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Original Research Article

Malnutrition as a predictor of adverse outcomes of febrile neutropenia in children with acute lymphoblastic leukemia during induction phase chemotherapy

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ABSTRACT

Background: Adequate nutrition is an important concern in children with leukemia. Malnutrition impairs immune function, leading to increased incidence of infection, poor quality of life, as well as death. Febrile neutropenia (FN) has a high prevalence in children with acute lymphoblastic leukemia (ALL) and a poor outcome as well.
Methods: This prospective observational study was done in the department of pediatrics hematology and oncology (PHO), BSMMU, from January 2021 to October 2021. A total of 60 patients of ALL were selected purposively. Patients were evaluated by taking anthropometric parameters before getting chemotherapy and were prospectively followed up for the development and outcome of FN until recovery. Statistical analysis was performed by using SPSS (Statistical package for the social sciences) for Windows version 26.0.
Result: Analysis of nutritional status as a risk factor for FN based on anthropometric indices, was found statistically significant for, weight for height (≤5 years) p=0.036, OR=0.24 (95% CI= 0.06-0.958), weight for age p=0.006, OR=0.23 (95% CI=0.07-0.67), but for BMI for age (>5 years) p=0.28, OD=0.28 (95% CI=0.02-3.19), and height for age p=0.513, OD=0.66 (95% CI=0.18-2.33) no statistically significant value was found. In this study, we found mortality rate was 15%. The mortality rate was significantly worse (27.3%) for patients who were malnourished at diagnosis as compared to those who were well nourished (7.9%) at diagnosis.
Conclusions: FN and its complications are more common in malnourished children with ALL. Malnutrition is associated with adverse outcomes of FN in children with ALL.

Keywords: Malnutrition, FN, ALL, Induction, Chemotherapy

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood accounting for approximately 80% of all cases of childhood leukemia.[1] Children with ALL have a five-year event-free survival rate of about 80%, whereas adults have a rate of about 40%.[2] Malnutrition is a major problem in children with cancer. Compared with adults, children are at a greater risk for nutritional depletion since they have a more rapid metabolic rate and greater caloric need for growth and development.[3] Malnutrition, which includes under and over-nutrition, harms health, health-related quality of life, and adverse consequences in the outcome of childhood cancer.[4] Malnourished children, in general, have considerable changes in their immune systems as compared with well-nourished children. These include decreased microbicidal, chemotactic, and phagocytic activities of leukocytes, along with an alteration in the cytokine profile. These changes might be potentially amplified by childhood acute leukemias and chemotherapeutic intervention, making these children more susceptible to infection.[5] Malnutrition in patients with cancer is related to factors associated with the treatment and the disease itself and sometimes economic and social conditions. Food intake, energy expenditure, nutrient absorption, and metabolism, as well as complications such as oral and gastrointestinal toxicity and nephrotoxicity caused by drugs used to treat malignancy and infections, play an important role in the etiology of malnutrition in cancer.[6] Nutritional screening, assessment, and nutritional care planning are considered crucial in children with cancer. Malnutrition has been associated with poorer coping with intensive cancer treatment regimens, increased risk for complications and infections, poor quality of life, higher relapse rates, and lower survival rates.[7] Childhood cancer patients who are obese at the time of diagnosis pose a unique set of challenges for oncologists. Obesity can make chemotherapy more difficult to administer regarding the determination of the dose.[8]

Furthermore, obesity has been linked to reduced survival, increased drug toxicity-related mortality, and higher risk of infection. Infection is one of the major causes of mortality and morbidity in patients being treated for ALL.

Despite treatment advancement, FN has a high prevalence in children with ALL and a poor outcome as well, but the adverse risk factors associated with FN in ALL are not well established.[9] Although malnutrition is a common occurrence in children with ALL in our country, there is a dearth of studies exploring the role of nutritional status in patients suffering from ALL, as malnutrition increases the incidence of infection and decreases the survival rate.[10] Thus, this topic was selected to assess the effect of malnutrition on adverse outcomes among ALL patients suffering from FN.

Objective

General objective

General objective was to assess the effect of malnutrition on developing FN in children with ALL during induction phase chemotherapy.

Specific objectives

Specific objectives were to know the age and sex distribution of the respondents, to analyze the nutritional status of the study subjects and to observe the comparison of the severity of neutropenia to nutritional status.

METHODS

This prospective observational study was done in the department of PHO, (Bangabandhu Sheikh Mujib medical university) BSMMU, from January 2021 to October 2021. A total of 60 patients of ALL were selected purposively. A total of 60 patients were selected as study subjects by purposive sampling technique as per inclusion and exclusion criteria.

Inclusion criteria

Children aged 1 year to <18 years, patients of ALL receive chemotherapy during the induction phase, patients who developed neutropenic fever and patients who were willing to give consent were included.

Exclusion criteria

Patients with relapsed ALL, patients getting palliative chemotherapy, patient receiving nutritional support on NG-tube or parenteral nutrition and patients who did not give consent to participate in the study were excluded.

The anthropometric measurements that were taken were body weight, height, and BMI for age. Anthropometric indices were calculated using reference median as recommended by the "national centre for health statistics" (NCHS) WHO 2009, reference values growth chart and classified according to standard deviation (SD) units (termed as Z-score) based on WHO criterion (WHO, 2009). Children (1-18 years) who were less than two standard deviations below the reference median (<-2SD) were considered underweight (weight-for-age), and stunted (height-for-age), respectively. For children ≤5 years of age, weight-for-height was used to interpret the nutritional status; severe malnutrition was considered <-3 standard deviations (SD), moderate malnutrition as -3 to <-2 SD, and good nutrition as -2 to +2 SD. For children >5 years of age, the body mass index (BMI) percentile was used to interpret the nutritional status, 5^{th}-85^{th} as normal weight, 85^{th} ≤95^{th} as overweight, and 95^{th} or more as obese. All the necessary investigations were done. Statistical analysis was performed by using SPSS for Windows version 26.0. Descriptive statistics (numbers

and percentages) were calculated for all variables and statistical analysis was also applied to find associations between variables using the Chi-square test. A $p<0.05$ was considered as significant. Risk estimation was calculated by using the Odds ratio through cross tabulation, with a 95% confidence interval. Ethical clearance was taken from the ethical committee of BSMMU. Informed written consent was obtained from the participants.

RESULTS

This study shows majority (83.30%) were age group <10 years. Mean ± SD 5.44±3.79 (Figure 1).

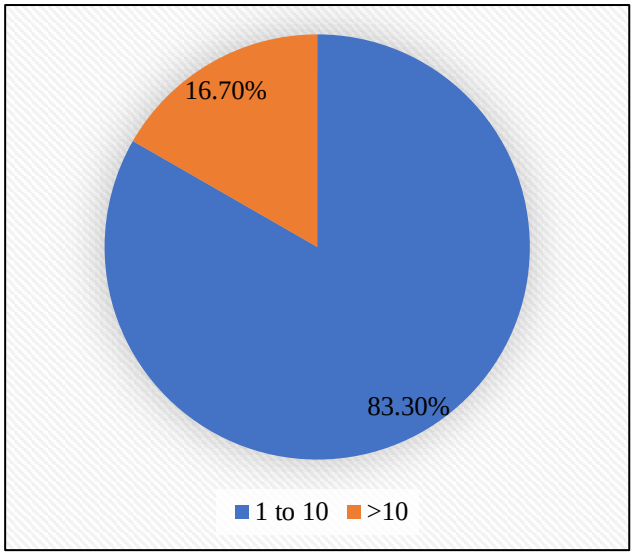

Figure 1: Age distribution of the respondents (n=60).

This study shows majority (83.30%) were age group <10 years. Mean ± SD 5.44±3.79 (Figure 1).

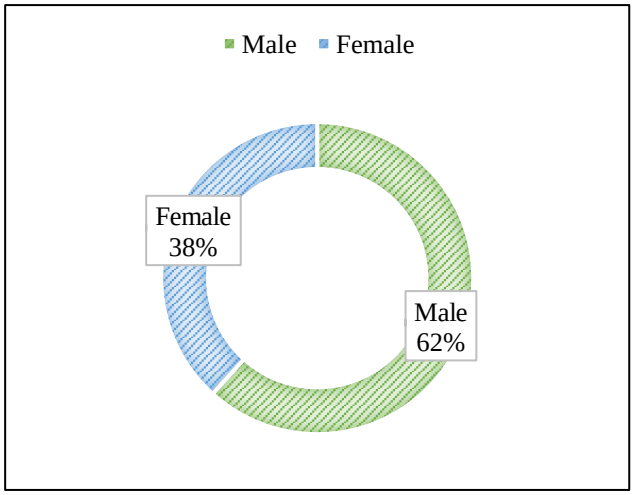

Figure 2: Sex distribution of the study subjects (n=60).

Regarding sex majority (61.70%) were male and 38.3% were female. Male female ratio 1.5:1 (Figure 2).

Table 1: Distribution of the study patients by nutritional status (n=60).

Nutritional status	N	Percentages (%)
Weight for height (WHZ) (≤ 5 years) (kg)		
Wasted	16	26.7
Well-nourished	26	43.3
BMI (> 5 years) (kg/m^2)		
Malnourished	6	10.0
Well-nourished	12	20.0
Weight for age (WAZ) (1-18 years) (kg)		
Underweight	26	43.3
Normal weight	34	56.7
Height for age (HAZ) (1-18 years) (cm)		
Stunted	12	20.0
Normal height	48	80.0

In this series, weight for height (≤5 years) shows 16 (26.7%) were malnourished and 26 (43.3) were well nourished, BMI for age (>5 years) shows 6 (10.0%) were malnourished and 12 (20.0%) were well nourished. Weight for age (1-18 years) shows 26 (43.3.%) were underweight and 34 (56.7%) had normal weight and height for age (1-18 years) shows 12 (20%) were stunted and 48 (80%) had normal height (Table 1).

The mean age of diagnosis was found to be higher (7.38±4.76) in the high-risk group compared to the low-risk group (4.10±2.06). The t test detected significant differences ($p<0.001$) in the mean age of diagnosis between the two risk groups. There is no statistical difference was found regarding gender, paternal and maternal education, and socioeconomic status between the two risk groups but a statistically significant difference ($p<0.008$) was found regarding behavioral patterns among the two risk groups (Table 2).

The Table shows that, the analysis of nutritional status as a risk factor for FN based on anthropometric indices, it was found statistically significant for, weight for height (≤five years) p=0.036, OR=0.24 (95% CI= 0.06-0.958), weight for age p=0.006, OR=0.23 (95% CI=0.07-0.67), but for BMI for age (>five years) p=0.28, OD=0.28 (95%CI 0.02-3.19), and height for age p=0.513, OD=0.66 (95% CI 0.18-2.33) no statistically significant value was found. It was found that nutritional status is associated with adverse outcomes of the FN, but we did not find it as a strong risk factor, as the odds ratio was not significant (Table 3).

A statistically significant difference was found in the severity of neutropenia and nutritional status; WHZ ($p<0.001$) and BMI for age (p=0.019) (Table 4).

A statistically significant difference was found between the two groups regarding microbiologically documented septicemia (p=0.006*) and the death (p=0.042*) (Table 5).

Table 2: Characteristics of subjects according to risk groups FN, (n=60).

Variables	Low risk, (n=35) (%)	High risk, (n=25) (%)	Total, (n=60) (%)	P value
Age at diagnosis (In years)	4.01±2.06	7.38±4.76	5.41±3.80	<0.001*
Gender				
Male	22 (62.9)	15 (60.0)	37 (61.7)	0.822
Female	13 (37.1)	10 (40.0)	23 (38.3)	
Paternal education				
Primary	1 (2.8)	2 (8.0)	3 (5.0)	0.369
Secondary	24 (68.6)	13 (52.0)	37 (61.7)	
Graduation	10 (28.6)	10 (40.0)	20 (33.3)	
Maternal education				
Primary	13 (37.1)	12 (48.0)	25 (41.7)	0.178
Secondary	19 (54.3)	8 (32.0)	27 (45.0)	
Graduation	3 (8.6)	5 (20.0)	8 (13.3)	
Socioeconomic status				
Lower	5 (14.3)	2 (8.0)	7 (11.7)	0.489
Middle	20 (57.1)	18 (72.0)	38 (63.3)	
Higher	10 (28.6)	5 (20.0)	15 (25)	
Behavioral pattern				
Followed advice	27 (77.1)	11 (44.0)	38 (63.3)	0.008*
Did not follow the advice	8 (22.9)	14 (56.0)	22 (36.7)	

Figures in the parentheses indicate the corresponding percentage; Chi-squared Test (χ^2) was done to analyze the data**,** *significant.

Table 3: Univariate logistic regression analysis of nutritional status as a risk factor for FN, (n=60).

Nutritional status	Low risk, (n=35) (%)	High risk, (n=25) (%)	P value	OR 95, CI%
Weight for height (WHZ) (≤5 years)				
Wasting	8 (22.9)	8 (32.0)	0.036*	0.24, 0.06-0.95
Well-nourished	21 (60.0)	5 (20.0)		
BMI (>5 years)				
Malnourished	1 (2.9)	5 (20.0)	0.288	0.28, 0.02-3.19
Well-nourished	5 (14.2)	7 (28.0)		
Weight for age (WAZ)				
Underweight	10 (28.6)	16 (64.0)	0.006*	0.23, 0.07-0.67
Normal weight	25 (71.4)	9 (36.0)		
Height for age (HAZ)				
Stunted	6 (17.1)	6 (24.0)	0.513	0.66, 0.18-2.33
Normal height	29 (82.9)	19 (76.0)		

Figures in the parentheses indicate the corresponding percentage; Chi-squared Test (χ^2) was done to analyze the data**,** *significant.

Table 4: Comparison of severity of neutropenia to nutritional status, (n=60).

Nutritional status	Profound neutropenia, (n=29) (%)	Severe neutropenia, (n=31) (%)	Total, (n=60) (%)	P value
WHZ (≤ 5 years)				
Wasting	12 (41.30)	4 (12.93)	16 (38.1)	<0.001*
Well-nourished	5 (17.24)	21 (67.74)	26 (61.9)	
BMI (> 5 years) (kg/m^2)				
Malnourished	9 (31.10)	1 (3.22)	10 (55.6)	0.019*
Well-nourished	3 (10.34)	5 (16.12)	8 (44.4)	

P value reached from the chi-square test, *significant.

Table 5: Comparison of adverse outcome with nutritional status, (n=60).

Adverse outcome	Well-nourished, (n=38) (%)	Malnourished, (n=22) (%)	Total, (n=60) (%)	P value
Microbiologically documented septicemia	3 (7.9)	8 (36.4)	11 (18.3)	0.006*

Continued.

Adverse outcome	Well-nourished, (n=38) (%)	Malnourished, (n=22) (%)	Total, (n=60) (%)	P value
Shock	3 (7.9)	5 (22.7)	8 (13.3)	0.103
Need for PICU admission	2 (5.3)	4 (18.2)	6 (10)	0.108
Death	3 (7.9)	6 (27.3)	9 (15)	0.042*

Figures in the parentheses indicate the corresponding percentage; Chi-squared Test (χ^2) was done to analyze the data, *significant.

DISCUSSION

In this study age range was from 1 year to <18 years and the mean age was 5.44±3.79. The age group was divided into two groups: <10 years and ≥10 years. Most of the subjects 50 (83.3%) belong to the age group <10 years and others belonging to ≥10 years are 10 (16.7%). Male: female ratio was 1.5:1. Another study in India, conducted by Kumar et al reported that of the 25 cases with ALL, 6 were in the age range of 1-4 years, 7 were between 4 to 8 years, and remaining between 8-12 years.[11] In this series, weight for height (≤ 5 years) shows 16 (26.7%) were malnourished and 26 (43.3) were well nourished, BMI for age (>5 years) shows 6 (10.0%) were malnourished and 12 (20.0%) were well nourished. Weight for age (1-18 years) shows 26 (43.3.%) were underweight and 34 (56.7%) had normal weight and height for age (1-18 years) shows 12 (20%) were stunted and 48 (80%) had normal height. Zalina et al observed that the prevalence of malnutrition was higher in children with newly diagnosed leukemia. They found that underweight (<-2 SD for weight-for-age) was observed in 37.3% of the children while 17.6% of them were stunted (<-25D for height for age).[12] In the present study, the mean age of diagnosis was found to be higher (7.38±4.76) in the high-risk group compared to the low-risk group (4.10±2.06). The t test detected significant differences (p<0.001) in the mean age of diagnosis between the two risk groups. Hapsari et al found that poor socioeconomic status was a risk factor for FN (p=0.032).[13] However, Agnes et al found that socioeconomic status was not statistically significant (p=0.83) for FN.[14] In our study, analysis of nutritional status as a risk factor for FN based on anthropometric indices was found statistically significant for, weight for height (≤5 years) p=0.036, OR=0.24 (95% CI .06-.958), weight for age p=0.006, OR=0.23 (95% CI=0.07-0.67), but for BMI for age (>5 years) p=0.28, OD=0.28 (95% CI=0.02-3.19), and height for age p=0.513, OD=0.66 (95% CI-0.18-2.33). In this study, nutritional status was associated with adverse outcomes of FN, but we did not find it as a strong risk factor, as the odds ratio was not significant. Chaudhury et al found a significant association between wasting and the occurrence of life-threatening complications in children aged less than 5 years (WHZ p=0.036), while no association was found between stunting (HAZ p=0.360) and death or life-threatening complications. Patients with malnutrition tended infection infection-related complications during initial therapy in comparison to normal nutritional status.[15] A statistically significant difference was found in the severity of neutropenia and nutritional status in this study; WHZ (p<0.001) and BMI for age (p=0.019). Another study by Roy et al found that 23.33% of the patients with severe malnutrition showed absolute neutrophil count (ANC) below 100, whereas that was 14.03% with normally nourished children. A fall in ANC is proportional to poor nutritional status and the incidence of FN was significantly higher in the severe malnutrition group (p<0.001).[16] A statistically significant difference was found between the two groups regarding microbiologically documented septicemia (p=0.006*) and death (p=0.042*) in the recent series. We found mortality rate was 15%. Mortality was significantly worse (27.3%) for patients who malnourished at diagnosis compared to those who were well nourished (7.9%) at diagnosis. A similar finding was also found by Loeffen et al survival was significantly worse (p=0.01) for patients who were malnourished at diagnosis than for those who were well nourished at diagnosis.[17] In study, found 4 overweight and 2 obese patients. Among them, 4 overweight patients developed high-risk FN, and 1 obese patient died. Lange et al showed that patients with high BMI are associated with poor outcomes after cancer chemotherapy.[18] Recent research suggests that relationship between obesity, cancer, and cancer therapy is more complicated than previously thought. Growth factors and lymphokines, which are either directly secreted by adipocytes or synthesized in the context of metabolic syndrome, have potential to change chemotherapy's anticancer effects and toxicity. Cancer cell proliferation is known to be influenced by insulin-like growth factor 1 and leptin.[19] Obesity-related lymphokines such as tumor necrosis factor, adiponectin, interleukin-6 and-8, vascular endothelial growth factor, and pre-B-colony-enhancing factors may increase toxicity by affecting inflammation and oxidation, as well as change tumor biology by affecting angiogenesis and cancer cell growth.[20]

Limitations

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

CONCLUSION

FN and its complications are more common in malnourished children with ALL. Malnutrition is associated with adverse outcomes of FN in children with ALL. Both under- and over-nutrition have adverse consequences on the outcome of childhood cancer.

Recommendations

Severe underweight, profound neutropenia predisposes the development of FN. These patients require close

observation. Moreover, to get robust data further studies should be conducted involving a large sample size and multiple centers in this regard.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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