



## Disease-related malnutrition in children with cancer: what's the risk and impact on patient outcome

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### Abstract

**Background:** Malnutrition in children with cancer is a common problem, particularly in low-income countries. Risk factors, effects on outcome, and feasible interventions are important to comprehend in managing patients.

**Objectives:** To identify the risk and impact of malnutrition in children with cancer.

**Method:** The authors searched for articles through PubMed and Google Scholar, using a combination of the following keywords: "Impact and Risk", "Effects of Malnutrition", and "Children with Cancer". Article searches were performed in July to September 2021. The articles reviewed in this manuscript are English language articles, with full text available. A total of 31 articles were used in this review.

**Discussion:** Children with cancer are at risk of suffering from malnutrition. Malnutrition occurs due to energy imbalance and results from multifactorial interactions, including type of tumors and therapy. Malnutrition can contribute to poor clinical outcome and decreased quality of life. Management of malnutrition in pediatric patients with cancer include screening and nutritional interventions with suitable route of administration based on patient condition.

**Conclusion:** Pediatric cancer patients are at increased risk of malnutrition, with a disproportionate burden between low- and middle-income versus high-income countries. Malnutrition is a threat to pediatric cancer patients because it can interfere with the course of chemotherapy treatment, although chemotherapy is considered to have a role in triggering malnutrition itself. Malnutrition has a short-term and long-term impact on children with cancer such as delays in treatment, impaired growth and development, to the emergence of other medical problems that lead to a worsening quality of life. Malnutrition is considered to cause high rates of morbidity and mortality in pediatric cancer patients. Malnutrition should be carefully screened and assessed early as it affects patient outcome.

**Keywords:** malnutrition, cancer, risk, outcome

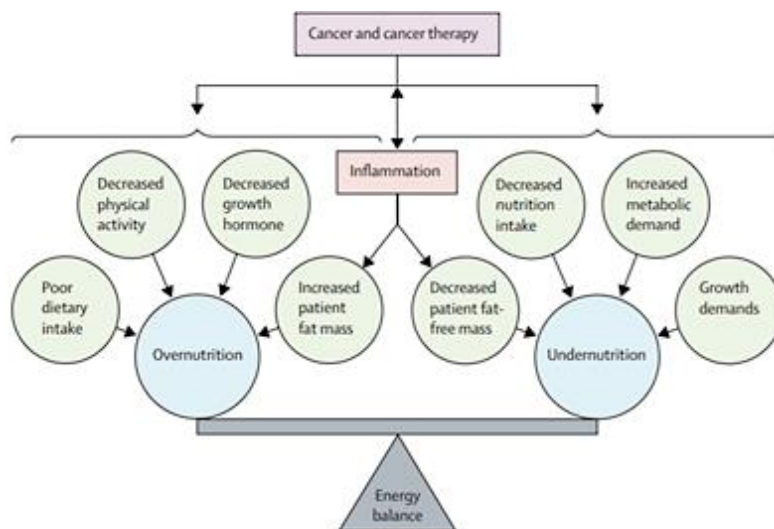
### Introduction

Children with cancer are at increased risk of severe mortality and morbidity. An important challenge is the inequality of survival rates between children in

high-income and low-income countries. According to the World Health Organization, in high-income countries, where comprehensive services are generally accessible, more than 80% of children with cancer are cured while in low- and middle-income countries (LMICs), less than 30% are cured. Some contributing factors of this inequality include diagnostic delay, advanced disease, lack of diagnostic accuracy, lack of accessible therapy, treatment abandonment, death due to toxicity as

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**Figure 1.** Energy balance in pediatric cancer<sup>3</sup>

treatment side effects, and avoidable relapse. Due to its magnitude, WHO considers childhood cancer a public health issue and therefore developed the Global Initiative for Childhood Cancer. The Global Initiative aims to “at least achieve 60% survival and to reduce suffering for all children with cancer by 2030, by increasing capacity of countries to provide quality services for children with cancer as well as increasing prioritization of childhood cancer at the global, regional, and national levels”. The Global Initiative targeted that those efforts will be implemented across 6-10 countries by 2019-2020 and 18-25 countries by 2021-2023.<sup>1</sup>

Managing childhood cancer as well as its comorbidities is an important goal of the WHO, Malnutrition is one of well-known comorbidities of childhood cancer patients. Successful childhood cancer management is in line with the second Sustainable Development Goals (SDG)<sup>2</sup>, which is “end hunger”, as the Global Initiative stated that “Reducing cancer and malnutrition improves childhood cancer outcome”.

It is well known that significant association exists between childhood cancer and malnutrition. The main problem that arises from the aforementioned association is the likely impact on patient outcome, i.e. the effect of malnutrition in childhood cancer and its influence on variables such such as mortality, treatment outcomes, and other clinical conditions. This review will describe disease-related

malnutrition in children with cancer, as well as its risk and impact on patient outcome.

## Methods

The authors searched for articles through PubMed sources and Google Scholar, using a combination of keywords including “Impact and Risk”, “Effects of Malnutrition”, and “Children with Cancer”. Article searches were performed in July to September 2021. The articles reviewed in this manuscript are English articles, with full text is available. After screening through the titles and abstracts of the articles found for relevancy to the topic, 31 articles were used in this review.

## Risk factors of malnutrition in children with cancer

Children with cancer are at increased risk of malnutrition. Malnutrition can manifest as undernutrition or overnutrition, as pediatric cancer interferes with energy balance. The interference of cancer with energy balance occurs through the process of inflammation for both overnutrition and undernutrition. For overnutrition, contributing factors include poor dietary intake, decreased physical activity, decreased growth hormones, decreased nutrition intake; whereas for undernutrition, contributing factors include

decreased nutrition intake, increased metabolic demand, and growth demands (Figure 1).<sup>3</sup>

Several risk factors for malnutrition can be categorized into three factors such as the characteristics of tumor itself, factors related to treatment, factors related to symptoms, demographics, anthropometry, and dietary intake. Characteristics of tumor itself include solid tumors in advanced stages (such as neuroblastoma, Wilms tumor, rhabdomyosarcoma, Ewing sarcoma), central nervous system tumors (craniopharyngioma, medulloblastoma, astrocytoma, ependymoma), high-risk acute lymphoblastic leukemia, lymphoma, nasopharyngeal carcinoma, as well as multiple relapsed and high-risk leukemias.<sup>4</sup> More specifically, tumor characteristics can be further divided into high risk factor for undernourishment, moderate risk factor for undernourishment, and high risk factor for fat accumulation (Table 1).<sup>5</sup>

The second contributing factors (factors related to treatment) include gastrointestinal tract irradiation, high-dose cranial/craniospinal radiotherapy, prolonged corticosteroid therapy with large doses, major abdominal surgery, undergoing haematopoietic stem cell

transplantation (HSCT) or presenting graft vs host disease. Symptoms that are considered contributing factors to malnutrition include nausea, vomiting, diarrhea, and severe mucositis. Compared to other demographical groups, infants have higher risk of malnutrition. Anthropometry risk factors include weight-for-high (W/H) or body mass index (BMI) for age (A) BMI/A Z-score of less than -2 or more than +2, mid-upper arm circumference (MUAC) of less than percentile 10 or more than percentile 90, and weight loss or poor weight gain during the last few weeks. Factors related to dietary intake include unmet energy and protein needs for the last few days.<sup>4</sup> More practically, patients with childhood cancer have taste and smell dysfunction, altered appetite regulation (variability in ghrelin and leptin levels), and disturbed eating habits (such as lack of exposure to a variety of nutritious foods during treatment).<sup>6</sup> Specifically, taste dysfunction seemed to be more prominent than smell.

A study by Lemos et al.<sup>7</sup> in Brazil showed that the prevalence of malnutrition in children and adolescents with cancer, both solid and hematological, were higher compared to those without cancer. This study, performed in a total of

**Table 1.** Tumor types associated with malnutrition for pediatric oncology patients. Adapted from Bauer et al.<sup>5</sup>

<b>High risk factor for undernourishment</b>	<b>Moderate risk factor for undernourishment</b>	<b>High risk factor for fat accumulation</b>
Solid tumor with advanced stages	Nonmetastatic solid tumors	Acute lymphoblastic leukemia receiving cranial irradiation
Wilms tumor	Uncomplicated acute lymphoblastic leukemia	Craniopharyngioma
Neuroblastoma stage III and IV	Advanced diseases in remission during maintenance treatment	Malignancies with large and prolong doses of corticosteroid therapy or other drugs increasing body fat stores
Rhabdomyosarcoma		Total body or abdominal or cranial irradiation
Ewing sarcoma		
Medulloblastoma		
Multiple relapsed leukemia and lymphoma		
Head and neck tumors		
Post stem cell transplantation (graft vs host disease)		
Diencephalic tumors		

1154 patients, showed that at the diagnosis of disease, the BMI of 12.2% of children in the solid tumor group and 9.52% of children in the hematologic group were below the adequate threshold, therefore classified as undernourished. Interestingly, this study found that malnutrition could be masked in some types of tumors, especially when the evaluation of malnutrition was performed by using only BMI. Therefore, multiple anthropometrical measurements other than BMI such as weight, height, triceps skinfold thickness (TSFT), mid-upper arm circumference (MUAC), arm muscle circumference (AMC), and percentage weight loss should be used as evaluation tools.

In malnourished children diagnosed with cancer, the problems became more complex. The side effects of a worsening nutritional status are mainly found during treatment, such as a decrease in the child's tolerance for chemotherapy, changes in drug metabolism due to inadequate absorption and digestion, decreased immunity due to malnutrition, increased risk of infection and decreased quality of life of children. This impact varies greatly from child to child. Malnutrition in children with cancer is dynamic and its development tend to become more visible during subsequent treatment.<sup>13</sup>

A clinical study reported that about 28% pediatric cancer patients have a high risk of experiencing severe malnutrition. This is further exacerbated by the increased risk of mortality and infection which are significantly increased by malnutrition and rapid weight loss in the initial phase of treatment (3-6 months after diagnosis).<sup>24</sup> Chemotherapy is a common treatment for cancer patients. Although needed, it also plays an active role in triggering nutritional problems in children. Chemotherapy agents affect and damage other normal cells in the body, such as cells of the digestive tract, mouth, hair follicles, and bone marrow. Depending on the type and dose of the drug given and the length of treatment, side effects of chemotherapy include canker sores (mucositis), stomatitis, dysphagia, changes in taste and smell, anemia, depression, anorexia, anxiety, nausea, vomiting and diarrhea may lead to malnutrition. Almost about 84% of children (boys and girls) with cancer have below normal Body Mass Index. On the other hand,

chemotherapy is very necessary for treatment, but poor nutritional status will disrupt the course of treatment.<sup>25</sup>

The incidence of malnutrition in children with cancer not only affects the frequency and continuity of chemotherapy, but also gives birth to other clinical problems, such developmental and growth disorders. Malnutrition among pediatric oncology patients has been recognized as a negative prognostic factor associated with increased morbidity or decreased survival. Moreover, these children are at greater risk of experiencing nutritional deficiencies due to their faster metabolic rate and greater caloric requirements for growth and development.<sup>26</sup> This increases the likelihood of malnutrition, leading to children with cancer experiencing growth delays such as stunting, especially in children with cancer at an early age. Poor nutritional intake and inadequate treatment have the potential to disrupt cognitive brain development. This demonstrated that untreated malnutrition worsens the children's quality of life.<sup>27</sup> Considering the burden severity of malnutrition in children in cancer, malnutrition in children with cancer should be well screened. Before using any specific screening tools, history taking is critical as an initial step. Important aspects to ask during history taking include current patient clinical state (subjective symptoms, treatment given, treatment effect nutrient intake, absorption and retention), patient history (dietary pattern before cancer diagnosis, previous data on growth, previous antitumor therapy and its effect on nutritional status), developmental status (feeding skill milestone and swallowing function), food allergies and intolerance, medications with special attentions to gastrointestinal side effects), family history, and social history.<sup>8</sup>

Nutrition screening tool for childhood cancer (SCAN) is a screening tool specifically developed to diagnose malnutrition in childhood cancer, with a score of three or more indicating at risk of malnutrition (**Table 2**). In an explanation of this questionnaire by Murphy et al.<sup>9</sup> type of cancer that is considered high risk depends on hospitals criteria and include patients on high risk treatment protocols, infants, and the presence of

comorbidities. In addition, treatment that are considered high intensity are chemotherapy, radiotherapy, and HSCT. Signs of undernutrition include visible muscle wasting, edema (including bilateral pedal), skin manifestations (dry, thin, shiny or wrinkled), hair manifestations (thin, sparse and easily pulled out), or evidence of micronutrient deficiencies.

productivity of life, greater levels of psychological distress, and higher susceptibility of infections. On the other hand, long-term consequences include growth impairment, reduced final height, decreased long-term survival (in several tumor types), impairment of several functions (motor, cognitive, and neurodevelopment), increased risk for several medical conditions (metabolic syndrome, secondary

**Table 2.** Nutrition screening tool for childhood cancer. Adapted from Murphy et al (2016)

Item	
Does the patient have a high risk cancer?	1
Is the patient currently undergoing intensive treatment?	1
Does the patient have any symptoms relating to the GI tract?	2
Has the patient had poor intake over the past week?	2
Has the patient had any weight loss over the past month?	2
Does the patient show signs of under nutrition?	2
<b>Total</b>	
Score indication	
≥3 At risk of malnutrition – Refer to dietitian for further assessment	

### The impact of disease-related malnutrition in patient outcome

The burden of malnutrition in childhood cancer is unequally distributed between low-and-middle income countries and high-income countries. More than 80% of children and adolescents with cancer are found in low-and-middle income countries. At the same time, low-and-middle income countries also face undernutrition as another entity, making the burden even greater.<sup>10</sup>

Malnutrition in pediatric cancer patients poses several consequences that influence outcome. The consequences can be generally categorized into short-term and long-term. Short-term consequences include wasting of muscle and fat mass, decreased tolerance of chemotherapy, unfavorable response to chemotherapy, treatment delays, fatigue, biochemical disturbances (anemia and hypoalbuminemia), delayed recovery of normal marrow function, changes in body composition, drug dose alteration, decreased quality and

cancers, aging) increased mortality rate, retardation of skeletal maturation, abnormal bone mineral density, and decreased quality of life.<sup>5</sup> The overall long-term impact is the accumulated result of the previous short-term impacts. Poor nutritional status affects the patient's survival ability and is closely related with an increase in patient treatment failure. The incidence of under-nutrition and malnutrition has been investigated as risk factors for the patient's worsening condition, posing critical risks for the child's growth and development. Limited nutritional reserves despite large nutritional requirements rendered the patients more vulnerable to high morbidity and mortality rates.<sup>30</sup> Magri Teles et al.<sup>31</sup>'s study on 155 pediatric cancer patients reported 18.1% patients had a Z-score of <-2 for BMI, and had to be treated with intubation/mechanical ventilation.

Besides those short-term and long-term consequences, clinical consequences of malnutrition in patients with cancer include increased infection risk, poor wound healing, poor quality of life, and

possible increased referral to tertiary care centers. Specifically, related to the cancer itself, malnutrition results in a reduced response to cancer treatment, increased side effects, and a possibility of reduced survival.<sup>11</sup> In addition, pediatric cancer patients with malnutrition have worse quality of life. Brinksma et al.<sup>12</sup> studied quality of life of 104 children aged 2–18 years diagnosed with hematological, solid, or

acute lymphoblastic leukemia (ALL) patients who already presented with overnutrition at the time of diagnosis also had poorer outcome such as higher rates of minimal residual disease at the end of induction therapy as well as poorer event-free survival, regardless of their minimal residual disease status.<sup>10</sup>

A study by Pribnow et al.<sup>14</sup> in Nicaragua showed

**Table 3.** Classification of malnutrition. Adapted from Pribnow et al.<sup>14</sup>

Classification	Item
Adequate nutrition	triceps skinfold thickness (TSFT) > 10 <sup>th</sup> percentile AND
	Mid-upper arm circumference (MUAC) > 10 <sup>th</sup> percentile AND
	Body mass index (BMI) > 5 <sup>th</sup> percentile AND
	Serum albumin > 3.5 g/dL (when available)
Moderate malnutrition	TSFT 5-10 <sup>th</sup> percentile OR
	MUAC 5-10 <sup>th</sup> percentile OR
	BMI 3-5 <sup>th</sup> percentile OR
	Serum albumin 3.2-3.5 g/dL (when available)
Severe malnutrition	TSFT <5 <sup>th</sup> percentile OR
	MUAC <5 <sup>th</sup> percentile OR
	BMI <3 <sup>rd</sup> percentile OR
	Serum albumin <3.2 g/dL (when available)

brain malignancies. They found that undernutrition and weight loss were associated with worse physical and social functioning domains of health-related quality of life, whereas overnutrition and weight gain affected the emotional and social domains.

A review by Barr and Mosby<sup>10</sup> reported that malnutrition in pediatric patients results in altered tolerance of chemotherapy, comorbidities, abandonment of treatment, relapse of disease, and death. Regarding altered tolerance of chemotherapy, the specifics are perturbations of drug metabolism, with resulting delays in chemotherapy, increased toxicity, and compromised survival. In addition, this review also stated that underweight or overweight/obese patients, using acute myelogenous leukemia (AML) patients as an example, had lower survival chance. Malnutrition at the time of diagnosis of malignancy is also a risk factor of unfavorable outcome.<sup>13</sup> Overweight/obese pediatric

that that the proportion of pediatric cancer patients with adequate nutritional status was 59.1%, higher compared to a proportion of 52.9% of event-free survival in moderately and severely malnourished patients. The study classified adequate nutrition, moderate malnutrition, and severe malnutrition as shown in **Table 3** (moderate and severe malnutrition are grouped together as inadequate nutrition).<sup>14</sup> Types of cancer included in this study were ALL, AML, Hodgkin lymphoma, Burkitt lymphoma, and Wilms tumor. Among the aforementioned types, Wilms tumor (85.7%), followed by Burkitt lymphoma (75%), and AML (74.%) had the highest percentage of inadequate nutrition among each group.

Malnutrition also increased the risk of febrile neutropenia in childhood cancer. A study by Agnes et al.<sup>15</sup> in Indonesia showed a significant correlation between malnutrition and febrile neutropenia in patients with ALL. In addition, a recent study in

India found that malnutrition, in this case severe underweight, together with profound neutropenia and non-remission status of bone marrow served as predisposing factors of recurrent fever in patients with ALL.<sup>16</sup>

A study by Sakthikumar on 306 children with cancer showed that 37% had poor nutritional status at the time of diagnosis. (9.52%). This risk factor for the impact of malnutrition can lead to poor treatment outcomes that lead to recurrence, severity and even death.<sup>28</sup> Significantly, the type of tumor greatly affects the child's survival and severe impact. Low BMI values are significantly associated with poor histologic response in patients with tumor necrosis (90%) and worsening of the condition in children with Ewing sarcoma.<sup>29</sup>

A systematic review of 46 studies reviewing the prevalence of malnutrition in pediatric cancer patients as well as the effects of pediatric cancer and its treatment on nutritional status showed that the prevalence range of undernutrition and overnutrition in pediatric cancer patient is 0% to 65% and 8% to 78%, respectively.<sup>17</sup> In particular, a study by Mejia-Arangure assessed in this systematic review that is considered strong in quality, showed that in patients with ALL, undernutrition is associated with higher risk of mortality.<sup>18</sup>

## **What's the goal/target of cancer management?**

### **Discussion**

The goal of cancer management can first be classified into therapeutic and palliative goals. Therapeutically, cancer management aims to improve function and outcome by preventing and treating undernutrition, enhance antitumor treatment effects, reduce adverse effects of antitumor therapies, and improve quality of life. Regarding the first goal (preventing and treating undernutrition), in curative oncology treatment, nutritional intervention aims to “reduce the number of complications and to shorten hospitalization”; whereas in palliative oncology treatment, the aim of nutritional intervention is to “sustain or enhance recovery of patient performance in everyday life, their well-being and their quality of life.”<sup>19</sup>

In general, to achieve the nutritional goals for pediatric cancer patients, several steps can be taken. First, nutritional status should be assessed. After nutritional status is assessed, the requirement is calculated and gastrointestinal function is evaluated. Then, route of food administration is determined and food regimen is decided. Route of food administration varies, depending on patient indications (**see Table 4**). Finally, evaluation of result is performed. The process should be patient-centered with team-based collaboration.<sup>5</sup>

Specifically, the goal of nutrition management in cancer patients can be broken down to be specific points. First, to reduce stress, as some patients has a desire to eat, but unable to do so due to their cancer conditions. Second, to ensure food safety, as cancer patients has specific dietary requirements to prevent further infection and complications, by having neutropenic diet, low bacteria diet, and sterile food. Third, to stimulate the gut, as the gut muscle needs to be stimulated or it will atrophy. Fourth, to meet caloric requirements, as calorie requirement during treatment are usually higher, and protein requirement are also higher. Fifth, to meet micronutrients and macronutrients requirements, by a balanced combinations of carbohydrate, lipids, protein, mineral, vitamin, and fiber.<sup>5</sup>

## **When is the critical time to optimize the management of cancer by stage?**

Regarding the time of optimization, nutritional assessment of pediatric cancer should be frequently performed. In addition, nutrition intervention should be initiated early when deficit are detected. In general, nutrition therapy should be started if undernutrition already exist or if it is anticipated that the patient will be unable to eat at 7 days. During chemoradiation, intensive dietary advice and oral nutrition supplement is advised to increase dietary intake to prevent therapy association with weight loss and interrupted radiation therapy. During chemotherapy, routine enteral nutrition during chemotherapy has no effect of tumor response to chemotherapy or on chemotherapy associated unwanted effect.<sup>8</sup>

**Table 4.** Nutritional strategies for children with cancer. Adapted from Bauer et al.<sup>5</sup>

Nutritional strategies	Indications
Enteral route	In all patients with functional gastrointestinal tract Meeting > 95–100% of estimated energy needs
Tube feeding (nasogastric)	Inability to ingest full energy requirements (.90%) through oral diet for 3–5 d Severe mucositis <3 d
PEG jejunostomy	Inability to meet full energy needs through tube diet for 3–5 d Severe vomiting for 3–5 d Weight loss despite tube feeding
Parenteral nutrition	Altered gastrointestinal absorption for 3–5 d Severe vomiting and diarrhea Severe pancreatitis Intestinal manifestation of graft vs. host disease Paralytic ileus

### Benefit of improving disease-related malnutrition in patient with cancer during cancer treatment?

Evidence showed that improving disease-related malnutrition in pediatric cancer patient will lead to more favorable outcomes. A review by Barr and Mosby suggested that restoration of lean body mass, mainly skeletal muscle, is an important aim of nutritional intervention. The review also discussed the impact of nutritional interventions in pediatric patients with leukemia in low- and middle-income countries. It was shown that in particular, fortified snack was shown to be beneficial in improving nutritional status and tolerance of chemotherapy.<sup>10</sup> A study in Malawi explored a peanut-butter based ready-to-use-therapeutic food (RUTF) called ‘chiponde’. This study showed that the preoperative nutritional status of children with Wilms’ tumor during neo-adjuvant chemotherapy was improved using the aforementioned food as an intervention. In addition, it also improve tumor response significantly.<sup>20</sup> A study in Guatemala by Antillon et al.<sup>21</sup> showed that an RUTF based on a mixture of maize and soy flours called ‘incaparina’ is beneficial for improving the prognosis of ALL patients who were malnourished at the time of diagnosis. Energy-enriched formula given through nasogastric tube also showed beneficial effect in improving nutritional status of pediatric cancer patients. A trial conducted by Broeder et al.<sup>22</sup> showed that energy-

enriched formula was more effective in improving the nutritional status of children with cancer. In that study, the authors compared two equal volumes of tube feeding, standard (1 kcal/mL) versus a high energy density (1.5 kcal/mL) on 27 children with solid tumor undergoing intensive phase treatment with weekly assessments of nutritional status. The same author also conducted a study showing that aggressive nasogastric tube feeding protocol has a positive impact to improve nutritional status of newly diagnosed pediatric cancer patients,<sup>23</sup> as well as to decrease the occurrence of infection in pediatric cancer patients with solid tumor.<sup>24</sup> A more recent evidence from a study by Sacks et al.<sup>32</sup> also supported the aforementioned results, showed that proactive enteral tube feeding is feasible and beneficial for children with cancer.

### Conclusion

In conclusion, pediatric cancer patients are at increased risk of malnutrition, with a disproportionate burden between low- and middle-income versus high-income countries. Malnutrition is a threat to pediatric cancer patients because it can interfere with the course of chemotherapy treatment, although chemotherapy is considered to have a role in triggering malnutrition itself. Malnutrition has a short-term and long-term impact on children with cancer such as delays in treatment, impaired growth and development, to the emergence of other medical problems that lead to a worsening quality of life.



Malnutrition is considered to cause high rates of morbidity and mortality in pediatric cancer patients, and should be carefully screened and assessed early as it affects patient outcome. Management of malnutrition should be in line with the therapeutic or palliative goals of cancer treatment. Correcting disease-related malnutrition in pediatric cancer patients, including using an energy-fortified formula administered via a nasogastric tube, has shown beneficial effects.

### Conflict of Interest

Authors declared no conflict of interest regarding this article.

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