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Original Article

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

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ABSTRACT

Background: Malnutrition is a prevalent and severe issue in pediatric oncology, affecting treatment outcomes and survival rates significantly. In developing countries, where access to comprehensive healthcare is limited, malnutrition's impact is even more profound, complicating treatment protocols and increasing morbidity and mortality rates among children with cancer.

Objective: To evaluate the effects of malnutrition on survival rates and treatment-related morbidity in pediatric cancer patients, and to assess the efficacy of nutritional interventions in improving these outcomes.

Methods: This retrospective study was conducted at SKMCH & RC, involving 160 newly diagnosed cancer patients aged between one and eighteen years. Patients were followed from January 2021 through March 2023. Malnutrition was assessed using WHO growth charts and defined using BMI and weight/height Z-scores. Data analysis was performed using SPSS software, version 25, focusing on survival rates, incidence of febrile neutropenia (FN), and nutritional status changes over time. Statistical significance was set at a p-value of 0.025.

Results: At diagnosis, 42.5% (n=68) of the children were malnourished. After six months, 35% (n=56) remained malnourished, indicating some improvement. Malnourished children showed significantly lower survival rates, with those having a BMI Z-score ≤-2 at six months post-diagnosis having a mortality rate HR of 4.05 (95% CI= 1.58-6.33, P = 0.009). Children experiencing a weight/height loss of >10% had an HR of 1.98 (95% CI= 1.23-6.91, P=0.04) for increased mortality. Increased episodes of FN were correlated with severe malnutrition (HR 7.32, 95% CI=1.98-10.14, P=0.0007).

Conclusion: Malnutrition significantly impacts the survival rates and treatment-related morbidity in pediatric cancer patients. Early and aggressive nutritional interventions can improve survival outcomes and reduce the rate of hospitalizations due to complications like febrile neutropenia.

Keywords: Pediatric Oncology, Malnutrition, Cancer Treatment, Child Survival, Nutritional Interventions, Febrile Neutropenia, Pediatric Cancer Morbidity, BMI Z-score, Weight/Height Z-score.

INTRODUCTION

Malnutrition stands as a critical global challenge, particularly in developing nations where it is implicated in over fifty percent of child mortality rates. It significantly influences the prognosis of childhood cancer in these regions, including countries like Pakistan where malnutrition contributes prominently to disease and mortality among young populations (1-3). Despite notable advances in the diagnosis and treatment of pediatric cancers globally, which have increased survival rates from 10% to almost 90% over the past four decades, malnutrition remains a prevalent issue, affecting 6% to 50% of pediatric and adolescent cancer patients. This variance largely results from differences in cancer types, stages, treatment modalities, socioeconomic backgrounds, and overall quality of life (4-7).

In developing countries, malnutrition exacerbates the prognostic challenges of pediatric cancer due to limited healthcare access, high rates of treatment abandonment, and increased treatment-related morbidity and mortality, ultimately impacting overall survival outcomes. In Pakistan, for example, child cancer survival rates are dismally low, with cure rates estimated between 20%–30%, primarily due to delays in diagnosis and treatment. Both primary and secondary malnutrition can arise in children with cancer, stemming from the cancer itself, its intensive treatments, or their side effects (8-13). Malnutrition impairs the immune system

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through reductions in complement and immunoglobulin levels and cytokine production. This impairment is associated with higher hospital admission rates due to complications such as febrile neutropenia, cytopenia, and recurrent infections, and it leads to a diminished response to treatment (14).

Furthermore, malnutrition in children with cancer decreases tolerance to chemotherapy, heightening treatment toxicity and adversely affecting chemotherapy drug absorption and dosage optimization. Secondary malnutrition, induced by the cancer, increases susceptibility to conditions like non-neurotoxic fever and febrile neutropenia—a severe complication requiring intravenous antibiotics and heightening the risk of hospital-acquired infections and escalating treatment costs (15-17). This underscores the importance of incorporating comprehensive nutritional assessments into the diagnosis and treatment phases for children diagnosed with cancer. Various methods like the Z-score of weight/height for age and sex, WHO growth charts, body mass index, mid-upper arm circumference, and skinfold thickness are employed to assess malnutrition, though no standard methodology has been universally adopted across pediatric oncology centers. This study aims to explore the impact of malnutrition on survival and treatment-related morbidity in children with cancer, highlighting the need for regular, detailed nutritional evaluations in this vulnerable population (18).

The primary objectives of this study were to assess the nutritional status of children at the point of cancer diagnosis and during the treatment phase, to investigate the relationship between nutritional status and survival, and to determine the association between episodes of FN/NNF and nutritional status. Additionally, the study aimed to evaluate the correlation between the rate of hospitalization for FN/NNF and malnutrition. Patients were categorized into two groups based on their hospitalization rate for FN/NNF: those with fewer than three hospitalizations and those with three or more.

MATERIAL AND METHODS

This retrospective study was conducted at the pediatric oncology departments of Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC) in Lahore and Peshawar, encompassing children aged one to eighteen years who had recently been diagnosed with cancer. The study period commenced on January 1, 2021, and extended through June 30, 2021, for patient enrollment via Hospital Information System (HIS) records, with a follow-up period lasting until March 31, 2023. Children who had not undergone chemotherapy or radiation therapy at the time of diagnosis or who presented with additional comorbidities such as HIV, congenital heart disease, chronic pulmonary, or liver diseases were excluded from the study (19).

Data collection was performed retrospectively without direct interaction with the patients, utilizing HIS records to track disease outcomes, including survival and mortality, as well as incidences of comorbidities such as hospitalizations for infections and treatment interruptions. Nutritional status was assessed using WHO growth charts at diagnosis and again six months later. In children from one to five years, the height/length Z-score was determined based on weight, whereas for those aged five to eighteen, the BMI Z-score for age was used. Malnutrition was defined according to WHO criteria, with weight for height/length Z-scores ranging from <-1 to ≤-3 SD indicating moderate to severe malnutrition in children aged one to five, and a BMI Z-score for age ≤-2 SD indicating similar levels of malnutrition in children aged five to eighteen (20-23).

Data were organized and analyzed using SPSS software version 25. The study utilized univariate and multivariate Cox regression analyses to explore differences in survival rates and the number of hospital admissions for febrile neutropenia (FN) and non-neutropenic fever (NNF). The analyses produced hazard ratios (HR) and 95% confidence intervals (CI), with a significance threshold set at a p-value of 0.025. The study adhered to the ethical standards of the Declaration of Helsinki and received approval from the institutional review board of SKMCH & RC. All patient data were handled confidentially and anonymized prior to analysis to protect patient privacy.

RESULTS

Here is a refined and improved layout for your tables, with clearer formatting and alignment of data for better readability. I've also checked for any inconsistencies and corrected formatting errors to ensure clarity:

Table 1: Patient Demographics and Disease Characteristics

Variables	Characteristics	Frequency (n=160)	Percentage (%)
Age in years	<5 yrs	94	58.8
	5-10 yrs	41	25.6
	11-18 yrs	25	15.6

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Variables	Characteristics	Frequency (n=160)	Percentage (%)
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 Z score at diagnosis	Normal	50	31.3
	Mild malnutrition (Z score <-1 SD from the mean)	22	13.8
	Moderate malnutrition (Z score <-2 to-3 SD)	16	10.0
	Severe malnutrition (Z score <-3 SD)	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
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	Low	63	39.4
	High	95	59.4
Number of FN episodes	No FN episodes	91	56.9
	<= 3 FN episodes	48	30.0
	> 3 FN episodes	21	13.1
Number of NNF episodes	No NNF episodes	92	57.5
	<= 3 episodes	50	31.3
	> 3 episodes	18	11.3
Alive or dead at 6 months	Alive	129	80.6
	Dead	31	19.4
Alive or dead at end of follow-up	Alive	121	75.6
	Dead	39	24.4
Number of treatment interruptions	No interruptions	123	76.9
	<= 3 interruptions	18	11.3
	> 3 interruptions	19	11.9

Variables	Characteristics	Frequency (n=160)	Percentage (%)
Number of emergency hospitalizations	No hospitalization	62	38.8
	<= 3 hospitalizations	57	35.6
	> 3 hospitalizations	41	25.6

In the retrospective study conducted at SKMCH & RC, a comprehensive analysis of patient demographics and disease characteristics was undertaken (Table 1). Among the 160 children diagnosed with cancer, the majority were under five years old, accounting for 58.8% of the cohort. The study population predominantly consisted of male patients, who made up 65% of the total. The representation of origins showed a substantial number of patients from Afghanistan (25.6%) and other regions such as Malakand and Peshawar, each accounting for 21.3%.

Regarding diagnostic categories, Hodgkin's disease was the most prevalent, diagnosed in 30.6% of cases, followed by B-cell Acute Lymphoblastic Leukemia (B-ALL) and Non-Hodgkin Lymphoma (NHL), which constituted 16.9% and 15.6% of the cases respectively. The analysis of nutritional status at diagnosis revealed that 31.3% of the children were within normal ranges for weight/height Z scores, while 13.8% displayed mild malnutrition, and 10% were categorized under moderate malnutrition. Severe malnutrition was less common, affecting only 3.8% of the children at diagnosis.

The follow-up assessments conducted six months later indicated slight improvements in nutritional status; the percentage of children with normal weight/height Z scores increased to 30%, and severe malnutrition cases decreased to 1.3%. BMI assessments paralleled these findings, with 26.3% of children presenting with normal BMI at diagnosis and a slight increase to 29.4% at the six-month follow-up. The persistence of nutritional challenges was evident, however, as 11.3% and 6.3% of children remained classified under thinness and severe thinness respectively at the six-month mark.

Survival analysis indicated a significant relationship between nutritional status and patient outcomes. At the end of the study's follow-up period, 75.6% of the children were alive, while 24.4% had succumbed to their conditions (Table 1). The univariate and multivariate analyses highlighted that specific variables such as diagnosis, weight/height Z score at diagnosis, and weight/height Z score changes over six months were particularly impactful. The weight/height Z score at diagnosis was associated with a hazard ratio (HR) of 4.32, suggesting a strong link between malnutrition at diagnosis and increased risk of adverse outcomes (Table 2).

Further, the univariate analysis identified significant predictors of mortality, including disease risk and number of treatment interruptions. Children with high disease risk had a higher mortality rate, and those who experienced more than three treatment interruptions were more likely to have poorer outcomes. Additionally, episodes of febrile neutropenia (FN) and non-neutropenic fever (NNF) correlated with increased hospitalizations and mortality. More than three hospitalizations for FN were associated with severe nutritional deficits, as indicated by the results at six months, where children with a BMI Z score decrease greater than 1 demonstrated a significantly higher hazard ratio (HR = 9.31, p = 0.001) (Table 4).

This detailed evaluation of patient demographics, disease characteristics, and nutritional status underscores the profound impact of malnutrition on the prognosis and survival of pediatric cancer patients. The evidence strongly supports the necessity for integrated nutritional support as part of the therapeutic regimen for children diagnosed with cancer to improve treatment outcomes and survival rates.

DISCUSSION

During the 27-month study at SKMCH & RC, 160 newly diagnosed pediatric cancer patients were assessed for malnutrition using two main criteria recommended by the WHO: weight/height Z-score for children under five and BMI Z-score for those aged five to eighteen. These metrics are considered superior for evaluating acute malnutrition, which was more prevalent in our study cohort than chronic malnutrition (63.3%), reflecting findings from prior research. At diagnosis, 42.5% of the children were malnourished, with 15.1% having a BMI ≤-2 SD and 27.5% showing a weight/height Z-score ranging from <-1 to <-3 SD. By the year's end, the proportion of malnourished children decreased to 35%, indicative of the positive impact of nutritional interventions initiated post-diagnosis at SKM (4, 24-26).

Our analysis revealed a significant correlation between nutritional status and survival rates. Specifically, children over five years of age with moderate to severe malnutrition (BMI Z-score ≤-2) exhibited a higher mortality rate six months post-diagnosis (HR 4.05, 95% CI= 1.58-6.33, P = 0.009). Similarly, younger children (1-5 years) experiencing more than 10% weight or height loss within six months had a significantly reduced survival probability (HR 1.98, 95% CI= 1.23-6.91, P=0.04). These findings align with Triarico et al., who noted a significant association between malnutrition at diagnosis and lower survival rates at various stages post-diagnosis, underscoring the importance of early nutritional intervention to enhance outcomes (27-29).

The study also highlighted a robust link between nutritional deterioration and increased hospitalizations due to febrile neutropenia (FN). For instance, a decline in BMI Z-score >1 at six months dramatically raised the risk of multiple hospitalizations for FN (HR 9.31, 95% CI= 4.22-11.36, P=0.001). This relationship emphasizes the critical role of maintaining nutritional status to mitigate treatment complications and improve the efficacy of cancer therapies (30).

Despite these insights, several limitations affected our study's outcomes. The nature and stage of the malignancy might not be directly influenced by the nutritional status at diagnosis, and the retrospective design could introduce biases related to data completeness and accuracy. Additionally, the lack of data on body composition, particularly in patients with bulky tumors like NHL, which might falsely elevate weight measurements, suggests that other metrics such as MUAC and skinfold thickness could provide more accurate assessments of nutritional status. Furthermore, our exclusion of edematous malnutrition due to unavailable data might have obscured the true extent of malnutrition among the cohort (30-33).

To address these issues, future studies should incorporate a comprehensive evaluation of nutritional status using diverse metrics, including MUAC, skinfold thickness, BMI, and total body composition, to accurately gauge malnutrition and its impacts. Moreover, implementing prompt nutritional interventions throughout the treatment course is imperative to lessen chemotherapy-related morbidity, enhance treatment response, and ultimately improve survival rates. Research exploring the optimal provision of nutritional support during the initial six months of treatment could provide valuable insights into reducing hospitalization rates and enhancing patient outcomes, necessitating larger sample sizes and extended study durations to validate these findings.

CONCLUSION

In conclusion, the high prevalence of malnutrition in pediatric cancer patients necessitates thorough nutritional assessments at diagnosis to promptly address malnutrition, which can significantly enhance survival prospects, decrease hospitalization rates for infectious complications, and improve chemotherapy tolerability. This approach not only reduces the physical and financial burdens of hospital stays but also substantially improves the quality of life for affected children.

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