.

Table 3. Comparison of Estimates of Body Composition in Children with ALL and Children in the Control Group

| Variable | Children with ALL (n= 39) | Children in control group (n= 39) | p value |
|---|---|---|---|
| TBK (g) | 22.1 ± 9.3 | 23.0 ± 8.3 | 0.638 |
| TBK (mmol) | 564.5 ± 238.3 | 588.6 ± 212.3 | 0.638 |
| BCM (kg) | 5.2 ± 2.2 | 5.4 ± 2.0 | 0.638 |
| FFM (kg) | 12.8 ± 4.2 | 12.7 ± 3.2 | 0.945 |
| FM (kg) | 4.1 ± 2.2 | 3.7 ± 1.1 | 0.379 |
| %BCM | 30.5 ± 4.3 | 32.3 ± 6.7 | 0.157 |
| %FFM | 76.4 ± 4.1 | 77.2 ± 3.9 | 0.354 |
| %FM | 23.6 ± 4.1 | 22.8 ± 3.9 | 0.354 |
| BCMI (kg/m$^2$) | 4.6 ± 0.8 | 4.7 ± 0.9 | 0.527 |
| FFMI (kg/m$^2$) | 11.4 ± 0.9 | 11.3 ± 0.6 | 0.470 |
| FMI (kg/m$^2$) | 3.6 ± 1.1 | 3.4 ± 0.8 | 0.276 |

Values are Mean ± SD; *p value < 0.05 analyzed by independent t test; TBK, Total body potassium; BCM, Body cell mass; FFM, Fat free mass; FM, Fat mass; BCMI, Body cell mass index; FFMI, Fat free mass index; FMI, Fat mass index.

Table 4. Comparison of Nutrient intake of Children with ALL and Children in the Control Group

| Variable | Children with ALL (n= 39) | Children in control group (n= 39) | p value |
|---|---|---|---|
| Energy (kcal) | 1217.0 ± 280.2 | 1169.4 ± 295.4 | 0.766 |
| Energy (kcal/kg body weight) | 75.6 ± 18.3 | 74.1 ± 19.9 | 0.967 |
| Protein (g) | 40.5 ± 10.5 | 36.1 ± 9.3 | 0.558 |
| Fat (g) | 41.8 ± 12.7 | 39.0 ± 12.7 | 0.777 |
| Fiber, total crude (g) | 4.1 ± 1.9 | 3.5 ± 1.6 | 0.528 |
| Carbohydrate (g) | 170.6 ± 38.6 | 169.4 ± 43.8 | 0.254 |
| Iron (mg) | 9.2 ± 3.2 | 10.5 ± 7.2 | 0.003* |
| Calcium (mg) | 613.3 ± 230.2 | 527.3 ± 254.4 | 0.594 |

Values are Mean ± SD; *p value < 0.05 analyzed by independent t test.

%BCM is lower in children with ALL, with a difference of ~25% between the children with ALL and children in the control group. The correlation between AMA and BCM was r = 0.658 and r = 0.621 in children with ALL and children in the control group respectively (Figure 2).

In children with ALL (n = 20), the mean serum total protein (6.6 ± 0.3 g/dl), albumin (4.3 ± 0.6 g/dl), urea (18.8 ± 11.9 mg/dl), creatinine (0.5 ± 0.1 mg/dl) and potassium (4.3 ± 0.7 mEq/L) were within the reference ranges. Hemoglobin was significantly lower when compared to children in the control group (9.6 ± 1.8 vs 12.5 ± 1.0 g/dl) p=<0.001. Although there was no significant differences in any of the lipid parameters between the children with ALL and children in the control group, the children with ALL had a trend of higher values; TC (155.4 ± 48.0 vs 134.0 ± 25.9 mg/dl), HDL-C (56.7 ± 16.5 vs 46.5 ± 9.2 mg/dl), LDL-C (96.0 ± 23.9 vs 85.3 ± 20.1 mg/dl ), TG (150.0 ± 85.5 vs 101.8 ± 36.2 mg/dl) when compared to children in the control group.

Nutrient intake of the children with ALL and children in the control group were similar, with no significant differences between the two groups of children, except for iron intake which was significantly lower in the children with ALL compared to children in the control group (Table 4). According to the SCAN assessment, gastrointestinal symptoms such as nausea and constipation were present only in two children and poor appetite in the preceding week was reported in ten children. At diagnosis, children with ALL were mostly sedentary and in bed for most of the day.

## Discussion

The present study measured the nutritional status and body composition of children with ALL at diagnosis and compared it with age and sex matched control children. The prevalence of underweight and overweight/obesity was 17.9% and 7.7% respectively in children with ALL based on the classification of the WHO growth standards [25]. Earlier studies have reported large heterogeneity in the prevalence rates of undernutrition varying from 6.8% to 66% in children from 2 to 18 y, using different classifications [32-35]. Similarly, while the prevalence of overweight/obesity in our study was 7.7%, previous studies have found a higher prevalence ranging from 13.4% to 33.5% [12,36-38]. Body weight at diagnosis has been shown to be a significant predictor of weight gain during the course of therapy [38], with BMI z scores at diagnosis showing a significant correlation with the BMI z scores even a decade later [39], and children who were overweight/obese at the time of diagnosis were ~12 times more likely to remain in the overweight/obese category at the end of their treatment, compared to those who were underweight or normal weight at diagnosis [37]. Children who were overweight/obese at diagnosis were at risk for mortality associated with treatment [40]. Interpreting and comparing data on nutritional status from different studies is challenging as several factors may influence the findings such as disease condition, socioeconomic status, type of anthropometric tools for the assessment of nutritional status, lack of uniformity in defining cutoffs for undernutrition, overweight/obesity and variations in the nutritional status and body composition caused by differences in ethnicity, environmental, and dietary factors.

Anthropometric measurements of the children of both groups in the present study were similar, except for waist circumference, which was higher in children with ALL. This was consistent with previous studies in children with haematological cancer from North Mexico and North Carolina who had a comparable nutritional status to healthy children at the time of diagnosis, when assessed through anthropometric measurements [41,42]. Similarly in Indian children with ALL [34], BMI and body composition measured by DEXA were not significantly different from healthy children at diagnosis. These studies also noted that children with ALL, had lower lean muscle mass and higher %FM, when compared to normal healthy children. It is possible that the acute nature of hematological disease conditions such as ALL, may not cause substantial changes at diagnosis in anthropometric measurements and body composition, in comparison to solid tumors [43]. The exact cause of the higher WC observed in children with ALL of the present study is unclear and more studies are needed to confirm these findings.

BCM, which is independent of hydration status was measured for the first time in Indian children with ALL and they were observed to have lower 50$^{th}$ and 75$^{th}$ percentiles for %BCM, when compared to children in the control group. While there is no data available on BCM at diagnosis in children, the limited available data in children with ALL from other countries suggest a significant decrease in BCM as cancer treatment advances, along with a significant increase in %FM; Australian children with different types of cancer undergoing treatment had significantly lower BCMI z scores when compared with age and sex matched control children [44]. Low muscle mass at the time of diagnosis of cancer has shown to be associated with poor outcomes such as weakness, muscle wasting, impaired flexibility, and functional mobility which could lead to insulin resistance [45,46] and this is particularly important in Indian children who have lower muscle mass [18]. The lower amount of BCM, which is the metabolically active tissue, in children with ALL

at diagnosis may result in several issues such as lower tolerance to chemotherapy, increased susceptibility to infections, impaired inflammatory responses and treatment related complications [47]. While it may not be possible to measure BCM in clinical settings, AMA which is a commonly used index to assess the nutritional status in pediatric cancer patients [43,48] has shown strong correlations with lean muscle mass [34]. The moderate correlation observed between AMA and BCM in both groups of children at the time of diagnosis in our study, suggests that AMA could be used as a potential surrogate for BCM for initial screening of muscle mass.

The children from both groups had similar nutrient intakes and met the recommended nutrient requirements for Indian children [49], which may have been due to the fact that the children were diagnosed early, before there was any impact on the dietary intake caused either by ALL or the side effects of treatment. However, a significantly lower intake of iron was observed in the children with ALL, which corresponded with significantly lower hemoglobin levels in children with ALL compared to the children in the control group.

The limitations of this study include single site measurements with a small sample size and the cross-sectional study design. However, this study using accurate measurements of anthropometry and body composition adds valuable data to the limited literature on the nutritional status and body composition of Indian children with ALL.

In conclusion, the present study suggests that Indian children with ALL at diagnosis have similar anthropometric measurements and body composition when compared to children in the control group. This could be because the nutrient intakes were not different and gastrointestinal symptoms were minimal in children with ALL in the early stage of diagnosis. However, although not significant, the BCM of the children with ALL was lower compared to the children in the control group. These findings have clinical relevance as the children with ALL may be considered normally nourished like their healthy peers if anthropometric measurements are solely used for nutritional assessment. The undernutrition/ and overweight maybe 'hidden and untreated', thus affecting the long-term prognosis. As treatment is initiated and continued, it can be accompanied by nutritional side effects such as reduced food intake, increased gastrointestinal symptoms and decreased physical activities, which adversely affect BCM. Hence it is important to measure and monitor the BCM closely throughout treatment. The study also suggests that appropriate nutritional interventions need to be planned for better clinical outcomes in children with cancer in India and other LMICs, rather than just providing high energy diets which may lead to weight gain and higher body fat during treatment, increasing the risk for non-communicable diseases. Studies with more children across different regions of India with longitudinal study designs are needed to understand the influence of nutritional status at diagnosis and during treatment on the long-term clinical outcome of Indian children with pediatric cancer.

## Author Contribution Statement

RK designed the research (conception, overall research plan, and study oversight); DP wrote the initial drafts of the manuscript; DP and VR were involved in the recruitment and data collection; KGB was involved in the body composition analysis and interpretation; VB and AP facilitated the recruitment of children into the study and critically reviewed the draft; SS performed the statistical analysis; RK, SS, AJM and DP were involved in the interpretation of results; RK, TR, AJM critically reviewed the draft and improvised it. RK has primary responsibility for the final content. All authors have read and approved the final manuscript.

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*Ethical Consideration*

The study was approved by the Institutional Ethical Committee, St. John's Medical College and Hospital, Bengaluru. The study was registered in the clinical trial registry of India. CTRI registration number (CTRI/2019/11/022181).

*Conflict of interest*

The authors report no conflict of interest.

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