Evaluation of Nutritional Status in Pediatrics with Acute Lymphocytic Leukemia in Hematology Unit – Children Welfare Teaching Hospital

Ahmed Salih Marzoog1, Besmah Mohammed Ali2, Raghad Majid AlSaeed3
[1] M.B.Ch.B. F.I.B.M.S. Pediatric Consultant. Membership of Clinical Nutrition. Fatema AL-Zahraa hospital for Obstetrics & Pediatrics. Baghdad /Iraq
[2] M.B.Ch.B. F.I.B.M.S. Community Medicine, Consultant. Public Health Department. Ghazi Al-Hariri Teaching Hospital, Baghdad Medical City, Iraq.
[3] M.B.Ch.B. F.I.B.M.S. Consultant Pediatric Hemato-Oncologist. Children Welfare Teaching Hospital, Baghdad Medical City, Iraq
E-mail: ahmedsalihmarzook@yahoo.com

Abstract
Background: Acute leukemia is the most cancer has frequency in children, malnutrition is one of the common complications of children with cancer, and malnutrition has been identified as a significant factor in treatment tolerance, increased morbidity, poor prognosis, reduced quality of life, and higher healthcare expenses. Nutritional assessment and early intervention in pediatric cancer patients could minimize the side effects of treatment, improve their survival, and reduce the risk of nutritional morbidity with a positive impact on quality of life. Objective: Assess the nutritional status of children with newly diagnosed acute lymphoblastic leukemia at time of diagnosis and follow up after 1 and 3 months of chemotherapy. Patients & Methods: a retrospective analysis done on newly diagnosed acute lymphoblastic leukemia patients aged less than 14 years old admitted to hematology unit of Children Welfare Teaching Hospital over a one-year period from 1/1/2021 to 1/1/2022. The patients are divided into two groups: under 5 years and above 5 years. Weight for height WHO Child Growth Standards median was used in the first group (under 5 years) and body mass index /age for children > 5 years of age to interpret their data to define underweight, wasting, overweight and obesity. Anthropometric data were collected from medical records upon diagnosis, at 1, and 3 months of chemotherapy. Results: The total number of patients included in current study was 94; being 52 (55.3%) of them males and 42 of them (44.7%) females. One third of patients was between the age 2-5 years 32 (34%), and 5-10 years 31 (33%) with mean age 2.6 ± 0.953 SD. AT diagnosis, there were 71 patients (75.5%) with normal nutritional status (≥ -2 to ≤ +1) ,18 patients (19.2%) were underweight with further categorization as moderate underweight (≥ -3 to < -2) in 12 patients (12.8%) and 6 patients (6.4%) were severely underweight (< -3). Overweight and obesity were seen in only 5 patients (5.4%). After 1 month of chemotherapy, there is a drop in underweight into 12 patients, in contrast after 3 months, which shows increase to 18 patients (19.2%). Overall wasting rate follows the same pattern of fluctuation of underweight (17,12 ,18 patients) (18%, 12.7%, 19.2%) respectively. The most common age group affected by wasting was (5-10) years old; 9 patients (29.1 %) from total 31 patients with a significant P value (0.052); mostly moderate wasting 6 patients versus 3 patients with severe wasting. Overall unintentional weight loss occurred in half of the patients 47 (50%) at one month which increased to 56 patients (59.6%) after 3 month of chemotherapy. Weight gain developed in 32 patients (34%) after one month which decreased to 28 patients (29.8%) after 3 months. Male gender had higher rate of wasting (< -2SD) 11 patients (21.1%) from total 52 males than female patients 6 (14.2 %) from total 42 females. On the other hand, a female patients developed a dangerous (>10% weight loss) during a period of 3 months of chemotherapy, 8 (19%) than male 6 (11.5%). The most common age group developed (> 10 %) weight loss was (>10) years old with a significant P value (0.08); 13 patients (68.4%) from 19. The majority of patients 80 (85.1%) had normal stature (-2 to +3) while 10 patients (10.7%) were stunted with a higher rate in female (11.9%) than male (9.6%). A higher rate of stunting was in below 2 years' age group (33.3%) with a significant P value (0.008).Conclusions: malnutrition present in a significant percentage of patients with acute lymphoblastic leukemia, so adequate nutrition is an important in such children, to ensure optimal treatment and outcome.

1. Introduction

It is estimated that more than 400,000 new cases of pediatric cancer are diagnosed throughout the world each year 1. Pediatric cancer is a potentially curable disease, with survival rates exceeding 80% in high-income countries, as opposed to low-income countries where it ranges between 15% and 45% 2.Malnutrition is the main nutritional disorder that occurs in children with cancer, and has been defined as a state in which a deficiency of energy, protein, and other nutrients, causes measurable adverse effects on the structure and functioning of organs and body tissues as well as

doi.org/10.31838/hiv23.02.42 Received: 11.10.22, Revised: 12.11.22, Accepted: 04.12.22

the clinical course of a disease 3,4.The incidence of malnutrition at the time of diagnosis of cancer in children appears to be less than adult. Some children were malnourished at the time of diagnosis and their malnourishment was reported to have increased during the therapy for malignancy, especially if their treatment involved intensive chemotherapy or bone marrow transplantation5. Undernourishment is reported in 6% to 65% of cases in children with cancer and being overweight in 8% to 78%. The prevalence varies depending on the study population 6-9.

American Society of Parenteral and Enteral Nutrition (ASPEN) defined malnutrition 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 outcomes10. It may be a subsequent to an imbalance in composition, and utilization of energy, nutrients or both. It may also be a result of cancer or its aggressive treatment and concomitant toxicities. Mucositis and appetite disorders, dysgausia, and xerostomia would alleviate risk of inadequate intake leading to further increased risk of malnutrition11.

There are several clinical, biochemical and physiological indicators to diagnose malnutrition in children with cancer; such as the patient's age, the deficit of specific micronutrients and the presence or absence of infection12. The severity of their malnutrition is determined mainly by anthropometric indicators, that are the indexes of weight-for-height (w/h) and weight-for-age (w/a), which indicates acute malnutrition, height-for-age (h/a) which indicate a delay in growth or chronic malnutrition; and the Body Mass Index (BMI), which is a figure that can diagnose a patient for being underweight, overweight or obesity13.

Lack of conclusive guidelines for assessing or identifying children and young ALL patients who are at risk of malnutrition makes it quite difficult to obtain a precise rate of malnutrition in this population, yet an approximation rate of 46% was reported11.

Hypotheses have been developed that suggest malnutrition impairs the ability of the immune response against infections due to cytokine hormone function alterations 14 and micronutrient deficiencies 15,16. It also impairs the effectiveness of cancer treatments because of pharma kinetic and pharmacodynamics changes that are explained by an altered metabolic state 17. Likewise, it has also been associated with a poorer quality of life and poorer physical, social and emotional performances 18.

2. Patients & Methods

This is a retrospective analysis was done in hematology unit of Children Welfare Teaching Hospital / Baghdad Medical City. It includes all newly diagnosed ALL patients aged less than 14 years old over one -year period from 1st.January 2021 to 1st. January 2022

Data including (patient name, residence, date of birth, gender, date of admission, date of diagnosis, type of leukemia, investigations) and growth parameters were collected from electronic archived medical records.

Diagnosis based on bone marrow aspirate and flow cytometry; all cases were treated according to UKALL 2019 protocol.

Growth parameters at diagnosis, at 1-, and 3-months including weight in (kg) and height in (cm) all were taken from the records. Body Mass Index (BMI) was calculated by an equation: weight (kg) / square of height in meters. BMI used to screen for overweight and obesity in children and teens age 5 through 14 years, whereas the weight-for-height ratio was used for patients below 5years.

There are different systems used to compare a child to the reference; standard deviation scores (Z-scores), percent of median and percentiles. Percentiles are adequate when full between 3rd to 97th percentiles (2 standard deviations) but inconvenient out of this range. Therefore, WHO recommend using standard deviation score (Z – score) as widely recognized as the best system for analysis and presentation of anthropometric data owing to its advantages over the other methods and it is the most appropriate descriptor of malnutrition19.The z-score scale is linear and, therefore, a fixed interval. This is not true for percentiles 20.

The patients are divided into two groups: under 5 years and above 5 years. In the first group (under 5 years), weight for height WHO Child Growth Standards median was used to interpret their data to define wasting, overweight and obesity as follows:

Table (1) Weight-for-Length /Height Z-Score Cutoffs (Birth to 5 Years) 21,22	
Nutritional status	**Z-score range**
Obese	> +3
Overweight	> +2 to ≤+3
Risk of overweight	> +1 to ≤ +2
Normal	**≥ -2 to ≤ +1**
Moderately wasted	≥ -3 to < -2
Severely wasted	< -3

The other group (5-19 years), BMI-for-age WHO Growth Reference median was used to interpret their data as follows:

Table (2) BMI-for-Age Z-Score Cutoffs (5 to 19 Years) 21,22	
Nutritional status	**Z-score range**
Obese	> +2
Overweight	> +1 to ≤ +2
Normal	≥ -2 to ≤ +1
Moderately wasted	≥ -3 to < -2
Severely wasted	< -3

Underweight is defined as the children with weight-for-age Z-score (WAZ) <−2SD and severe underweight is defined as the children with WAZ <−3SD in both two groups.

Table (3) Weight-for-Age Z-Score Cutoffs [21,22]	
Nutritional status	Z-score range
Normal	≥ -2 to ≤ +1
Moderately underweight	≥ -3 to < -2
Severely underweight	< -3

Unintentional weight loss was considered sever weight loss as follows:

	Table (4) Significant unintentional weight loss 23
% weight loss	Time frame
>2%	1 week
>5%	1 month
>7.5%	3 months
>10%	6 months

Height for age WHO Growth reference median was used for both two groups to define stunting:

Table (5) Length/Height-for-Age Z-Score Cutoffs (Birth to 19 Years) 21,22	
Nutritional status	Z-score range
Normal	≥ -2 to ≤ +3
Moderately stunted	≥ -3 to < -2
Severely stunted	< -3

Mid-upper arm circumference (MUAC) is another simple and noninvasive anthropometric indicator often included in assessing nutritional status and predicting mortality rate. It reflects the amount of muscle mass and subcutaneous fat. It is measured on a straight left arm, mid-way between the tip of the shoulder and the tip of the elbow. Unfortunately, these important measures are not routinely done in our patients.

3. Statistical analysis

Statistical analysis was done using SPSS program, data were expressed by means ± Standard Deviation. Comparisons of proportions was performed by crosstab using Chi-Square test. For all tests, P value of <0.05 was considered as statistically significant.

4. Results

The total No. of patients included in current study was 94; 52 (55.3%) male and 42 (44.7%) female with M: F ratio of 1.23:1. Most of the cases were from Baghdad 45 patients (45.8%), followed by Diyala 17 patients (18%) and Kut 11 patients (11.7%).
The majority of patients was 2-5 years old 32 (34%) and 5-10 years 31 (33%) with mean age was 2.6 ± 0.953 SD.

Table (6) Demographic data		
Gender	Frequency	Percent
Male	52	55.3
Female	42	44.7
Age		
< 2 years	12	12.8
2-5years	32	34.0
5-10 years	31	33.0
> 10 years	19	20.2
Total	94	100

From weight /age WHO Z score at time of diagnosis, the results revealed that 71 patients (75.5) were in normal nutritional status (≥ -2 to ≤ +1) ,18 patients (19.2%) were underweight with further categorization as moderate underweight (≥ -3 to < -2) in 12 patients (12.8%) and 6 patients (6.4%) were severely underweight (< -3). Overweight and obesity were seen in only 5 patients (5.4%).
Following the same patients after induction period (> 1 month) of chemotherapy, the results revealed that there is a drop in underweight into 12 patients (12.7%); 10 patients (10.6%) were moderately underweight and 2 patients (2.1%) were severely underweight.
In contrast at 3 months of chemotherapy (interim maintenance), the results showed that there was an increase in percentage of underweight into 18 patients (19.2%); 14 patients (14.9%) were moderately underweight and 4 patients (4.3%) were severely underweight.

Table (7) Nutritional Status of patients according to weight /age WHO Z score at diagnosis, 1, and 3 months of chemotherapy									
Over wt. & Obese (> +1SD)		Total Under wt.	Severe Under wt. (< -3 SD)		Moderate Under wt. (< -2 SD)		Normal (-2 to+1)		
%	No.		%	No.	%	NO	%	No.	
5.4	5	18 (19.2)	6.4	6	12.8	12	75.5	71	At Diagnosis
5.3	5	12 (12.7 %)	2.1	2	10.6	10	81.9	77	After 1 month
2.2	2	18 (19.2 %)	4.3	4	14.9	14	78.7	74	After 3 months

Overall wasting rate at diagnosis was 17 patients (18%) which decline to 12 patients (12.7%) after one month of chemotherapy then increased to 18 patients (19.2%) after 3 months as shown in below table.

Table (8) Nutritional status of patients according to Weight-for-Length/Height Z-Score in under 5 years old and BMI-for-Age Z-Score in (5 to 18 Years) old									
Over wt. & Obese (> +1 SD)		Total wasting	Severe Wasting (< -3 SD)		Moderate Wasting (≥ -3 to < -2) SD		Normal (≥ -2 to ≤ +1) SD		
%	No.		%	No.	%	NO.	%	No.	
7.5	7	17 (18.1 %)	9.6	9	8.5	8	74.5	70	At Diagnosis
5.3	5	12 (12.7%)	2.1	2	10.6	10	81.9	77	After 1 month
2.2	2	18 (19.2%)	4.3	4	14.9	14	78.7	74	After 3 months

Overall unintentional weight loss occurred in half of the patients 47 (50%) at one month which increased to 56 patients (59.6%) after 3 month of chemotherapy. At one month of chemotherapy, the results showed that the 17 patients (18.1%) developed (5-10%) weight loss which increased to 24 patients (25.5%) and another 16 patients (17%) developed (2-5%) weight loss which increased to 20 patients (21.3%). Further weight loss (> 10%) demonstrated in 14 patients (14.9%) which decrease at 3 months to 12 patients (12.8%). Weight gain developed in 32 patients (34%) after one month which decreased to 28 patients (29.8%) after 3 months.

Table (9) Weight changes after one month and 3 months of chemotherapy

Wt. gain		No Wt. loss		Total wt. loss	>10 %		5-10%		2-5%		
%	No	%	No.		%	No.	%	No.	%	No.	
34	32	16	15	47 (50%)	14.9	14	18.1	17	17	16	After one months
29.8	28	10.6	10	56 (59.6%)	12.8	12	21.3	20	25.5	24	After 3 month

The results revealed that male gender had higher rate of wasting (< -2SD, moderate & severe) 11 patients (21.1%) from total 52 males than female patients 6 (14.2 %) from total 42 females while about equal sex ratio in normal nutritional status and obesity.

Table (10) The relationship between gender & nutritional status

		> -2 < +1 Normal	> +1 < +2 Overweight	> +2 Obese	< -2 Moderate Wasting	< -3 severe Wasting	Total %
gender	male	37	1	3	5	6	52
		71.2%	1.9%	5.8%	9.6%	11.5%	
	female	33	0	3	3	3	42
		78.6%	0.0%	7.1%	7.1%	7.1%	
Total		70	1	6	8	9	94
		74.5%	1.1%	6.4%	8.5%	9.6%	100

Regarding weight changes in relation to gender, the results showed that half of patients 47 (50%) developed weight loss mostly in female (54.7%) versus male (46.1%). Also the results showed that female patients developed a dangerous (>10%) weight loss during a period of 3 months of chemotherapy 8 (19%) than male 6 (11.5%). Less weight loss (5-10%) was higher in male patients 10 (19.2%) than female 7 (16.7%). Weight gain was mostly in male gender 21(40.4%) patients from total 52 than female 11(26.2%) patients from total 42.

Table (11) gender & weight changes relationship

		2-5%	5-10 %	> 10%	Total wt. loss	No wt. loss	Wt. gain	Total %
Sex	male	8	10	**6**	24	7	21	52
		15.4%	19.2%	**11.5%**	46.1%	13.5%	40.4%	100
	female	8	7	**8**	23	8	11	42
		19.0%	16.7%	**19.0%**	54.7	19.0%	26.2%	100
Total		16	17	**14**	47	15	32	94
		17.0%	18.1%	**14.9%**	50%	16.0%	34.0%	100

The majority of patients 80 (85.1%) had normal stature (-2 to +3) while 10 patients (10.7%) were stunted with a higher rate in female (11.9%) than male (9.6%).

Table (12) gender in regard to WHO.Ht Z score

		-2 to +3 normal	-2 to -3 moderately stunted	< -3 severely stunted	Tall stature	
Sex	male	45	4	1	2	52
		86.5%	7.7%	1.9%	3.8%	100%
	female	35	2	3	2	42
		83.3%	4.8%	7.1%	4.8%	100%
Total		80	6	4	4	94
		85.1%	6.4%	4.3%	4.3%	100%
			10 (10.7%)			

Regarding the relation of age with nutritional status. The most common age group affected by wasting was (5-10) years old; 9 patients (29.1 %) from total 31 patients with a significant P value (0.052); mostly moderate wasting 6 patients versus 3 patients with severe wasting.

Table (13) Relationship between Age & Nutritional status

	> -2 < +1 Normal	> +1 < +2 (Overweight	> +2 Obese	< -2 Moderate Wasting	< -3 severe Wasting	Total
< 2 years	7	0	3	0	2	12
	58.3%	0.0%	25.0%	0.0%	16.7%	100%
2-5years	26	0	3	1	2	32
	81.2%	0.0%	9.4%	3.1%	6.2%	100%
5-10 years	21	1	0	**6**	**3**	**31**
	67.7%	3.2%	0.0%	**19.4%**	**9.7%**	**100 %**
> 10 years	16	0	0	1	2	19
	84.2%	0.0%	0.0%	5.3%	10.5%	100%
Total	70	1	6	8	9	94
	74.5%	1.1%	6.4%	8.5%	9.6%	100%

In regard age and its relationship with weight loss. The most common age group developed (> 10 %) weight loss was (>10) years old with a significant P value (0.08); 13 patients (68.4%) from 19.

Table (14) Age & Wt. Loss relationship

		< 5%	> 5%	> 10%	Wt. loss	No wt. loss	Increased Body Wt.	Total
Age	< 2 years	1	0	6	7	2	3	12
		8.3%	0.0%	50.0%	58.3%	16.7%	25.0%	100%
	2-5years	6	6	2	14	6	12	32
		18.8%	18.8%	6.2%	43.75%	18.8%	37.5%	100%
	5-10 years	4	6	3	13	5	13	31
		12.9%	19.4%	9.7%	42%	16.1%	41.9%	100%
	> 10 years	5	5	3	13	2	4	19
		26.3%	26.3%	15.8%	68.4%	10.5%	21.1%	100%
Total	16	17		14	47	15	32	94
	17.0%	18.1%		14.9%	50 %	16.0%	34.0%	100%

Relationship between age and height showed that a higher rate of stunting was in < 2 years' age group (33.3%) with a significant P value (0.008).

Table (15) Relationship between Age and height

		-2 to +3 (normal)	-2 to -3 moderately stunted	< -3 severely stunted	Tall stature	Total
Age years	< 2	8	1	3	0	12
		66.7%	8.3%	25.0%	0.0%	100%
	2-5	30	0	0	2	32
		93.8%	0.0%	0.0%	6.2%	100%
	5-10	27	3	1	0	31
		87.1%	9.7%	3.2%	0.0%	100%
	> 10	15	2	0	2	19
		78.9%	10.5%	0.0%	10.5%	100%
Total		80	6	4	4	94
		85.1%	6.4%	4.3%	4.3%	100%

5. Discussion

Studies show that well-nourished patients can tolerate treatment better with fewer complications, while patients who are malnourished experience more treatment delays or interruptions and longer hospital stays 24.

Current study showed a slight males predominance over females (55.3 %) with male: female ratio of 1.23:1. This is in agree with Ali AM etal study 25 in Egypt (55.8%, M/F 1.4:1), Antillon F etal study 26 in Guatemala (53.9%, M/F 1.2:1), Huibers MH etal study 27 in Malawi (58.3, M/F 1.4:1). Khalid A etal study 28 which shows male to female ratio 1.5:1, Sonowal R etal study 29 in India with 2.4:1 male to female ratio; but disagree with that mentioned in Kadir RA etal study 30 in Basrah which shows same sex ratio, these differences might be related to different number of cases analyzed in each study.

Because there were no standard guidelines to assess the nutritional status in oncology patients, so many different clinical practices were used in the study e.g. Wt. / age to detect underweight, Wt. / Ht to detect wasting, BMI / age to detect overweight and obesity and Ht / age to detect stunting. The most accurate methods of assessment are Mid upper arm circumference (MUAC) and triceps skinfold thickness (TSFT) measurements, but these measures are not routinely done in the unit to assess nutritional status).

From Wt. / age WHO Z score chart, the majority of patients (75.5%) were in normal nutritional status at diagnosis. This was in agree with González HR et al study 31 in Colombia (83.8%), Yazbeck et al study 32 in Lebanon (74.8%), Sneha LM et al study 33 in India (73.6), in Ali AM et al study 25 (60%) and Huang J et al study 34 in China, but differ than that mentioned in Kadir RA etal study 30 (50%), Sonowal R etal study 29 (47.5%), Antillon F etal study 26(46.9%), Huibers MH etal study 27 (36.5), and Khalid A et al study 28 (35.1%).

The rate of underweight at diagnosis was (19.2%) mostly moderate underweight ((≥ -3 to < -2 SD) as in Aggarwal P et al study 35 (19.1%), Yazbeck et al study 32 in Lebanon (25.2%), and Sneha LM et al study 33(26.4%). Higher than that in Ali AM et al study 25 (9.3%), González HR et al study 31 (6.8%), and lower than that in Kadir RA et al study 30 (40%), Sonowal R et al study 29 (52.5%), and Khalid A et al study 28 (64.9%), these might be attributed do different of socio-economic status of cases in different countries enrolled in each study.

After induction therapy (>1 month), the rate of underweight decreased into (12.7%). This is can be related to side effects of steroids used with chemotherapy. This is in contrast to Yazbeck et al study 32 in Lebanon in which the patients remained almost the same at the end of treatment. By following the same patients after 3 months of chemotherapy, there was again increase in rate of underweight (19.2%). This is in agree with Kadir RA et al study 30 in Basra in which patients followed

the same fluctuation in weight, height and BMI but contrast to Antillon F et al study 26 which showed a decrease in underweight from (53.1%) at diagnosis into (47.8%) after 3 months of chemotherapy. This is can be explained due to side effects of chemotherapy e.g. decrease oral intake, mucositis and febrile neutropenia.

The rate of wasting followed the same pattern of fluctuation at diagnosis, 1, and 3 months of chemotherapy (18.1% ,12.7%, 19.2%) respectively. This was in agree Kadir RA etal study 30 and Huang J etal study 34 in which the rate was decreased from (40%) at diagnosis into (35%) after one month of chemotherapy.

The most common age group affected by wasting was (5-10) years old with a significant P value (0.052). This was compatible with Ali AM et al study 25 (78.6%), Huibers MH et al study 27(63.5%), and Sonowal R et al study 29

A higher rate of wasting in male gender (21.1%) than female (14.2%) as in same in Kadir RA et al study 30 and Ali AM et al study 25. While the female developed more significant dangerous (>10%) weight loss during a period of 3 months of chemotherapy (19%) than male (11. 5%). Also, the rate of stunting which indicate chronic malnutrition was higher in female patients (11.9%) than male (9.6%) and this might explain a significant weight loss in female .

A half of patients (50%) developed weight loss after 1 month of chemotherapy and further reduction (59.6%) after 3 months. A lower percentage was found in Sneha LM et al study 33 in India (38.8%), and Hill R et al study 36 (17%); these might be attributed to differences of chemotherapy protocols intensity between different centers and their remote side effects.

A significant association was found between weight loss and (>10 years) age group with p value (0.08).

The impact of obesity development during treatment on survival outcomes is yet unknown in childhood ALL, but the presence of obesity at diagnosis has been showed to be linked to an increased risk of relapse in ALL patients 10 years of age or older 37. Weight gain developed after 1and 3 months of chemotherapy (34%,29.8%) respectively. Withycombe JS etal study 38 shows a lower rate (3.9%) experienced greater than or equal to a 20% increase in kilograms (weight) during Induction.

A higher rate of stunting was in < 2 years' age group (33.3%) with a significant P value (0.008) at diagnosis.

6. Conclusions

Malnutrition present in a significant percentage of patients with ALL. So, adequate nutrition is an important in such children, to ensure optimal treatment and outcome.

7. Recommendations

More attention should be paid to nutritional status as optimum nutritional support can play a vital role in the outcome of induction of remission in childhood ALL. Include MUAC and TST measurements in routine practice in our hospital. Taking height and weight measures in each visit to the patient will help in further monitoring of nutritional status as malnutrition and obesity are risk factors for relapse in future. Because of many limitations in the study as it is retrospective, the results demonstrate the need for a laregr prospective studies to evaluate nutrition as an independent risk factor in the outcome of childhood malignancies.

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