Malnutrition Assessment in Pediatric Acute Lymphoblastic Leukemia in Upper Egypt and Its Effect on Induction Response

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Abstract:

Background: Nutritional status in children with acute lymphoblastic leukemia (ALL) is important. The impact of malnutrition at diagnosis on the induction response is still controversial. This study aimed to assess the prevalence of malnutrition in children with ALL at the time of diagnosis and to evaluate its relation with patients' characteristics and response to the induction therapy.
Methods: A prospective study was conducted on 43 newly diagnosed ALL patients, aged 2-18 years, from January 2020 to November 2020. All patients were treated according to the modified St. Jude Total XV protocol. Response evaluation was done by bone marrow aspiration and minimal residual disease (when available). The nutritional assessment was done at the presentation by the STRONG kids screening tool and anthropometrics done were weight for age (WFA), body mass index for age (BMI for age), and arm anthropometry (mid-upper arm circumference/ triceps skinfold thickness (MUAC/TSFT).
Results: Median age was 6 years, 55.8% were males, 79% lived in rural areas, and 69.8% belonged to the moderate socioeconomic status category. The rapid early response was achieved in 79.1% and 90% had complete remission post-induction. About one-third had high malnutrition risk. The prevalence of undernutrition was 9.3% by WFA, 32.5% by BMI/A, 67.4% by MUAC, and 30.2% by TSFT. Patients with undernutrition had a significant association with malnutritional risk (p=0.006) and induction failure (p=0.031).
Conclusion: There was a high prevalence of malnutrition in pediatric ALL patients in South Egypt. Undernutrition had a significant association with malnutrition risk and induction failure.

Keywords: Malnutrition, Pediatric, Leukemia, Induction response.

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Introduction:

Acute lymphoblastic leukemia (ALL), the most common malignancy in children, has a dramatic improvement in the last four decades, due to the advances in treatment protocols and supportive care [1]. Nutrition plays a fundamental role in cancer management. Pediatric malnutrition has been defined by the American Society of Parenteral and Enteral Nutrition (ASPEN) as "an imbalance between nutrient requirements and intake, results in cumulative deficits of energy, protein or micronutrients that may negatively affect growth, development and other relevant outcomes" [2].

Most of the children with cancer live in countries with limited resources, where the prevalence of malnutrition may exceed 50%, which is often related to many factors, such as socioeconomic status [3]. In ALL patients who are malnourished at diagnosis, chemotherapy is found to be more toxic and less effective compared to those with adequate nutritional status. The poor nutritional status can influence the outcome through an altered metabolism of antineoplastic drugs, decreased tolerance to chemotherapy, and increased infection rates [4].

The effect of nutritional status at diagnosis on the response to the remission induction phase of ALL is controversial. In Egypt, few studies have examined specifically the association between malnutrition and induction failure. Our objectives were to determine the prevalence of malnutrition in children with ALL at the

time of diagnosis in a tertiary care center in Upper Egypt and evaluate the relation between malnutrition and patients' criteria and their response to remission-induction therapy.

Patients and Methods:

This prospective observational study included 43 newly diagnosed pediatric ALL patients who were admitted to the Pediatric Oncology and Hematological Malignancies Department at South Egypt Cancer Institute (SECI), Assiut University during the period from January 2020 to the end of November 2020. The study was reviewed and approved by the Institutional Review Board of SECI, Assiut, Egypt. Informed consent was taken from the child's parents before including the patient in the study.

This study included all newly diagnosed ALL patients aged from 2 to 18 years old at presentation with the exclusion of patients who received previous treatment outside SECI before admission, and those with relapse or on palliative care. Patients who had chronic illness or comorbidities e.g., diabetes mellitus, inflammatory bowel disease, congenital heart disease, celiac disease, cerebral palsy, etc. were also excluded.

Demographic characteristics of the patients such as age, gender, residence, and socioeconomic status (SES) using the Arabic Version of Family Socioeconomic Scale (revised version 2010) [5] were collected.

The diagnosis was done through history taking and clinical examination, and laboratory investigations included complete blood picture (CBC), bone marrow (BM) examination by morphology, cytochemistry, flow cytometry, and cytogenetics (when available). All patients were stratified according to National Cancer Institute (NCI)/Rome classification for ALL [6] and treated according to the modified St. Jude Total XV protocol [7]. Response evaluation was done by Bone marrow aspirate (BMA), and Cerebrospinal Fluid (CSF) on day 15 and post-induction on day 42. BMA either in D15 or post-induction is classified into M1 (<5% blasts), M2 (<25% blasts), or M3 (≥25% blasts) remaining in the bone marrow [8]. Minimal Residual Disease (MRD) analysis (when available) was done by flow cytometry and interpreted as positive or negative (defined by using a threshold of 0.01% residual leukemia blasts) [9]. CSF evaluation was considered positive if contains >5 nucleated cells/mm3 with morphologically identified blasts by cytocentrifugation [6].

Rapid early response (RER) is defined by M1 response on day 15, however slow early response (SER) is considered in the patients with M2 and M3 responses [10]. Complete remission (CR) is the absence of leukemic blasts in peripheral blood and CSF and less than 5% blasts on BMA smears (M1), together with restoration of normal hematopoiesis with no evidence of extramedullary disease [8]. Induction failure was defined as either morphological persistence of leukemic blasts in BM or extramedullary site (s) after the completion of the induction therapy [10].

Nutritional assessment:

- Nutritional screening:

Patients underwent nutritional screening using the Screening Tool for Risk of Impaired Nutritional Status and Growth (STRONG kids) tool for hospitalized patients. It consists of 4 key items including global subjective assessment, the nutritional risk of the patient's disease (presence of high-risk disease or predicted major surgery), nutritional intake and losses (decreased food intake, diarrhea, and vomiting), and loss or absence of weight gain. Based on the overall scores (0 to 5), malnutrition risk is categorized into low risk (score 0), moderate risk (score 1 to 3), and high risk (score 4 to 5). According to a nutritional follow-up proposal based on risk category by Hulst et al, the "high risk" group should receive a consultation with a dietician after admission to make an adequate nutritional plan, and the "moderate risk" group should receive a critical look at their nutritional intake, and the nutritional risk re-assessed after one week, while the "low risk" group should check weight regularly according to hospital policy [11].

- Anthropometrics and nutritional status evaluation:

Anthropometrics using weight for age (WFA), height for age (HFA), and body mass index for age (BMI/A), which is measured from 2 to 5 years Z scores using WHO z-scores using Anthro software of World Health Organization (WHO) [12], and from 5 to 18 years z-scores using Reference of Growth Parameters for Egyptian School Children and Adolescents aged from 5 to 19 Years [13]. Arm anthropometry (Mid-upper arm circumference (MUAC) and triceps skinfold thickness (TSFT) were measured from 2 to 5 years using WHO Z scores [12], and from 5 to 18 years using Mramba et al. 2017 Circumference that accords with WHO standards [14].

Nutritional status was classified according to WHO guidelines into two groups for WFA, HFA: normal-patients with z-score > -2 standard deviation (SD) from mean WFA and HFA; underweight or stunted patients with z-score > -2 SD from mean WFA and HFA [15]. For BMI- for age, it was categorized into three groups: undernourished – patients with z-score > -1 SD from mean BMI-for-age (-1 to -1.99 mild undernutrition, -2 to -2.99 moderate undernutrition, ≤ -3 severe undernutrition) [16]; normal – patients between -1 SD and +1 SD from mean BMI/A; and over-nourished – patients > +1 SD from mean BMI/A [>+1SD overweight, >+2SD obese]. MUAC/TSFT measurements were used: z scores between −1 and +1 were considered to show adequate nutrition and z scores ≤ −1 were considered undernutrition [17,18]. All measurements used in the current study were performed by previously trained nutritionists from the institution. Also, serum albumin level was used as a biochemical marker, hypoalbuminemia was considered if it was lower than 3.5mg/dL [19].

Statistical analysis:

All statistical calculations were done using SPSS (statistical package for the social science; SPSS Inc.,

Chicago, IL, USA) version 22 [20]. Data were statistically described in terms of mean ± standard deviation (±SD), or median and range when not normally distributed, frequencies (number of cases), and relative frequencies (percentages) when appropriate. For comparing categorical data, Fisher's exact test was performed. P-value is always 2 tailed sets significant at 0.05 level.

Results:

Table (1) shows the demographic data of 43 patients included in the study. The median age was 6 years, with most of the patients were below the age of 10 years old (76.7%). Most of the patients were males (55.8%). Seventy-nine percent were from rural areas. Thirty (69.8%) patients belonged to the moderate SES category. Thirty-seven patients (86%) had a B-precursor ALL. About fifty-one percent were stratified as high risk.

The response evaluation by BMA was done for 39 patients at D15 (BMA was not done in 4 patients (2 were covid-19 positive, one had acute pancreatitis and sepsis, and one had fracture lumbar spine with casting) showed RER was achieved in 79.1%. Post-induction evaluation was done in 42 patients (one patient died due to septic shock) revealed CR was recorded in 90.1%. MRD analysis at the end of the induction phase was done only for 21 (48.8%) of the patients, it revealed negative results in 13 patients (61.4%), while persistent MRD was documented in 8 patients (38.1%)}.

Nutritional screening using the STRONG kid's tool revealed that most of ALL patients (67.4%) were rated to have a moderate risk for malnutrition at diagnosis, while 32.6% were at high risk.

The nutritional assessment revealed that the prevalence of malnutrition at presentation ranged widely from 9.3% using WFA, to 67.6% by MUAC as shown in table (2). For nutritional status evaluated by BMI/A, the median z score was -0.014, ranging between (-3.32 to 2), 60% were normally nourished, 7% were over nourished (of those 2.3% were obese), and 32.5% were undernourished (mild in 8, moderate in 5, and severe in one case). Hypoalbuminemia was recorded in 20 (46.5%).

The relation between the nutritional status using BMI/A with other criteria of the studied patients was demonstrated in table (3). Undernutrition was more observed in patients who had B-precursor cell phenotype, while T cell phenotype was associated with overnutrition with no significant relation in between (P= 0.069). The undernutrition at presentation had significantly associated with malnutrition risk (P= 0.006), and induction failure (p= 0.031). Analysis of post-induction MRD results (which was done only in 21 patients) showed there was a higher percentage of MRD positive results in malnourished patients (undernourished and over nourished) versus the normally nourished ALL with no statistical difference (p=0.350).

Table (1): Demographic characteristics of pediatric ALL patients (n= 43).

Characteristics	N	(%)
Age (years)		
• Mean ± SD	6.88 ± 3.84	
• Median (range)	6 (2 – 16)	
• Age groups		
<10	33	(76.7)
≥10	10	(23.3)
Sex		
• Male	24	(55.8)
• Female	19	(44.2)
Residence		
• Rural	34	(79.1)
• Urban	9	(20.9)
Socio-economic status class		
• Low	4	(9.3)
• Moderate	30	(69.8)
• High	8	(18.6)

Quantitative data are presented in the form of mean±SD and median (range), qualitative data are presented in the form of a number (percentage).

Table (2): Nutritional status in 43 ALL pediatric patients at diagnosis.

Variable	N	(%)
Weight for age (z score)		
• Normal	39	(90.7)
• Underweight	4	(9.3)
Height for age (z score)		
• Normal	40	(93)
• Stunted	3	(7)
BMI /A (z score)		
• Normal	26	(60.4)
• Overnutrition	3	(7)
• Undernutrition	14	(32.6)
MUAC (z score)		
• Normal	14	(32.6)
• Undernutrition	29	(67.4)
TSFT (z score)		
• Normal	30	(69.8)
• Undernutrition	13	(30.2)
Serum albumin		
• Normal	23	(53.5)
• Hypoalbuminemia	20	(46.5)
Strong kids score		
• Low risk	0	(0.0)
• Moderate risk	29	(67.4)
• High risk	14	(32.6)

BMI/A; body-mass index for age, MUAC; mid-upper arm circumference, TSFT; triceps skin-fold thickness. Qualitative data are presented in the form of a number (percentage).

Table (3): The relation between body mass index for age and patients' characteristics, nutritional risk, and response in pediatric ALL patients (n=43).

Variable	BMI categories						*P-value**
	Normal (n=26)		Under nutrition (n=14)		Over nutrition (n=3)		
Age groups (years)							
• 2-10 (n= 33)	21	(80.8)	11	(78.6)	1	(33.3)	0.237
• ≥10 (n=10)	5	(19.2)	3	(21.4)	2	(66.7)	
Gender							
• Male (n= 24)	13	(50.0)	9	(64.3)	2	(66.7)	0.705
• Female (n= 19)	13	(50.0)	5	(35.7)	1	(33.3)	
Socio-economic status class							
• Low (n=5)	2	(7.7)	3	(21.4)	0	(0)	
• Moderate (n= 30)	19	(73.1)	10	(71.4)	1	(33.3)	0.166
• High (n=8)	5	(19.2)	1	(7.2)	2	(66.7)	
Immunophenotyping							
• Pre B-cell (n= 37)	23	(88.5)	13	(92.9)	1	(33.3)	0.069
• Pre T-cell (n= 6)	3	(11.5)	1	(7.1)	2	(66.7)	
Risk stratification							
• SR (n= 21)	12	(46.2)	8	(57.1)	1	(33.3)	0.715
• HR (n= 22)	14	(53.8)	6	(42.9)	2	(66.7)	
Strong kids score							
• Low (n=0)	0	(0)	0	(0)	0	(0)	
• Moderate (n= 29)	21	(80.8)	5	(35.7)	3	(100)	0.006*
• High (n= 14)	5	(19.2)	9	(64.3)	0	(0)	
Early Response (n=39)	24	(92.3)	12	(85.7)	3	(100)	
• RER (n= 34)	22	(84.6)	10	(71.4)	2	(66.7)	0.517
• SER (n= 5)	2	(7.7)	2	(14.3)	1	(33.3)	
End of induction (morphology) (n=42)	26	(100)	13	(92.9)	3	(100)	
• Complete remission (n=39)	26	(100)	11	(84.6)	2	(66.7)	0.031*
• No remission (n= 5)	0	(0)	2	(14.3)	1	(33.3)	
End of induction (MRD) (n=21)	12	(46.2)	7	(50)	2	(66.7)	
• <0.01 (n=13)	9	(75)	3	(42.4)	1	(50)	0.350
• ≥0.01 (n=8)	3	(25)	4	(57.1)	1	(50)	

RER, rapid early response; SER, slow early response; SR, standard-risk; HR, high-risk; MRD, minimal-residual disease. Qualitative data are presented in the form of numbers (percentage). * Fisher's exact test was used, significance defined by $p < 0.05$.

Discussion:

Adequate nutrition is essential for growth and development in children [21]. Cancer-related malnutrition can be a result of the primary disease or its therapy. Patients with undernutrition at diagnosis in developing countries have been found to have inferior outcomes, however, this is not for the patients treated in developed countries [22]. To our knowledge, this is the first study performed in Upper Egypt to evaluate the nutritional status assessment of ALL patients at diagnosis and study its effect on the response to the remission-induction phase.

In the current study, there was a male predominance (55.8%), the mean age of the included patients was 6.8 years, with the majority of ALL patients (76.7%) aged less than 10 years, which is comparable to many studies [23,24].

Most of ALL patients (79.1%) resided in rural areas that agree to the study of Darwish et al [25], these findings can be explained by what stated by the World Bank that Upper Egypt is predominantly rural with 75% of its young people living in rural areas [26]. Furthermore, we found that about 70% of the cases belonged to the moderate SES level, the same was reported by Osman et al and Darwish et al in South Egypt [25,27].

The assessment of nutritional risk by the STRONG kids revealed a higher frequency of a high-risk group for malnutrition (32.6%) than other studies in high-income countries (HICs) such as that study conducted by Yoruk and his colleagues who found that the rates of patients with moderate and high risk for malnutrition at diagnosis were 73 and 27% respectively [28].

In this study, undernutrition ranged from 9.3 to 67.6% varying according to the method of assessment. It is higher than many reports from developed countries [22,29], however, this percentage was lower than other studies from Asia and South America [3,24,30].

In general, the prevalence of malnutrition defined by BMI and arm anthropometry z- scores is higher than that estimated by the WFA z-score [31]. In childhood cancers, malnutrition evaluation with weight-based measures has drawbacks as body weight can be distorted by tumor masses, hydration status, organomegaly, ascites, or edema. Arm anthropometry is independent of tumor load, so it is a better indicator of nutritional status [32].

On the other hand, we observed that only 7% of ALL patients had z- scores > +1 SD, however, many reports from HICs revealed high percentages of overweight and obesity ranging from 14 to 29% [1,33–35].

Children with cancer in low- and middle-income countries (LMICs) are especially disadvantaged with many challenges such as undernutrition which may be caused by the influence of socioeconomic conditions, lack of adequate education, and health support that can increase the nutritional risk [36]. However, in HICs, overweight and obesity are public health issues that affect cancer outcomes, especially those with acute leukemia [21].

On analysis of the relation of patients' criteria by BMI categories, we found that undernutrition is slightly frequent in males, patients less than 10 years, and in B precursor cell phenotype with no statistically significant difference, the same was observed by Orgel and his colleagues [22].

The study revealed that screening for malnutrition risk using the STRONG kids' tool was effective in predicting malnutrition status in ALL patients, as we found that among normally nourished ALL patients, 19.2% were rated to have a high risk for malnutrition, versus 64.3% of the undernourished patients. This represents the importance of assessing the nutritional risk in ALL patients at diagnosis, so it can help to raise the clinician's awareness about the nutritional status in children at diagnosis and enables them to refer children at risk for early dietary intervention. this

Nutritional assessment at the time of diagnosis can influence the response to treatment [37,38]. In our study, RER was observed in 84.6% of normally nourished versus 71.4% of undernourished patients, also, CR post induction was 100% in normally nourished versus 84.6% in undernourished patients. This is consistent with what was reported by a study by Khaled in Pakistan who observed that RER was recorded in 21.8 and 32.8% of malnourished and well-nourished patients, while post-induction CR was observed in 63% versus 69.1% respectively [39]. Other reports showed no relation between nutritional status and remission outcome of patients with ALL postinduction therapy [30,34].

Because of our limited resources, we did not have the facility to do MRD for all patients. Although MRD was done for about half of the cases, we noticed high persistent MRD end of induction in malnourished ALL patients. The data about the relationship between persistent MRD post-induction therapy and undernutrition are scarce and conflicting. A study conducted by the Children Oncology Group showed no association between BMI subgroups and MRD post-induction [34]. However, the study of Orgel et al found that obesity was an independent predictor of persistent MRD in pediatric ALL [40].

The exact mechanism that which undernutrition affects the outcome of children with cancer is not fully understood, but it may involve altered immune function, modified cellular bioenergetics, and changes to epigenetic influences on cellular control. Weight loss and abnormal body composition, together with impaired micronutrient status, may impact disease response and resistance to therapy [41].

Conclusion:

There was a high prevalence of malnutrition in pediatric ALL patients in South Egypt. Undernutrition had a significant association with malnutrition risk and induction failure. The limitations of this study are the

small sample size and limited resources. So, we need larger studies to be promoted as well as encourage routine surveillance of nutritional status, consistent with local resources, by established methods to raise the outcome of children with cancer.

List of Abbreviations:

ALL	Acute Lymphoblastic leukemia
SES	Socioeconomic Status
BMA	Bone Marrow Aspirate
MRD	Minimal Residual Disease
RER	Rapid Early Response
SER	Slow Early Response
CR	Complete Remission
WHO	World Health Organization
WFA	Weight for Age
BMI/A	Body Mass Index for Age
MUAC	Mid- Upper Arm Circumference
TSFT	Triceps Skin Fold Thickness
SD	Standard Deviation
LMICs	Low Middle-Income Countries
HICs	High Income Countries

Authors' Contributions:

All authors made substantial contributions to the conception or design of the work, acquisition, analysis, or interpretation of data.

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None.

Conflict of Interest:

The authors declare that they have no conflict of interest**.**

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