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ORIGINAL ARTICLE

Impact of Malnutrition on Survival and Treatment Related Morbidity of Cancer in Children

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ABSTRACT

Aim: To find out the impact of malnutrition on survival and treatment-related morbidity of cancer in children and to raise awareness among health care professionals to critically address the issues of malnutrition at diagnosis and during various treatment phases of cancer in children.
Methods: This is a retrospective study, all children of age 1 year to 18 years newly diagnosed with cancer presented to the Pediatric Oncology Department SKMCH &RC from January 1, 2021, to June 30, 2021, were included in the study, and their data was collected from the HIS system. The enrolled patients in the study were followed up further for disease outcome from July 1, 2021, till March 31, 2023, through HIS notes with no direct contact with the patients. Newly diagnosed children with cancer having other co-morbidities like HIV, congenital heart disease, chronic lung and liver disease, and others were excluded, and those patients who had not received any chemotherapy or radiotherapy after diagnosis were also excluded from the study.
Results: The sample comprised of one hundred and sixty pediatric cancer patients. On admission, 68 (42.5%) of all the children newly diagnosed with cancer were malnourished using weight for height Z score of < -3 to < -1SD for children below 5 years of age and BMI ≤ -2Z score for children aged 5 to 18 years. The rate of infections (frequency of 3+ hospitalizations for FN episodes and NNF) was enhanced by malnutrition in the initial phase of treatment (6 months after diagnosis) (p.Tag 0.025). Using univariate and multivariate approach, it was revealed that weight loss more than 10 percent and BMI score reduction by more than 1 to 6 months were associated with the survival and infections independently. In addition, analysis of one variable at a time also revealed high correlation between the two variables: treatment interruptions and malnutrition.
Conclusion: The timely intervention of a condition requires a thorough evaluation of nutritional status at diagnosis and close monitoring for malnutrition during the initial treatment phase, which may potentiate the treatment response to chemotherapy and decrease treatment interruptions. This will prevent prolonged hospitalization for infections in childhood cancer patients and will possibly increase the survival rate.
Keywords: Pediatric cancer, Nutritional assessment, Malnutrition, febrile neutropenia, weight/height Z-score, Survival

INTRODUCTION

Malnutrition is one of the major global problems of developing countries. It accounts for at least half of the childhood deaths across the world. In developing countries like Pakistan, where malnutrition is one of the fundamental causes of morbidity and mortality among children, it may seriously affect the outcome of cancer in children in terms of survival and treatment-related morbidity. When we look at the whole scenario; international; in the last 40 years; for many other childhood cancers the survival rate has risen from 10% to nearly 90% today.

The prime factors that have contributed to the high cure rate include; improvement in diagnostic techniques, innovation in the type of therapies used, and improvement in the supportive care. However, still, malnutrition is a common complication, ranging from a mild and moderate one in children and adolescents with cancer, the prevalence being between 6 percent and 50 percent, depending on the type and stage of the disease, the treatment modality, and the general standard of living. In developing countries, where limited healthcare facilities, high rates of treatment abandonment, treatment-related morbidity, and mortality affect the overall prognosis of cancer in children and adolescents, malnutrition is contributing another worse prognostic factor to the outcome of cancer in children. In Pakistan, limited data is available on the survival rate of cancer in children. However, the trend shows that only 20%–30% are cured, owing mainly to treatment delays and misdiagnosis.

The cause of malnutrition can be primary or secondary due to malignancy itself or its aggressive multimodal treatment and its adverse effects[10]. Malnutrition causes a decrease in cytokines, complements, and immunoglobulin levels that leads to a deficient immune system[11]. This makes the child prone to infections, febrile neutropenia, cytopenia, and a poor response to chemotherapy that initiates the cycle of repeated hospital admissions.

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Malnutrition can seriously affect overall survival because of a decrease in tolerance to chemotherapy, decreasing event-free survival and increasing treatment-related morbidity[12-15]. It may decrease the suboptimal absorption of chemotherapeutical drugs and tolerated dose delay the time to appointments, and be responsible for the weak treatment effect. Disease related malnutrition causes immunocompetence to decline, patients become susceptible to infections and febrile neutropenia-FN due to hormonal changes and altered cytokines production response. For FN, the following was observed: fever (body temperature ≥38.5°C) with neutropenia (absolute neutrophilic count ≤0.5 x 10^9/L) hospitalization becomes mandatory for pediatric patients in order to administer intravenous antibiotic therapy[20,21].

As a result, the number of hospitalizations in children and adolescents with cancer having malnutrition increased significantly, causing higher treatment costs and compromising quality of life (QoL)[22]. That is why nutritional assessment must be a vital component of the history and physical examination of children with cancer at the time of diagnosis and during the treatment phase. Nutritional imbalance in children can be measured using various indicators such as Z-score, WHO recommended growth charts for weight-for age, height-for-age, weight for height, body mass index, mid-upper arm circumference, and skin fold thickness.[23,24] This study aims to explore the impact of malnutrition on cancer survival and treatment-related morbidity in children, as there is no universal algorithm for detecting malnutrition.

METHODOLOGY

This is a retrospective study conducted at the Pediatric Oncology Department SKMCH & RC Lahore and Peshawar and included children aged 1 year to 18 years newly diagnosed with cancer. Newly diagnosed children with cancer having other comorbidities like HIV, congenital heart disease, chronic lung and liver disease, and other chronic illnesses, and those patients who haven't received any chemotherapy or radiotherapy after diagnosis were excluded from the study.

The study started retrospectively from January 1, 2021, to June 30, 2021, for enrolment of the patients through HIS notes without any direct contact with the patients. The enrolled patients were further followed up from July 1, 2021, to March 31, 2023, through HIS notes for disease outcome (no patients died and survived), morbidities like hospitalizations for infections (FN and other NNF), and treatment interruptions. Data collected from HIS was stored in and analyzed through SPSS software.

The nutritional status of the study population was assessed at diagnosis and at 6 months after diagnosis by WHO growth charts: weight for height/length Z score in 1 year to 5 year-old children and BMI for age Z score in children aged >5 years to 18 years.

In our study, malnutrition was defined by WHO criteria: weight for height/length Z score < -1 to ≤-3 SD in 1 year to 5 year old children and BMI Z score for age ≤ -2 SD (moderate to severe malnutrition) in children aged >5 years to 18 years. These are the measuring tools for acute malnutrition in children.

According to WHO growth charts, acute malnutrition is defined by: Weight for Height Z score for children aged 1 to 5 years:

- Mild malnutrition Z Score ≤ -1 SD from the mean
- Moderate malnutrition : Z score ≤ - 2 & ≥ -3 SD from the mean,
- Severe malnutrition: Z score < -3 SD from the mean

While in children of age >5-18 yrs it is defined by :BMI Z score for age

a)Severe thinness : < -3 SD from the mean

b)Thinness : ≤ -2 & ≥ -3 SD from the mean.

As acute malnutrition is more prevalent in cancer in children according to previous studies, we took weight for height Z score in under 5 years and BMI z score for age in above 5-18 years age children, which are more reliable tools according to WHO and UNICEF data[28].

In our study, we defined morbidity by:

1. The number of episodes of febrile neutropenia (FN) and no neutropenic fever (NNF); and
2. The number of hospitalizations of children with cancer for FN and NNF.

Survival was defined by several children with cancer surviving after the start of treatment till the end of the follow-up duration of the study.

RESULTS

This study included 160 pediatric patients who were getting treatment from the Shaukat Khanum Memorial Cancer Hospitals trust-wide. The frequencies and percentages for demography and disease characteristics were calculated for all patients and are presented in Table 1. 104(65%) patients were male and 56(35%) patients were female. The highest number of patients was Afghanis (41.5%), comparative to other regions, while 34(21.3%) patients were from the Malakand agency and 34(21.3%) patients were from the Peshawar region. Just 5(3.1%) patients were from other provinces of Pakistan, contributing very little proportion to the study population. So most patients totaling 55(96.9%) were from Pakhtoon-dominant regions like Khyber Pakhtunkhwa and Afghanistan.

The median age was calculated to be around 8 years at the time of diagnosis. The patient age, which was less than <5, was the highest group 94 (58.8%). Concerning the patients between 5-10 years was 41 (25.6%) and above 11-18 years was 25(15.6%). Following patient diseases, the highest number of patients—49(30.6%)—were affected by Hodgkin lymphoma. Similarly, 27(16.9%) patients were diagnosed with B-All and 25(15.6%) were affected by NHL. Furthermore, 15(9.4%) patients were having bone sarcoma. The largest number of patients who had high disease risk was 95(59.4%), and low disease risk was reported as 63(39.4%).

A total of 68(42.5%) patients were malnourished at diagnosis, of whom 24(15.1%) patients had BMI ≤-2 SD from the mean, while the remaining 44(27.6%) had a weight/height z score < -1 to ≤-3 SD from the mean. At 6 months, the number of malnourished children reduced to a total of 56(35%), with 15 (9.3%) patients having a BMI ≤ -2 SD and 41(39%) having a weight/height z score < -1 to < -3 SD from the mean.

As far as FN is concerned, the number of FN episodes that are less than or equal to three FN episodes was 48 (30.0%). The number of emergency hospitalizations across the hospitals for pediatric patients was calculated, and the number of patients who were not hospitalized was reported as 2 (38.8%). Moreover, the majority of the patients 92 (57.5%) had no neutropenic fever. In the data analysis, 129(80.6%) patients were alive at the end of the study period, while 31(19.4%) died during the study period. Concerning treatment interruptions, those patients who had treatment interruptions were 123(76.9%) in the treatment phase.

Table 1.Abbreviations:DI khan: Dera Ismail Khan,, NHL:Non Hodgkin lymphoma-ALL: B cell acute lymphoblastic leukemia,T-ALL: T cell acute lymphoblastic leukemia ,B sarcoma: Bone sarcoma, S-sarcoma:,soft tissues sarcoma, CNS tumors: central nervous system tumors, FN: Febrile neutropenia, NNF: Non-neutropenic fever, BMI.

Table 2: A univariate and multivariate analysis of survival on patient demographic features and disease characteristics was performed by using the SPSS latest version. A univariate analysis was checked to create the association of one dependent variable with the independent variables at a time. Similarly, multivariate statistical analyses were accomplished by using a step-wise regression method. The P-value was checked at statistical significance,The study found that various factors, including age, origin, diagnosis, BMI at 6 months, weight/height Z score at diagnosis, weight/height z score at 6 months, and number of FN episodes, were significantly correlated with lower survival rates. Other variables, such as disease risk, emergency hospitalizations, non-neutropenia, and treatment interruptions, were also significantly correlated with lower survival rates. In multivariate analysis, diagnosis, weight/height Z score, and weight/height z score were significantly associated with lower survival rates, and weight/height z score at 6 months (HR = 3.41, CI = 1.84-11.32, p = 0.0003) were significantly associated with lower survival rates in multivariate analysis. This study's fundamental feature is that it focuses on the impact of malnutrition on survival and treatment-related morbidities like hospitalization rate and treatment interruptions. In light of this risk factor's potential for management, an individualized assessment of our kids and teenagers would be required going forward. Furthermore, this demographic is very vulnerable and needs nutritional care. A proper nutritional intervention may help cancer patients better tolerate their medication, as numerous studies have already shown.

Table 3: At 6 months, we checked the relationship between BMI Z-score, weight/height, and survival time. During 6 months, a BMI Z-score decrease of >1 and a weight/height of >10% were established individually in 29(24.2%) and 37(30.5%) patients. The incidence of death in patients aged 5-18 with moderate to severe malnutrition was significantly higher at 6 months post-diagnosis, with survival significantly reduced in patients aged 1-5 years with weight/height loss >10% and in patients aged above 5-18 years with a BMI Z-score decrease >1.

Table 4: In 6 months, we determined the relationship between hospitalization status in patients with FN. Patients from moderately to severely malnourished (BMI Z ≤ -2) at 6months and patients who experienced a decrease in BMI Z score >1 were [HR 7.05, 95% CI= 2.69-8.42, P=0.026] and [HR 9.31, 95% CI= 4.22-11.36, P=0.001] respectively.05, 95% CI= 2.69-8.42, P=0.026) and BMI Z-score decrease >1 (HR 9.31, 95% CI= 4.22-11.36, P=0.001). One has several hospitalizations for FN>3 in mid-treatment after diagnosis.

Furthermore, patients with more than three FN had higher hospitalization rates within the group with weight/height loss >10% at month 6 (HR 7.32; 95% CI 1.98-10.14; P=0.0007).

Table 1: Patient D
emographics and Disease Characteristics (n=160)

Variables	Characteristics	Frequency	%age
Age in years	<5yrs	94	58.8
	5-10yrs	41	25.6
	11-18yrs	25	15.6
Gender	Male	104	65.0
	Female	56	35.0
Origin	Afghan	41	25.6
	Bannu DI Khan	12	7.5
	Hazara	7	4.4
	Kohat	8	5.0
	Malakand	34	21.3
	Mardan	19	11.9
	Peshawar	34	21.3
	Other provinces	5	3.1
Diagnosis	Hodgkin	49	30.6
	NHL	25	15.6
	B-All	27	16.9
	T-All	3	1.9
	BSarcoma	15	9.4
	S-sarcoma	4	2.5
	CNS tumor	4	2.5
	Others	33	20.6
Weight/Height Zscore at diagnosis	normal	50	31.3
	Mild malnutrition(Zscore < -1SD from the mean	22	13.8
	Moderate malnutrition(zscore<-2 to-3 SD from the mean)	16	10.0
	Severe malnutrition (zscore <-3SD from the mean)	6	3.8
weight /height Z score at 6 months	normal	48	30.0
	Mild malnutrition	24	15.0
	moderate malnutrition	15	9.4
	severe malnutrition	2	1.3
	Total	89	55.6
BMI at diagnosis	Normal	42	26.3
	Thinness	18	11.3
	Severe thinness	6	3.8
BMI at 6 months	normal	47	29.4
	thinness	10	6.3
	severe thinness	5	3.1
disease risk	Total	62	38.8
	low	63	39.4
	high	95	59.4
number of FN episodes	no FN episodes	91	56.9
	Less than or equal to 3 FN episodes	48	30.0
	greater than 3 FN episodes	21	13.1
No of non neutropenic fever (NNF)	no NNF	92	57.5
	less than or equal to 3 episodes	50	31.3
	greater than 3 episodes	18	11.3
Alive or dead at 6 months	Alive	129	80.6
	dead	31	19.4
Patient alive or dead at the end of follow-up	alive	121	75.6
	dead	39	24.4
No of treatment interruptions	no treatment interruptions	123	76.9
	< or equal to 3	18	11.3
	>than 3	19	11.9
number of emergency hospitalizations	no hospitalization	62	38.8
	less than or =3 hospitalizations	57	35.6
	>3 than no of hospitalizations	41	25.6

Table 2: Univariate and Multivariate analysis of survival on patients' demographic featuresand disease characteristics.

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age in years	1.29	1.21-1.44	0.007	1.09	0.25-4.31	0.78
Gender	0.89	2.23-1.42	0.72	2.05	1.41-5.65	0.65
Origin	4.56	5.31-7.41	0.032	1.96	0.21-3.00	0.83
Diagnosis	13.07	6.25-21.31	0.002	6.98	3.74-9.12	0.009*
Weight/Height Z score at diagnosis	4.32	1.71-6.32	0.002	2.35	1.36-2.23	0.005*
weight /height z sore at 6 months	2.31	3.69-9.67	0.009	3.31	1.84-11.32	0.0003*
BMI at diagnosis	6.17	2.35-6.21	0.001	1.85	1.09-7.28	0.32
BMI at 6 months	3.98	1.87-3.14	0.001	2.32	1.11-5.23	0.45
disease risk	6.32	3.17-5.78	0.006	3.21	2.33-5.32	0.96
number of FN episodes	3.23	1.25-2.34	0.007	1.27	1.12-3.21	0.67
Non neutropenic fever	3.86	2.88-3.78	0.002	2.14	1.96-5.22	0.321
Number of treatment interruptions	2.86	2.75-6.47	0.0003	1.86	1.09-4.32	0.173
number of emergency hospitalizations	1.99	1.12-4.36	0.003	0.96	1.26-6.21	0.95

Table 3: Impact of BMI Z-score and weight/height on survival at different times

		HR	No. (%)	95% CI	P value
Diagnosis	BMI Z-score ≤-2	3.2	9(6.21)	0.79-9.54	0.34
6 months	BMI Z-score ≤-2	4.05	21(17.5)	1.58-6.33	0.009
	BMI Z-score decrease >1	3.21	37(30.5)	1.30-4.63	0.03
	Weight/height loss>10%	1.98	29(24.4)	1.23-6.91	0.04
	Weight/height loss> 5%	2.53	69(27.2)	1.96-4.39	0.864

Table 4: Impact of nutritional status on the incidence of >3 hospitalizations for FN at Different times.

		HR	No. (%)	95% CI	P value
At Diagnosis	BMI Z-score ≤-2	2.1	9(6.21)	0.86-7.32	0.45
At 6 months	BMI Z-score ≤-2	7.05	21(17.5)	2.69-8.42	0.026
	BMI Z-score decrease >1	9.31	37(30.5)	4.22-11.36	0.001
	Weight/height loss>10%	7.32	30(25.2)	1.98-10.14	0.0007
	Weight/height loss > 5%	1.88	63(52.5)	1.46-7.23	0.968

DISCUSSION

Our study included a total of 160 newly diagnosed patients with cancer, performed over a period of total 27 months. We took 2 different parameters: weight/height z score in under 5 years and BMI z score above 5-18 years of age for assessment of malnutrition in children with cancer, as these two are better assessment tools for acute malnutrition according to WHO recommendations. Mid-upper arm circumference (MUAC) is also one of the assessment tools for acute malnutrition, but it was not available retrospectively in our hospital information system (HIS). In our study, we were measuring acute malnutrition in children, which is more common in children with cancer (63.3%), as compared to chronic malnutrition.

A total of 68(42.5%) patients were malnourished at diagnosis, of whom 24(15.1%) patients had a BMI ≤-2 SD from the mean, while the remaining 44(27.6%) had a weight/height z score < -1 to <-3 SD from the mean. At 6 months, the number of malnourished children reduced to a total of 56(35%), with 15 (9.3%) patients having a BMI ≤ -2 SD and 41(39%) having a weight/height z score < -1 to < -3 SD from the mean. This decrease in the number of malnourished children may be attributed to nutritional care provided at SKM after the enrolment of patients for the treatment of cancer and studies are similar with prior studies.[12,15,18,22]

We checked survival at 6 months by looking for association between BMI Z-score, weight for height loss, and survival time. During 6 months, a BMI Z-score decrease of >1 and a weight/height of >10% were established individually in 29 (24.2%) and 37 (30.5%) patients. The incidence of death in patients of age more than 5–18 years with moderate to severe malnutrition (BMI Z-score ≤ -2) was considerably greater at 6 months (HR 4.05, 95% CI = 1.58–6.33, P = 0.009) after diagnosis. Furthermore, survival was significantly reduced in patients of age 1–5 years when there was weight/height loss >10% at 6 months (HR 1.98, 95% CI = 1.23-6.91, P = 0.04). In addition to that, survival was significantly decreased for patients aged above 5–18 years with a BMI Z-score decrease >1 at 6 months (HR 3.21, 95% CI = 1.30–4.63, P = 0.03) the findings support with.[25-31]

The study found a significant association between hospitalizations and nutritional status for FN in the first 6 months of treatment, with patients from moderate to severely malnourished reporting multiple hospitalizations and a higher number of hospitalizations in patients with weight/height loss.

Our study supplemented the already existing data in the literature. In fact, previously Triarico et al. 29 also reported that outcomes involving malnutrition at diagnosis and at 3 months and 6 months of diagnosis were actually significantly poor in survival. It was possible to identify a significant relationship between malnutrition during the first stage of treatment (3-6 months from the diagnosis) and lower survival, adjusted by 5-year expected survival according to diagnosis. Therefore, considering all the previous studies, including our study, it could be said that improving the control of the nutritional status during the beginning of the treatment can increase the survival rates 30-33. Moreover, Triarico etal. 29 demonstrated the correlation between early weight losses within the first 3-6 months of diagnosis. Additionally, a rate of FN episodes. The most important advantage of the current study is that it has pointed out an impact of malnutrition and weight loss on survival and on hospitalization for FN among childhood cancer patients. Since malnutrition is a better manageable risk factor in the future a detailed assessment of our children and adolescents is highly required and adequate nutrition support to this vulnerable group should be provided. The study while interpreting the data could be raised, like:

1. Nature and stage of malignancy couldn't be impacted directly on nutritional status at diagnosis.
2. The retrospective nature of the study.
3. Lack of information on body composition, some of the bulky tumours likely contribute to weight gain; in that case, we should have taken MUAC and skin fold thickness as another assessment tool for malnutrition, but that is not routinely taken at first presentation at SKM.
4. We didn't take edematous malnutrition (kwashiorkor) in our study as data on the presence and absence of edema along with a low BMI Z score and a low weight for height Z SC score was not available in HIS. This could confound the study and may falsely mask the number of actual malnourished patients at diagnosis and during the treatment phase.

Based upon the above limitations of the study, we will recommend the following: A thorough assessment of nutritional status by MUAC, skinfold thickness, BMI, weight, and height with full body composition should be taken. Edematous malnutrition should not be ignored, as this can falsely increase the weight for height/age. Timely nutritional intervention during the treatment is needed to improve the treatment response, reduce the chemotherapy-related morbidities, and enhance the survival rates. Furthermore, prospective studies are needed to look for an association of optimum nutritional care during the first 6 months of the treatment phase with survival and hospitalization rates, which will definitely need a larger sample size and prolonged study duration.

CONCLUSION

Due to the high prevalence of malnutrition in childhood cancer, thorough nutritional assessment of patients at diagnosis is strongly needed so that timely intervention of malnutrition can be provided to enhance the possible survival rates, decrease the hospitalization rates for infectious diseases, and improve the tolerability of chemotherapy. This will definitely reduce the cost of hospitalization rates and the misery of children with malignancies.

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1. Conception and design of or acquisition of data or analysis and interpretation of data.

2. Drafting the manuscript or revising it critically for important intellectual content.
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