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ORIGINAL ARTICLE

IMPACT OF NUTRITIONAL STATUS ON INDUCTION MORTALITY IN PAEDIATRIC ACUTE LYMPHOBLASTIC LEUKAEMIA

Muhammad Tahir[1]✉, Awais Arshed[1], Tariq Ghafoor[1], Sumaira Khalil[1], Tanzeela Farah[1], Noor Un Nisa[1]

ABSTRACT

OBJECTIVE: To study the impact of nutritional status on induction mortality among pediatric patients suffering from acute lymphoblastic leukemia (ALL).

METHODS: This descriptive analytical study was conducted on pediatric ALL patients who completed induction chemotherapy in Pediatric Oncology Department Combined Military Hospital, Rawalpindi, Pakistan from 1st January 2012 to 30th June 2021. All patients of ALL diagnosed on basis of National Comprehensive Cancer Network Clinical Practice Guidelines, aged 1-18 years were included. Patients who left before completion of induction chemotherapy or refused to participate were excluded. Cases were divided into three groups based on nutritional status. Induction chemotherapy was given as per UKALL 2011 protocol.

RESULTS: Out of 926 patients diagnosed with ALL, 586 (63.3%) were males and 340 (46.7%) were females. Mean age of patients was a 5.83±3.627 years. Majority of the patients (n=679, 73.3%) were well-nourished; and 161 (17.4%) and 86 (9.3%) were moderately and severely malnourished, respectively. About 49.8% (n=461) patients received standard risk chemotherapy protocol with three-drug induction and 50.2% (n=465) received four-drug induction chemotherapy. Infection was the most common complication in 742 (80.1%) patients. Overall induction mortality was 12.9% (n=119/926) in all patients including 9.54% (n=44/461) in standard-risk and 16.12% (n=75/465) in high-risk patients (p=0.003). Induction mortality was significantly high in malnourished-group (17.8%) and 12.2% in normally-nourished children (p=0.008).

CONCLUSION: Nutritional status and risk group at time of diagnosis emerged as predictors of induction mortality among ALL patients. Considerable number of patients died during induction phase of treatment. Malnourished children have a high mortality rate.

KEY WORDS: Acute lymphoblastic leukemia (Non-MeSH); Pediatrics (MeSH); Mortality (MeSH); Malnutrition (MeSH); Pakistan (MeSH).

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1: Pediatric Oncology Department, Combined Military Hospital (CMH), Rawalpindi, Pakistan.

Email✉: drmaliktahir48@gmail.com

Contact #: +92-333-9379891

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignant condition.[1] Outcome of children managed with this condition depends upon several factors and usually, clinicians try to find out these factors at the time of diagnosis to alter the management plan for individual patients.[2] Though treatment response is usually adequate in most of the patients and they achieve remission but still, a considerable number of patients expire during the induction phase of chemotherapy.[3]

Nutrition is an important factor in children with cancer as it not only affects the prevention, pathogenesis, of oncological patients but also influences supportive care and survival.[2,4] Multiple studies have been done in the west to look for the factors related to treatment outcome in patients with ALL. Annalisa Paviglianiti published a review in 2020 highlighting the impact of body mass index on outcomes among children suffering from various types of leukemias. It was revealed that being overweight was associated with poor survival after the treatment and being underweight was associated with increased treatment toxicity.[5] Yazbeck N, et al. in 2016 reported the worse outcomes in malnourished children with ALL at diagnosis as compared with well-nourished children.[6] Similarly, Antillon F, et al. (2013) published that malnutrition was a common finding and related to poor outcomes among the patients suffering from ALL.[7]

Because of reducing bone marrow reserve, malnutrition is a poor prognostic factor in ALL patients.[8] Alterations in drug metabolism in children with cancer have been reported leading to delay in chemotherapy, enhanced toxicity, and decrease overall survival.[9,10] Lobato-Mendizabal et al. reported a decreased survival of 26% in undernourished patients as compared to 83% in well-nourished.[11] Mejia-Arangure JM, et al. in Mexico, reported increased mortality in induction in children with undernutrition.[12]

A recent local study by Ghafoor et al. documented that malnutrition adversely affects the treatment outcome in pediatric AML. It is significantly associated with increased treatment-related mortality, mainly due to infection and decreased disease-free and overall survival.[13] We targeted ALL patients for the same purpose and planned this study with the rationale to look for the impact of nutritional status on induction mortality among pediatric patients suffering from ALL.

TABLE I: CHARACTERISTICS OF STUDY PARTICIPANTS ACCORDING TO THE RISK

Parameters		Standard Risk (n=461)	High Risk (n=465)	Total (n=926)	P value
Age (years)	1-3	126 (27.3%)	77 (16.5%)	203 (21.9%)	0.000
	>3-10	335 (72.6%)	216 (46.4%)	551 (59.5%)	
	>10	0	172 (36.9%)	172 (18.5%)	
Gender	Male	283 (61.3%)	303 (65.1%)	586 (63.2%)	0.234
	Female	178 (38.6%)	162 (34.8%)	340 (36.7%)	
Fever	Yes	394 (85.4%)	385 (82.7%)	779 (84.1%)	0.266
	No	67 (14.5%)	80 (17.2%)	147 (15.8%)	
Pallor	Yes	451 (97.8%)	429 (92.2%)	880 (95%)	0.000
	No	10 (2.1%)	36 (7.7%)	46 (5%)	
Bruising	Yes	152 (32.8%)	160 (34.5%)	312 (33.7%)	0.627
	No	309 (67%)	304 (65.5%)	613 (66.3%)	
Hemoglobin (mg/dl)	<7	246 (53.3%)	196 (42.2%)	442 (47.7%)	0.000
	7-10	165 (35.8%)	180 (38.7%)	345 (37.2%)	
	>10	50 (10.8%)	89 (19.1%)	139 (15%)	
Platelets (cells/L)	$<50\times10^9$	307 (66.6%)	271 (58.3%)	578 (62.4%)	0.29
	$50\text{-}150\times10^9$	112 (24.3%)	136 (29.2%)	248 (26.8%)	
	$>150\times10^9$	42 (9.1%)	58 (12.5%)	100 (10.8%)	
White Blood Cell Count (cells/L)	$<50\times10^9$	461 (100%)	178 (38.3%)	639 (69.0%)	0.000
	$=50\times10^9$	0	287 (61.7%)	287 (31%)	
Nutritional Status	Normally Nourished	326 (70.7%)	353 (75.9%)	679 (73.3%)	0.114
	Moderately Malnourished	92 (20%)	69 (14.8%)	161 (17.4%)	
	Severe Malnourished	43 (9.3%)	43 (9.2%)	86 (9.3%)	
Induction death	Yes	44 (9.5%)	75 (16.1%)	119 (12.9%)	0.003
	No	417 (90.5%)	390 (83.9%)	807 (87.1%)	

METHODS

This prospective study was conducted at the Pediatric Oncology Department, Combined Military Hospital from July 2011 to June 2021. All patients of ALL diagnosed on basis of National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines[14] between the age of 1 and 18 years were included in this study. Patients who left before the completion of induction chemotherapy or refused to participate in the study were excluded.

After ethical approval from the ethical review board committee and informed consent from the patients and/or their caregivers, patients fulfilling the above-mentioned inclusion and exclusion criteria were included in the study. Data was recorded and maintained in electronic media by the data manager under the guidance and supervision of a Paediatric Oncologist. The nutritional status of the patients was determined by Centers for Disease Control and Prevention (CDC) growth chart using the parameter of weight for age and gender. The cases were classified as normally nourished, moderately malnourished and severely malnourished, if the weight for age Z-sco re was < -2, -2 to -3 and <-3, respectively.[15]

For induction chemotherapy patients were divided into standard and high risk according to National Cancer Institute (NCI) Classification based on age, WBC count, and cytogenetic abnormalities.[16] Standard risk group received dexamethasone, vincristine, and asparaginase while the high-risk group received dexamethasone, vincristine, asparaginase, and daunorubicin as per the United Kingdom National Randomised Trial For Children and Young Adults with Acute Lymphoblastic Leukaemia and Lymphoma 2011 (UKALL 2011) protocol.[17] Patients were followed up for 29 days and induction death was defined as the death of the patient with cause-related to underlying ALL.[18] Age, gender, risk group, and nutritional status were correlated with induction death in our study population.

Characteristics of patients, nutritional status, and induction death were analyzed by using descriptive statistics. Chi-square was used to determine the relationship of age, gender, risk group, and nutritional status with induction death in our study population. All statistical analysis was performed using Statistics Package for Social Sciences version 24.0. Differences between groups were considered significant if p-values were =0.05.

RESULTS

A total of 926 patients diagnosed with ALL and completed induction chemotherapy at our department during the study period were included in the analysis. At diagnosis, the mean age was 5.83±3.627 years with a range of 1-17 years. Out of 926 patients, 586 (63.3%), were male while 340 (36.7%) were female. Table I and II summarized the general characteristics and their relation with risk group and malnutrition of study participants.

Majority of the patients (n=679, 73.3%) were well-nourished, 161 (17.4%) and 86 (9.3%) were moderately and severely malnourished, respectively. Maximum patients 766 (82.7%) had a diagnosis of Pre-B ALL.

About 49.8% (n=461) patients received standard risk chemotherapy

TABLE II: CHARACTERISTICS OF STUDY PARTICIPANTS ACCORDING TO THE NUTRITIONAL STATUS

Parameters		Normally Nourished	Moderately Malnourished	Severely Malnourished	P value
Age (years)	1-3	140 (68.9%)	48 (23.6%)	15 (7.3%)	0.05
	>3-10	411 (74.7%)	89 (16.1%)	50 (9.0%)	
	>10	128 (73.9%)	24 (13.8%)	21 (12.1%)	
Gender	Male	427 (72.8%)	106 (18.0%)	53 (9.0%)	0.741
	Female	252 (74.1%)	55 (16.1%)	33 (9.7%)	
Fever	Yes	560 (71.8%)	141 (18.1%)	78 (10.0%)	0.06
	No	119 (80.9%)	20 (13.6 %)	8 (5.4%)	
Pallor	Yes	648 (73.6%)	154 (17.5)	78 (8.8%)	0.15
	No	31 (67.3%)	7 (15.2%)	8 (17.3%)	
Bruising	Yes	244 (78.2%)	51 (16.3%)	17 (5.4%)	0.009
	No	434 (70.7%)	110 (17.9%)	69 (11.2%)	
Hemoglobin (mg/dl)	<7	319 (72.1%)	84 (52.1%)	39 (45.3%)	0.693
	7-10	260 (38.3%)	53 (32.9%)	32 (37.2%)	
	>10	100 (14.7%)	24 (14.9%)	15 (17.4%)	
Platelets (cells/L)	$<50 \times 10^9$	418 (61.6%)	107 (66.4%)	53 (61.6%)	0.723
	$50\text{-}150 \times 10^9$	189 (27.8%)	36 (22.3%)	23 (26.7%)	
	$>150 \times 10^9$	72 (10.6%)	18 (11.2%)	10 (11.6%)	
White Blood Cell Count (cells/L)	$<50\times10^9$	450 (70.6%)	123 (19.3%)	64(10.0%)	0.022
	$=50\times10^9$	229 (79.2%)	38 (13.1%)	22 (7.6%)	
Risk Groups	Standard Risk	326 (70.7%)	92 (19.9%)	43 (9.2%)	0.11
	High Risk	353 (75.9%)	69 (14.8%)	43 (9.2%)	
Infection		538 (79.5%)	129 (80.6%)	75 (87.2%)	0.234
Induction death		79 (11.6%)	21 (13%)	19 (22.1%)	0.024

protocol with three-drug induction and the rest received four-drug induction chemotherapy.

The most common presenting complaint was pallor in 880 (95%) patients while fever was the initial complaint of 799 (84.1 %) patients. Mean hemoglobin was 7.39±2.56 g/dl, and the mean number of platelets was $67.7\pm95.59\times10^9$/L with 578(62.4%) patients having platelets less than 50×10^9/L. The mean WBC count was $57.6\pm3.39\times10^9$/L (range, 0.29-996), around one-third had a WBC of more than $50x10^9$/L. Almost half of the patients were treated with standard-risk treatment (49.8%) and 465 cases with high risk (50.2%). Infection was the most common complication in 742 patients (80.1%). Overall induction mortality was 12.9% (n=119/926) in all patients including 9.54% (n=44/461) in standard-risk and 16.12% (n=75/465) in high-risk patients (p=0.003).

Induction death was 11.63% in well-nourished patients and 13.04%, and 22.09% in moderately and severely malnourished patients (p-value 0.024).

DISCUSSION

This study prospectively evaluated one of the largest cohorts of pediatric patients with ALL from a single center in Pakistan. Malignancies are a major cause of mortality and morbidity across the globe.[1] Cancer related to the hematopoietic system has been lethal as well and has a major impact on mortality and morbidity. The situation becomes more complex when clinicians have to deal with patients of the younger age group who are more prone to adverse effects of cytotoxic drugs. Management strategies could be altered and become patient-specific if high-risk groups are identified at the time of diagnosis and managed accordingly. We planned this study with the rationale to look for the impact of nutritional status on induction mortality among pediatric patients suffering from ALL.

Kedenczki O, et al.[19] from Hungary studied the impact of nutritional status in children with malignancies and concluded that around 30% of patients were under-nourished in their study and mortality risk was higher among patients with weight loss exceeding 20%.

An Indian study evaluated pre-treatment undernutrition, and folate, and B12 deficiency in children with ALL, and their correlation with complications and outcome of induction chemo-therapy.[20] They studied 50 children of ALL and revealed that nutritional deficiencies at the time of diagnosis adversely affect the outcome in patients managed for ALL. Our study was quite large as compared to this Indian study and we analyzed data over 10 years and generated similar findings. In the present study, malnourishment was associated with poor outcomes during induction chemotherapy.

Hafiz MG, et al. studied similar parameters on a sample population from Bangladesh and concluded that under-nutrition was common in patients at the time of diagnosis in childhood ALL and undernourished children were more prone to suffer from infection, prolonged duration of induction, long hospital stay, and even death.[21] Induction death was the main outcome of our study and around 13% of our study participants died during the induction phase. Malnourishment emerged as a predictor of induction death in our study.

Diakatou & Vassilakou published a review of the international literature from 2014 to 2019 regarding the nutritional status of pediatric cancer patients at diagnosis and correlations with treatment, clinical outcome, and the long-term growth and health of survivors. They summarized that malnutrition is related to adverse short and long-term outcomes in pediatric patients suffering from various types of malignancies.[22]

We did not have the facility of parenteral nutrition in our department. We did prescribe oral nutritional supplements to the patients but most of them were unable to take them because of decreased appetite due to chemotherapy effects, with a resultant decrease in complement, cytokines, and immunoglobulin levels and probably impaired immune system and decrease tolerance of chemotherapy. During episodes of nausea and vomiting as a result of chemotherapy nasogastric feeding can be helpful.

These results reflect the outcome of standard treatment offered in our setting and could not be generalized to other settings of our country.

CONCLUSION

A considerable number of patients suffering from ALL died during the induction phase of treatment. Nutritional status at the time of diagnosis emerged as predictors of induction mortality among patients suffering from ALL.

As a modifiable risk factor, early monitoring of every pediatric ALL patients' nutritional status as well as timely nutritional intervention could improve induction remission outcomes and overall survival. Further research is needed to assess whether nutritional support before starting chemotherapy and during induction chemotherapy will mitigate the effect of malnutrition in ALL.

REFERENCES

1. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J 2017;7(6):e577. https://doi.org/10.1038/bcj.2017.53.
2. Sas V, Moisoiu V, Teodorescu P, Tranca S, Pop L, Iluta S, et al. Approach to the Adult Acute Lymphoblastic Leukemia Patient. J Clin Med 2019;8(8):1175. https://doi.org/10.3390/jcm8081175.
3. Bhojwani D, Howard SC, Pui CH. High-risk childhood acute lymphoblastic leukemia. Clin Lymphoma Myeloma 2009;9(Suppl 3):S222-30. https://doi.org/10.3816/CLM.2009.s.016.
4. Rogers PC. Importance of nutrition in pediatric oncology. Indian J Cancer 2015k;52:176-8. https://doi.org/10.4103/0019-509X.175830.
5. Paviglianiti A. A review on the impact of body mass index on outcomes in pediatric leukemia. J Blood Med 2020;18;11:205-12. https://doi.org/10.2147/JBM.S232655.
6. Yazbeck N, Samia L, Saab R, Abboud MR, Solh H, Muwakkit S. Effect of Malnutrition at Diagnosis on Clinical Outcomes of Children With Acute Lymphoblastic Leukemia. J Pediatr Hematol Oncol 2016;38(2):107-10. https://doi.org/10.1097/MPH.0000000000000428.
7. Antillon F, Rossi E, Molina AL, Sala A, Pencharz P, Valsecchi MG, et al. Nutritional status of children during treatment for acute lymphoblastic leukemia in Guatemala. Pediatr Blood Cancer 2013;60(6):911-5. https://doi.org/10.1002/pbc.24377.
8. Lobato-Mendizábal E, Ruiz-Argüelles GJ, Marín-López A. Leukaemia and nutrition I: Malnutrition is an adverse prognostic factor in the outcome of treatment of patients with standard-risk acute lymphoblastic leukaemia. Leuk Res 1989;13(10):899-906. https://doi.org/10.1016/0145-2126(89)90043-x.
9. Marín-López A, Lobato-Mendizabal E, Ruiz-Argüelles GJ. Malnutrition is an adverse prognostic factor in the response to treatment and survival of patients with acute lymphoblastic leukemia at the usual risk. Gac Med Mex 1991;127(2):125-31.
10. American Society of Parenteral and Enteral Nutrition. Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients. Section IV: Nutrition assessment - Pediatrics. J Parenter Enteral Nutr 2002;26 (Suppl 1):13SA-17SA. https://doi.org/10.1177/0148607102026001011.
11. Murry DJ, Riva L, Poplack DF. Impact of nutrition on pharmacokinetics of anti-neoplastic agents. Int J Cancer 1998; Suppl 11: 48-51. https://doi.org/10.1002/(sici)1097-0215(1998)78:11+<48::aid-ijc14>3.0.co;2-3.
12. Mejia-Arangure JM, Fajardo-Gutierrez A, Reyes-Ruiz NI et al. Malnutrition in childhood lympho-blastic leukemia: A predictor of early mortality during the induction-to-remission phase of the treatment. Arch Med Res 1999;30:150-3. https://doi.org/10.1016/s0188-0128(98)00026-8.
13. Ghafoor T, Ahmed S, Khalil S, Farah T. Impact of Malnutrition on Treatment Outcome of Paediatric Acute Myeloid Leukemia. J Coll Physicians Surg Pak 2020;30(10):1021-5. https://doi.org/10.29271/jcpsp.2020.10.1021.
14. Puckett Y, Chan O. Acute lymphocytic leukemia. [Updated 2020;18]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021. Available from URL: https://www.ncbi.nlm.nih.gov/books/NBK459149/
15. Jafari S, Fouladgar M, Naeeni MM, Fakhri M, Fatemi SA, Heidari K, et al. Body mass index, weight-for-age, and stature-for-age indices in iranian school children in relation to weight and growth disorders: a population-based survey. Int J Prev Med 2014;5(Suppl 2):S133-8. https://doi.org/10.4103/2008-7802.157674.
16. Schultz KR, Pullen DJ, Sather HN, Shuster JJ, Devidas M, Borowitz MJ, et al. Risk- and response-based classification of childhood B-precursor acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). Blood 2007;109(3):926-35. https://doi.org/10.1182/blood-2006-01-024729.
17. Goulden NJ, Kirkwood AA, Moppett J, Samarasinghe S, Lawson S, Rowntree C, et al. UKALL 2011: randomised trial investigating a short induction dexamethasone schedule for children and young adults with acute lympho-

blastic leukaemia. Blood 2017;130 (Supplement 1):141. https://doi.org/10.1182/blood.V130.Suppl_1.141.141.

18. Nakagawa S, Kato M, Imamura T, Imai C, Koh K, Kawano Y, et al. In-Hospital Management Might Reduce Induction Deaths in Pediatric Patients With Acute Lymphoblastic Leukemia: Results From a Japanese Cohort. J Pediatr Hematol Oncol 2021;43(2):39-46. https://doi.org/10.1097/MPH.0000000000001926.

19. Kadenczki O, Nagy AC, Kiss C. Prevalence of Undernutrition and Effect of Body Weight Loss on Survival among Pediatric Cancer Patients in Northeastern Hungary. Int J Environ Res Public Health 2021;4;18(4):1478. https://doi.org/10.3390/ijerph18041478.

20. Tandon S, Moulik NR, Kumar A, Mahdi AA, Kumar A. Effect of Pre-treatment Nutritional Status, Folate and Vitamin B12 Levels on Induction Chemotherapy in Children with Acute Lymphoblastic Leukemia. Indian Pediatr 2015;52(5):385-9. https://doi.org/10.1007/s13312-015-0642-x.

21. Hafiz MG, Mannan MA. Nutritional status at initial presentation in childhood acute lymphoblastic leukemia and its effect on induction of remission. Mymensingh Med J 2008;17(2 Suppl):S46-51.

22. Diakatou V, Vassilakou T. Nutritional Status of Pediatric Cancer Patients at Diagnosis and Correlations with Treatment, Clinical Outcome and the Long-Term Growth and Health of Survivors. Children (Basel) 2020;7;7(11):218. https://doi.org/10.3390/children7110218.

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

MT: Conception and study design, analysis and interpretation of data, critical review, approval of the final version to be published

AA & TG & SK: Acquisition, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

TF & NUN: Analysis and interpretation of data, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

KMUJ web address: www.kmuj.kmu.edu.pk
Email address: kmuj@kmu.edu.pk