Original Articles

Influence of Nutritional Status of Children with Acute Lymphoblastic Leukemia (ALL) on Treatment Outcome after Completion of Induction

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Abstract

Background: *Malnutrition and cancer both influences tolerance and response to treatment especially ALL. Malnutrition increases morbidity, mortality, reduces the effectiveness of treatment and impairs the quality of life significantly.*

Objective: *Assessment of the nutritional status and its influence on treatment outcome children with Acute Lymphoblastic Leukemia (ALL) before and after induction chemotherapy.*

Materials & Methods: *This prospective observational study included 72 children with ALL, aged 1-15 years, was conducted from January to December 2014 in the Department of Pediatric Hematology and Oncology, BSMMU. The anthropometric measurements (weight-for-age, height-for-age, weight-for-height, MUAC, BMI) hematological and biochemical parameter (serum albumin, total protein) were measured. The children got induction chemotherapy according to the UK ALL 2003 (modified) protocol.*

Results: *Among the study population, 18(39.1%) were underweight, 8(17.4%) were stunted, 16(34.8%) were wasted, MUAC for age 14(56.0%) and BMI for age 12(57.1%) were malnourished, 10.9% had low total proteins (<5.7g/dl), 37.0% low serum albumin (<3.2g/dL). Mean anthropometric measurements and biochemical parameters were higher among the survivors compared to non-survivors. Significant difference was found between the well-nourished and the malnourished group according to WAZ. Complications like febrile neutropenia, treatment delay, number of transfusion (PRBC) requirement were more in malnourished group.*

Conclusion: *Malnutrition is widely prevalent in children with ALL and a major determining factor in treatment planning, complications and final outcome.*

Keywords: *Acute Lymphoblastic Leukemia (ALL), Malnutrition, Anthropometric measurements, Impact of nutritional status, Treatment outcome.*

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Introduction:

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. It represents 25%-30% of all childhood cancers and approximately 75% of all cases of childhood leukemia. A sharp peak of ALL incidence is observed at 2-5 years of age.[1-3] The results of the treatment of ALL in children depend not only on the biologic diversity of the leukemia cells and on the individual variability of drug metabolism, but also on the nutritional and socioeconomic status of the leukemic child.[4,5] Malnutrition is a major

problem in children with cancer.[6] Compared with adults, children are at a greater risk for nutritional depletion since they have a more rapid metabolic rate and greater caloric needs for growth and development.[7] Protein energy malnutrition (PEM) has been identified as a major health problem in Bangladesh. The majority of PEM cases (nearly 80%) falls in the mild and moderate categories and frequently goes unrecognized.[4,5] The effects of PEM on the therapeutic response of children with cancer are obviously relevant. Disease related malnutrition occurs frequently in patients with cancer and is a major cause of morbidity and mortality.[8] Isenring et al. in his study found that incidence of malnutrition in cancer patients ranges between 40% to 80%[9] and Tong et al. found the prevalence of malnutrition in cancer patients ranges from 50% to 80%.[10] The outcome of treatment in patients with ALL is clearly related to their nutritional status.[11-13] Roy et al. and Linga et al. in their study found malnutrition in ALL patients and its effect on tolerance to chemotherapy, especially in the first few months of intensive therapy.[14,15] The event-free survival of children with ALL in developed countries has increased substantially in the last 2 decades. Although the prognosis of ALL has also improved in underdeveloped countries, the figures for event-free survival are lower, even when aggressive protocols are used.[16,17] Unfavorable nutritional status could contribute to this observation. Mexican investigators demonstrated, for the first time, that malnutrition was an adverse prognostic factor in the outcome of children with standard risks ALL.[12] Malnutrition is prevalent on large scale in hospitalized patients, which increases morbidity and mortality, reduces the effectiveness of medical treatment in hospitals, and impairs the quality of life significantly.[14]

The aim of this study was to assess the influence of under nutrition in children with ALL and to observe its effect on tolerance to chemotherapy in terms of the incidence and severity of complications. The other aim is to establish malnutrition as a prognostic factor in children with ALL at the onset of chemotherapy in terms of survival and recurrence-free survival.

Materials and Methods:

This prospective observational study included 72 children newly diagnosed as ALL, aged 1-15 years. With the approval of the institutional review board the study was done January 2014 to December 2014 in the Department of Pediatric Hematology and Oncology, BSMMU.

The anthropometric measurements, hematological and biochemical parameterwere taken. Anthropometric indices were calculated using reference median as recommended by NCHS (WHO-2000), NHANES and classified according to standard deviation units termed as Z score. Children less than two standard deviations of the reference median (<-2 SD) are considered as underweight (weight-for-age), stunted (height-for-age) and wasted (weight-for-height), MUAC for age (<-2SD) malnutrition, BMI for age <5th centile underweight respectively. Total serum proteins < 5.7 g/dL[2,6] and Serum albumin <3.2 g/dL was considered low.[7] The children got induction according to the UK ALL2003 (modified) protocol. They were in regular follow up. Data regarding blood counts, hematological support, bone marrow remission status and complications during and at the end of induction were analyzed and compared to find out the impact of nutritional status on treatment outcomes in different groups. Statistical analysis was done using t-test and chi-square test. Data were analyzed using the statistical package for social sciences (version 16.0 for windows). P value<0.05 was considered statistically significant.

Results:

Total 72 patients were enrolled this study. Among them 46 patients were alive, 13 patients died, 11 patients discharged on risk bond and 02 patients were lost of follow up. All the admitted patients got UKALL 2003 protocol (modified). Maximum number 43 (59.0%) were in the age group 2-6 years, followed by 16 (22.2%) in the age group of 7-11 years and the range was from 1 years to 15 years. (Table-I)

Table-I

Age & gender distribution of study population (n=72)

	Frequency (%)	Mean Age
Age		
≤2	6 (8.3)	1.77 ± 0.23
2 – 6	43 (59.7)	3.66 ± 0.91
7- 11	16 (22.2)	8.47 ± 1.19
12 – 15	7 (9.7)	13.71 ± 1.11
	72 (100)	5.55 ± 3.57
Gender		
Male	54 (75)	
Female	18 (25)	

Among the leukemia patients (of the 46 survivors) nutritional status at diagnosis, at D_{15} and after induction among survivors (n=46). No statistically significant difference was found among newly diagnosed and day 15 of induction. In case of BMI for age significant difference (*p value* 0.008) was found among newly diagnosed and after completion of induction therapy. (Table-II)

In case of low S. Total Protein and S. Albumin levels significant difference was found among newly diagnosed and day 15 of induction, were statically significant. In term of low S. Albumin levels was found significant difference among newly diagnosed and after completion of induction therapy, was statically significant. (Table-III)

Anthropometric parameters of survivors were compared with those of non-survivors and the mean weight for age was also found to be higher (-1.5 ± 3.4) for survivors as compared to non-survivor's groups (-2.0 ± 1.27). Here no significant difference in the mean weight for age value of survivors as compared to non-survivors. (Table-IV)

Table-II

Nutritional status of ALL patients at diagnosis, at D_{15} and after induction among survivors (n=46)

	At diagnosis	At D_{15}		After completion of induction	
	n (%)	n (%)	*p value*	n (%)	*p value*
Under weight (WAZ <-2SD)	18 (39.1)	21 (45.7)	0.453	14 (30.4)	0.289
Stunting (HAZ <-2SD)	8 (17.4)	8 (17.4)	1.000	10 (21.7)	0.625
Wasting (WHZ <-2SD)	16 (34.8)	17 (37.0)	0.453	11 (23.9)	0.453
MUAC <-2SD (n=25)	14 (56.0)	18 (72.0)	0.125	13 (52.0)	1.000
BMI < 5^{th} percentile (n=21)	12 (57.1)	14 (66.7)	0.625	4 (19.0)	0.008

Table-III

Biochemical parameters of ALL patients at diagnosis, at D_{15} and after induction among survivors (n=46)

	At Diagnosis	At D15		After completion of induction	
	n (%)	n (%)	*p value*	n (%)	*p value*
S.Total Protein <57 g/L	5 (10.9)	20 (43.5)	0.001	5 (10.9)	1.000
S. Albumin <32 g/L	17 (37.0)	34 (73.9)	0.001	5 (10.9)	0.004

Table-IV

Comparison of anthropometric parameters of survivors (n=46) and non survivors (n=13)

Anthropometric parameters	Survivors			Non survivors		*p value*
	At diagnosis [Mean±SD]	At D_{15} [Mean±SD]	After completion of induction [Mean±SD]	At diagnosis (13 pt.) [Mean±SD]	At D_{15} (9 pt.) [Mean±SD]	
WAZ	-1.5 ± 3.4	-1.1 ± 2.2	-0.1 ± 3.0	-2.0 ± 1.27	-1.4 ±1.28	0.343
WHZ	-1.5 ± 1.9	-1.4 ± 2.0	-0.9 ± 2.0	-1.3 ± 1.48	-0.9±1.4	0.892
HAZ	-0.8 ± 1.2	-0.7 ± 1.2	-0.7 ± 1.5	-1.1 ± 1.2	-1.03 ±1.7	0.433
MUAC	14.2 ± 1.8	13.6 ± 1.7	14.2 ± 1.9	13.3 ± 0.90	14.6 ± 4.0	0.254
BMI	13.4 ± 1.6	13.5 ± 1.6	15.0 ± 1.6	14.2 ± 2.8	15.3 ± 3.3	0.383

The biochemical parameters were also compared between survivors and non survivors. Serum Albumin values were lower but not statically significant (*p value* 0.119) among the non-survivors. Although S.Total Protein also low in the non-survivor group, none of them achieved statistical significance. (Table-V)

Comparison of outcome of children with malignancy between well-nourished and mal nourished group. A significant difference was found using WFA for febrile neutropenia, number of blood transfusion (PRBC) between malnourished and well-nourished patients. We have also found there is significant difference for requirement of PRBC in term of malnourished MUAC for age. Although no significant difference was found among any outcome variable in relation to any of HAZ, WFH, BMI and MUAC. Significant difference between the well-nourished and the malnourished group according to WAZ. Complications like febrile neutropenia, treatment delay, number of transfusion (PRBC) requirement were more in the malnourished group. (Table-VI)

Table-V

Comparison of biochemical parameters of survivors (n=46) and non survivors (n=13)

Biochemical parameters	Survivors			Non survivors		*p value*
	At diagnosis [Mean±SD]	At D_{15} [Mean±SD]	After completion of induction [Mean±SD]	At diagnosis (13) [Mean±SD]	At D_{15} (9) [Mean±SD]	
S.Total Protein (g/dl)	67.8 ± 8.9	57.7 ± 7.8	64.4 ± 6.2	66.4 ± 9.2	50.7 ± 8.4	0.621
S.Albumin (g/L)	33.1 ± 5.4	29.0 ± 4.7	37.0 ± 4.5	30.5 ± 5.4	26.1 ± 3.8	0.119

Table-VI

Comparison of outcome of children with ALL patients between well-nourished and malnourished group (n=59)

Parameter	Nutrition	No. of patients (%)	Febrile neutropenia	Infection	No. of transfusion	
					PRBC	Platelet
WAZ	mn	24 (40.7)	1.52 ± 0.513 *(P-0.01)*	1.91±0.90	3.26±1.45 *(P-0.017)*	4.81±3.41
	wn	35 (59.3)	1.16 ± 0.38	1.47±1.02	2.35±1.29	4.06±2.37
HAZ	mn	12 (20.3)	1.37 ±0.51	1.60±0.89	2.83±1.11	5.00±3.60
	wn	47 (79.7)	1.30±0.46	1.65±1.01	2.68±1.50	4.32±2.57
WFH	mn	18 (30.5)	1.36±0.50	1.44±0.72	3.00±1.11	4.36±2.27
	wn	41 (69.5)	1.30±0.46	1.72±1.07	2.60±1.53	4.40±3.25
BMI	mn	31 (52.5)	1.41±0.50	1.76±0.83	2.93±1.52	4.77±3.16
	wn	28 (47.5)	1.17±0.39	1.50±1.16	2.46±1.27	4.00±2.44
MUAC	mn	18 (30.5)	1.23±0.43	1.50±0.84	3.35±1.53 *(P-0.004)*	4.41±1.93
	wn	41 (69.5)	1.35±0.48	1.71±1.05	2.45±1.29	3.30±2.21

** wn= well-nourished, mn= malnourished FN=Febrile Neutropenia, Only significant p values are shown.

Table-VII

Comparison of outcome of children with ALL patients between well-nourished and mal nourished group (n=59)

Parameter	Nutrition	Mortality	Remission/response	Treatment delay
WAZ	mn	6 (46.2)	20 (38.5)	13.05 ± 5.62
				P-0.034
	wn	7 (53.8)	32 (61.5)	9.5 ± 3.46
HAZ	mn	4 (30.8)	9 (17.3)	8.87 ± 6.42
	wn	9 (69.2)	43 (82.7)	11.31 ± 5.42
WFH	mn	4 (30.8)	17 (32.7)	9.56 ± 5.00
	wn	9 (69.2)	35 (67.3)	11.60 ± 5.86
BMI	mn	7 (53.8)	27 (51.9)	13.66 ± 8.13
	wn	6 (46.2)	25 (48.1)	8.44 ± 5.07
MUAC	mn	4 (30.8)	15 (28.8)	10.64 ± 4.37
	wn	9 (69.2)	37 (71.2)	11.00 ± 6.13

** mn= malnourished , wn= well-nourished

Discussion:

In the past few years, there has been great improvement in the survival of children with cancer. Hence, the emphasis now is not just on the longevity but also on the quality of life of these children. Very few studies are available in Indian literature regarding the prevalence of malnutrition in childhood malignancies.[6]

In this study peak age of ALL children was between 2 to 6 years. Most of the subjects 43(59.7%) belongs to age 02 to 06 yrs. Next group of patients 16 (22.2%) observed in 7-11 yrs of age group. Another study in India, reported that of the 25 cases with ALL, 6 were in the age range of 1-4 years, 7 between 4 to 8 years and the remaining between 8-12 years.[13] Another cross-sectional study conducted in University Kebangsaan Malaysia Medical Centre demonstrated that subjects comprised 32 (62.7%) males and 19 (37.3%) females. Most of the subjects (41.2%) were in the age group of 4 to 6 years.[18] We also found that out of 72 cases 54(75.0%) were male and 18(25.5%) were female. Male: female ratio was 3:1.

In this study malnutrition among the leukemia patients (of the 46 survivors), at diagnosis 18(39.1%) were underweight, 14(56.0%) were malnutrition MUAC-for-age (of 25 survivors) and 12(57.1%) were underweight BMI-for-age (of 21 survivors). At day 15 among the leukemia patients 18(72.0%) were malnutrition (MUAC-for-age). No statistically significant difference was found among newly diagnosed and day 15 of induction. In comparison Van Eys J also found in his study, 28.2% prevalence of malnutrition by weight for height at the time of diagnosis of cancer in children.[19] Smith et al.[20] also found that HFA and WFA were unaffected, but 20% of patients were malnourished by MAC which were similar to our study.[20] Ogur et al. in his study found WFH was unaffected but 27% patients were mal-nourished by MAC and TSF (Triceps Skin Fold).[21]

This study showed no significant difference in the mean weight for age value of survivors as compared to non-survivors. Jain et al. found mean weight for height were higher for survivors as compared to non-survivors. The mean MAC, TSF and MAMC were also higher in survivors than non-survivors in each of the individual malignancy groups, though not statistically significant.[6]

Among the leukemia patients (of the 46 survivors) difference of s. albumin and s. total protein was found among newly diagnosed, day 15 of induction and after completion of induction but which was not statistically significant. Jain et al. observed that biochemical parameters detected a much lower prevalence of malnutrition as compared to anthropometric parameters.[6] Similar observations were found in other studies[19,21-23]

We studied the impact of nutritional status on the disease pattern i.e., incidence of relapse, treatment

delays, and complications (e.g., febrile neutropenia, bleeding and infection). In the total study population, children malnourished by WAZ were observed to have statistically significant higher rates of febrile neutropenia episodes (p-0.013), increase no. of transfusion (p-0.017) and a greater incidence of delay in treatment (p-0.034). We also found significant difference (p-0.004) for requirement of PRBC transfusion in term of malnutrition MUAC for age. No significant difference was found among the others outcome variable in relation to any of the parameters (HAZ, WHZ, MUAC, and BMI) used and there is no significant difference of mortality among the malnourished as compared to well-nourished group. Jain et al. found children malnourished by WFH were observed to have statistically significant lower rates of achievement of remission, poor response to therapy and a greater incidence of delay in, treatment.[6] Various other studies have also found similar results of malnourished child by WFH.[24-27] Roy et al. found that under nutrition adversely affect the final outcome, treatment tolerance and treatment complications in children with ALL.[14] Zalina et al. did not find significant differences in the nutritional status among a sample of children with leukemia at different stages of treatment.[18]

Conclusion:

The percentage of malnutrition among the children with ALL was higher at diagnosis. Febrile neutropenia, requirement of blood transfusion & treatment delay was more in malnourished children with ALL. The nutritional status of children with ALL should be monitored periodically during chemotherapy.

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