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THE NUTRITIONAL STATUS OF PEDIATRIC CANCER PATIENTS: NUTRITIONAL RISK SCREENING TOOLS AND NUTRITIONAL THERAPY

PhD thesis

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Abbreviations

AMC: Arm Muscle Circumference

BIA: Bioelectrical Impedance Analysis

BMI: Body Mass Index

CNS: Central Nervous System

CPN: Central Parenteral Nutrition

CVC: Central Venous Catheter

CT: Computed Tomography

DEXA: Dual-Energy X-ray Absorptiometry

EN: Enteral Nutrition

ESPEN: European Society of Clinical Nutrition and Metabolism

FAQ: Food Amount Questionnaire

FFQ: Food Frequency Questionnaire

HRQOL: Health-Related Quality of Life

LBM: Lean Body Mass

MNA: Mini Nutritional Assessment

MRI: Magnetic Resonance Imaging

MUAC: Mid-Upper Arm Circumference

MUST: Malnutrition Universal Screening Tool

NRS: Nutritional Risk Screening

NS: Nutritional Status

ONS: Oral Nutritional Supplements

PG-SGA: Patient Generated Subjective Global Assessment

PN: Par**e**nteral Nutrition

PNET: Primitive Neuroectodermal Tumor

PNRS: Pediatric Nutritional Risk Score

PNST: Pediatric Nutrition Screening Tool

PPN: Partial Parenteral Nutrition

PVC: Peripheral Venous Catheter

PROs: Patient Reported Outcomes

PYMS: Pediatric Yorkhill Malnutrition Score

QOL: Quality of Life

SCAN: Nutrition Screening Tool in Childhood Cancer

SGA: Subjective Global Assessment

STAMP: Screening Tool for the Assessment of Malnutrition in Pediatrics

STRONG: Screening Tool for Nutritional Status and Growth

STRONGkids: Screening Tool for Nutritional Status and Growth

TPN: Total Parenteral Nutrition

TSFT: Triceps Skinfold Thickness

WFH: Weight-for-Height

WHO: World Health Organization

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1. Introduction

1.1. Baseline characteristics of pediatric cancer patient population

The incidence rate of pediatric cancer is slowly but constantly increasing; in addition to this under diagnosis is also a major problem in developing countries. According to a study from 2019, approximately 43% of childhood cancer cases are undiagnosed globally (Ward et al., 2019). Cancer is one of the leading causes of death by disease for children, with approximately 400,000 new cases diagnosed globally each year among children aged 0-19 years (Johnston et al., 2021; Ward et al., 2019). The number of new cases, as well as the different cancer types may substantially vary by geographic location. Although the number of new pediatric cancer patients seems to be significantly smaller than the number of adult cancer patients, the global burden of childhood cancer is underestimated.

Economic differences might also substantially influence the outcome of malignant diseases in children. The estimated 5-year net survival for childhood cancer is about 80% in high-income countries, and could be as low as 20% in low-income countries. The aim of WHO's Global Initiative for Childhood Cancer, which was announced in 2018 September, is to reach at least 60% survival rate by 2030 (WHO 2018). Even though survival rates seem to increase year by year, two-thirds of pediatric cancer survivors experience at least one of the followings: secondary cancer, organ damage, infertility, setback in growth and development, impaired cognitive abilities and psycho-socio impact. Late effect from treatment, which is classified as severe or life-threatening, occurs in one quarter of the cases (Landier et al., 2015; Dickerman 2007).

In order to achieve better clinical outcome appropriate nutritional screening and therapy are required as it has been suggested in a number of previous studies (Barr 2015; Brinksma et al., 2015). Similarly to adult cancer patients these studies have revealed that optimizing nutritional status of the patients have a positive effect on event free survival, treatment toxicity and quality of life as well (Orgel et al., 2014). Since there are no specific clinical nutrition guidelines on how to assess the nutritional status (NS)

and how to provide adequate nutrition support for pediatric cancer patients, it can be challenging for professionals.

1.1.1. Prevalence and mortality

Childhood tumors differ from adult diseases in many ways. The spectrum of malignancies varies on a broad spectrum by involved organ and cell types. The most common categories of childhood cancers include leukemia, brain tumors, lymphomas and solid tumors (Ward 2015). According to a large clinical register, between the years 2001-2010 the most common cancers were leukemia, followed by central nervous system (CNS) tumors, and lymphomas in children aged 0–14 years based on 284 649 cases (Steliarova-Foucher et al., 2017). CNS tumors are slightly more prevalent in case of male children and it seems that children aged 0-14 are more susceptible according to a British study (Arora et al., 2009). In Hungary there are also various types of solid tumors, however neuroblastoma, medulloblastoma, PNET (primitive neuroectodermal tumor) and astrocytoma are diagnosed in children the most often (Louis et al., 2016). In our country between 2000-2008 leukemia and CNS tumors were leading, both with 27%. The incidence of CNS tumors in Hungary is higher than elsewhere, however, the cause of this phenomenon is unknown (Maródi 2013). These are followed by tumors of the peripheral nervous system, lymphomas and childhood kidney tumors. Of these, neuroblastoma and Wilms tumor (similar to the much rarer retinoblastoma and hepatoblastoma) are rarely encountered in adulthood. In adolescence, lymphomas are replaced by leukemia in terms of incidence. However, the incidence of germ cell tumors, bone and soft tissue sarcomas tend to increase. Tumors originating from endocrine organs are also becoming more pronounced. On the other hand, breast-, gastrointestinal-, and uterine tumors appear to be exceptionally rare in children aged 0-14 years. Even the biological behavior of morphologically identical malignancies is not the same at the different stages of life, especially during the growing phase. Thus, the course and prognosis of acute lymphoblastic leukemia differ significantly during congenital, infant, childhood phase and in the elderly. Neuroblastoma in infants and young children (younger than 1.5 years) is one of the tumors with a relatively favorable outcome, in contrast to the prognosis of the disease in the elderly (Maródi 2013).

In our country there are about 200-250 new pediatric oncology diseases per year, out of which approximately 45% of the patients are treated at the 2nd Department of Pediatrics of Semmelweis University, which is also the Center of the Hungarian Children's Oncology Working Group. The National Childhood Cancer Registry has also been also operated at our clinic and has been functioning as the database of the Hungarian Pediatric Oncology Network since 1971. The Registry collects data on epidemiology, treatment effectiveness as well as on the rate of survival (Borgulya et al., 2004; Garami et al., 2014; Gallo et al., 2022).

Table 1. The most common tumor types in children

Global incidence of pediatric cancer (aged 0-19) ≈ 400.000 cases/year	**USA**	**Europe**	**Hungary**
Number of cases/year	15.780	35.000	200-250
Leukemia	28%	35%	27%
CNS (Brain and spinal cord tumors)	26%	15%	27%
Neuroblastoma	6%	5-7%	10%
Wilms tumor	5%	6-7%	5,5%
Lymphoma	8%	5-22%	12%
Rhabdomyosarcoma	3%	5-8%	2%
Retinoblastoma	2%	3-4%	2-3%
Bone cancer (including Ewing and osteosarcoma)	3%	6%	4,8%

Sources: (Steliarova-Foucher 2017; Maródi 2013; Vassal et al., 2014).

Patient care is provided in three wards. The Department of Hematology (1A) treats malignant and non-malignant hematological diseases, primarily patients with leukemia and lymphoma, due to the modern equipment intensive care unit background can also be provided. The Oncology Department (1B) treats and cares for patients with bone tumors, soft tissue tumors, ophthalmology and kidney tumors, whereas the Neuro-Oncology Department (2A) provides treatment for children with malignancies as a national onco-hematology center (Garami et al., 2014).

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It has been long ascertained that the nutritional status in case of chronic wasting diseases, especially in case of childhood cancer, does influence the outcome of the disease, the course of the therapy, including treatment tolerance and infection risk, not to mention the quality of life (QOL) and the cost of care. It is also known that the tumor itself means a risk for malnutrition, especially in case of children (Barr 2015; Schoeman 2015).

1.1.2. Quality of life

Since the survival rate of pediatric cancer patients is improving, the quality of life and its determining factors are becoming a critical issue and therefore should also be taken into consideration. Concern regarding long term survivors' health-related quality of life (HRQOL) has emerged as physical (e.g. cardiovascular, endocrine, gastrointestinal, musculoskeletal, nervous, pulmonary, and genitourinary systems (DeLaat and Lampkin 1992)), psychological, social, cognitive, and academic late effects all have become evident to influence HRQOL (Copeland 1992; Madan-Swain and Brown 1991; Varni et al., 1998). HRQOL can be defined as the impact of disease and treatment on the patient's self-perceptions of functioning in a number of different domains (Guyatt et al., 1993; Jenney et al., 1995; Pal 1996). Generic measures of the health status of children usually include the physical, mental and social dimensions (Vivier et al., 1994), however Aaronson has defined a multidimensional core set of domains to be included (Aaronson 1991). Thus apart from the disease- and treatment-related symptoms, physical-, psychological-, social- functioning additional dimensions (beyond the primary set) depending on the specific type of cancer should be added, e.g. cognitive functioning in case of brain tumor (Aaronson 1991).

Data demonstrate that children as young as 5 years of age can reliably and validly self-report their HRQOL when an age-appropriate instrument is used (e.g. pain visual analogue scale) (Sherman et al., 2006). The evidence supports that including pediatric parent proxy-report is recommended when pediatric patients are too young, cognitively impaired, or too ill to complete a HRQOL instrument, however, it cannot be used as a substitute for child self-report (Varni et al., 2007). According to Varni and colleagues, pediatric Patient Reported Outcomes (PROs) should be considered as the standard for HRQOL measurement in pediatric oncology clinical trials and research in which patient HRQOL is investigated.

As a number of previous studies highlighted the role of nutritional status as an impact on the quality of life (QOL), it has been widely accepted and documented (Caro et al., 2007; Murphy et al., 2015; Orgel et al., 2014; Barr 2015; Bechard et al., 2016). According to these sources the assessment of nutritional status should include the

evaluation of QOL to be able to optimize nutritional interventions for the individual requirements of the patients.

Nutritional status and food intake are adversely affected by oncology treatments (Connor et al., 2006; Bergkvist and Wengstrom 2006; Guren et al., 2006; Van Cutsem and Arends 2005). Progressive wasting of skeletal muscle mass may occur even before weight loss becomes noticeable (Laviano et al., 2005) leading to cancer cachexia (Argiles 2005; Fearon et al., 2006). Typical symptoms of cancer cachexia are weight loss, anorexia (lack of desire to eat), early satiety, reduced food intake, reduction in adipose tissue and lean body mass, fatigue, and even anemia (Laviano et al., 2005).

It can be concluded that individualized nutritional intervention should be provided simultaneously with the antineoplastic treatment to enhance performance status and QOL as well (Segura et al., 2005). Nevertheless, we have to differentiate between the curative phase - when nutritional intervention is aimed at increasing patients' response, treatment tolerance and QOL, at the same time reducing complications and morbidity – and palliative care – when nutritional care focuses on managing symptoms and maintaining QOL, or if possible improving it (Van Custem and Arends 2005).

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1.1.3. Nutritional status

Defining malnutrition in children

The term ’malnutrition’ covers a pathological state resulting from inadequate nutrition including, undernutrition due to insufficient intake of energy and other nutrients. By undernutrition one means stunting (low weight for age), wasting (low weight for height), and underweight (protein-energy malnutrition). Malnutrition also covers overnutrition (overweight and obesity) due to excessive consumption of energy and other nutrients and as well as deficiency diseases due to insufficient intake of one or more specific nutrients such as vitamins and minerals (Ge et al., 2001).

Many factors play a role in the development of malnutrition, such as inadequate social and environmental conditions, overly strict diets, chronic diarrhea and/or vomiting, anorexia, depression, disturbance of food intake, maldigestion, malabsorption (caused by e.g. tumor, inflammatory bowel disease, ulcer), conditions with accelerated metabolism and/or increased protein breakdown (e.g. severe injury, burns, sepsis, persistent fever), as well as diagnostic procedures or therapies (e.g. chemotherapy, radiation) may also contribute to its development. (Dipasquale et al., 2020). Figure 1. shows the interaction between the most typical forms and the factors.

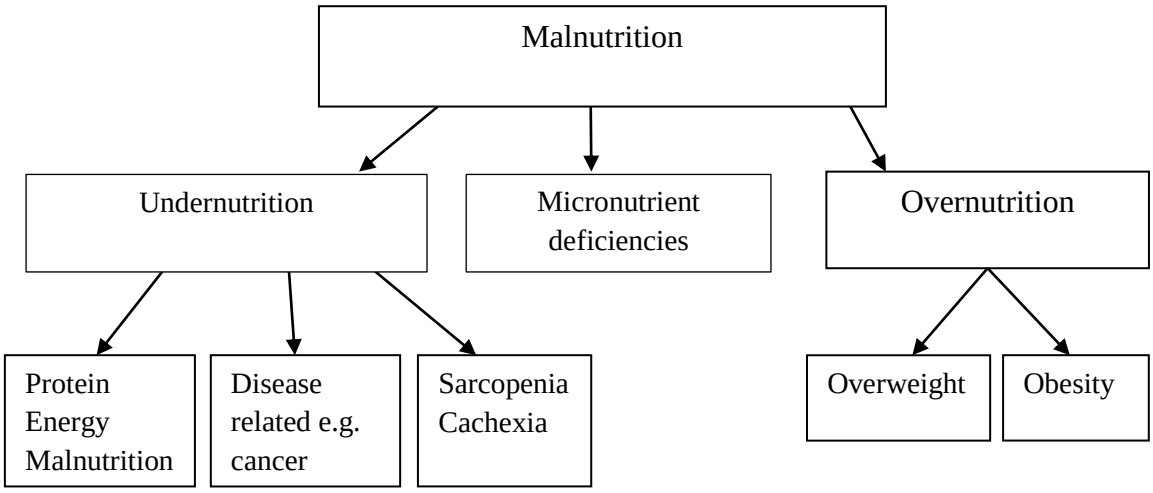

Figure 1. Malnutrition categories

The consequences of malnutrition affect the entire body, including the function and recovery of every organ system (Saunders and Smith 2010). In the ESPEN (European Society of Clinical Nutrition and Metabolism) Guideline on nutrition in adult cancer patients it is also highlighted that weight loss and decrease in BMI negatively influence survival. The grading scheme (grades 0-4) predicts overall survival, where 0 means best, 4 means worst prognosis (Arends et al., 2017). Another study suggested that 71.7% of the body mass loss was lean body mass (LBM) (Silver et al., 2007).

Muscle protein loss severely impairs quality of life and negatively affects physical function as well as treatment tolerance. Studies on the body composition of children with cancer have shown that it is specifically skeletal muscle loss that affects tumor-related malnutrition, whether or not it is associated with fat loss (Barr 2015; Schoeman 2015). The loss of skeletal muscle mass cannot be prevented with nutritional therapy alone, thus pediatric patients also need regular physiotherapy, appropriate for their underlying disease. According to recent clinical studies that examine the role of exercise in pediatric oncology, its implementation during therapy is feasible and well tolerated and has a remarkably positive impact on this patient group (Joffe et al., 2019; Morales et al., 2018; Rustler et al., 2017).

The detrimental effects of sarcopenia, which means a progressive loss of skeletal muscle mass and function, have been established not only in adult but in young patients as well. Sarcopenia can occur in case of depleted, normal, or excess fat mass, the latter of which is called sarcopenic obesity (Yip et al., 2015; Mei et al., 2016). Both sarcopenia and sarcopenic obesity have been important prognostic indicators in a wide range of adult malignancies (Feliciano et al., 2017; Argiles 2005; Go et al., 2016). However, there are more and more studies which claim that especially ALL patients experience significant decrease in skeletal muscle mass within the first 6 months of initiating treatment protocols (Rayar et al., 2013). Furthermore, they tend to develop sarcopenic obesity while undergoing therapy (Orgel et al., 2018).

Severe deterioration in nutritional status cannot be completely cured without residual symptoms, thus it is important to monitor patients' nutritional status regularly and initiate early nutritional intervention before severe deficiencies develop (Arends et al., 2017). Regarding the feasibility and effectiveness of different nutritional interventions

among children with cancer is still not elucid and is an opportunity for further inquiry (Peterson et al., 2017; Ladas et al., 2005).

Nutritional risk screening requires adequate screening methods and screening tools that take into account all the factors that affect nutritional status (e.g. underlying disease, stage of the disease, patient's somatic development etc.). This topic is discussed extensively in the next section.

1.2. Nutritional risk screening methods designed for pediatric patients

According to the proposal of the European Society of Clinical Nutrition and Metabolism (ESPEN), screening methods validated according to age group and underlying diseases should be used to identify those who, due to their unfavorable nutritional status have a risk of malnutrition. After evaluating their nutritional status and the effect of their treatment on the nutritional status, further actions should be decided, ranging from the establishment of a nutritional status that does not require further action, to the need for regular follow-up or to the necessity for initiating immediate nutritional support therapy (Cederholm et al., 2015).

In recent decades, a number of malnutrition risk screening methods have become accepted due to their clinical applicability and reliability. These screening tools include nearly identical variables, such as weight loss, body mass index (BMI), signs of nutritional difficulty (e.g., loss of appetite or decreased food intake), and the classification of the severity of the underlying disease. ESPEN recommends validated methods for age group and disease, such as the Nutritional Risk Screening (NRS) 2002, the Mini Nutritional Assessment (MNA) or the Malnutrition Universal Screening Tool, (MUST) for adults and the Screening Tool for Nutritional Status and Growth (STRONG) for children (Cederholm et al., 2015). In case of those patients who are at increased risk due to their nutritional status, the type and underlying mechanism of the nutritional problem should be identified. In this way, the necessary clinical steps can be determined and individual nutrition therapy can be planned.

Based on ESPEN's professional recommendation, nutritional screening should be mandatory in all clinical and health care settings, given the internationally proven fact that malnutrition is a serious clinical risk factor for patients with acute and chronic disease to improve the outcome of the underlying disease and the quality of life. If a validated, sufficiently specific and sensitive screening method is used, the number of patients at risk will be higher than those who are truly malnourished. Determining the nutritional status of those who are at risk and deciding what to do with them is the task and responsibility of the so-called nutrition support teams (NSTs) (Cederholm et al., 2015). NSTs are multi-professional working groups including experts (physicians, dieticians, nurses, and pharmacists) in the field of clinical nutrition (Nightingale 2010).

The predictability and specificity of a good screening tool is high. Thus, it is expected to be reliable, relatively easy to apply, not very expensive, furthermore, repeatable and independent of the examiner. It is very difficult to find a screening tool which meets all the above mentioned criteria. There are a great number of tools which have been developed to meet one or the other criterion, as a result various screening tools are used these days in the adult and pediatric health care settings as well (Gallo et al., 2022).

1.3. Pediatric nutritional risk screening tools

There are several risk screening tools mentioned in the literature for assessing the nutritional status of children. The screening tools are always tailored to the patient population and the possibilities of the institutions that develop them; therefore it is not possible to choose a generally accepted one which could be used as the best (Gallo et al., 2018). Table 2 summarizes the most commonly used pediatric screening tools, their main features and components.

STRONGkids (Screening Tool for Nutritional Status and Growth is a score system which can be used to screen hospitalized children in general pediatric care institutions. The screening sheet evaluates four aspects: 1. external signs of malnutrition; 2. nutritional intake and loss (severe vomiting / diarrhea, decreased nutrient intake in recent days, on-going nutritional therapy, insufficient nutrient intake due to pain), 3. weight loss and the absence of weight gain in recent weeks, months. Criterion 4 refers to the presence of severe underlying illness or expected major surgery. Severe illnesses are already classified as moderate risk and therefore require action e.g. nutritional intervention (Huysentruyt et al., 2013).

The advantage of this method is that its application does not require invasive examination, measurement, special training, thus the existence of the risk can be detected quickly and easily, but it is not disease specific. It can also be used in groups of patients where BMI and weight-for-height (WFH) measurements do not show reliable results (e.g. preterm infants, patients with Duchenne muscular dystrophy, cerebral palsy).

The disadvantage of STRONG is its low negative predictive value, thus chances of over diagnosis are significant. It is of little use in specialized institutions, because many patients with underlying diseases are considered to be at increased risk of malnutrition (e.g. cystic fibrosis, celiac disease, inflammatory bowel disease, infections, chronic wasting diseases (including metabolic, pulmonary, cardiac, renal, hepatic, and intestinal diseases, as well as tumors). Preterm infants, burn patients, bronchopulmonary dysplasia, anorexia nervosa, trauma, and mental retardation are all regarded as increased

risk of malnutrition, however, an adequately controlled celiac disease or mental retardation should not necessarily be associated with malnutrition.

STRONGkids have been performed in several institutions in Hungary and was considered to be appropriate for the assessment of malnutrition risk, despite the fact that the screening was performed on a variety of patients according to their underlying disease, so the patient population was heterogeneous. After screening with STRONGkids it was recommended to focus on malnutrition, and in order to avoid the complications of malnutrition to provide dietetic counsel and if necessary special sip feeds, regardless of the cause of malnutrition (Müller et al., 2012).

Pediatric Nutrition Screening Tool (PNST) was created as a simplified method of STRONGkids. It is also not specific for the underlying disease, but it takes into account recent unintended weight loss / weight gain, decreased nutrient intake in recent weeks, and external signs of malnutrition or overeating (White et al., 2016).

Patient Generated Subjective Global Assessment (PG-SGA) is an age-appropriate version of the original Subjective Global Assessment (SGA) developed for acute nephrology, oncology, and neurology patients which can be used irrespectively of the age, metabolic demand, and physical examination of the patient. Its score system evaluates body weight, nutrient intake, clinical signs of malnutrition, functional capacity, metabolic requirement, and the physical examination of the patient. Categorization of patients based on the previously mentioned parameters is considered to be suitable for follow – up (Secker and Jeejeebhoy 2007).

Pediatric Nutritional Risk Score (PNRS) was developed for pediatric inpatients above the age of one month. It is a simple and fast questionnaire, which is independent of the patient groups. Its three criteria include nutrient intake and loss, diet-related pain, and the presence of an underlying disease with a risk of malnutrition. On the other hand, it is not detailed enough to be safely used in a wide range (Sermet-Gaudelus et al., 2000).

Pediatric Yorkhill Malnutrition Score (PYMS) is a screening tool, which classifies change in BMI percentile, recent weight loss, nutrient intake, and the underlying

disease. It was developed to for hospitalized children above the age of 1. Its application does not require special training, its specificity is 92%, and its sensitivity is 59% (Gerasimidis et al., 2011).

Screening Tool for the Assessment of Malnutrition in Pediatrics (STAMP) gives scores on the underlying disease, nutrient intake, as well as weight and height data. It was developed for hospitalized children, aged 2-17. It is suitable to screen repeatedly and thus monitor changes. The sensitivity of this tool is 72%, whereas specificity is 90% (McCarthy et al., 2012).

Nutrition Screening Tool in Childhood Cancer (SCAN) is a disease specific pediatric, non-anthropometric data assessment tool, which was published in 2016 based on six factors: type of tumor risk, need for current intensive care, gastrointestinal side effects, degree of nutrient intake in the previous week, weight loss in the last month, and clinical signs of malnutrition. This tool is considered to be fast, inexpensive, accurate, and easy to record knowing the patient's documentation. It should be highlighted that it has 100% sensitivity, 39% specificity, 56% positive predictive value, and 100% negative predictive value (Murphy et al., 2016). The feasibility of SCAN is limited by the fact that at the first admission of the patient, the type of the tumor and what risk it means is not yet known.

Subjective Global Nutritional Assessment for Children (SGNA) is suitable for the nutritional assessment of pre-operative patients. It includes recording the underlying disease, weight change, weight-to-height ratio, food intake and possible gastrointestinal symptoms, measuring functional capacity and the physical examination of the patient. The disadvantage of this tool is that it can only be performed with the involvement of a pediatrician (Erkan 2014).

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Table 2. Summary of the different pediatric screening tools

Screening tool	Tool Components				Disease specific
	Anthropometric data	Change in eating habits (amount, frequency, appetite, intake)	Clinical information	Other	
STRONGkids		X	X	Pre-existing nutrition intervention	No
PG-SGA	X	X	X		No
PNRS		X	X		No
PYMS	X	X	X		No
STAMP	X	X	X		No
SGNA	X	X	X	Diagnosis, physical findings	No
SCAN		X	X	Diagnosis, severity of the disease	Yes

1.4. Other methods for nutritional assessment

Assessing nutritional status is not easy; moreover, it requires time and expertise. Therefore, it is necessary to select those pediatric patients first, who are potentially at risk, and who should definitely be screened. There are direct and indirect methods for assessing nutritional status; however, a reliable assessment requires the knowledge of several parameters. Considering the changes in body weight alone for example is not always indicative, since edema may mask weight loss (Gallo et al., 2018).

Indirect methods in children

1.4.1. Anthropometric measurements

Body weight, body height, skin fold thickness, upper arm circumference can be obtained by physical examination. This data combined with the evaluation of certain biochemical parameters (transthyretin, possibly prealbumin) are suitable for determining nutritional status. However, they cannot be used to measure the distribution of body weight or to assess body composition (body fat – muscle mass ratio). In order to determine body composition, special devices should be used.

1.4.2. Nutritional status indicators

BMI percentile: in case of children it is useful to determine the BMI percentile. Percentiles are used to rank an individual on a growth chart and indicate where he fits in the context of the reference population. The adult BMI values and categories are not relevant for the characterization of children's nutritional status, since their body composition changes continuously until they reach adulthood. Therefore, growth charts have been developed to assess the nutritional status of boys and girls. In Hungary these are based on the data of the National Longitudinal Child Growth Survey (Joubert et al., 2006).

WHO weight-for height (WFH) %: the method recommended by the WHO to calculate the weight-for-height percentage (the percentage of the patient's current body weight relative to the 50th percentile body weight corresponding to his current height). According to the literature, it has similar reliability to BMI percentiles. The number

indicates the following main categories: mild malnutrition 80-90 %; severe <70 %; in the case of obesity it is greater than 120% (WHO 2006).

1.4.3. Food recalls and questionnaires

Nutritional data collection, which is the responsibility of dieticians, can also be used to determine nutritional status. In addition to the 24-hour food recall, a Food Amount Questionnaire (FAQ) or the retrospective Food Frequency Questionnaire (FFQ) could be applied to assess the patients' nutritional intake (Vilela et al., 2019). This method is the same in case of adults, there are no differences regarding questions included in food recalls and questionnaires.

Direct methods in children

1.4.4. Body composition measurements

Bioelectric Impedance Analysis (BIA): body composition analysis based on BIA provides segmental information on the ratio of different body tissues. It is quick, painless, non-invasive, does not cause radiation exposure, therefore, it can be repeated as often as required. Another advantage is that it can be used for nutritional risk screening, assessing nutritional status, as well as for controlling and monitoring the effectiveness of nutritional therapy (Fuller et al., 2020).

Dual Energy X-ray Absorptiometry (DEXA): A body composition analyzing method such as DEXA is used to calculate the whole body's bone density and mineral content, as well as the weight and proportion of fat and soft tissue. Due to the parameters of the device, the test cannot be performed above a certain height and weight, and since the measurement involves a small amount of radiation exposure, it can only be repeated at certain intervals (Shepherd et al., 2017).

Computed tomography (CT) and Magnetic Resonance Imaging (MRI):

CT and MRI imaging methods are primarily used to determine the amount of visceral fat, and are used to estimate the mass of skeletal muscle and bone tissue, as well as internal organs. Due to the radiation exposure of the CT scan, the evaluation of the nutritional status could only be considered if the examination is required for other reasons as well (Faron et al., 2020). In Hungary to analyze nutritional status by these methods are out of question due to limited access and the time-consuming evaluation of the findings.

1.5. The aims and methods of nutrition therapy

Nutrition therapy is used to support mental and physical well-being, to prevent or decrease the development of malnutrition, moreover, to treat metabolic changes caused by malnutrition. The purpose of nutritional interventions is to maintain or increase food intake in accordance with the increased needs associated with the disease. Furthermore, nutrition therapy aims to maintain skeletal muscle mass, physical performance and to correct or alleviate metabolic changes, which may occur due to deteriorating nutritional status. In chronic wasting diseases e.g. cancer, it is particularly important to avoid malnutrition that worsens the prognosis. Inadequate food intake is very common in case of pediatric tumor patients, which negatively affects immune functions, and may prolong hospitalization and treatment due to complications. The tools and methods of nutrition therapy are discussed in the next section.

1.5.1. Dietetic counseling

The first level of nutrition therapy is nutritional counseling by a dietician. Professional counseling should be a regular, committed, and thorough communication process designed to help the patient understand the forms of nutrition by which he can change his lifestyle and eating habits in order to overcome the disease. The most ideal way to increase the patient's energy and protein intake is to consume normal food prepared with appropriate cooking techniques selected for the purpose. In addition to counseling, oral nutritional supplements (ONS) are often needed to meet the specific needs of the underlying disease. If oral nutrient intake is still insufficient, enteral or parenteral supplementation is indicated, depending on the functioning of the digestive system, as prescribed by a physician experienced in nutritional therapy (Arends et al., 2017).

Based on a thorough survey in 2005 67% of the institutions reported that nutrition education is provided to all newly diagnosed pediatric cancer patients. In most institutions registered dieticians were responsible for nutrition education; however diet technicians, nurses, and physicians also contributed to educating patients on nutrition. Institutions reported that dietary recommendations were generally practitioner-specific and did not use standardized educational protocols (Ladas et al., 2006).

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1.5.2. Clinical nutrition

Clinical nutrition is an essential part of effective therapy and healing work. The process of providing optimal clinical nutrition - from malnutrition risk screening, assessing nutritional status, to effective nutrition therapy applied in a timely manner - is an interdisciplinary mission. Based on international experience, the coordination of the process can be carried out effectively by a nutrition support team (NST) as it was mentioned before. To provide clinical nutrition, which is in the best interest of the patient, the expertise and commitment of the NST staff responsible for treating the underlying disease is essential. In Table 3 below we can see the Dutch Malnutrition Steering Group's guideline on the nutritional intake versus requirement and recommended supplementation (Dutch Malnutrition Steering Group 2011).

Table 3. Dutch Malnutrition Guideline on nutritional intake and supplementation

Intake versus requirement	Supplementation
100 % of requirements	• No supplementation necessary
75-100% of requirements	• Energy and protein rich food • Consider oral nutritional supplements
50-75 % of requirements	• **Oral nutritional supplement**
25-50% of requirements	• If possible: oral nutritional supplements • If not: **tube feeding** • Consider parenteral nutrition if the enteral nutrition is inadequate
< 25 % of requirements	• For < 21-28 days: **nasogastric tube** feeding • For > 21-28 days: **tube feeding via PEG** • Consider parenteral nutrition if the enteral nutrition is inadequate

Source: (Dutch Malnutrition Steering Group 2011)

1.5.2.1. Enteral Nutrition (EN)

Enteral nutrition is one form of "artificial nutrition" and includes both feeding via nasogastric/enteral or percutaneous (gastric or jejunal) tube as well as ONS. Thus, enteral nutrition comprises all forms of nutritional support that imply the use of dietary foods for special medical purposes as defined in the European legal regulation of the commission directive 1999/21/EC of 25th March 1999 (Lochs et al., 2006). Enteral nutrition is a safe, effective and generally well tolerated approach of nutritional therapy in patients with normal functioning gastrointestinal tract. The main goal of EN is prevention or treatment of malnutrition in order to improve outcome. The 2006 ESPEN guidelines on EN have reviewed and analyzed several interventional studies to create evidence-based recommendations for the use of EN in different diseases and clinical settings (Lochs et al., 2006). Taking the evidence levels into consideration (provided by the ESPEN guidelines) regarding oncological cases, patients with severe nutritional risk benefit from nutritional support 10-14 days prior to major surgery, even if surgery has to be delayed (level of evidence: A). During radio- or radio chemotherapy using intensive dietary advice and oral nutritional supplements to increase dietary intake and to prevent therapy-associated weight loss and interruption of therapy is highly recommended (level of evidence: A). However, during chemotherapy routine EN does not seem to be useful (level of evidence: C) (Lochs et al., 2006).

Oral Nutritional Supplements (ONS): these are sterile liquids (e.g. Nutridrink), semi solids (e.g. Fresubin Yocréme) or modular formulae - usually powders (e.g. Calogen, Protifar, Fantomalt) which provide not only macro but micro nutrients as well (see Table 4). ONS may be prescribed for patients who are unable to meet their nutritional requirements by diet alone. Thus the role of ONS is to complement nutritional intake, however, dietetic advice on how to improve oral intake should be provided simultaneously. Despite the fact, that there is limited amount of research regarding dietary counseling, certain studies found that dietary counseling resulted in comparable increase in weight to ONS use (Baldwin and Weekes 2012). Other studies in this area have claimed that increasing the energy density of meals through food enrichment can boost patients' overall caloric intake up to 30% (Odlund et al., 2003).

Table 4. The most common types of ONS - Formulas

Type of ONS	Characteristics of ONS
Juice style	Volume ranges from 200-220 ml with an energy density of 1.25-1.5 kcal/ml. They are fat free.
Milkshake style	Volume ranges from 125-220 ml, energy density ranges from 1-2.4 kcal/ml. Available with added fiber.
High-energy powders	Volume ranges from 125-350 ml, ideally made up with full cream milk to give an energy density of 1.5-2.5 kcal/ml.
Soup	Volume ranges from 200-330ml. Some are ready mixed and others are a powder and can be made up with water or milk to give an energy density of 1–1.5 kcal/ml.
Semi-solid/dysphagia range	Range of presentations from thickened liquids (stage 1 and 2) to smooth pudding styles (stage 3), with an energy density of 1.4-2.5 kcal/ml.
High protein	Range of presentations; jellies, shots, milkshake style containing 11-20g of protein in volumes ranging from 30–220 ml.
Low volume high concentration shots	These are fat and protein based products that are taken in small quantities (shots), a dose is typically 30-40 ml taken 3-4 times daily.

Source: (Russel 2007)

It is important to note that all versions of the above-mentioned ONS formulas are available in Hungary.

Tube feeding: the gastro-intestinal tract can be accessed via a number of places. We differentiate between trans nasal access – nasogastric (goes to the stomach) and nasojejunal (goes to the jejunum). The feeding tube can also be placed directly to the stomach or the jejunum; these are called Percutaneous Endoscopic Gastrostomy (PEG) and Percutaneous Endoscopic Jejunostomy (PEJ) respectively. Gastrostomy and jejunostomy can also be performed by surgical procedures.

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Deciding which feeding route is to be applied depends on various factors, including the underlying disease, the estimated duration of tube feeding, the preference and compliance of the patient. After selecting the appropriate feeding route, the feeding solution should also be carefully chosen (Sobotka 2011).

1.5.2.2. Parenteral Nutrition (PN)

The most important goal of parenteral nutrition is to provide a nutrient mixture closely related to the patient's requirements and to avoid complications at the same time. Although PN has been debated over the past decades it is essential for pediatric patients who cannot be adequately fed orally and/or enterally e.g. who are treated at intensive care units (ICU). According to the updated ESPEN guideline PN should only be used if other alternatives are not feasible, or would be unsafe to use. However, whenever it is possible PN should always be combined with at least some minimal EN in order to maintain the barrier function of the gastrointestinal lining (Singer et al., 2009; Howard and Bokhurst-de van der Schueren 2011). According to the some guideline, patients receiving less than their targeted enteral feeding after 2 days should be considered for supplementary or partial PN. This recommendation is only Grade C since meta-analysis results are conflicting (Simpson and Doig 2005; Singer et al., 2009).

Methods of delivering PN

Total Parenteral Nutrition (TPN) or Partial Parenteral Nutrition (PPN): PN, especially TPN can induce adverse effects, therefore enteral feeding is encouraged whenever possible to limit both the amount and the length of PN therapy. TPN means that it is the only source of nutrition the patient receives, whereas in case of PPN it is provided as a supplement and the patient has another source of nutrition as well.

PN via central or peripheral venous catheter: feeding via a central venous catheter (CVC) means that the catheter is placed in a larger, high-flow vessel e.g. vena cava inferior. In case of feeding via a peripheral venous catheter (PVC) the feeding catheter delivers the nutrients into a small vein. Centrally administered PN can fully cover the

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nutritional needs, since vessel tolerance to hyperosmolar solutions is usually not a limitation. Peripheral PN may provide less than the overall needs for macro- and micronutrients as the amounts given may be limited by venous intolerance as well as the more limited flow rates into a smaller vessel (Singer et al., 2009).

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2. Objectives

Assessing the nutritional status of pediatric cancer patients and providing adequate nutrition therapy have received considerable attention in recent years. Numerous research groups published multiple articles focusing on the effect of nutritional status and body composition changes during treatment, however no specific guideline is available regarding the assessment of NS in children with cancer. Furthermore, until 2016, there was no screening tool validated for pediatric cancer patients either. In addition, there is no exact recommendation or algorithm on how nutrition therapy should be provided for pediatric cancer patients.

The aims of the present study were:

1. First of all, to investigate whether the recognition of unfavorable nutritional status at hospital admission and the subsequent intensified nutrition support have an effect on
   (i) complications during anti-cancer treatment,
   (ii) disease progression of the underlying illness,
   (iii) recovery, and survival in pediatric patients with solid tumors.

2. To present our new self-developed, easy-to-use nutritional risk screening method, called Nutritional Risk Screening for Pediatric Cancer (NRS-PC):
   (i) Comparing NRS-PC to another tool, which had been validated for children with tumors, and to objective bio-impedance measures.
   (ii) It was also intended to recommend a screening algorithm which can be easily used in pediatric oncology facilities specifically.

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3. Methods

3.1. The effect of nutritional support on the disease progression and survival

In the first part of our study we analyzed data from 145 children (0-18 years) undergoing complex treatment (including chemotherapy) with solid tumors at the 2nd Department of Pediatrics, Semmelweis University (Budapest, Hungary) between 2009 and 2014. Our retrospective data collection was approved by the Hungarian Scientific and Research Ethics Committee (number: 86748/AOGY2/2016). The last follow-up was done on 25th April 2019. During the study period, in total 160 pediatric cancer patients were treated at the neuro-oncological unit, and only 15 of them did not have full medical records. Therefore, we had access and analyzed the data of 90.6% of the treated pediatric cancer patients (Gallo et al., 2022).

The incidence of the different types of solid tumors can be seen in Table 5. By high risk tumor we mean those specific tumor types which require aggressive treatment protocols (based on clinical and histopathological findings, classified by pediatric oncologists). The study period was divided into two three-year periods: *Period 1* before the nutrition support team (2009-2011) and *Period 2* after starting intensified nutrition support (2012-2014). It is important to mention that we have selected this type of oncological patient group particularly since there was no change in the treatment protocol - except for the intensified nutrition therapy provided by our NST - during these years. The proportion of the different tumor types was similar in the two periods as it can be seen in Table 5. Each tumor type was treated (surgery, chemo-, and radiation therapy) according to its standard medical protocols (Gallo et al., 2022).

Table 5. Incidence and diagnosis of tumors in the two periods (Gallo et al., 2022)

Tumor types	Period 1. (2009-2011)	Period 2. (2012-2014)	Total N	Total %
Neuroblastoma	19	18	37	25.5%
Medulloblastoma	14	12	26	17.9%
Ewing sarcoma	15	15	30	20.7%
PNET	4	4	8	5.5%
Ependymoma/glioma	3	3	6	4.1%
Hepatoblastoma	2	6	8	5.5%
Other	16	14	30	20.7%
Total	73	72	145	

During *Period 1* no nutrition support team was involved, and therefore malnutrition risk screening was not compulsory. We could not identify malnutrition risk using our screening tool. We could only rely on the medical documents; there were only few patients clearly recognized as „being at risk". At the beginning of 2012 the NST (including physicians, nurses, dieticians, and pharmacists), was established at our department and in *Period 2* malnutrition risk screening was introduced as compulsory in case of every hospital admission. To draw attention to children being at risk of malnutrition our self-developed nutrition status screening sheet, named Nutrition Risk Screening for Pediatric Cancer (NRS-PC) was used. Our screening takes into consideration both the objective and clinical aspects of nutritional status: the BMI percentile (below 10 or 3 percentile), factors that determine the patient's nutritional and gastrointestinal status (lost more than 1 kg since showing the symptoms, changes in stool, vomiting etc.), as well as other aspects related to the general status of the patient (decrease in physical activity, appetite and the amount of food intake). Patients at risk of malnutrition according to the malnutrition risk screening test (BMI percentile <5 or BMI percentile <10 plus at least two positive responses to questions from 3 to 8 were provided with extra nutritional support during *Period 2*. Between 2012-2014 all patients were screened and if they were found to be at risk of malnutrition they were given nutrition support based on professional dietetic standards (Gallo et al., 2022).

Besides the diagnosis (presence of high risk or CNS tumor) and the outcome (survival) the following parameters were recorded and analyzed for each patient: age, gender (male or female), body height and body weight at the beginning and at the end of the oncological treatment, number of days spent in hospital, number of chemotherapy days, number of antibiotic and antimycotic treatment days, number of transfusions, presence of nutritional risk (weight-for-height percentile below 10 at the beginning of the treatment), presence of positive malnutrition risk (during the treatment), length of nutrition therapy, presence and type of nutrition support (oral, enteral or parenteral). In our sample the following tumor types were considered as CNS tumors: neuroblastoma, medullobalstoma, PNET, ependymoma/glioma and other rarely occurring tumor types, astrocytoma, atypical teratoid rhabdoid tumor (AT/RT), plexus choroideus carcinoma (Gallo et al., 2022).

Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared. Weight-for-height, height-for-age, weight-for-age and body mass indexes were interpreted by using the Z-score classification system. Z-scores were calculated as the difference between the observed and the median value of the reference population divided by the standard deviation value of the reference population. Reference data (according to age/height and gender) were obtained from 'The National Longitudinal Child Growth Survey' published by the Hungarian Central Statistics Office in 2006 (Joubert 2006). Weight-for-height percentiles were calculated from weight-for-height Z-scores and were selected as the index referring to growth during the treatment period (Mwangome 2014; Gallo et al., 2022).

3.1.1. Differences between the characteristics of the two Periods

To compare the two periods, Fisher test was used regarding gender, age, presence of high risk tumor, presence of CNS tumor, presence of nutritional risk during the treatment**,** the presence of positive malnutrition risk during the treatment, presence of nutrition therapy, presence of enteral or parenteral nutrition and presence of antimycotic treatment. To determine differences in the measured variables (length of treatment, number of days spent in hospital, number of chemotherapy days, number of antibiotic

treatment days, number of transfusions, weight-for-height percentile at the beginning of the treatment) between the two study periods, separate general linear models were used (Gallo et al., 2022).

3.1.2. Changes in weight-for-height percentile before and after treatment

To see the differences regarding the change in weight-for-height percentile before and after treatment, we created 4 groups according to the two periods and the survival within 4 years after the beginning of treatment (Period 1 died, Period 1 survived 4 years, Period 2 died, Period 2 survived 4 years). General linear mixed model was fit to the data with random effects for each child (Pinheiro and Bates 2000). The fixed effects were the above mentioned 4 groups, the time of measurement (before or after treatment) and their interaction. The response variable was weight-for-height percentile. For multiple comparisons the Tukey-Kramer correction was used. All analysis was performed in R 3.4.4. The significance level was set at $P < 0.05$ (Gallo et al., 2022).

3.1.3. Survival analysis

Survival curves were constructed using the Kaplan-Meier method (package survival in R). Log-rank test of equality across strata for categorical variables was performed. We analyzed the independent contribution to tumor survival of several prognostics with univariable and multivariable regression methods based on the Cox proportional hazards model. Variables were entered into the model using a forward selection approach, starting with the most significant variable (based on the unadjusted p-value) and then continuing in order of significance. After completing the survival analysis for the whole dataset (n=145), it was repeated separately for *Period 1* (n=73) and *Period 2* (n=72) as well (Gallo et al., 2022).

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3.2. Different nutritional screening tools and recommended screening algorithm

In the second part of our study we analyzed data from 109 pediatric oncology patients (age 3-18) at the 2nd Department of Pediatrics, Semmelweis University (Budapest, Hungary) who were inpatients between 2017 and 2018. Data were collected during the different phases of the disease: *Diagnosis* (the time between histological sampling and the initiation of cancer treatment – usually a couple of days or maximum few weeks), *Active treatment* (intensive chemotherapy until the last day of intravenous chemotherapy), *Maintenance* (oral low-dose chemotherapy mostly in leukemia and some soft tissue sarcomas) and *Post therapy* (during the follow-up period, after completing all therapies) with the approval of the Hungarian Scientific and Research Ethics Committee (number: 86748/AOGY2/2016). During the study period, in total 156 bio-impedance measures were done, however some patients were measured more than once, but only if they proceeded to the next phase of the disease. 14 of the patients had a disease relapse, which means the reappearance of their malignancy (Gallo et al., 2021).

Bio-impedance measures were performed by a clinical dietician who is also member of the nutrition support team. Patients were on an empty stomach; those who were physically fit enough to stand alone for 1.5 minutes were measured by InBody 720, and those who were not, were measured by InBody S10 in a seated position (InBody Co. Ltd. 13850 Cerritos Corporate Drive, Unit C, Cerritos, CA 90703; Gallo et al., 2021).

Recorded parameters were the following: name, age (date of birth), diagnosis, date of the measurement, phase of the disease, weight, height (using standardized scales and stadiometers); calculated parameters were: SCAN score and NRS-PC score. BMI and body composition parameters including muscle mass and body fat percentage were determined by the InBody devices. BMI, muscle mass and body fat percentage were compared against normal range values. Three categories were set up regarding BMI, muscle mass and body fat mass: low, normal, and high which were also determined and provided by the InBody devices (Gallo et al., 2021).

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The three different screening tools

3.2.1. SCAN

Nutrition screening tool for childhood cancer is a simple and quick tool to identify children with cancer who are at risk of malnutrition (see Figure 2). It was validated and published in 2016. SCAN includes six Yes or No questions and if the total score is ≥3 it means being at risk of malnutrition. The patient has to be referred to a dietician for further assessment (Gallo et al., 2021).

Nutrition screening tool for childhood cancer (SCAN)

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
	Total

Score indication

≥3 At risk of malnutrition – Refer to dietician for further assessment

Figure 2. The questionnaire of SCAN nutrition screening tool for pediatric cancer (Gallo et al., 2021)

3.2.2. NRS-PC

Nutrition risk screening for pediatric cancer, which is our self-developed screening tool. Similarly to SCAN it is also an easy-to-use questionnaire with a score system (see Figure 3). Apart from six questions regarding weight loss, physical activity, change in nutrition habits, stool and other gastrointestinal symptoms the BMI percentiles are also taken into consideration (Gallo et al., 2021).

NRS-PC (Nutrition Risk Screening for Pedatric Cancer) Questionnaire

- New or returning patient:
- Name:
- Date of birth:
- Department (ward):
- Weight: (kg)
- Height: (cm)
- Age:
- Diagnosis:
- Does the patient receive any nutritional supplement? Yes or No
- Does the patient have a feeding tube upon admission? Yes or No
- BMI percentile <10? Yes or No
- BMI percentile <5? Yes or No

Questions	YES	NO
1. More than 1 kg weight loss since tumor associated complaints and symptoms		
2. Change in nutrition habits: reduced amount of food consumed		
3. Change in nutrition habits: fewer occasions (compared to previous number of meals)		
4. Stool is more frequent than usual or change in consistency		
5. Increased vomiting compared to earlier		
6. Reduced physical activity compared to earlier (before diagnosis)		
NRS-PC score (number of positive responses from Questions 1-6)		

Date:

Screening done by (name of the person):

Figure 3. The questionnaire of NRS-PC nutrition screening tool for pediatric cancer (Gallo et al., 2021)

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3.2.3. BIA

Bioelectrical Impedance Analysis is used to measure body composition. InBody 720 and S10 are medical-grade body composition analyzers, which rely on four technological milestones (8-point tactile electrode system, direct segmental measurements, multiple frequencies, no estimations) to provide accurate and precise results that are highly correlated to gold-standard methods (Fuji et al., 2017). The software in the device, when assessing body composition, evaluates three categories (low, normal or high) regarding BMI, muscle mass and body fat percentage.

One of our primary goals was to evaluate NRS-PC to muscle mass, and to compare the result to the data of bio-impedance measurement. Based on the evaluation two categories were created: a, low muscle mass and b, normal and high muscle mass. The individual muscle mass values were defined by the body composition analysis, provided by InBody 720 or S10 devices. A receiver-operator characteristic curve was used to assess the relationship between muscle mass category and the different cut-off scores of the NRS-PC. The area under the curve (AUC) was calculated to measure classifier performance (Gallo et al., 2021).

4. Results

4.1. Results regarding the effect of nutritional support on the disease progression and survival

4.1.1. The comparison of *Period 1* and *Period 2*

We collected data of 73 patients (45 male, 28 female) between 2009-2011 (*Period 1*, without intensified nutrition support) and of 72 patients (39 male, 33 female) between 2012-2014 (*Period 2*, with intensified nutrition support). The characteristics of the study subjects are summarized in Table 6.

Table 6. Characteristics of the study subjects (Gallo et al., 2022)

Study periods	**Period 1 (2009-2011)**	**Period 2 (2012-2014)**	**P- value**
N (children)	73	72	
Percent of males	61.6%	54.2%	0.403
Number of patients with CNS tumor	54 (74.0%)	45 (62.5%)	0.156
Number of patients with high risk tumor	14 (19.2%)	18 (25.0%)	0.429
Mean (SD) time from diagnosis to end of treatment (days)	802 (489)	512 (329)	<0.001*
Mean (SD) number of days spent in hospital	116 (57)	120 (65)	0.698
Mean (SD) number of chemotherapy days	38 (27)	33 (18)	0.166
Mean (SD) number of antibiotic treatment days	37 (29)	40 (33)	0.600
Received antimycotic treatment	32 (47.8%)	21 (29.1%)	0.036*
Mean (SD) weight-for-height percentile at the beginning of the treatment	37.5 (32.0)	33.5 (30.4)	0.441
Presence of malnutrition risk during the treatment period	N/A	47 (65.3%)	
Presence of malnutrition risk based on BMI Z-score	24 (32.9%)	26 (36.1%)	0.729
Average number of nutrition therapy days	22.4	54.2	0.043*
Presence of prolonged parenteral nutrition (>7 days)	14 (19.2%)	7 (9.7%)	0.156
Presence of enteral nutrition (oral and/or tube feeding)	22 (30.1%)	35 (48.6%)	0.028*

The mean (SD) age at the beginning and at the end of treatment in *Period 1* was 6.3±5.6 and 8.3±5.5 years, and in *Period 2* it was 6.7±5.4 and 8.1±5.7 years, respectively. The ratio of males, the presence of CNS tumor, and the presence of high risk tumor did not differ significantly among the two periods (Fisher-test, $p>0.05$ in all cases). However, there was a significant difference in the presence of malnutrition risk during the treatment period (Fisher-test, $p<0.001$) and the length of nutrition therapy in *Period 2* compared to *Period 1*(Mann-Whitney test, $p<0.05$). Furthermore, antimycotic treatment was two times less needed (Fisher test, $p=0.036$, odd ratio= 2.2) in *Period 2* compared to *Period 1* (Gallo et al., 2022).

The time from diagnosis to the end of treatment was significantly shorter in *Period 2* compared to *Period 1* (general linear models, $p<0.001$). However, the number of days spent in hospital, the number of chemotherapy days, the number of antibiotic treatment days did not differ significantly between the two periods (general linear models, $p>0.05$ in all cases) (Gallo et al., 2022).

4.1.2. Analyzing weight-for-height percentile before and after treatment

In *Period 1*, after treatment, the weight-for-height percentiles were significantly higher in those children who survived compared to the children who died (General linear mixed model with Tukey post-hoc test, $p=0.008$). So in *Period 1*, those who died within 4 years after the beginning of the treatment had a significantly larger decrease in the weight-for-height percentiles after treatment compared to those who survived at least 4 years. Contrary to these, changes in weight-for-height percentiles did not differ significantly in *Period 2* (General linear mixed model with Tukey post-hoc test, $p=0.341$) among children who died and children who survived 4 years after the beginning of the treatment, see Figure 4 (Gallo et al., 2022).

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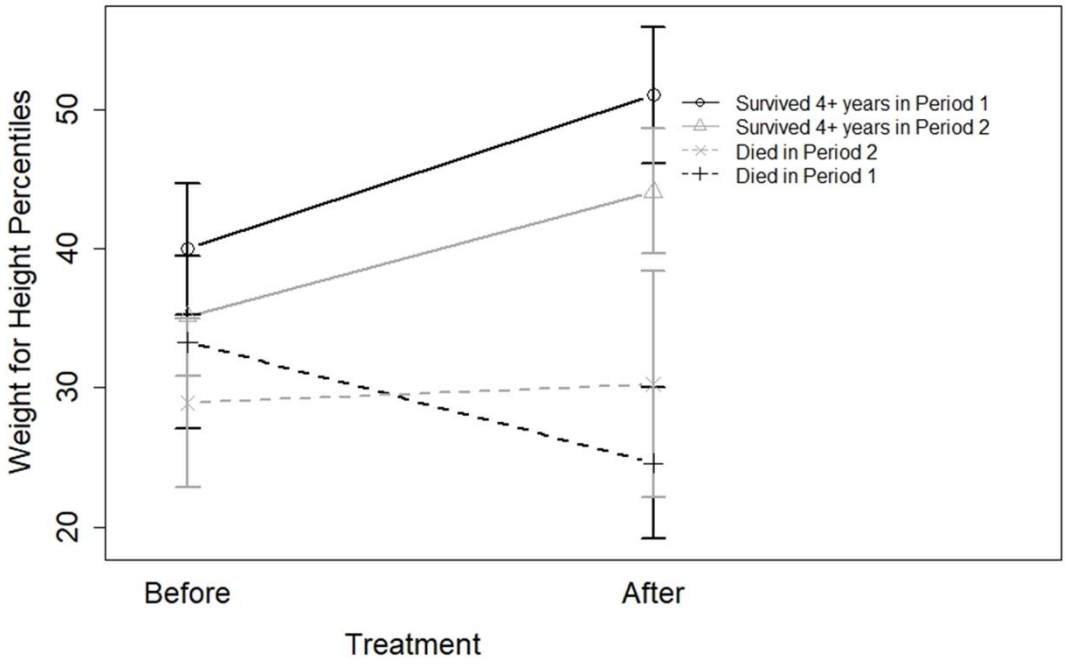

Figure 4. Correlation between weight-for-height percentiles and 4-year survival (Gallo et al., 2022)

4.1.3. Survival probability in the two periods

The minimal follow-up period was 4 years, therefore in both study periods we could calculate the ratio of children surviving at least 4 years. In *Period 1*, 35.6% (26/73) of the children died within 4 years after the beginning of the treatment, while in *Period 2* only 25.0% (18/72). Taking the entire study period into consideration we can see that the median (min – max) follow up time in *Period 1* was 8.7 (7.0 – 10.0) and in *Period 2* 5.5 (4.0- 6.9) years. During the whole study period 39.7% (29/73) of the children who had started treatment in *Period 1* died, whereas in *Period 2* only 26.4% (19/72). Kaplan Meier Curve analysis performed at the two periods as demonstrated by Figure 5. A clear trend can be seen since survival was more favorable in *Period 2* compared to *Period 1*, however the difference was not significant (p=0.130) (Gallo et al., 2022).

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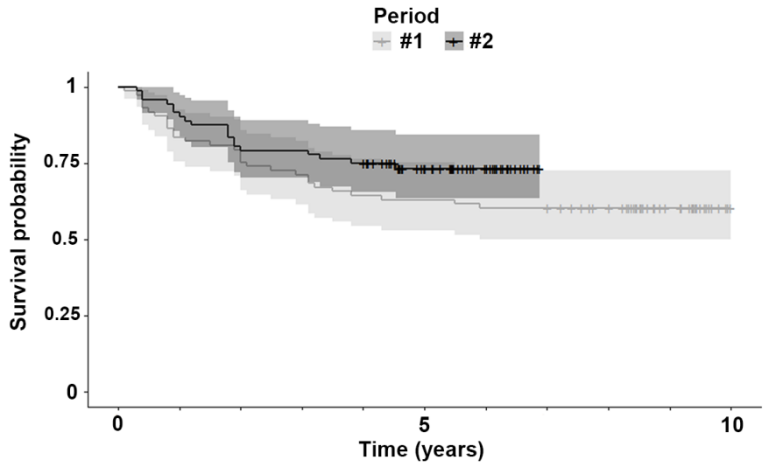

Figure 5. Kaplan Meier curve in *Period 1* and *2* (Gallo et al., 2022)

The univariate Kaplan Meier analysis and log rank tests demonstrated shorter survival in CNS tumor patients and in children showing a decrease of weight-for-height percentile during treatment (Figure 6 A and B). All the other measured factors (age, gender, presence of high risk tumor, presence of antimycotic treatment, presence of nutritional risk at the beginning of the treatment (weight-for-height percentile <10), presence of positive malnutrition risk during the treatment, presence and type of nutrition therapy (enteral or parenteral) did not affect survival significantly ($p>0.05$ in all cases). Multivariable cox hazard proportional analysis confirmed that decrease in weight-for-height percentile during treatment and the presence of CNS tumor are significant predictors of a less favorable survival (Figure 7) (Gallo et al., 2022).

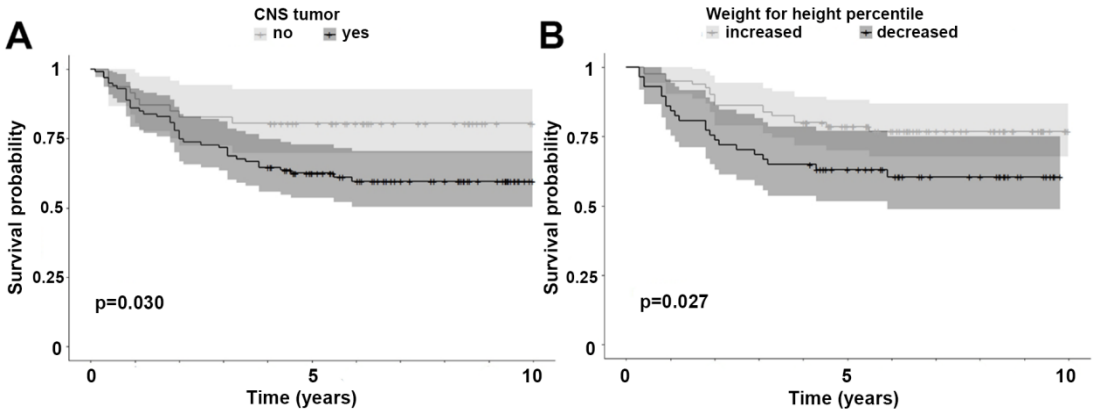

Figure 6. A and B. Survival probability in case of CNS tumor and decreased weight-for-height percentile (Gallo et al., 2022)

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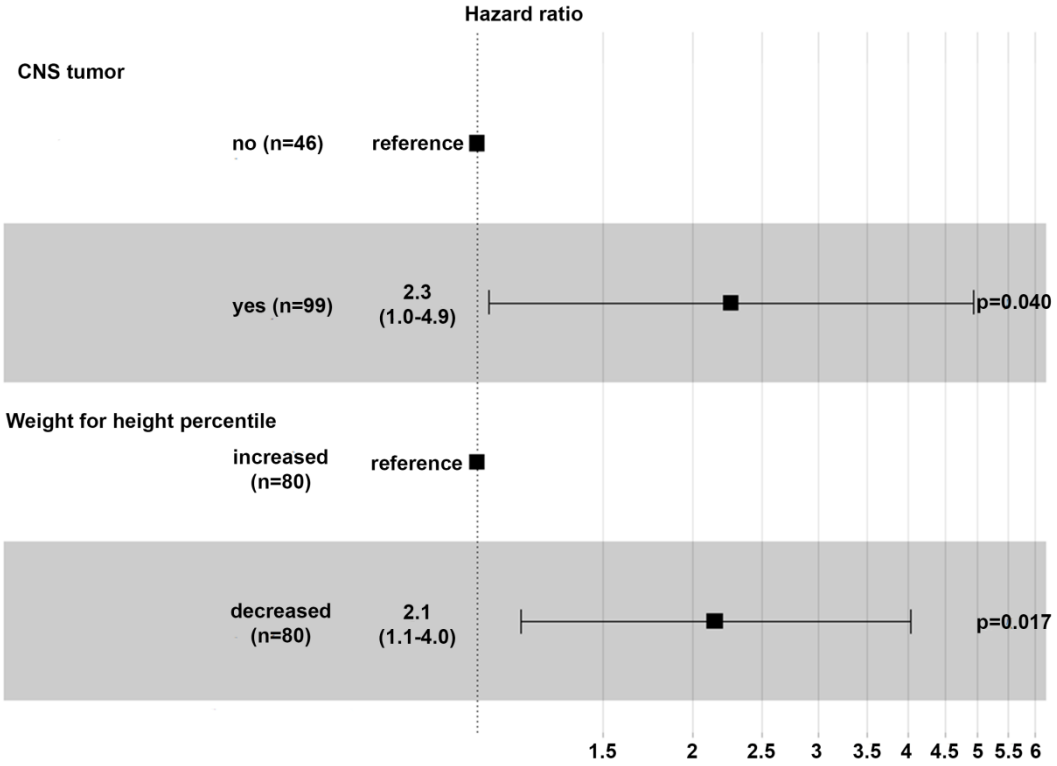

Figure 7. Survival probability demonstrated by multivariable cox hazard proportional analysis (Gallo et al., 2022)

Conducting the analysis only on data of *Period 1* (before the introduction of the NST), the univariate Kaplan Meier analysis and log rank tests revealed significantly shorter survival in children showing a decrease of weight-for-height percentile during treatment (Figure 8 A). All the other measured factors did not affect the survival significantly ($p>0.05$ in all cases). Multivariable cox hazard proportional analysis showed that decrease in weight-for-height percentile during treatment was a significant predictor of a less favorable survival in *Period 1* (Figure 8 B) (Gallo et al., 2022).

In *Period 2* (after initiating intensified nutrition support), none of the measured factors affected the survival significantly ($p>0.05$ in all cases) according to the univariate Kaplan Meier analysis, the log rank tests and the multivariable cox hazard proportional analysis (Figure 8 C) (Gallo et al., 2022).

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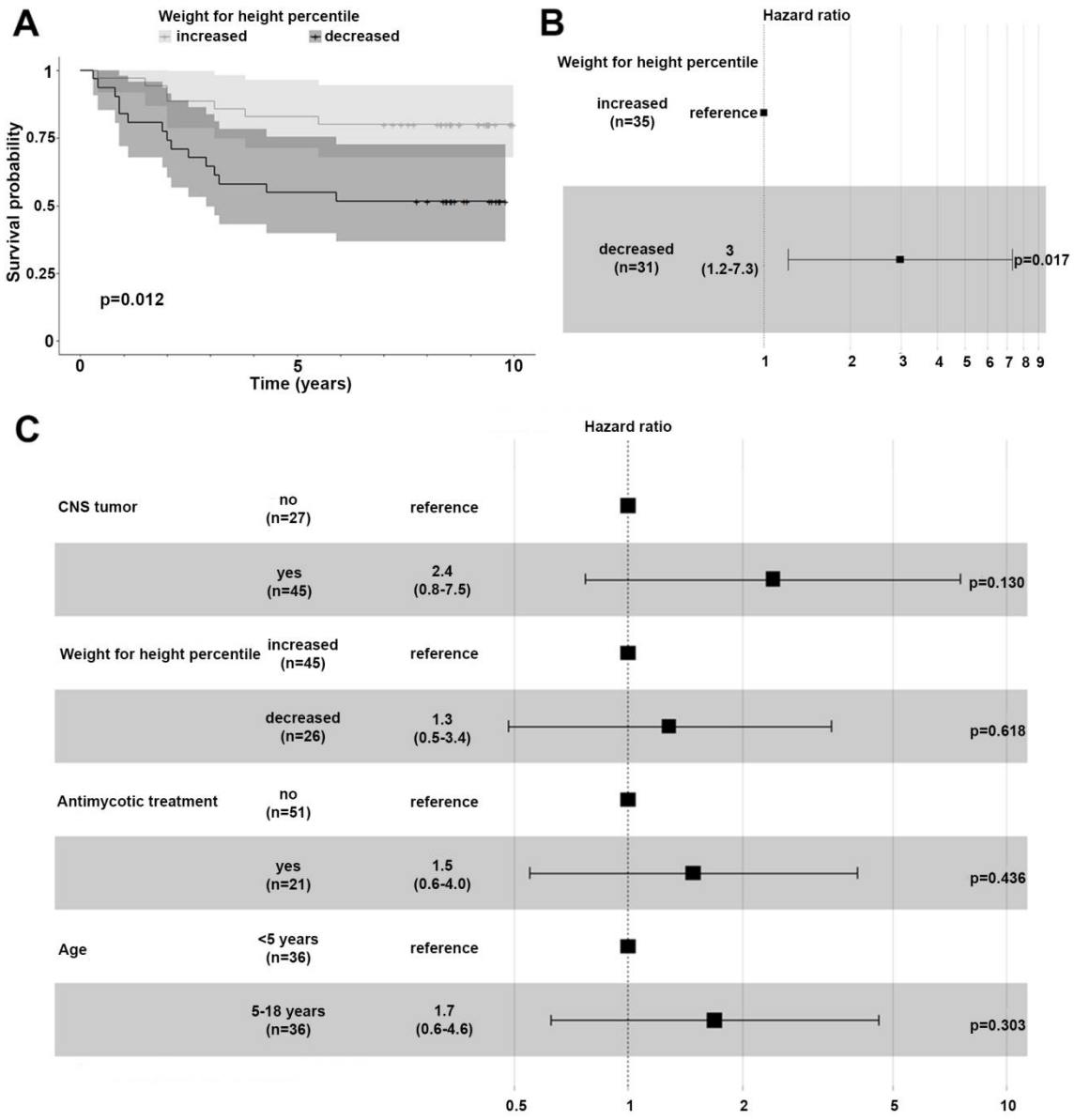

Figure 8 A, B and C. Survival probability before and after introducing NST (Gallo et al., 2022)

4.1.4. Nutrition therapy

Although there was no NST in *Period 1* some of the patients were given nutrition therapy, usually in the intensive care units (ICUs) and mainly in the form of parenteral nutrition. Therefore, parenteral nutrition for at least 7 days was given to twice as many patients in *Period 1,* although statistically this difference is not significant (Table 6).

In *Period 2* nutrition therapy was the responsibility of the NST and the decision was made after the consideration of other important factors (e.g. the condition of the digestive tract). Comparing the number of patients who were provided with enteral nutrition (oral nutrition support and tube feeding) in *Period 1* and *2* the difference is significant (Table 6). This means it was a more preferred way of nutrition support in *Period 2*. If we consider the average number of nutrition therapy days a significant difference has been found: 22.4 days in *Period 1*, 54.2 days in *Period 2*, p=0.043. Nutrition therapy was started earlier, as soon as malnutrition risk was detected, and was provided for a longer period of time in *Period 2* (Gallo et al., 2022).

4.2. Results regarding different nutritional screening tools and recommended screening algorithm

In the investigation of screening tools data of 109 patients were analyzed (n= 64 males). Some of the children underwent repeated assessments at different phases of their disease as seen in Table 7. 77 patients went through one assessment, 21 two and 11 patients three assessments. Children had a mean age of 11.3 years (range: 3-21 years, SD = 4.8 years). 45 patients were treated with hematologic malignancies, 23 with Ewing-sarcoma and osteosarcoma, 21 with brain and spinal tumors, 20 with other malignancies. 14 of the patients had a disease relapse (Gallo et al., 2021).

Table 7. The characteristics of the study subjects (Gallo et al., 2021)

Time point of the disease	Number of cases (n=)	Male-Female ratio	Average age (years)±SD	Lost patients (n=)	Relapse (n=)	SCAN score	NRS-PC score
Diagnosis	44	29:15	10.5±3.5	1	9	3.4±2.0	1.0±1.3
Active treatment	36	22:14	14.5±3.5	4	1	3.4±1.6	1.2±1.3
Maintenance	34	19:15	9.5±4.5	0	0	2.9±1.7	0.5±1.0
Post therapy	36	22:14	11.5±2.5	1	4	1.7±1.4	0.4±0.9

4.2.1. Validation of NRS-PC to SCAN

As a first step, NRS-PC was compared to SCAN, a validated nutrition assessment tool used in pediatric oncology, to identify cut off scores for NRS-PC. According to Murphy et al. (2016), a child was classified at risk of malnutrition if the SCAN score was equal or greater than three. A receiver-operator characteristic curve was used to assess the relationship between SCAN and the different cut-off scores of the NRS-PC. The area under the curve (AUC) showed a high classifier performance see Figure 9 (AUC = 0.9). A cut off score of one on the NRS-PC resulted in 98% [95% CI: 90, 100] sensitivity, 62% [95% CI: 51, 71] specificity, a positive predictive value of 58% [95% CI: 47, 68] and a negative predictive value of 98% [95% CI: 91, 100]. This means that in our

sample one child considered malnourished by the SCAN would have been undetected with our questionnaire. A cut off score of two would decrease the sensitivity to 86% [95% CI: 77, 93], while increasing the specificity to 77% [95% CI: 65, 86]. As we aimed to identify all children at risk of malnutrition sensitivity was prioritized over specificity (Gallo et al., 2021).

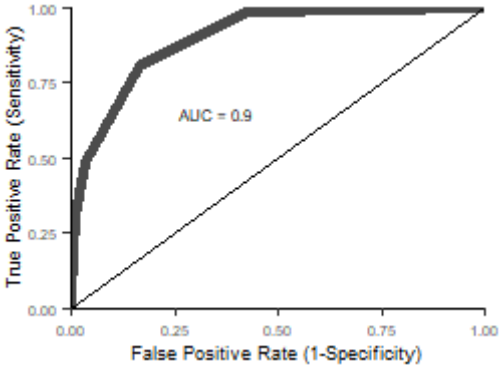

Figure 9. ROC curve demonstrating the predictive value of NRS-PC to SCAN with a cut off score of 3 (Gallo et al., 2021)

4.2.2. Evaluation of NRS-PC to bio-impedance measures

In order to evaluate NRS-PC to muscle mass measured by bio-impedance analysis low muscle mass and normal or high muscle mass categories were set up. A ROC curve was used to assess the relationship between the muscle mass category and the different cut-off scores of the NRS-PC. The area under the curve (AUC) was calculated to measure classifier performance. Sensitivity, specificity, negative and positive predictive values were calculated to each cut-off score and were reported in Table 8. Ideally, a measurement tool should have a 100% sensitivity to identify every child who has low muscle mass. A cut off score of one would give a sensitivity of 75% with 60% specificity. In our sample, this means that 13 children would have been incorrectly classified to the group of normal muscle mass, while 40 children would be incorrectly classified to the low muscle mass group (Gallo et al., 2021).

Table 8. Validation of NRS-PC to muscle mass. 95% confidence intervals are in [] (Gallo et al., 2022)

Cut off score	Sensitivity	Specificity	Negative predictive value	Positive predictive value
1	0.75 [0.62, 0.86]	0.6 [0.49, 0.69]	0.82 [0.71, 0.9]	0.5 [0.39, 0.61]
2	0.7 [0.59, 0.79]	0.71 [0.58, 0.81]	0.64 [0.52, 0.75]	0.76 [0.65, 0.85]
3	0.62 [0.53, 0.71]	0.82 [0.65, 0.93]	0.38 [0.26, 0.5]	0.92 [0.84, 0.97]
4	0.59 [0.5, 0.68]	0.9 [0.68, 0.99]	0.25 [0.16, 0.37]	0.97 [0.91, 1]
5	0.54 [0.45, 0.62]	1 [0.29, 1]	0.04 [0.01, 0.12]	1 [0.95, 1]

4.2.3. Comparison of NRS-PC and SCAN predictive value regarding muscle mass

To evaluate whether the SCAN or the NRS-PC questionnaire was a more sensitive tool to identify patients with reduced muscle mass, we did ROC analysis and compared the AUC values of both questionnaires with the DeLong method. The AUC of 0.67 [95% CI: 0.58, 0.75] of the SCAN was significantly lower (Z = -2.46, p-value = 0.014) than in the case of the NRS-PC (AUC = 0.75, [95% CI: 0.67, 0.82]), indicating that NRS-PC has better classifier properties to identify children with lower muscle mass see Figure 10 (Gallo et al., 2021).

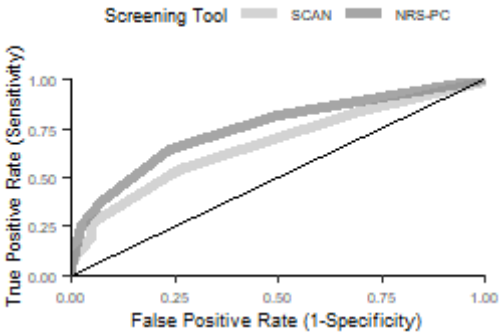

Figure 10. ROC curve demonstrating the predictive value of the SCAN and the NRS-PC for low muscle mass (Gallo et al., 2021)

The AUC of NRS-PC (0.75) was significantly larger than the AUC (0.67) of SCAN.

4.2.4. Evaluating the NRS-PC and SCAN at different phases of the disease

Patients were assessed at different phases of the course of their treatment. The description of the four phases and the number of participant in each case are shown in Table 9. To assess whether the classifier performance of NRS-PC differs at the different phases of the treatment, ROC analysis was performed. The AUC values at the different phases did not differ significantly from each other (Gallo et al., 2021).

Table 9. Comparison of SCAN and NRS-PC at different phases of the disease (Gallo et al., 2021)

	Description	Number of cases	NRS-PC AUC	SCAN-AUC	Z	p
	Assessment after diagnosis	44	0.67 [0.49 0.86]	0.62 [0.45 0.8]	0.88	0.381
	Active treatment	36	0.78 [0.63 0.93]	0.7 [0.53 0.86]	1.29	0.196
	Maintenance	35	0.77 [0.62 0.93]	0.64 [0.46 0.81	1.8	0.072
	Assessment post therapy	37	0.82 [0.67 0.96]	0.67 [0.49 0.84]	1.57	0.115

4.2.5. Evaluating BMI categories

Classifier performance of both questionnaires was evaluated in the three BMI categories separately. There were no significant differences in the AUC values of the two screening tools, however, in the low and normal BMI groups the result of the DeLong test approached significance. In the low BMI group, SCAN had better classifier properties, whereas in the normal BMI group, NRS-PC seemed to be better. Nevertheless, neither of the tests had sufficient sensitivity in the low BMI group (see Table 10 and 11) (Gallo et al., 2021).

Table 10. Comparison of SCAN and NRS-PC at different BMI categories (Gallo et al., 2021)

	Number of cases	NRS-PC AUC	SCAN-AUC	Z	p
Low	27	0.5 [0.22 0.78]	0.62 [0.31 0.93]	-1.86	0.063
Normal	99	0.72 [0.61 0.81]	0.64 [0.54 0.75]	1.75	0.081
High	25	0.83 [0.54 1]	0.74 [0.22 1]	0.77	0.439

Table 11. Comparison of low and high nutritional risk patients (Gallo et al., 2021)

For categorical variables, chi square tests, for age independent samples t-test were used for comparison.

		Low risk	High risk	p
Gender	Male	37	56	0.150
	Female	16	43	
Relapse	No	47	91	0.720
	Yes	6	8	
Phase	1	10	34	< 0.001
	2	7	29	
	3	13	22	
	4	23	14	
BMI category	Low	3	24	0.001
	Normal	35	64	
	High	15	10	
Age		10.7	11.6	0.270

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4.2.6. Comparing children under and over NRS-PC cut-off

Comparing children at low risk for malnutrition to those at high risk according to NRS-PC no significant differences were found in gender, the proportion of patients after relapse or age. However, there was a significant difference in the phase of the disease and the BMI category of the patients. There were more high risk patients in phases 1-3, whereas less in phase 4. It is also clear that children in the low BMI category were almost all at high risk (except for 3 patients) for having low muscle mass (Gallo et al., 2021).

5. Discussion

5.1. Nutritional status of pediatric cancer patients

The role of nutrition in children with cancer is indisputable as it influences several cancer control parameters including treatment, recovery, and survival (Sala et al., 2004; Rogers et al., 2015). It is also widely accepted that nutritional status (NS) will be affected during the course of the disease due to treatment and supportive care. Based on previous studies we can see that NS usually deteriorates and malnutrition tends to become more prominent (Antillon et al., 2013; Brinksma et al., 2012; Jaime-Pérez et al., 2008; Reilly et al., 2009). In the majority of studies, patients are categorized into 3 categories, namely hematologic, solid, and brain malignancies (Antillon et al., 2013). It is observed that patients in the ALL group were overweight more often than the rest of the study group (Połubok et al., 2017). It is important to highlight that the time of cancer development is not the same for all diagnoses. If cancer develops more rapidly (e.g. hematological malignancies against solid tumors) the shortage of weight is lower, thus there is not enough time to develop severe nutrition deficiencies (Połubok et al., 2017).

Improving NS is childhood cancer patients has the potential to impact on the outcome, regarding morbidity and mortality as well as QOL (Barr, 2015; Rogers et al., 2015). Identifying alterations in NS and managing it is still challenging for the following reasons. Data available on the prevalence of poor NS at diagnosis and at the different phases of the disease are highly inconsistent among pediatric patient groups along with developed and developing countries. Furthermore, the diversity of definitions for malnutrition and the methodology used to assess NS regarding criteria and cut-off points makes it very difficult to accurately estimate the prevalence of cancer related malnutrition (Diakatou et al., 2020). In addition, practical guidelines or nutrition care models to prevent and treat malnutrition are scarce and recommendations apply for adult cancer patients (Muscaritoli et al., 2021; Sirvent-Ochando et al., 2021).

5.2. Screening malnutrition

Both previous and recent studies have investigated the issue of weight change in children diagnosed with cancer. Most authors assessed the NS by analyzing BMI, mid-upper arm circumference (MUA, triceps skinfold thickness (TSFT), and arm muscle circumference (AMC). Based on their results it can be concluded that despite adequate BMI, the other 3 parameters presented malnutrition. In the study of Maia-Lemos the overall prevalence of undernutrition was 10.8%, 27.3%, 24.5% and 13.6%, based on BMI, TSFT, MUAC, and AMC respectively (Maia-Lemos et al., 2016). Similarly, in a large Indian study the prevalence of undernutrition at the time of diagnosis was very high, ranging from 40–80% depending on the method used for assessment, being highest with MUAC and lowest with BMI (Shah et al., 2015). In an Italian study nutritional risk has been assessed with SRONGkids and BMI Z-scores. The analysis showed that all patients were at risk for malnutrition at diagnosis. 90 patients (71.4%) presented a moderate risk (STRONGkids 2 or 3), whereas the other 36 (28.6%) were at high risk (STRONGkids 4 or 5). However, based on BMI Z-scores 16 patients (12.7%) presented mild undernutrition, 2 patients (1.6%) presented moderate and 4 patients (3.1%) showed severe undernutrition (Triarico et al., 2019). Nutritional assessment at the time of diagnosis, is probably the most appropriate time to prevent the deterioration of NS since malnutrition worsens as the disease progresses, consequently the longer the diagnosis is delayed, the higher the risk of malnutrition. Although there is no gold-standard for assessing NS, it is advisable not to rely on BMI alone, but to utilize complementary measurements e.g. anthropometric, BIA or even malnutrition risk screening tools (Sala et al., 2004; Sala et al., 2012; Eys, 1998; Maia-Lemos et al., 2016).

In the second part of our study on pediatric cancer patients we provided a comparative analysis of the already validated SCAN, our self-developed NRS-PC score system and bio-impedance measures, the latter of which present objectively measured body composition parameters owing to a modern clinically used device.

It is known that among pediatric oncology patients the prevalence of malnutrition is high (Martin et al., 2006; Co-Reyes et al., 2012). Therefore, screening for malnutrition risk to identify and triage patients who need further assessment and nutritional intervention may contribute to the solution of this problem. It is vital to have a

nutritional screening tool which is quick, easy to use and can be performed by the nursing staff, since in busy pediatric hospitals and oncology units dieticians have limited capacity and in some centers NSTs might not be available.

There are certain validated nutrition screening tools for pediatric patients as it was mentioned before e.g. STRONGkids, PYMS, STAMP, PNST etc., however, these have been designed for general patients (Huysentruyt et al., 2013; Gerasimidis et al., 2011; McCarthy et al., 2012; White et al., 2016). STRONGkids, which is highly recommended in the European Union - since it is fast and easy to use -, can also be used in case of general pediatric diseases. According to STRONGkids all cancers belong to the „medium risk" category, thus it does not distinguish malnourished cancer patients (Huysentruyt et al., 2013).

Prior to 2012 only weight loss was considered as an indicator of malnutrition risk, but there was no nutrition assessment at our hospital. In 2012 with the foundation of the nutrition support team (NST) we started to develop our own disease specific malnutrition risk screening tool in order to find a quick and simple process to identify children who are malnourished or at risk of malnutrition. This is essential in case of pediatric cancer patients to be able to decide who is in need of further assessment, dietetic counsel, oral nutritional supplementation or any other nutritional intervention. In our second study we aimed to assess whether NRS-PC is suitable for these purposes and could be used at any phase of the disease. Since SCAN was already available during our study period it was possible to use both SCAN and NRS-PC on our sample.

Previously, SCAN was evaluated against pediatric SGNA, in that study 32 subjects were involved, whereas in our study the data of 109 patients were analyzed (Murphy et al., 2016). In Murphy's SCAN article air displacement plethysmography - Body Pod Body Composition System - was used to measure body volume, fat mass and fat free mass, whereas we used bio-impedance measures and InBody body composition devices. In a 2019 study these methods were compared to dual energy x-ray absorptiometry (DXA) and was concluded that both Body Pod and InBody 770 overestimate fat free mass and underestimate fat mass and percent body fat (Antonio et al., 2019). This

however, does not influence our results. Relying on this information and the cited article, both methods are acceptable for body composition analysis.

5.3. Developing a screening algorithm

Prior to 2016, until the validation of SCAN there was no available screening tool for pediatric cancer patients, therefore we have started to develop NRS-PC. First and foremost, we wanted to compare SCAN and our NRS-PC questionnaire in order to decide which was more sensitive to identify patients with reduced muscle mass. Although body composition studies in pediatric cancer are limited and existing literature in this area has largely focused on hematologic malignancies, it is known that the loss of muscle mass adversely affect clinical outcome and survival both in adult and pediatric cancer patients (Rier et al., 2016; Joffe et al., 2019). Our results indicated that NRS-PC has better classifier properties to identify children with lower muscle mass. However, evaluating the NRS-PC and SCAN at the different phases of the disease we found that they did not differ from each other significantly. Regarding the three BMI categories (low, normal, high) there were no significant differences between them, although in the low and normal BMI groups the DeLong test approached significance (Gallo et al., 2021).

As children in the low BMI category were almost all at high risk and as the ROC curve of NRS-PC does not show appropriate validity to identify those who have low muscle mass, we suggest bio-impedance measures in every patient with low BMI. In our sample, there were only two children who had normal muscle mass in spite of their low BMI (Gallo et al., 2021).

In case of normal BMI, we need further studies to assess whether the NRS-PC is sensitive enough to identify approximately all patients with low muscle mass. In our sample, a first screening with NRS-PC would result in overlooking 13 children with low muscle mass. However, out of the 13 children, 3 did have normal muscle mass at the subsequent assessment, 1 had similarly low muscle mass and we did not have data from the other 9. Existing literature reinforces that during the course of cancer therapy body composition can change considerably (Murphy et al., 2015; Brinksma et al., 2015; Suzuki et al., 2018; Yang and Chois 2019). Therefore, longitudinal data would be

advantageous to decide whether it is safe to rely on NRS-PC without bio-impedance measures (Gallo et al., 2021).

In the high BMI group, we suggest screening with NRS-PC first. None of the patients with low muscle mass would have been undetected in our sample with this strategy, and out of the three children who were identified being at high risk, at the subsequent assessments two had low muscle mass (Gallo et al., 2021).

As a conclusion we suggest screening high BMI patients first with NRS-PC. However, in case of low BMI bio-impedance measures provide more precise information on muscle mass and nutritional risk. Further data are needed to decide whether the NRS-PC is sensitive enough in case of normal BMI patients (Gallo et al., 2021). See Figure 11 for an overview of assessing nutritional status and a recommended algorithm.

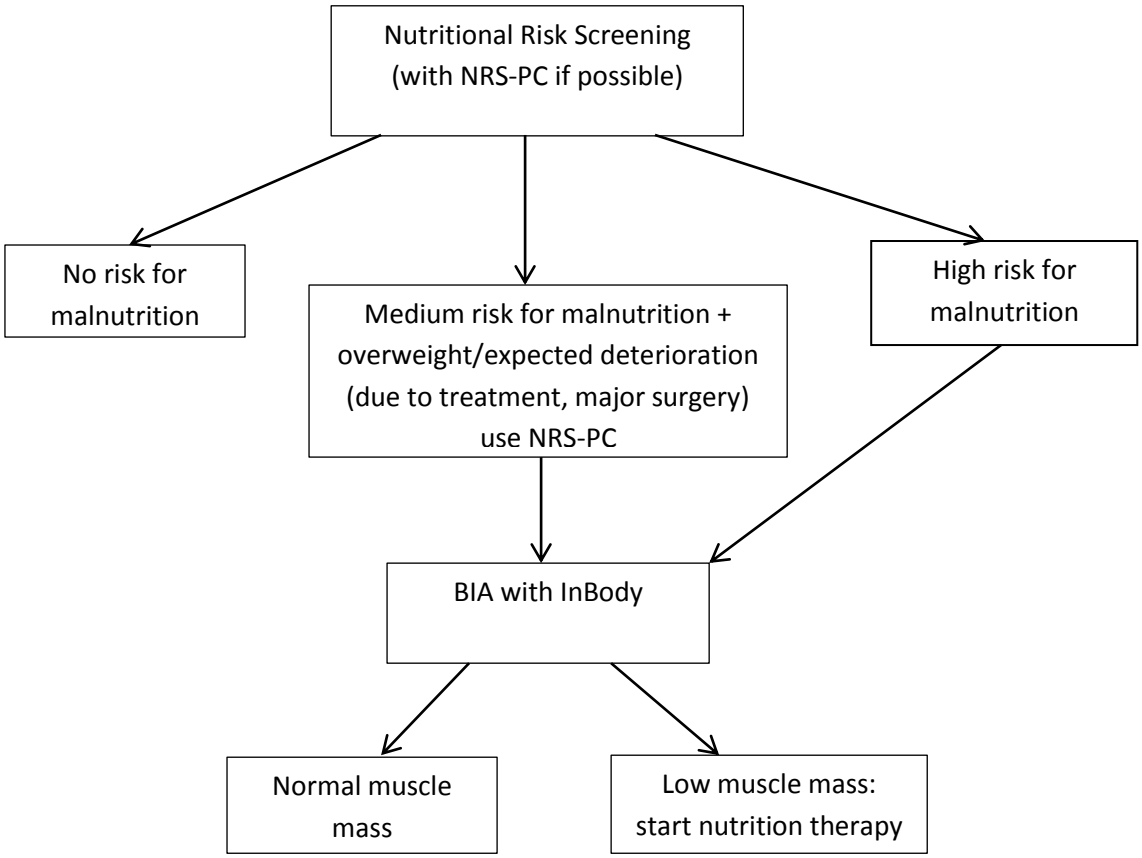

Figure 11. Assessing nutritional status algorithm

5.4. Disease progression and survival

In the first part of our study we investigated two similar periods; the only difference was regular malnutrition risk screening and intensified nutrition support, which was provided by a professional team in *Period 2*. The focus of our study was on disease progression and survival in pediatric patients with solid tumors undergoing chemotherapy. In *Period 1* dietetic counsel was given only to the very severely malnourished patients based on the subjective judgment of the pediatric physician, since no nutrition risk screening tools were applied. In this period, the physician decided on the nutrition therapy – when to start it and how it should be provided. In *Period 1* parenteral nutrition was preferred during hospital stay since it was easier to administer through the central vein catheter (Gallo et al., 2022).

In *Period 2* nutrition therapy was the responsibility of the NST and the decision was made after the consideration of other important factors (e.g. the condition of the digestive tract). Since 2012 our self-developed nutrition status screening sheet (NRS-PC) was used to evaluate malnutrition risk and to decide on further assessment or interventions. Our study would highlight the importance of NSTs work in pediatric units, where cancer patients are treated (Gallo et al., 2022).

Comparing the two study periods differences have been found in the length of time from diagnosis to end of treatment, in the presence of antimycotic treatment and in the type and length of nutrition therapy. During *Period 2*, using our own screening tool a higher prevalence of malnutrition risk have been found 65.3% compared to the results of the EuroOOPS study group which was 32.6% (Sorensen et al., 2008). However, it has to be noted that in that international multicenter study NRS-2002 was used to assess malnutrition risk and the patient population was more heterogeneous. In another study 45% of pediatric patients with cancer were considered malnourished based on body cell mass (Murphy et al., 2010; Gallo et al., 2022).

Time from the beginning to the end of treatment was significantly shorter and there were significantly two times less need for antimycotic treatment in *Period 2* compared to *Period 1*. Former studies also confirm that poor nutritional status is associated with

higher risk of hospital acquired infections (Co-Reyes et al., 2012; Bechard et al., 2016). Nutrition support provided for critically ill and adult cancer patients has been proved to be of key importance in previous studies as well. In order to maintain muscle mass, which is inversely associated with the length of hospital stay, lower survival rate, infections and lower quality of life, nutrition support is essential (Bechard et al., 2016; Arends et al., 2016, Gallo et al., 2022).

We expected to prove that nutrition therapy was significantly more effective in patients with high risk tumors. Furthermore, it was also assumed we could detect differences between the two periods in the number of hospital admissions, however, no significances were found. It is clear that in *Period 1* if nutrition therapy was needed, and it was mainly provided in the form of parenteral nutrition. However, according to the ESPEN guideline on the nutrition in cancer patients the enteral route would be preferred whenever it is possible (Arends et al., 2016). When malnutrition risk is not discovered early enough, enteral nutrition may not be feasible.

Survival rate was better, although not significant in *Period 2* compared to *Period 1*. This result is in line with previous studies which have already described the positive effect of appropriate nutritional status on the disease outcome (Caro et al., 2007). It is assumed that longer follow-up, a larger sample of patients and further research in the future would help make this difference significant.

Our data shows that malnutrition effects survival because if weight loss occurs during the treatment, survival is significantly worse. During *Period 1* there was no NST, and those who died had 3-times larger odd for a decrease in weight-for-height percentiles during the treatment. In *Period 2*, with the help of the NST the weight loss of those who died and surviving children were similar.

It is known that in case of CNS tumors the prevalence of malnutrition is high, which may contribute to an increased risk for mortality (Ravasco et al., 2003; Daren et al., 2016). Our survival analysis revealed that the presence of CNS tumor means increased mortality as it was shown on Figure 6A; however taking the multivariable model into consideration this difference is no longer significant.

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The results of this retrospective study demonstrate the need for regular malnutrition risk screening and NSTs. We believe that due to the nutrition support team's efforts, including regular nutritional status screening, malnutrition risk evaluation, timely and closely monitored nutrition therapy enable better disease control and outcome (Gallo et al., 2022).

Our results indicate the need for professional NSTs in large pediatric oncology units treating a great number of patients, since nutrition therapy cannot be planned individually or implemented appropriately without them. This may seem to be only a small step; however it is worth fighting against malnutrition in order to ensure better life prospects for children with cancer (Gallo et al., 2022).

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5.5. Limitations

In this single center study during the research period we had a limited number of patients who could be involved. We could not collect longitudinal data however, it would have been beneficial to follow patients from the diagnosis until the completion of their treatment in order to further evaluate the use and accuracy of the NRS-PC.

Although it was a relatively large-scale study, in which a relatively homogenic group of pediatric tumor patients were investigated, data was collected retrospectively in a single center. More patients could have been included from other departments or the time of our research may have been extended, however, by doing so the comparability of the two periods and the homogeneity of the patients would have decreased, and thus the impact of the nutrition support team could not have been evaluated.

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6. Conclusions

Assessing the nutritional status of pediatric cancer patients is proved to be very useful and can contribute to the necessary dietetic interventions. However, using specific screening tools and following a screening algorithm facilitates the assessment and provides more accurate information based on which better nutritional care can be administered.

In the first part of our research we intended to determine whether malnutrition risk screening and intensified nutrition support, provided by a professional nutritional team (NST), promoted disease progression and survival in pediatric patients with solid tumors. While patient characteristics and treatment protocols were identical in the two compared periods the presence of the nutritional support team and compulsory malnutrition risk screening were only available in *Period 2.* As a result of intensified nutrition support the time from diagnosis to completion of treatment and the need for antimycotic treatment reduced significantly. The total percentage of surviving children was 60.3% and 75.0% in *Period 1* and *2* respectively. Decrease in weight-for-height percentile during treatment and central nervous system tumors are significant predictors of a less favorable survival. We can conclude that malnutrition risk screening and intensified nutrition therapy have positive effects on NS and therefore patient survival in pediatric cancer patients.

In the second part of our study we aimed to present our self-developed nutritional risk screening method (NRS-PC), which we related to another validated tool (SCAN) and to objective bio-impedance measures. Based on our results, NRS-PC proved to have better classifier properties to identify children with lower muscle mass, therefore we can recommend it to be used as part of a screening algorithm at pediatric oncology facilities. As it was discussed in various studies it is of key importance to identify all children at risk of malnutrition, thus sensitivity should be prioritized over specificity. The prevalence of malnutrition among pediatric cancer patients is high as it was confirmed by a number of previous studies, and it cannot be determined by relying on the BMI of the patients. Therefore, further and more specific methods should be utilized. We managed to demonstrate that in case of low BMI patients bio-impedance measures are

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recommended, whereas in patients with high BMI, screening with NRS-PC first would be suggested.

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7. Summary

Cancer is one of the leading causes of childhood deaths; globally more than 300,000 cases are registered per year, including approximately 200-250 new cases in the 0-18 age group in Hungary. Nearly 50% of the patients are treated at the 2nd Department of Pediatrics, Semmelweis University. Many types of childhood tumors are associated with a high risk of malnutrition. A screening method specifically validated for children with tumors has only been available since 2016, whereas guidelines on nutrition therapy have only been developed for adult patients.

Malnutrition, or the risk for malnutrition, which can be low, moderate or high already exists in a significant percentage of patients at the time of diagnosis, thus recognizing this is particularly important. Body weight, height, and body mass index alone are not sufficient to recognize malnutrition or its risk. Therefore, the literature suggests special screening methods, anthropometric and body composition measurements.

Based on our experience, screening at hospital admission and also during anti-cancer treatment is also essential, for this purpose NRS-PC could be used. If the risk for malnutrition is moderate or severe BIA measurement is also recommended. Evaluating nutritional status thus determines the need for nutritional therapy, regarding its amount and the method of administration. Timely and adequately provided clinical nutrition is an essential part of the effective treatment and patient care, ideally overseen and carried out by a multidisciplinary nutrition therapy team. According to international experience, a physician, dietician, pharmacist, and other health care professionals (e.g. physiotherapist, nurse) experienced in nutrition therapy should be members of the nutrition team.

If we can maintain and preserve the optimal nutritional status or at least prevent the deterioration of NS in case of pediatric oncology patients throughout the different phases of the disease, we can have a positive effect on the course of the disease, survival and on the quality of life as well.

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8. Összefoglalás

A daganatos megbetegedések a gyermekkori halálesetek egyik vezető oka; éves szinten világszerte több mint 300.000 esetet, Magyarországon évente kb. 200-250 új esetet regisztrálnak a 0-18 éves korosztályban. Ezen betegek közel 50%-a a Semmelweis Egyetem 2-es számú Gyermekgyógyászati Klinikáján kerül ellátásra. A gyermekkori tumoros megbetegedések számos típusa magas alultápláltsági rizikóval jár. Kifejezetten tumoros gyermekekre validált szűrőmódszer csak 2016 óta létezik, táplálás terápiára vonatkozó útmutató pedig eddig csak felnőtt beteg ellátására készült.

Az alultápláltság, vagy annak különböző fokú rizikója már a diagnózis felállításakkor is a betegek jelentős százalékánál fennáll, ezért ennek felismerése különösen fontos. A testúly, a testmagasság és a testömeg index önmagukban nem elegendőek ahhoz, hogy az alultápláltság vagy annak rizikója felismerésre kerüljön. Ennek érdekében speciális szűrőmódszereket, antropometriai-, illetve testösszetétel méréseket javasol a szakirodalom.

Tapasztalatunk szerint a kórházi felvételkor történő szűrés és kezelések alatti nyomonkövetés is elengedhetetlen, erre a célra az általunk fejlesztett NRS-PC is használható. Ha az alultápláltság kockázata közepes vagy súlyos, BIA mérés is javasolt. Az így meghatározott tápláltsági állapot alapján véleményezhető a táplálás terápia szükségessége, annak mennyisége és módja. Az időben megkezdett, adekvát klinikai táplálás tehát a hatékony gyógyító munka nélkülözhetetlen része, melyet ideális esetben a multidiszciplináris táplálás terápiás munkacsoport felügyel és hajt végre. Nemzetközi tapasztalatok alapján táplálás terápiában jártas orvos, dietetikus, gyógyszerész, és egyéb egészségügyi szakdolgozók (pl.: gyógytornász, nővér) kell, hogy a táplálási team tagjait alkossák.

Eredményeink szerint amennyiben meg tudjuk őrizni és fenn tudjuk tartani a tumoros beteg gyermekek optimális tápláltsági állapotát, illetve legalább meg tudjuk előzni a tápláltsági állapot romlását a betegség kezdetétől a végéig, azáltal mindenképpen kedvező hatást tudunk gyakorolni a betegség lefolyására és a túlélésre, valamint az életminőségre egyaránt.

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10. Bibliography of the candidate's publications

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Original article

Different nutritional screening tools and recommended screening algorithm for pediatric oncology patients

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SUMMARY

Background & aims: Cancer is one of the leading causes of death for children; however, appropriate nutritional status can positively affect disease progression and outcome. The aim of this study was to present our self-developed nutritional risk screening method, relate it to another validated tool and to objective bio-impedance measures. We intended to recommend a screening algorithm which can be used in our pediatric oncology facilities.

Methods: We analysed data from 109 pediatric oncology patients (age 3–18) at the 2nd Department of Pediatrics, Semmelweis University between 2017 and 2018. The nutritional status was assessed by the Nutrition screening tool for childhood cancer (SCAN), Nutrition risk screening for pediatric cancer (NRS-PC) our own self-developed screening tool and Bio-impedance analysis (InBody 720 and S10). Classifier properties for low muscle mass measured by Bio-impedance analysis were compared for SCAN and NRS-PC in the overall sample and in the different phases of the disease.

Results: The AUC of 0.67 [95% CI:0.58,0.75] of the SCAN was significantly lower ($Z = -2.46$, $p = 0.014$) than in the case of the NRS-PC (AUC = 0.75 [95% CI:0.67,0.82]), indicating that NRS-PC has better classifier properties to identify children with lower muscle mass. No significant difference was found in the different phases of the disease.

Conclusions: Based on our results, we suggest screening high BMI patients first with NRS-PC. However, in case of low BMI bio-impedance measures provide more precise information on muscle mass and nutritional risk. Further data are needed to decide whether the NRS-PC is sensitive enough in normal BMI patients.

1. Introduction

Cancer is one of the leading causes of death for children, with approximately 300,000 new cases diagnosed each year among children aged 0–19 years [1,2]. The aim of WHO's Global Initiative for Childhood Cancer, which was announced in 2018 September, is to reach at least 60% survival rate by 2030 [3]. In order to achieve better clinical outcome appropriate nutritional screening and therapy are required as it has been suggested in a number of previous studies. Similarly to adult cancer patients these studies have revealed that optimising nutritional status of the patients have a positive effect on event free survival, treatment toxicity and quality of life as well [1,2,4]. Since there are no specific clinical nutrition guidelines on how to assess the nutritional state and how to provide adequate nutrition support for pediatric cancer patients, it can be challenging for professionals.

It has been long ascertained that the nutritional status in case of chronic wasting diseases, especially in case of childhood cancer, does influence the outcome of the disease, the course of the therapy, including treatment tolerance and infection risk, not to mention the quality of life and the cost of care [5,6]. It is also known that the tumour itself means a risk for malnutrition, especially in case of children. The most common categories of childhood cancers include leukaemia, brain tumors, lymphomas and solid tumours [7]. Several types of childhood cancers are associated with high

Abbreviations: SCAN, Nutrition screening tool for childhood cancer; NRS-PC, Nutrition risk screening for pediatric cancer; BIA, Bio-impedance analysis; AUC, area under the curve; ROC, receiver-operator characteristics; BMI, Body mass index; NST, Nutrition support team; LBM, Lean body mass.

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nutritional risk (e.g. AML and ALL - prevalence 33%, Brain and spinal tumors - prevalence 26%, Wilm's tumor Stage III and IV. – prevalence 5% Ewing-, and Osteosarcoma - prevalence 4%) since due to aggressive treatment protocols (surgery, stem cell transplant, chemo-, radiation therapy), which patients have to endure, nutritional status declines and thus the risk for malnutrition increases significantly.

It is already known that pediatric oncology patients tend to have lower fat free mass (FFM) at diagnosis and remains low during the treatment [8,9]. The decrease in fat free mass is often accompanied by increased fat mass, which strongly correlates with low or reduced physical activity [8,9]. Relying on BMI alone is misleading since it does not show the underlying body composition changes; therefore assessing the body composition is essential.

In the ESPEN Guideline on nutrition in cancer patients it is highlighted that weight loss and decrease in BMI negatively influence survival. The grading scheme (grades 0–4) predicts overall survival, where 0 means best, 4 means worst prognosis [10]. Another study suggested that 71.7% of the body mass loss was lean body mass (LBM) [11].

Although a number of screening tools have been developed, mainly for general pediatric patients, none of them met the specific requirements of pediatric cancer patients. Later in 2016 SCAN was published [12], the validity of which was tested against pediatric subjective global nutritional assessment (SGNA). In the present study we aimed to validate both SCAN and our self-developed screening tool (NRS-PC) to bio-impedance measures. As it was mentioned above, bio-impedance measures can assess the body composition (including fat free mass and fat mass) and it is of key importance when we decide on the nutrition therapy of children with cancer. The aim of our research was also to create a screening algorithm which would help professionals decide which screening method to use and when to use them.

2. Material and methods

In this study we analysed data from 109 pediatric oncology patients (age 3–18) at the 2nd Department of Pediatrics, Semmelweis University (Budapest, Hungary) who were inpatients between 2017 and 2018. Data were collected during the different phases of the disease: *Diagnosis* (the time between histological sampling and the initiation of cancer treatment – usually a couple of days or maximum few weeks), *Active treatment* (intensive chemotherapy until the last day of intravenous chemotherapy), *Maintenance* (oral low-dose chemotherapy mostly in leukemias and some soft tissue sarcomas) and *Post therapy* (during the follow-up period, after completing all therapies) with the approval of the Hungarian Scientific and Research Ethics Committee (number: 86,748/AOGY2/2016). During the study period, in total 156 bio-impedance measures were done, however some patients were measured more than once, but only if they proceeded to the next phase of the disease. 14 of the patients had a disease relapse, which means the reappearance of their malignancy.

Bio-impedance measures were performed by a clinical dietician who is also member of the nutrition support team. Patients were on an empty stomach; those who were physically fit enough to stand alone for 1.5 min were measured by InBody 720, and those who were not, were measured by InBody S10 in a seated position (InBody Co. Ltd. 13,850 Cerritos Corporate Drive, Unit C, Cerritos, CA 90703).

Recorded parameters were the following: name, age (date of birth), diagnosis, date of the measurement, phase of the disease, weight, height (using standardized scales and stadiometers); calculated parameters were: SCAN score and NRS-PC score. BMI and body composition parameters including muscle mass and body fat percentage were determined by the InBody devices. BMI, muscle mass and body fat percentage were compared against normal range values. Three categories were set up regarding BMI, muscle mass and body fat mass: low, normal, and high which were also determined and provided by the InBody devices.

Three different screening tools were used to assess the nutritional status of the patients:

SCAN: nutrition screening tool for childhood cancer is a simple and quick tool to identify children with cancer who are at risk of malnutrition. It was validated and published in 2016. SCAN includes six Yes or No questions and if the total score is ≥ 3 it means being at risk of malnutrition. The patient has to be referred to a dietician for further assessment (For further details see Appendix 1).

NRS-PC: nutrition risk screening for pediatric cancer, which is our self-developed screening tool. Similarly to SCAN it is also an easy-to-use questionnaire with a score system. Apart from six questions regarding weight loss, physical activity, change in nutrition habits, stool and other gastrointestinal symptoms the BMI percentiles are also taken into consideration (For further details see Appendix 2). Scores are given according to the number of positive answers (Questions 1–6).

BIA Bioelectrical Impedance Analysis is used to measure body composition. InBody 720 and S10 are medical-grade body composition analyzers, which rely on four technological milestones (8-point tactile electrode system, direct segmental measurements, multiple frequencies, no estimations) to provide accurate and precise results that are highly correlated to gold-standard methods [13]. Our final results included three categories (low, normal or high) regarding BMI, muscle mass and body fat percentage (one by one) that has been shown to determine body composition independently of age, ethnicity or gender.

One of our primary goals was to evaluate NRS-PC to muscle mass measured by bio-impedance analysis. Based on these measures two categories were created: low muscle mass and normal or high muscle mass. The individual muscle mass values were defined by the body composition analysis, provided by InBody 720 or S10 devices. A receiver-operator characteristic curve was used to assess the relationship between muscle mass category and the different cut-off scores of the NRS-PC. The area under the curve (AUC) was calculated to measure classifier performance.

2.1. Statistical analysis

Descriptive statistics were used for the presentation of demographic data. A receiver-operator characteristic curve was used to assess the relationship between SCAN, NRS-PC and bio-impedance measures. To compare children who were at low and at high risk for malnutrition according to NRS-PC we used Chi-square test (categorical variables) and t-test (continuous variables). Significance was set at $p < 0.05$. All statistical analysis was done in R (version 3.6.1), for receiver-operator characteristic curve analysis, ROCR and epiR packages were used.

3. Results

The data of 109 patients were analyzed (n = 64 males). Some of the children underwent repeated assessments at different phases of their disease (see Table 1). 77 patients went through one assessment, 21 two and 11 patients three assessments. Children had a mean age of 11.3 years (range: 3–21 years, SD = 4.8 years). The incidence of the different tumor types can be seen is Table 2. 14 of the patients had a disease relapse.

Table 1
The characteristics of the study subjects.

Phase of the disease	Number of cases (n =)	Male: Female ratio	Age (years)	Lost patients (n =)	Relapse (n =)	SCAN score	NRS-PC score
Diagnosis	44	29:15	10.5 ± 3.5	1	9	3.4 ± 2.0	1.0 ± 1.3
Active treatment	36	22:14	14.5 ± 3.5	4	1	3.4 ± 1.6	1.2 ± 1.3
Maintenance	34	19:15	9.5 ± 4.5	0	0	2.9 ± 1.7	0.5 ± 1.0
Post therapy	36	22:14	11.5 ± 2.5	1	4	1.7 ± 1.4	0.4 ± 0.9

Data are expressed as mean ± SD.

Table 2
The incidence of different tumor types.

Tumor types	Number of patients (n =)
ALL	39
AML	6
Ewing sarcoma and Osteosarcoma	23
Brain and spinal tumors (Medulloblastoma, Neuroblastoma, PNET – Central nervous system)	21
Other (Wilms-tumor, Hepatoblastoma, Melanoma, Colon cancer etc.)	20

3.1. Validation of NRS-PC to SCAN

As a first step, NRS-PC was compared to SCAN, a validated nutrition assessment tool used in pediatric oncology, to identify cut off scores for NRS-PC. According to Murphy et al. (2016), a child was classified at risk of malnutrition if the SCAN score was equal or greater than three. A receiver-operator characteristic curve was used to assess the relationship between SCAN and the different cut-off scores of the NRS-PC. The area under the curve (AUC) showed a high classifier performance (AUC = 0.9) (Fig. 1). A cut off score of one on the NRS-PC resulted in 98% [95% CI: 90, 100] sensitivity, 62% [95% CI: 51, 71] specificity, a positive predictive value of 58% [95% CI: 47, 68] and a negative predictive value of 98% [95% CI: 91, 100]. This means that in our sample one child considered malnourished by the SCAN would have been undetected with our questionnaire. A cut off score of two would decrease the sensitivity to 86% [95% CI: 77, 93], while increasing the specificity to 77% [95% CI: 65, 86]. As we aimed to identify all children at risk of malnutrition sensitivity was prioritised over specificity.

4. Evaluation of NRS-PC to bio-impedance measures

In order to evaluate NRS-PC to muscle mass measured by bio-impedance analysis low muscle mass and normal or high muscle mass categories were set up. A ROC curve was used to assess the relationship between the muscle mass category and the different cut-off scores of the NRS-PC. The area under the curve (AUC) was calculated to measure classifier performance. Sensitivity, specificity, negative and positive predictive values were calculated to each cut-off score and were reported in Table 3. Ideally, a measurement tool should have a 100% sensitivity to identify every child who has low muscle mass. A cut off score of one would give a sensitivity of 75% with 60% specificity. In our sample, this means that 13 children would have been incorrectly classified to the group of normal muscle mass, while 40 children would be incorrectly classified to the low muscle mass group.

4.1. Comparison of NRS-PC and SCAN predictive value regarding muscle mass

To evaluate whether the SCAN or the NRS-PC questionnaire was a more sensitive tool to identify patients with reduced muscle mass, we did ROC analysis and compared the AUC values of both questionnaires with the DeLong method. The AUC of 0.67 [95% CI: 0.58, 0.75] of the SCAN was significantly lower (Z = −2.46, p-value = 0.014) than in the case of the NRS-PC (AUC = 0.75 [95% CI: 0.67, 0.82]), indicating that NRS-PC has better classifier properties to identify children with lower muscle mass (Fig. 2).

4.2. Evaluating the NRS-PC and SCAN at different phases of the disease

Patients were assessed at different phases of the course of their treatment. The description of the four phases and the number of participant in each case are shown in Table 4. To assess whether the classifier performance of NRS-PC differs at the different phases of the treatment, ROC analysis was performed. The AUC values at the different phases did not differ significantly from each other.

4.3. Evaluating BMI categories

Classifier performance of both questionnaires was evaluated in the three BMI categories separately. There were no significant differences in the AUC values of the two screening tools, however, in the low and normal BMI groups the result of the DeLong test approached significance. In the low BMI group, SCAN had better classifier properties, whereas in the normal BMI group, NRS-PC seemed to be better. Nevertheless, neither of the tests had sufficient sensitivity in the low BMI group (see Tables 5 and 6).

4.4. Comparing children under and over NRS-PC cut-off

Comparing children at low risk for malnutrition to those at high risk according to NRS-PC no significant differences were found in gender, the proportion of patients after relapse or age. However, there was a significant difference in the phase of the disease and the

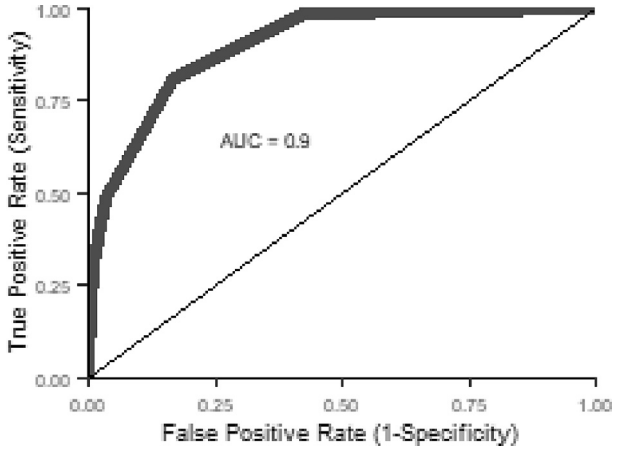

Fig. 1. ROC curve demonstrating the predictive value of NRS-PC to SCAN with a cut off score of 3.

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Table 3
Validation of NRS-PC to muscle mass. 95% confidence intervals are in [].

Cut off score	Sensitivity	Specificity	Negative predictive value	Positive predictive value
1	0.75 [0.62, 0.86]	0.6 [0.49, 0.69]	0.82 [0.71, 0.9]	0.5 [0.39, 0.61]
2	0.7 [0.59, 0.79]	0.71 [0.58, 0.81]	0.64 [0.52, 0.75]	0.76 [0.65, 0.85]
3	0.62 [0.53, 0.71]	0.82 [0.65, 0.93]	0.38 [0.26, 0.5]	0.92 [0.84, 0.97]
4	0.59 [0.5, 0.68]	0.9 [0.68, 0.99]	0.25 [0.16, 0.37]	0.97 [0.91, 1]
5	0.54 [0.45, 0.62]	1 [0.29, 1]	0.04 [0.01, 0.12]	1 [0.95, 1]

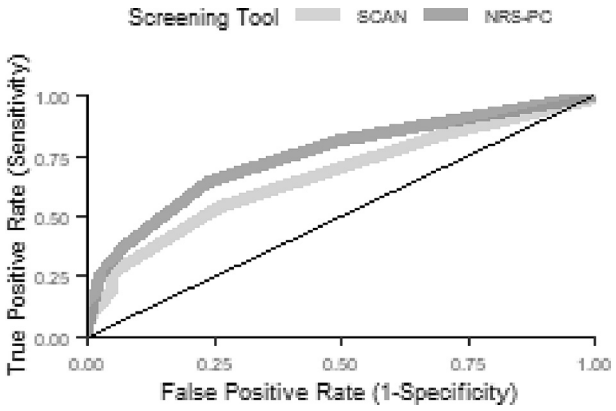

Fig. 2. ROC curve demonstrating the predictive value of the SCAN and the NRS-PC for low muscle mass. The AUC of NRS-PC (0.75) was significantly larger than the AUC (0.67) of SCAN.

BMI category of the patients. There were more high risk patients in phases 1–3, whereas less in phase 4. It is also clear that children in the low BMI category were almost all at high risk (except for 3 patients) for having low muscle mass.

5. Discussion

In the current study on pediatric cancer patients we provide a comparative analysis of the already validated SCAN, our self-developed NRS-PC score system and bio-impedance measures, the latter of which present objectively measured body composition parameters owing to a modern clinically used device.

It is known that among pediatric oncology patients the prevalence of malnutrition is high [14,15]. Therefore, screening for malnutrition risk to identify and triage patients who need further assessment and nutritional intervention may contribute to the solution of this problem. It is vital to have a nutritional screening tool which is quick, easy to use and can be performed by the nursing staff, since in busy pediatric hospitals and oncology units dieticians have limited capacity and in some centers NSTs might not be available.

There are certain validated nutrition screening tools for pediatric patients e.g. STRONGkids, Pediatric Yorkhill Malnutrition Score (PYMS), Screening Tool for Assessment of Malnutrition in Pediatrics (STAMP), Pediatric Nutrition Screening Tool (PNST), Subjective Global Nutritional Assessment (SGNA) however, these have been designed for general patients [16–20]. STRONGkids, which is highly recommended in the EU - since it is fast, and easy to use - can also be used in case of general pediatric diseases. According to STRONGkids all cancers belong to the „medium risk" category, thus it does not distinguish malnourished cancer patients [16].

Prior to 2012 only weight loss was considered as an indicator of malnutrition risk, but there was no nutrition assessment at our hospital. In 2012 with the foundation of the nutrition support team (NST) we started to develop our own disease specific malnutrition risk screening tool in order to find a quick and simple process to identify children who are malnourished or at risk of malnutrition. This is essential in case of pediatric cancer patients to be able to decide who is in need of further assessment, dietetic counsel, oral nutritional supplementation or any other nutritional intervention. In this study we aimed to assess whether NRS-PC is suitable for these purposes and could be used at any phase of the disease. Since SCAN was already available during our study period it was possible to use both SCAN and NRS-PC on our sample. Previously, SCAN was evaluated against pediatric SGNA, in that study 32 subjects were involved, whereas in our study the data of 109 patients were analysed [12]. In Murphy's SCAN article air displacement plethysmography - Body Pod Body Composition System - was used to measure body volume, fat mass and fat free mass, whereas we used bio-impedance measures and InBody body composition devices. In a 2019 study these methods were compared to dual energy x-ray absorptiometry (DXA) and was concluded that both Body Pod and InBody 770 overestimate fat free mass and underestimate fat mass and percent body fat [21]. This however, does not influence our results. Relying on this information and the cited article, both methods are acceptable for body composition analysis.

5.1. Developing a screening algorithm for the nutritional status of pediatric oncology patients

First and foremost, we wanted to compare SCAN and our NRS-PC questionnaire in order to decide which was more sensitive to identify patients with reduced muscle mass. Although body composition studies in pediatric cancer are limited and existing literature in this area has largely focused on hematologic malignancies, it is known that the loss of muscle mass adversely affect clinical outcome and survival both in adult and pediatric cancer patients [22,23]. Our results indicated that NRS-PC has better classifier properties to identify children with lower muscle mass. However, evaluating the NRS-PC and SCAN at the different phases of the disease we found that they did not differ from each other

Table 4
Comparison of SCAN and NRS-PC at different phases of the disease.

Description	Number of cases	NRS-PC AUC	SCAN-AUC	Z	p
Assessment after diagnosis	44	0.67 [0.49 0.86]	0.62 [0.45 0.8]	0.88	0.381
Active treatment	36	0.78 [0.63 0.93]	0.7 [0.53 0.86]	1.29	0.196
Maintenance	35	0.77 [0.62 0.93]	0.64 [0.46 0.81]	1.8	0.072
Assessment post therapy	37	0.82 [0.67 0.96]	0.67 [0.49 0.84]	1.57	0.115

Table 5
Comparison of SCAN and NRS-PC at different BMI categories.

	Number of cases	NRS-PC AUC	SCAN-AUC	Z	p
Low	27	0.5 [0.22 0.78]	0.62 [0.31 0.93]	−1.86	0.063
Normal	99	0.72 [0.61 0.81]	0.64 [0.54 0.75]	1.75	0.081
High	25	0.83 [0.54 1]	0.74 [0.22 1]	0.77	0.439

Table 6
Comparison of low and high nutritional risk patients (based on bio-impedance measurements). For categorical variables, chi square tests, for age independent samples t-test were used for comparison.

		Low risk	High risk	p
Gender	Male	37	56	0.150
	Female	16	43	
Relapse	No	47	91	0.720
	Yes	6	8	
Phase	1	10	34	<0.001
	2	7	29	
	3	13	22	
	4	23	14	
BMI category	Low	3	24	0.001
	Normal	35	64	
	High	15	10	
Age		10.7	11.6	0.270

significantly. Regarding the three BMI categories (low, normal, high) there were no significant differences between them, although in the low and normal BMI groups the DeLong test approached significance.

As children in the low BMI category were almost all at high risk and as the ROC curve of NRS-PC does not show appropriate validity to identify those who have low muscle mass, we suggest bio-impedance measures in every patient with low BMI. In our sample, there were only two children who had normal muscle mass in spite of their low BMI.

In case of normal BMI, we need further studies to assess whether the NRS-PC is sensitive enough to identify approximately all patients with low muscle mass. In our sample, a first screening with NRS-PC would result in overlooking 13 children with low muscle mass. However, out of the 13 children, 3 did have normal muscle mass at the subsequent assessment, 1 had similarly low muscle mass and we did not have data from the other 9. Existing literature reinforces that during the course of cancer therapy body composition can change considerably [8,9,24,25]. Therefore, longitudinal data would be advantageous to decide whether it is safe to rely on NRS-PC without bio-impedance measures.

In the high BMI group, we suggest screening with NRS-PC first. None of the patients with low muscle mass would have been undetected in our sample with this strategy, and out of the three children who were identified being at high risk, at the subsequent assessments two had low muscle mass.

6. Conclusions

As a conclusion we can affirm that assessing the nutritional status of pediatric cancer patients by any means is proved to be very useful and can contribute to the necessary dietetic interventions. Derived from our results we suggest screening high BMI patients first with NRS-PC. In case of low BMI bio-impedance measures provide more precise information on muscle mass and nutritional risk. Further data are needed to decide whether the NRS-PC is sensitive enough in case of normal BMI patients. Using specific screening tools and following a screening algorithm facilitates the assessment and supplies more accurate information based on which better nutritional care can be administered. The assessment of nutritional status and the implementation of nutrition therapy accordingly may contribute to better outcome and survival in pediatric cancer patients.

6.1. Limitations

In this single center study during the research period we had a limited number of patients who could be involved. In the current study we could not collect longitudinal data however, it would be beneficial to follow patients from the diagnosis until the completion of their treatment in order to further evaluate the use and accuracy of the NRS-PC.

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Author contribution statement

I declare that all authors approved the manuscript submitted.
Individual contribution is stated below:
Conception and design: NG, KH, ET, GK.
Data collection: NG, KC, EF.
Analysis and interpretation: NG, KC, ET, KH, GK.
Drafting of the manuscript: NG, KH, GK.
Revising the manuscript for content: NG, KC, ET, KH, EF, GK.

Conflict of interest

The authors declare that no conflict of interest exist in this study.

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Appendix A

Appendix 1
Nutrition screening tool for childhood cancer (SCAN).

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
	Total:

Score indication.
≥3 At risk of malnutrition – Refer to dietician for further assessment.

Appendix 2

NRS-PC (Nutrition Risk Screening for Pedatric Cancer) Questionnaire

- New or returning patient:
- Name:
- Date of birth:
- Department (ward):
- Weight (kg)
- Height (cm)
- Age:
- Diagnosis:
- Does the patient receive any nutritional supplement? Yes or No
- Does the patient have a feeding tube upon admission? Yes or No
- BMI percentile <10? Yes or No
- BMI percentile <5? Yes or No

Questions	YES	NO
1. More than 1 kg weight loss since tumor associated complaints and symptoms		
2. Change in nutrition habits: reduced amount of food consumed		
3. Change in nutrition habits: fewer occasions (compared to previous number of meals)		
4. Stool is more frequent than usual or change in consistency		
5. Increased vomiting compared to earlier		
6. Reduced physical activity compared to earlier (before diagnosis)		
NRS-PC score (number of positive responses from Questions 1–6)		

Date.
Screening done by (name of the person).

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The Effect of Nutritional Support on the Disease Progression and Survival in Pediatric Patients with Solid Tumors

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ABSTRACT

Cancer is one of the leading causes of death for children; however, appropriate nutritional status can positively affect survival. The aim of this study was to determine to what extent malnutrition risk screening and intensified nutrition support, provided by a professional team, promoted disease progression and survival in pediatric patients with solid tumors. 145 pediatric cancer patients (average age 6.3 ± 5.6 and 6.7 ± 5.4 years) with solid tumors undergoing chemotherapy participated in the study. Two 3-year periods were studied: 2009-2011 and 2012-2014. Patient characteristics and treatment protocols were identical, but in *Period 2*, with the foundation of our nutrition support team malnutrition risk screening was made mandatory upon every hospital admission. As a result of intensified nutrition support the time from diagnosis to completion of treatment (802 vs. 512 day, $p < 0.001$) and the need for antimycotic treatment reduced significantly (47.8% vs. 29.1%, $p = 0.036$). The total percentage of surviving children was 60.3% and 75.0% in *Period 1* and *2* respectively. Decrease in weight-for-height percentile during treatment and central nervous system tumors are significant predictors of a less favorable survival. Malnutrition risk screening and intensified nutrition therapy have positive effects on nutritional status and therefore patient survival in pediatric cancer patients.

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Introduction

It has been long ascertained that the nutritional status in case of chronic wasting diseases, especially in case of childhood cancer, does influence the outcome of the disease, the course of the therapy, including treatment tolerance and infection risk, as well as the quality of life and the cost of care (1).

Between the years 2001-2010 the most common cancers were leukemia, followed by central nervous system (CNS) tumors, and lymphomas in children aged 0–14 years based on 284 649 cases (2). In Hungary there are various types of solid tumors, however neuroblastoma, medulloblastoma, PNET (Primitive neuroectodermal tumor) and astrocytoma are diagnosed in children the most often (3). CNS tumors are slightly more prevalent in case of males and it seems that children aged 0-14 are more susceptible according to a British study (4). In our country there are about 250 new pediatric oncology diseases per year, out of which approximately 45% are treated at the 2nd Department of Pediatrics of Semmelweis University.

Treatment options depend on several factors, including the type of the tumor, the stage and grade when it is diagnosed, the age and overall health condition of the patient, severity of the symptoms. Treatment protocols and guidelines also help multidisciplinary teams, including nutrition support teams to provide the best care possible (5–7).

The risk of nutritional depletion is high due to the metabolic changes the tumor triggers, such as muscle wasting and weight loss (8). Symptoms and side effects (e.g. pain, stomach discomfort, diarrhea, nausea, vomiting) patients usually suffer from, especially during treatment, might impair food intake. Moreover, they may cause nutrient losses and may prevent nutrient absorption. The psychological effects, most often depression and anorexia, also have a negative effect on appetite; consequently the energy and nutrient intake is much lower than the desired amount. For all the above mentioned factors, the risk

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Table 1. Incidence and diagnosis of tumors in the two periods.

Tumor types	*Period 1* (2009–2011)	*Period 2* (2012–2014)	Total *N*	Total %
Neuroblastoma	19	18	37	25.5%
Medulloblastoma	14	12	26	17.9%
Ewing sarcoma	15	15	30	20.7%
PNET	4	4	8	5.5%
Ependymoma/glioma	3	3	6	4.1%
Hepatoblastoma	2	6	8	5.5%
Other	16	14	30	20.7%
Total	73	72	145	

of weight loss and malnutrition is extremely high. Approximately 40% of cancer patients have been found to have substantial protein energy malnutrition (9, 10).

It has become evident that in case of childhood cancer malnutrition has a negative impact on the outcome of the disease, and at the same time it is an important prognostic factor (7). Furthermore, in case of CNS tumors existing malnutrition at diagnosis, has a negative predictive effect and patients quit or discontinue therapy more often. In addition, weight other than optimum is a risk factor and while the event-free survival rate decreases, treatment toxicity increases (11). It is widely accepted that nutritional status affects the outcome and the quality of life of survivors; in addition, malnutrition increases morbidity and mortality (11–13).

Nutritional screening methods depend largely on the disease group and according to the above mentioned facts this is even more important in case of childhood cancer (14). SCAN (Nutrition Screening Tool for Childhood Cancer), which is the only validated screening tool, has only been available from 2016 (6).

Pediatric clinics or oncology units where childhood cancer patients are cared for are still challenged. Nutrition support teams (NST) could help this situation and could implement nutritional screening on a regular basis. In our department an official nutrition support team was established in 2012. Our aim was to analyze retrospectively the effect of regular malnutrition risk screening and intensified nutrition support on the treatment outcome in pediatric solid tumors by comparing two large patient populations treated in our pediatric center.

Material and Methods

In this study we analyzed data from 145 children (0–18 years) undergoing complex treatment (including chemotherapy) with solid tumors at the 2nd Department of Pediatrics, Semmelweis University (Budapest, Hungary) between 2009 and 2014. Our retrospective data collection was approved by the Hungarian Scientific and Research Ethics Committee (number: 86748/AOGY2/2016). The last follow-up was done on 25th April 2019. During the study period, in total 160 pediatric cancer patients were treated at the neuro-oncological unit, and only 15 of them did not have full medical records. Therefore, we had access and analyzed the data of 90.6% of the treated pediatric cancer patients.

The incidence of the different types of solid tumors can be seen in Table 1. By high risk tumor we mean those specific tumor types which require aggressive treatment protocols (based on clinical and histopathological findings, classified by pediatric oncologists). The study period was divided into two three-year periods: *Period 1* before the nutrition support team (2009–2011) and *Period 2* after starting intensified nutrition support (2012–2014). It is important to mention that we have selected this type of oncological patient group particularly since there was no change in the treatment protocol - except for the intensified nutrition therapy provided by our NST - during these years. The proportion of the different tumor types was similar in the two periods as it can be seen in Table 1. Each tumor type was treated (surgery, chemo-, and radiation therapy) according to its standard medical protocols.

During *Period 1* no nutrition support team was involved, and therefore malnutrition risk screening was not compulsory. We could not identify malnutrition risk using our screening tool. We could only rely on the medical documents; there were only few patients clearly recognized as „being at risk". At the beginning of 2012 the NST (including physicians, nurses, dietitians, and pharmacists), was established at our department and in *Period 2* malnutrition risk screening was introduced as compulsory in case of every hospital admission. To draw attention to children being at risk of malnutrition our self-developed nutrition status screening sheet, NRS-PC: Nutrition Risk Screening for Pediatric Cancer was used (see Appendices). Our screening takes into consideration both the objective and clinical aspects of nutritional status: the BMI percentile (below 10 or three percentile), factors that determine the patient's nutritional

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and gastrointestinal status (lost more than 1 kg since showing the symptoms, changes in stool, vomiting etc.), as well as other aspects related to the general status of the patient (decrease in physical activity, appetite and the amount of food intake). Patients at risk of malnutrition according to the malnutrition risk screening test (BMI percentile <5 or BMI percentile <10 plus at least two positive responses to questions from 3 to 8, see Appendix) were provided with extra nutritional support during *Period 2*. Between 2012-2014 all patients were screened and if they were found to be at risk of malnutrition they were given nutrition support based on professional dietetic standards.

Besides the diagnosis (presence of high risk or CNS tumor) and the outcome (survival) the following parameters were recorded and analyzed for each patient: age, gender (male or female), body height and body weight at the beginning and at the end of the oncological treatment, number of days spent in hospital, number of chemotherapy days, number of antibiotic and antimycotic treatment days, number of transfusions, presence of nutritional risk (weight-for-height percentile below 10 at the beginning of the treatment), presence of positive malnutrition risk (during the treatment), length of nutrition therapy, presence and type of nutrition support (oral, enteral or parenteral). In our sample the following tumor types were considered as CNS tumors: neuroblastoma, medullobalstoma, PNET, ependymoma/glioma and other rarely occurring tumor types, astrocytoma, atypical teratoid rhabdoid tumor (AT/RT), plexus choroideus carcinoma.

Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared. Weight-for-height, height-for-age, weight-for-age and body mass indexes were interpreted by using the Z-score classification system. Z-scores were calculated as the difference between the observed and the median value of the reference population divided by the standard deviation value of the reference population. Reference data (according to age/height and gender) were obtained from 'The National Longitudinal Child Growth Survey' published by the Hungarian Central Statistics Office in 2006 (15). Weight-for-height percentiles were calculated from weight-for-height Z-scores and were selected as the index referring to growth during the treatment period (16).

Statistical Analysis

Differences between the Characteristics of the Two Periods

To compare the two periods, Fisher test was used regarding gender, age, presence of high risk tumor, presence of CNS tumor, presence of nutritional risk during the treatment, the presence of positive malnutrition risk during the treatment, presence of nutrition therapy, presence of enteral or parenteral nutrition and presence of antimycotic treatment. To determine differences in the measured variables (length of treatment, number of days spent in hospital, number of chemotherapy days, number of antibiotic treatment days, number of transfusions, weight-for-height percentile at the beginning of the treatment) between the two study periods, separate general linear models were used.

Changes in Weight-for-Height Percentile before and after Treatment

To see the differences regarding the change in weight-for-height percentile before and after treatment, we created 4 groups according to the two periods and the survival within 4 years after the beginning of treatment (*Period 1* died, *Period 1* survived 4 years, *Period 2* died, *Period 2* survived 4 years). General linear mixed model was fit to the data with random effects for each child (17). The fixed effects were the above mentioned 4 groups, the time of measurement (before or after treatment) and their interaction. The response variable was weight-for-height percentile. For multiple comparisons the Tukey-Kramer correction was used. All analysis was performed in R 3.4.4 (18). The significance level was set at $P < 0.05$.

Survival Analysis

Survival curves were constructed using the Kaplan–Meier method (package survival in R). Log-rank test of equality across strata for categorical variables was performed. We analyzed the independent contribution to tumor survival of several prognostics with univariable and multivariable regression methods based on the Cox proportional hazards model. Variables were entered into the model using a forward selection approach, starting with the most significant variable (based on the unadjusted p-value) and then continuing in order of significance. After completing the survival analysis for the whole dataset ($n = 145$), it was repeated separately for *Period 1* ($n = 73$) and *Period 2* ($n = 72$) as well.

Results

Differences between the Two Periods

We collected data of 73 patients (45 male, 28 female) between 2009 and 2011 (*Period 1*, without intensified nutrition support) and of 72 patients (39 male, 33

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Table 2. Characteristics of the study subjects.

Study periods	*Period 1* (2009-2011)	*Period 2* (2012-2014)	P- value
N (children)	73	72	
Percent of males	61.6%	54.2%	0.403
Number of patients with CNS tumor	54 (74.0%)	45 (62.5%)	0.156
Number of patients with high risk tumor	14 (19.2%)	18 (25.0%)	0.429
Mean (SD) time from diagnosis to end of treatment (days)	802 (489)	512 (329)	<0.001*
Mean (SD) number of days spent in hospital	116 (57)	120 (65)	0.698
Mean (SD) number of chemotherapy days	38 (27)	33 (18)	0.166
Mean (SD) number of antibiotic treatment days	37 (29)	40 (33)	0.600
Received antimycotic treatment	32 (47.8%)	21 (29.1%)	0.036*
Mean (SD) weight-for-height percentile at the beginning of the treatment	37.5 (32.0)	33.5 (30.4)	0.441
Presence of malnutrition risk during the treatment period	N/A	47 (65.3%)	
Presence of malnutrition risk based on BMI Z-score	24 (32.9%)	26 (36.1%)	0.729
Average number of nutrition therapy days	22.4	54.2	0.043*
Presence of prolonged parenteral nutrition (>7 days)	14 (19.2%)	7 (9.7%)	0.156
Presence of enteral nutrition (oral and/or tube feeding)	22 (30.1%)	35 (48.6%)	0.028*

female) between 2012-2014 (*Period 2*, with intensified nutrition support). The characteristics of the study subjects are summarized in Table 2.

The mean (SD) age at the beginning and at the end of treatment in *Period 1* was 6.3 ± 5.6 and 8.3 ± 5.5 years, and in *Period 2* it was 6.7 ± 5.4 and 8.1 ± 5.7 years, respectively. The ratio of males, the presence of CNS tumor, and the presence of high risk tumor did not differ significantly among the two periods (Fisher-test, $p > 0.05$ in all cases). However, there was a significant difference in the presence of malnutrition risk during the treatment period (Fisher-test, $p < 0.001$) and the length of nutrition therapy in *Period 2* compared to *Period 1* (Mann-Whitney test, $p < 0.05$). Furthermore, antimycotic treatment was two times less needed (Fisher test, $p = 0.036$, odd ratio= 2.2) in *Period 2* compared to *Period 1*.

The time from diagnosis to the end of treatment was significantly shorter in *Period 2* compared to *Period 1* (general linear models, $p < 0.001$). However, the number of days spent in hospital, the number of chemotherapy days, the number of antibiotic treatment days did not differ significantly between the two periods (general linear models, $p > 0.05$ in all cases).

Changes in Weight-for-Height Percentile before and after Treatment

In *Period 1*, after treatment, the weight-for-height percentiles were significantly higher in those children who survived compared to the children who died (General linear mixed model with Tukey post-hoc test, $p = 0.008$). So in *Period 1*, those who died within 4 years after the beginning of the treatment had a significantly larger decrease in the weight-for-height percentiles after treatment compared to those who survived at least 4 years. Contrary to these, changes in weight-for-height percentiles did not differ significantly in *Period 2* (General linear mixed model with Tukey post-hoc test, $p = 0.341$) among children who died and children who survived 4 years after the beginning of the treatment (Figure 1).

Survival Analysis

The minimal follow-up period was 4 years, therefore in both study periods, we could calculate the ratio of children surviving at least 4 years. In *Period 1*, 35.6% (26/73) of the children died within 4 years after the beginning of the treatment, while in *Period 2* only 25.0% (18/72). Taking the entire study period into consideration we can see that the median (min–max) follow up time in *Period 1* was 8.7 (7.0–10.0) and in *Period 2* 5.5 (4.0–6.9) years. During the whole study period 39.7% (29/73) of the children who had started treatment in *Period 1* died, whereas in *Period 2* only 26.4% (19/72). Kaplan Meier Curve analysis performed at the two periods as demonstrated by Figure 2. A clear trend can be seen since survival was more favorable in *Period 2* compared to *Period 1*, however the difference was not significant ($p = 0.130$).

The univariate Kaplan Meier analysis and log rank tests demonstrated shorter survival in CNS tumor patients and in children showing a decrease of weight-for-height percentile during treatment (Figure 3A and B). All the other measured factors (age, gender, presence of high risk tumor, presence of antimycotic treatment, presence of nutritional risk at the beginning of the treatment (weight-for-height percentile <10), presence of positive malnutrition risk during the treatment, presence and type of nutrition therapy (enteral or parenteral) did not affect survival significantly ($p > 0.05$ in all cases). Multivariable cox hazard proportional analysis confirmed that decrease in weight-for-height percentile during treatment and

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the presence of CNS tumor are significant predictors of a less favorable survival (Figure 4).

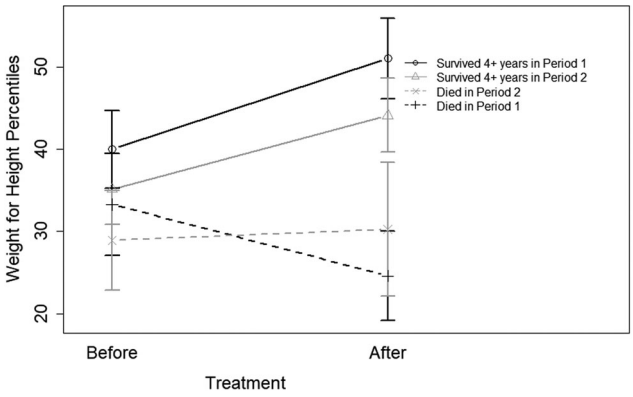

Figure 1. Changes in weight-for-height percentiles during treatment regarding survival (at least 4 years after the beginning of treatment) in the two study periods. (*Period 1*: before the nutrition support team (2009-2011) and *Period 2*: after starting intensified nutrition support (2012-2014)).

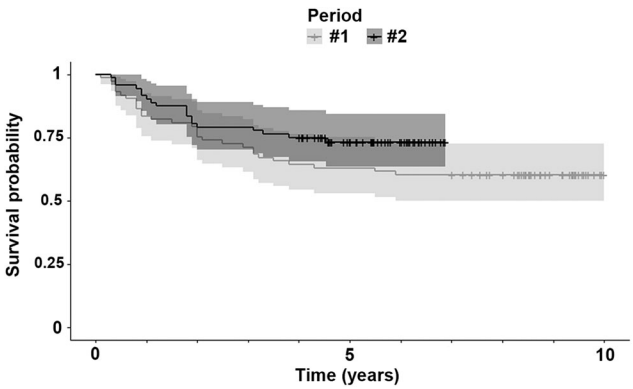

Figure 2. Kaplan Meier Curve analysis performed in the two periods with 95% CI.

Conducting the analysis only on data of *Period 1* (before the introduction of the NTS), the univariate Kaplan–Meier analysis and log rank tests revealed significantly shorter survival in children showing a decrease of weight-for-height percentile during treatment (Figure 5A). All the other measured factors did not affect the survival significantly ($p > 0.05$ in all cases). Multivariable cox hazard proportional analysis showed that decrease in weight-for-height percentile during treatment was a significant predictor of a less favorable survival in *Period 1* (Figure 5B).

In *Period 2* (after initiating intensified nutrition support), none of the measured factors affected the survival significantly ($p > 0.05$ in all cases) according to the univariate Kaplan Meier analysis, the log rank tests and the multivariable cox hazard proportional analysis (Figure 5C).

Nutrition Therapy

Although there was no NST in *Period 1* some of the patients were given nutrition therapy, usually in the ICU units and mainly in the form of parenteral nutrition. Therefore, parenteral nutrition for at least 7 day was given to twice as many patients in *Period 1*, although statistically this difference is not significant (Table 2).

In *Period 2* nutrition therapy was the responsibility of the NST and the decision was made after the consideration of other important factors (e.g. the condition of the digestive tract). Comparing the number of patients who were provided with enteral nutrition (oral nutrition support and tube feeding) in *Period 1* and 2 the difference is significant (Table 2). This means it was a more preferred way of nutrition support in *Period 2*. If we consider the average number

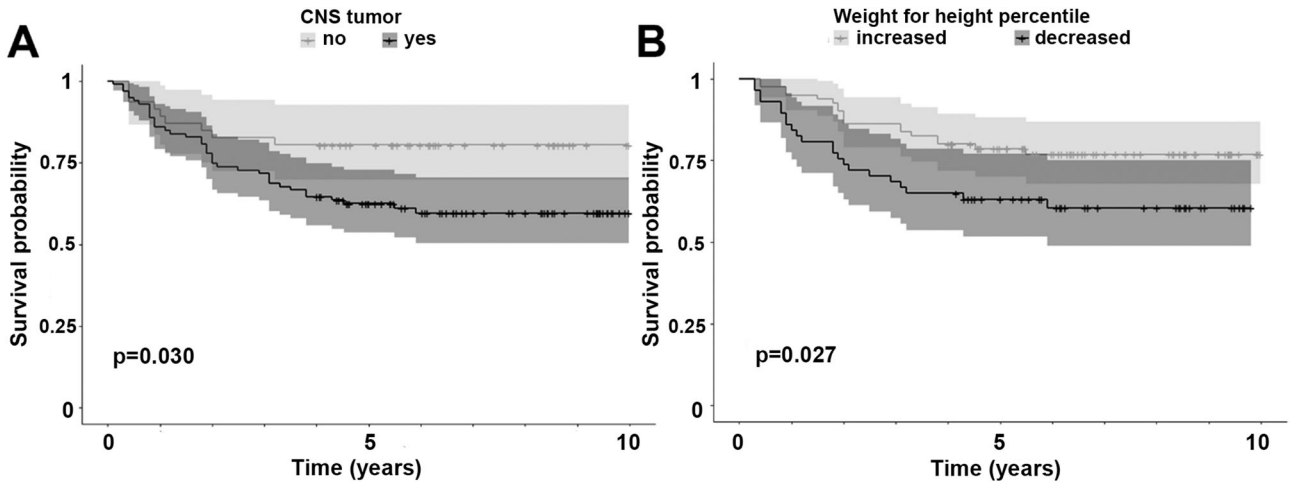

Figure 3. Kaplan Meier Curve analysis performed regarding CNS tumor (A), and the alteration of weight-for-height percentile (B) during treatment with 95% CI ($n = 145$).

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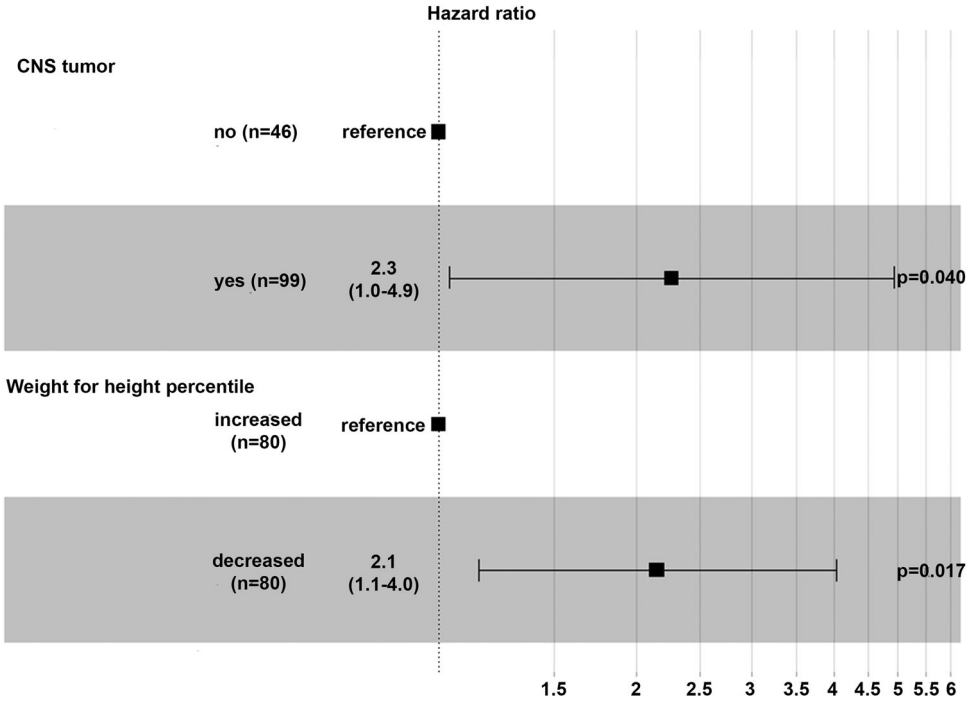

Figure 4. Final model of adjusted Cox Hazard analysis, predictors of tumor survival, multivariable analysis ($n = 145$).

of nutrition therapy days a significant difference has been found: 22.4 day in *Period 1*, 54.2 day in *Period 2*, $p = 0.043$. Nutrition therapy was started earlier, as soon as malnutrition risk was detected, and was provided for a longer period of time in *Period 2*.

Discussion

In this single center study we investigated two similar periods. The only difference was regular malnutrition risk screening and intensified nutrition support, which was provided by a professional team in *Period 2*. The focus of our study was on disease progression and survival in pediatric patients with solid tumors undergoing chemotherapy. In *Period 1* dietetic counsel was given only to the very severely malnourished patients based on the subjective judgment of the pediatric physician, since no nutrition risk screening tools were applied. In this period, the physician decided on the nutrition therapy – when to start it and how it should be provided. In *Period 1* parenteral nutrition was preferred during hospital stay since it was easier to administer through the central vein catheter.

In *Period 2* nutrition therapy was the responsibility of the NST and the decision was made after the consideration of other important factors (e.g. the condition of the digestive tract). Since 2012 our self-developed nutrition status screening sheet (NRS-PC) was used to evaluate malnutrition risk and to decide on further assessment or interventions. Our study would highlight the importance of NSTs work in pediatric units, where cancer patients are treated.

Comparing the two study periods differences have been found in the length of time from diagnosis to end of treatment, in the presence of antimycotic treatment and in the type and length of nutrition therapy. During *Period 2*, using our own screening tool a higher prevalence of malnutrition risk have been found 65.3% compared to the results of the EuroOOPS study group which was 32.6% (19). However, it has to be noted that in that international multicenter study NRS-2002 was used to assess malnutrition risk and the patient population was more heterogeneous. In another study 45% of pediatric patients with cancer were considered malnourished based on body cell mass (20).

Time from the beginning to the end of treatment was significantly shorter and there were significantly two times less need for antimycotic treatment in *Period 2* compared to *Period 1*. Former studies also confirm that poor nutritional status is associated with higher risk of hospital acquired infections (9, 21). Nutrition support provided for critically ill and adult cancer patients has been proved to be of key importance in previous studies as well. In order to maintain muscle mass, which is inversely associated with the length of hospital stay, lower survival rate, infections and lower quality of life, nutrition support is essential (21, 22, 26).

We expected to prove that nutrition therapy was significantly more effective in patients with high risk

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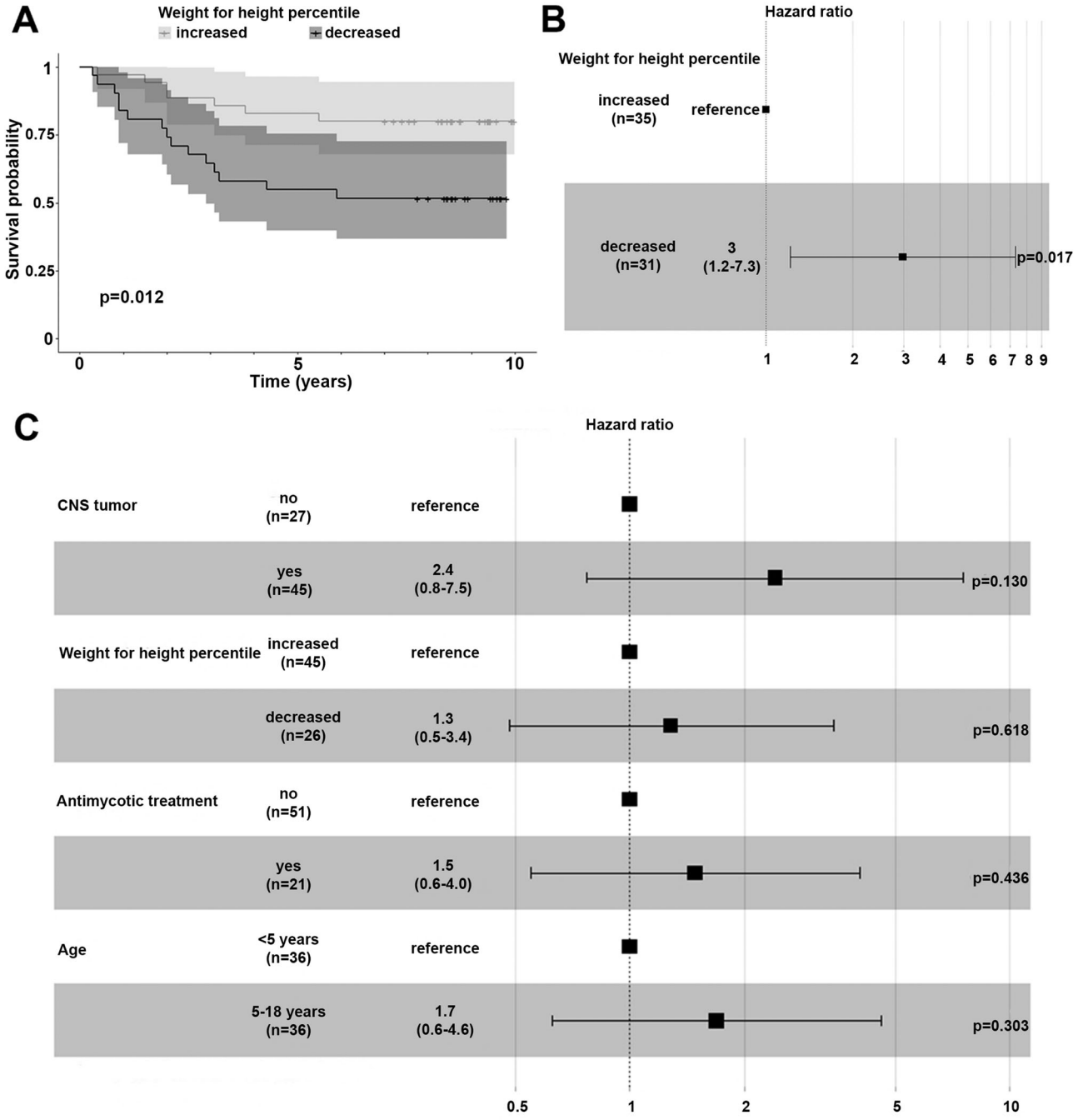

Figure 5. Panel A: Kaplan Meier Curve analysis performed regarding the presence of a decrease of weight- for-height percentile during treatment with 95% CI. Panel B and C: Final model of adjusted Cox Hazard analysis, predictors of tumor survival, multivariable analysis for *Period 1* (B) and *Period 2* (C).

tumors. Furthermore, it was also assumed we could detect differences between the two periods in the number of hospital admissions, however, no significances were found. It is clear that in *Period 1* if nutrition therapy was needed, and it was mainly provided in the form of parenteral nutrition. However, according to the ESPEN guideline on the nutrition in cancer patients the enteral route would be preferred whenever it is possible (22). When malnutrition risk is not discovered early enough, enteral nutrition may not be feasible.

Survival rate was better, although not significant in *Period 2* compared to *Period 1*. This result is in line with previous studies which have already described the positive effect of appropriate nutritional status on the disease outcome (1). It is assumed that longer follow-up, a larger sample of patients and further research in the future would help make this difference significant.

Our data shows that malnutrition effects survival because if weight loss occurs during the treatment,

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survival is significantly worse. During *Period 1* there was no NST, and those who died had 3-times larger odd for a decrease in weight-for-height percentiles during the treatment. In *Period 2*, with the help of the NST the weight loss of those who died and surviving children were similar.

It is known that in case of CNS tumors the prevalence of malnutrition is high, which may contribute to an increased risk for mortality (23,24). Our survival analysis revealed that the presence of CNS tumor means increased mortality as it is shown in Figure 3; however taking the multivariable model into consideration this difference is no longer significant.

The results of this retrospective study demonstrate the need for regular malnutrition risk screening and NSTs. We believe that due to the nutrition support team's efforts, including regular nutritional status screening, malnutrition risk evaluation, timely and closely monitored nutrition therapy enable better disease control and outcome.

Our results indicate the need for professional NSTs in large pediatric oncology units treating a great number of patients, since nutrition therapy cannot be planned individually or implemented appropriately without them. This may seem to be only a small step; however it is worth fighting against malnutrition in order to ensure better life prospects for children with cancer.

Limitations

Although it was a large-scale study, in which a relatively homogenic group of pediatric tumor patients were investigated, data was collected retrospectively in a single center. More patients could have been included from other departments or the time of our research may have been extended, however, by doing so the comparability of the two periods and the homogeneity of the patients would have decreased, and thus the impact of the nutrition support team could not have been evaluated.

In our study we applied the screening tool of our department (NRS-PC) since we could not find any validated screening tool specific for pediatric tumor patients at the beginning of our study.

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Author Contribution Statement

I declare that all authors approved the manuscript submitted.

Individual contribution is stated below:
Conception and design: NG, KC, ET, GK
Data collection: NG, KC, ET, ZsJ, MG, PH
Analysis and interpretation: NG, KC, ET, KN, GK
Drafting of the manuscript: NG, KN, GK
Revising the manuscript for content: NG, KC, ET, MG, PH, ZsJ, KN, GK.

Disclosure statement

The authors declare that no conflict of interest exist in this study.

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Appendix

NRS-PC (Nutrition Risk Screening for Pedatric Cancer) Questionnaire

- New or returning patient:
- Name:
- Date of birth:
- Department (ward):
- Weight:(kg)
- Height:(cm)
- Age:
- Diagnosis:
- Does the patient receive any nutritional supplement? Yes or No
- Does the patient have a feeding tube upon admission? Yes or No

Questions	YES	NO
1. BMI percentile <10		
2. BMI percentile <5		
3. More than 1 kg weight loss since tumor associated complaints and symptoms		
4. Change in nutrition habits: reduced amount of food consumed		
5. Change in nutrition habits: fewer occasions (compared to previous number of meals)		
6. Stool is more frequent than usual or change in consistency		
7. Increased vomiting compared to earlier		
8. Reduced physical activity compared to earlier (before diagnosis)		
Nutritional risk can be ascertained (being at risk)*		

Date: Screening done by (name of the person).
*BMI percentile <5 or BMI percentile <10 plus at least positive responses to questions from 3 to 8.

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A tápláltsági állapot szűréstől a táplálásterápiáig a gyermekgyógyászatban

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A cikkben az egészségügyi intézményekbe kerülő betegek tápláltsági állapot rizikószűrésének fontosságáról, tápláltsági állapotuk meghatározásának gyermekgyógyászatban alkalmazható módszereiről és a táplálásterápia szerepéről lesz szó.

A MALNUTRÍCIÓ MEGHATÁROZÁSA ÉS TÍPUSAI

A kóros tápláltsági állapot (malnutríció) egy vagy több tápanyag relatív vagy abszolút hiányának, illetve feleslegének következtében alakul ki. A hiányállapot az alultápláltság, a felesleg pedig az obezitás. Az éhezés vagy betegség miatt, illetve az öregedésből adódó alultápláltság olyan állapotnak tekinthető, amely az elégtelen táplálékbevitel vagy a nem megfelelő felszívódás eredménye, ami megváltozott testösszetételhez (csökkent zsírmentes testtömeg), valamint csökkent fizikai, szellemi funkcióhoz és a betegségek rosszabb klinikai kimeneteléhez vezet.[1]

A múlt század utóbbi évtizedeiben az alultápláltságot a nyugati országokban

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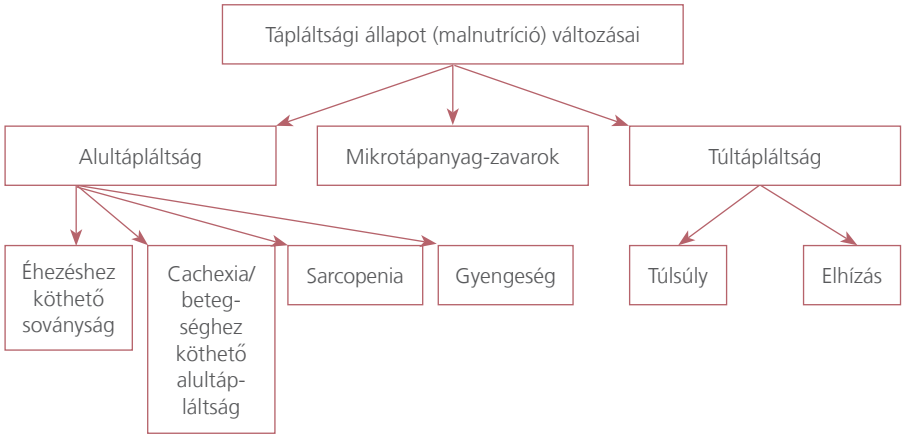

ÁBRA A malnutríció típusai

az általános proteinenergia malnutríció (PEM) fogalmával illették, mivel a táplálтsági hiányállapot leginkább a fehérjeenergia beviteli hiányának, illetve vesztésének kombinációjaként fordul elő. A PEM klinikai meghatározása és diagnosztikai kritériumai az idők során változtak.

Az alultápláltság létrejöttében számos tényező játszik szerepet, úgymint a nem megfelelő szociális és környezeti feltételek, a túl szigorú diéták, idült hasmenés és/vagy hányás, étvágytalanság, depresszió, anorexia, a táplálék felvételének, emésztésének, felszívódásának zavara (melynek oka lehet daganat, gyulladásos bélbetegség, fekély stb.), a felgyorsult anyagcserével és/vagy a fehérjék fokozott lebontásával járó állapotok (pl. súlyos sérülés, égés, szepszis, tartós láz). Továbbá a diagnosztikus eljárások vagy a terápia (pl. kemoterápia, besugárzás) következményei is hozzájárulhatnak kialakulásához. A legjellemzőbben kialakuló formák, illetve a tényezők közötti kölcsönhatást az *Ábra* mutatja.

A MALNUTRÍCIÓ DIAGNOSZTIKAI KRITÉRIUMAI – ESPEN KONSZENZUS

A Klinikai Táplálás és Metabolizmus Európai Társasága (ESPEN) javaslata szerint korcsoport, illetve alapbetegségek szerint validált szűrőmódszerekkel kell azonosítani azokat, akik kedvezőtlen táplálтsági állapotukból adódóan úgynevezett malnutrícióriziкóval rendelkeznek. A táplálтsági állapotuk optimálistól való eltérés irányának és mértékének, illetve a gyógyításuk táplálтsági állapotra való hatásának értékelése után kell dönteni a további teendőkről, ami terjedhet a teendőt nem igénylő táplálтsági állapot megállapításától a nyomon követés, a rizikószűrés megismétlésének szükségességétől az azonnali táplálásterápia megkezdéséig.

> Az ESPEN javaslata szerint korcsoport, illetve alapbetegségek szerint validált szűrőmódszerekkel kell azonosítani azokat, akik kedvezőtlen táplálтsági állapotukból adódóan úgynevezett malnutrícióriziкóval rendelkeznek.

Az utóbbi évtizedekben számos, malnutríciót szűrő módszer vált elfogadottá klinikai alkalmazhatóságuk, illetve megbízhatóságuk következtében. Ezek a szűrőmódszerek közel azonos változókat tartalmaznak, úgymint a fogyás, a „body mass index” (BMI, body mass index), a táplálkozási nehezítettség jelei (pl. étvágyvesztés vagy csökkent táplálékbevitel), valamint a meglévő betegség súlyosságának osztályozása. Az ESPEN korcsoportra és betegségre validált módszereket ajánl (felnőttek esetében ilyen a Nutritional Risk Screening (NRS) 2002, a rövidített Mini Nutritional Assessement (MNA), és a Malnutrition Universal Screening Tool (MUST) felnőttek, a Screening Tool for Nutritional Status and Growth (STRONG) pedig gyermekek esetében). A táplálтsági állapotukból adódóan fokozottan veszélyeztetettek körében azonosítani kell a táplálkozási probléma fajtáját és mögöttes mechanizmusát. Így meghatározhatók a szükséges klinikai lépések és megtervezhető az egyéni táplálásterápia.[2]

Az ESPEN szakmai ajánlása szerint a táplálтsági állapot szűrése minden klinikai és egészségügyi ellátás során kötelező, tekintettel a nemzetközileg bizonyított tényre, hogy az akut és krónikus betegségben szenvedő betegeknél a malnutríció komoly klinikai rizikófaktora az alapbetegség gyógyíthatóságának és a beteg további életminőségének alakulására. Validált, kellően specifikus és szenzitív szűrő módszer alkalmazása esetén a kockázattal rendelkezők száma nagyobb lesz, mint a valóban malnutrícióssoké. A kockázattal rendelkezők valós táplálтsági állapotának megállapítása és a teendők meghatározása klinikai táplálás témakörben járatos szakemberek, úgynevezett táplálkozási „team”-ek feladata.

GYERMEKEKRE ALKALMAZHATÓ TÁPLÁLTSÁGIÁLLAPOT-SZŰRŐ MÓDSZEREK

A gyermekek táplálтsági állapotának szűrésére több módszert ajánl a szakirodalom.[3,5,6] A szűrőmódszerek mindig az azt kidolgozó intézmények betegeihez, lehetőségeihez szabottak, ezért nem lehet köztük általánosan elfogadott, legjobban használhatót választani.

Gyermekgyógyászati általános betegellátó intézmények körében alkalmazható a *Screening Tool for Nutritional Status and Growth (STRONG) kids* pontrendszer. A szűrőlap négy szempontot értékel: (1) az alultápláltság külső jelei; (2) táplálkozási bevitel és veszteség (súlyos hányás/hasmenés, csökkent

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tápanyagbevitel az elmúlt napokban, folyamatban lévő táplálásterápia, fájdalom miatti elégtelen tápanyagbevitel), (3) súlycsökkenés, illetve a súlygyarapodás megállása az elmúlt hetekben, hónapokban. Súlyos alapbetegség vagy várható nagyműtét mint (4.) szempont alapján a közepes, ezért teendőt igénylő besorolást alkalmazza.[3]

A módszer előnye, hogy alkalmazása nem igényel invazív vizsgálatot, mérést, speciális képzettséget, így a rizikó megléte gyorsan és könnyen kideríthető, azonban betegségre nem specifikus. Jól alkalmazható azoknál a betegcsoportoknál is, ahol a BMI és a „weight-for-height = súly a hosszhoz (WFH) mérés nem mutat megbízható eredményt (pl. koraszülöttek, Duchenne-izomdisztrófiában vagy cerebralis paresisben szenvedők).

A STRONG hátránya alacsony negatív prediktív értéke, így a túldiagnosztizálás esélye jelentős. Szakintézményekben kevéssé jól alkalmazható, mert számos alapbetegségben szenvedő beteget alultápláltság szempontjából eleve fokozottan rizikósnak véleményez (pl. cisztás fibrózis, cöliákia, gyulladásos bélbetegségek, infekciók, krónikus senyvesztő betegségek, anyagcsere-, tüdő-, szív-, máj-, vese-, pancreas- és bélbetegségek, daganatos kórképek). Ide tartoznak még a koraszülött csecsemők, az égés, a bronchopulmonalis dysplasia, anorexia nervosa, trauma és mentális retardáció diagnózisok is, miközben egy adekvátan kontrollált cöliákia vagy mentális retardáció nem jár szükségszerűen alultápláltsággal.

> Korcsoport, illetve alapbetegségek szerint validált szűrőmódszerekkel kell azonosítani azokat, akik kedvezőtlen táplháltsági állapotukból adódóan úgynevezett malnutrícióirizikóval rendelkeznek.

A hazánkban több intézményben végzett STRONG módszert megfelelőnek tartották a malnutrícióirizikó felmérésére, bár a szűrést alapbetegségük szerint változatos betegcsoportokban végezték. A felmérés után az alultápláltságot javasolták keresni, majd az okoktól függetlenül tanácsadással és szükség szerint speciális tápszerek alkalmazásával javasolták a malnutríció következményeinek megelőzését.[4]

A szűrőmódszerek két alcsoportba sorolhatók, az antropometriai adatokat mellőző és az azokat figyelembe vevő módszerek csoportjába.

ANTROPOMETRIAI ADATOKAT MELLŐZŐ SZŰRŐMÓDSZEREK

A *Pediatric Nutrition Screening Tool (PNST)* a STRONG kids egyszerűsített módszereként jött létre. Az alapbetegség tekintetében ez szintén nem specifikus, figyelembe veszi az utóbbi időben bekö-

TÁBLÁZAT A leggyakrabban használt gyermekkori tápláltságiállapot-szűrő módszerek jellemzői

Szűrőmódszerek	Aktuális táplháltsági állapot	Súly-csökkenés	Csökkent tápérték-bevitel	Betegség súlyossága	Betegség specifikus	Módszer előnye	Módszer hátránya
PNRS Pediatric Nutritional Risk Score (Gyermekgyógyászati tápláltsági rizikó pontrendszer)	–	–	X	X	–	Gyors felvétel; speciális képzettséget nem igényel	Részletesség hiánya
STAMP Screening Tool for the Assessment of Malnutrition in Pediatrics (Szűrőeszköz a malnutríció értékelésére nél	X	–	X	X	–	72% szenzitivitás; 90% specificitás	Felvételéhez speciális képzettség szükséges
SGNA Subjective Global Nutritional Assessment for children (Szubjektív globális táplháltsági állapot értékelés gyermekekben)	X	X	X	X	Sebészet	Alkalmas a nagy kockázatú betegek kiszűrésére és megkülönböztetésére	Felvételéhez speciális képzettség szükséges
PYMS Pediatric Yorkhill Malnutrition Score (Yorkhilli gyermekgyógyászati malnutríció pontrendszer)	X	X	X	X	–	Felvétele speciális képzettséget nem igényel; 92% specificitás, 59% szenzitivitás	Kapacitáshiány (dietetikus bevonása szükséges)
STRONG kids Screening Tool for Nutritional Status and Growth (Szűrőeszköz a táplháltsági állapot és gyarapodás felmérésére)	X	X	X	X	–	Könnyű, gyors felvétel	Az alapbetegségből indul ki és nem a táplháltsági állapotból
SCAN Nutritional Screening Tool for Childhood Cancer (Táplháltsági állapot-szűrőeszköz gyermekkori daganatokban)	X	X	X	X	Onkológia	100% szenzitivitás;39% specificitás; 56% pozitív prediktív érték, 100% negatív prediktív érték; könnyű, gyors felvétel	Felvételekor még nincs pontos diagnózis; viszonyítási problémák

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vetkezett nem szándékos súlyvesztést/súlygyarapodás csökkenését, az utóbbi hetekben történt tápanyagbevitel csökkenését, valamint az alul- vagy túltápláltság külső jeleit.

A *Patient Generated Subjective Global Assessment (PG-SGA)* az eredeti, akut nefrológiai, onkológiai és neurológiai esetekre kidolgozott SGA-nak életkortól függetlenül alkalmazható változata. Pontrendszere a testsúlyt, a tápanyagbevitelt, a malnutríció klinikai tüneteit, a funkcionális kapacitást, a metabolikus igényt és a beteg fizikális vizsgálatát veszi figyelembe. Az így megállapított kategóriabesorolás-változásokat a beteg nyomon követésére is alkalmasnak tartják.

A *Pediatric Nutritional Risk Score (PNRS)* egyszerű, gyors, betegségcsoporttól függetlenül használható kérdőív. Három kritériuma a tápanyagbevitel és -veszteség, a táplálkozással összefüggő fájdalom, valamint a malnutríció kockázatával járó alapbetegség megléte. Hátránya, hogy széles körű biztonságos használathoz nem elég részletes.

ANTROPOMETRIAI PARAMÉTEREKET IS FIGYELEMBE VEVŐ SZŰRŐMÓDSZEREK

Előnyük a magas szenzitivitásuk és specificitásuk, felvételük azonban szükségszerűen lassabb és nehezebb.

A *Pediatric Yorkhill Malnutrition Score (PYMS)* szűrőlap a BMI percentil változását, utóbbi időben súlycsökkenést, a tápanyagbevitel mennyiségét és az alapbetegséget osztályozza. Felvétele speciális képzettséget nem igényel, specificitása 92%, szenzitivitása 59%.

A *Screening Toolforthe Assessment of Malnutritionin Pediatrics (STAMP)* pontot ad az alapbetegségre, a tápanyagbevitelre, a súly- és hosszadatokra. A módszer szenzitivitása 72%, specificitása 90%.[5,6]

BETEGSÉGSPECIFIKUS SZŰRŐMÓDSZEREK

NUTRITION SCREENING IN CHILDHOOD CANCER (SCAN)

A gyermekonkológiában 2016-ban jelent meg egy antropometriai adatokat nem értékelő, hat szűrőtényezőn (a daganat kockázati típusán, a jelenlegi intenzív ellátás szükségességén, az emésztőrendszeri mellékhatásokon, a megelőző heti táplálékbeviteli hajlandóság mértékén, az elmúlt hónapban mért súlycsökkenésen, illetve az alultápláltság klinikai jeleinek megfigyelhetőségén) alapuló módszer.

A módszer gyors, olcsó, pontos, a beteg dokumentációjának ismeretében felvétele könnyű. Kiemelendő 100%-os szenzitivitása, 39%-os specificitása, 56%-os pozitív prediktív értéke és 100%-os negatív prediktív értéke.[7]

> A tápláltsági állapot felmérésére számos módszer létezik, megbízható értékeléséhez több paraméter ismerete szükséges.

A SCAN elvégezhetőségét mérsékli, hogy a beteg első felvételekor a daganat kockázati típusa még nem ismert.

A *Subjective Global Nutritional Assessment for Children (SGNA)* preoperatív betegek tápláltsági állapotfelmérésére alkalmas. Magában foglalja az alapbetegséget, a súlyváltozást, a testsúly/testhossz arányát, a táplálékbevitel és az esetlegesen fennálló gasztrointesztinális tünetek rögzítését, a funkcionális kapacitás mérését, valamint a beteg fizikális vizsgálatának eredményét. Hátránya, hogy a módszer csak gyermekorvos bevonásával alkalmazható.[5]

A különböző szűrőmódszerek áttekintését lásd a *Táblázatban*.

A TÁPLÁLTSÁGI ÁLLAPOT MEGHATÁROZÁSA

A tápláltsági állapot felmérésére számos módszer létezik, megbízható értékeléséhez több paraméter ismerete szükséges (például kizárólag a testtömeg változásának figyelembevétele nem mindig kórjelző, hiszen pl. az oedema elfedheti a valódi fogyást).

Gyermekek esetében hasznos a BMI percentilis meghatározása. A tápláltsági állapot jellemzésére a felnőttkori határértékek nem mérvadók, mert a felnőttkor eléréséig folyamatosan változik a gyermekek testfelépítése. A fiúk és a lányok tápláltságának megítélésére léteznek kidolgozott értékelő táblázatok, melyeket az Országos Longitudinális Gyermeknövekedési vizsgálat adatai alapján készítettek.[11]

A WHO által ajánlott módszer a testsúly és a testhossz százalékos aránya (a beteg aktuális testsúlyának százalékos aránya az aktuális testmagasságához tartozó 50-es percentilis testsúlyhoz viszonyítva) számolása, mely a szakirodalmi adatok szerint a BMI percentilértékhez hasonló megbízhatóságú. Enyhe alultápláltság véleményezhető 80–90%-os érték, súlyos alultápláltság pedig 70% alatti érték esetében. Obezitást jelez a 120%-nál magasabb érték.[12]

A táplálkozási adatfelvétel is alkalmazható a tápláltsági állapot meghatározásához, mely dietetikus feladata. A 24 órás táplálékfogyasztás kikérdezése (foodrecall) mellett a mennyiségeket is feltüntető gyakorisági kérdőív (Food Amount Questionnaire, FAQ) vagy a visszatekintő, az egyes táplálékok fogyasztási gyakoriságának kikérdezésén alapuló (Food Frequency Questionnaire, FFQ) kombinációja használható.

Antropometriai mérések (testsúly, testmagasság, bőrredővastagság, felkar átmérője), fizikális vizsgálattal nyerhető adatok, illetve bizonyos biokémiai jellemzők (transthyretin, esetleg prealbumin) együttes értékelése alkalmas tápláltsági állapot meghatározására.

A felsorolt módszerek idő- és szakmaitapasztalat-igényesek, és alkalmazásukkal nem kaphatunk választ a testtömeg testtáji megoszlásáról, illetve a testösszetételről, arról, hogy zsír vagy izomtömeg képezi-e a mért értékeket. A testösszetétel megállapításához speciális vizsgáló eszközök alkalmazhatók.

A bioimpedancia (BIA) elvén működő testösszetétel-analízis az egyes szöveti arányokat testrészekre lebontva is megadja, fájdalommentes, noninvazív, nem jár sugárterheléssel, gyors, bármilyen gyakorisággal megismételhető. További előnye, hogy használható a tápláltsági állapot rizikószűrésére, a tápláltsági állapot mérésére, valamint a táplálásterápia hatékonyságának ellenőrzésénél nyomon követésre is.

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Az olyan testösszetétel-vizsgáló módszer, mint a „Dual Energy X-ray Absorptiometry" (DEXA, vagyis denzitometriás mérés) a teljes test csontsűrűségének és ásványianyag-tartalmának, valamint a zsír, illetve lágyszövet tömegének és arányának számítására alkalmas. A készülék paraméterei miatt a vizsgálat bizonyos testmagasság és testsúly felett nem végezhető el, és a mérés kisfokú sugárterheléssel jár, ezért csak meghatározott időközönként ismételhető módszer. A komputertomográfia (CT), valamint a mágnesrezonancia (MR) képalkotó módszerek elsősorban a zsigeri zsír mennyiségének meghatározására szolgálnak, a vázizom és a csontszövet, valamint a belső szervek tömegének becslésére használatosak. A CT-vizsgálat sugárterhelése miatt csak az egyéb okból végzett vizsgálat tápláltsági állapot szerinti értékelése merülhetne fel lehetőségként. Magyarországon e módszerek a korlátozott hozzáférés és a leletek tápláltsági állapot szerinti időigényes kiértékelése miatt nem jönnek szóba.

TÁPLÁLÁSTERÁPIA

A táplálásterápia a malnutríció kialakulásának megelőzésére, illetve a malnutríció okozta anyagcsere-változások kezelésére alkalmas módszer. A táplálási intervenciók célja, hogy fenntartsuk vagy növeljük a szervezet táplálékbevitelét, a betegséghez társuló fokozott szervezeti igényeknek megfelelően; korrigáljuk vagy enyhítsük a tápláltsági állapot romlása miatt kialakuló anyagcsere-változásokat; megőrizzük a vázizomzat tömegét és a fizikai teljesítőképességet. Krónikus senyvesztő betegségekben kiemelten fontos jelentőségű a prognózist rontó malnutríció elkerülése. Ilyen betegségben szenvedő gyermekeknél nagyon gyakori a nem megfelelő táplálékfelvétel, az *Ábrán* szereplő okok összessége miatt. Amennyiben a szájon át történő táplálékfelvétel bármilyen okból nem valósul meg, akkor időben el kell kezdeni a beteg úgynevezett mesterséges táplálását, a lehetőségek határáig az emésztőrendszerbe, vagyis enterális úton (szondatáplálás), további szükség esetén parenterális úton (vénás táplálás) is.[8]

Az izomfehérje-vesztés súlyos mértékben rontja az életminőséget és kedvezőtlenül hat a fizikai funkciókra, valamint a kezelés iránti toleranciára. Daganatos gyerekek testösszetételét vizsgáló tanulmányokból kiderült, hogy kifejezetten a vázizomvesztés az, ami a daganattal összefüggő malnutríciót befolyásolja, függetlenül attól, hogy társul-e hozzá zsírvesztés vagy sem.[8,9]

> A táplálásterápia a malnutríció kialakulásának megelőzésére, illetve a malnutríció okozta anyagcsere-változások kezelésére alkalmas módszer.

A vázizomvesztés kizárólag táplálásterápiás eszközökkel nem védhető ki, a beteg gyermekeknek rendszeres, alapbetegségüknek megfelelő mozgásterápiára is szükségük van. Súlyos tápláltsági állapotromlást teljes értékűen, maradványtünetek nélkül gyógyítani nem lehet, ezért fontos a betegek tápláltsági állapotának rendszeresen nyomon követése és a korai táplálásterápiás intervenció megkezdése, még a súlyos hiányok kialakulása előtt.[10]

A táplálásterápia első szintje a dietetikus szakember által végzett táplálkozási tanácsadás. A szakmai tanácsadásnak rendszeres, elkötelezett és alapos szakmai kommunikációs folyamatnak kell lennie, amelynek célja, hogy a beteg megértse azokat a táplálkozási formákat, melyek által hosszú távon, a betegség legyőzésének érdekében tudja megváltoztatni táplálkozási szokásait. A beteg energia- és fehérjebevitelének fokozására a legideálisabb mód a cél érdekében válogatott, megfelelő konyhatechnikai módszerekkel készített normál étel fogyasztása. Az alapbetegségből adódó sajátos igények kielégítésére gyakran a tanácsadás mellett orális táplálékkiegészítőkre (ONS) is szükség van. Amennyiben a szájon át történő tápanyagbevitel továbbra is elégtelen, akkor enterális vagy parenterális úton történő kiegészítés indikált, az emésztőrendszer működésétől függően, táplálásterápiában jártas orvos előírása szerint.[10]

A klinikai táplálás a hatékony gyógyító munka elengedhetetlen része. Optimális klinikai táplálást nyújtó folyamat – a tápláltsági állapotból adódó kockázat szűrésétől a tápláltsági állapot megállapításán át az idejében alkalmazott, hatékony táplálásterápiáig – interdiszciplináris küldetés. Nemzetközi tapasztalatok szerint a folyamat összehangolását hatékonyan olyan táplálási team tudja végezni, melynek táplálás témában járatos orvos, dietetikus, gyógyszerész és egyéb szakképesítésű egészségügyi dolgozók (pl. gyógytornász) egyaránt tagjai. A beteg érdekeinek mindenben megfelelő klinikai táplálásához nélkülözhetetlen az alapbetegség gyógyításáért felelős személyzet e témában való jártassága és elkötelezettsége is.

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GYERMEKGYÓGYÁSZAT 2022; 73. ÉVFOLYAM, 1. SZÁM

Tápláltsági állapot szűrés és szűrési algoritmus gyermek onkológiai betegeknél

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ÖSSZEFOGLALÁS A daganatos megbetegedések a gyermekkori halálesetek egyik vezető oka. Hazánkban évente 200–250 új esetet regisztrálnak a 0–18 éves korosztályban. A gyermekkori daganatok számos típusa fokozott alultápláltsági rizikóval jár. Kutatásunk célja volt, hogy bemutassuk saját fejlesztésű tápláltsági állapot szűrő módszerünket, és kidolgozzunk egy tápláltsági állapot szűrő algoritmust, amely gyermek onkológiai eseteket ellátó intézményekben alkalmazható. A tápláltsági állapotot felmérést 2017 és 2018 között 109 beteg bevonásával végeztük. A saját fejlesztésű szűrőmódszerünket már validált módszerekhez hasonlítottuk, hogy meg tudjuk állapítani a határpont értékét. Beigazolódott, hogy a saját fejlesztésű szűrőmódszerünk jobb tulajdonságokkal rendelkezett az kisebb izomtömegű gyermekek azonosítására.

KULCSSZAVAK alultápláltság, tápláltsági rizikószűrés, kockázatszűrő módszerek, gyermekkori daganat, gyermekonkológia

Bevezetés

A daganatos megbetegedések a gyermekkori halálesetek egyik vezető oka, melyet a hazai és nemzetközi statisztikai adatok is alátámasztanak (1, 2). Éves szinten világszerte több mint 300 000 eset kerül diagnosztizálásra, míg Magyarországon hozzávetőlegesen évente 200–250 új esetet regisztrálnak a 0-18 éves korosztályban. A betegek közel 50%-a a Semmelweis Egyetem II. Sz. Gyermekgyógyászati Klinikáján kerül ellátásra (3).

A korábbi nemzetközi kutatások eredményei azt igazolták, hogy a megfelelő tápláltsági állapot pozitívan befolyásolhatja a betegség lefolyását és kimenetelét, nemcsak felnőtt, hanem a gyermek onkológiai megbetegedések esetében is (4, 5). A túlélési ráta az elmúlt években folyamatosan emelkedett, azonban az egyes országokban nagy eltérés figyelhető meg. Azokban az országokban, ahol korán felismerésre kerül a betegség, idejében megkezdődik a kezelés, ennek részeként szükség esetén a táplálás terápia is, ott akár 80%-osak is lehetnek a túlélési mutatók (6, 7).

A gyermekkori tumoros megbetegedések számos típusa magas alultápláltsági rizikóval jár, pl. akut myeloid leukaemia (AML), központi-idegrendszeri daganatok, Wilms-tumor III. és IV. stádium, Ewing-, csont- és lágyrész-sarcoma (3). Az agresszív kezelési protokollok (műtét, őssejt-transzplantáció, kemo-, sugárterápia) következtében a betegek tápláltsági állapota romlik, és így jelentősen megnő a malnutríció kialakulásnak kockázata.

Bár többféle tápláltsági állapot szűrő módszert is fejlesztettek, főként általános gyermekgyógyászati betegek számára, ezek egyike sem felelt meg a daganatos betegek speciális követelményeinek (8-10). Később, csak 2016-ban jelent meg a SCAN (Nutrition screening tool for childhood cancer), amelyet az SGNA-hoz (Subjective Global Nutritional Assessment for Children) viszonyítottak (11).

Kutatásunk célja az volt, hogy bemutassuk saját fejlesztésű tápláltsági állapot szűrő módszerünket (NRS-PC – Nutrition risk screening for pediatric cancer) (lásd *1. ábra*), melyet a tumoros gyermekekre validált szűrőmódszerrel (SCAN) és az objektív bioimpedancia elvén alapuló mérésekkel is összevetettünk. Továbbá, célul tűztük ki egy olyan tápláltsági állapot rizikószűrő algoritmus kidolgozását, amely gyermekonkológiai eseteket ellátó intézményekben egyszerűen és jól alkalmazható, csökkentve ezáltal az ellátó intézményre és a szakmai erőforrásokra háruló terheket, valamint optimalizálva a betegellátás hatékonyságát.

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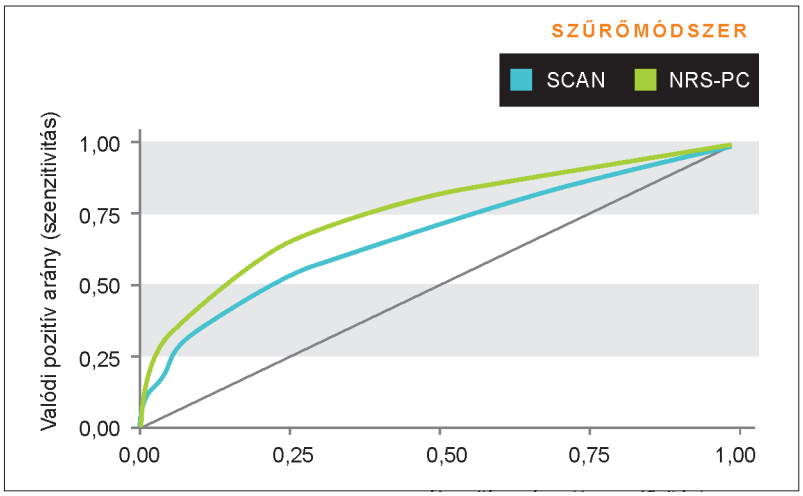

1. ábra: ROC görbe, amely a SCAN és az NRS-PC prediktív értékét mutatja alacsony izomtömeg esetén

Betegek és módszer

A Semmelweis Egyetem II. Sz. Gyermekgyógyászati Klinikáján, 2017 és 2018 között 109 onkológiai (3–18 éves) beteg adatait gyűjtöttük össze és elemeztük ki a négy betegségszakasz szerint (Diagnózis, Aktív kezelés, Fenntartó kezelés, Kezelés vége). A rögzített paraméterek a következők voltak: név, életkor (születési dátum), diagnózis, a mérés dátuma, a betegség szakasza, testsúly, testmagasság (hitelesített eszközök segítségével mérve). A számított paraméterek között SCAN és NRS-PC pontszám kerültek rögzítésre. A BMI-t (Testtömeg index) és a testösszetétel paramétereit, beleértve az izomtömeget és a testzsírszázalékot az InBody készülékek határozták meg, ezek az értékek összehasonlításra kerültek a normáltartomány értékeivel. Három kategóriát állítottunk fel a BMI, az izomtömeg és a testzsírszázalék tekintetében: alacsony, normál és magas, amelyeket szintén az InBody készülékek határoztak meg.

Így tehát a tápláltsági állapot felmérést három eszközzel végeztük: a már tumoros gyermekekre validált SCAN-nel, a saját fejlesztésű szűrőmódszerünkkel (NRS-PC), valamint a bioimpedancia elvén működő InBody 720 és S10 készülékekkel végzett testösszetétel-mérésekkel. A bioimepdancia mérésekkel igazolt alacsony izomtömeg meglétét, mely egy meghatározó kritérium, hasonlítottuk össze a SCAN és NRS-PC-vel kapott eredményekhez a teljes beteganyagra és az egyes betegségszakaszokra vonatkoztatva egyaránt.

Témakifejtés, eredmények

A 109 bevont beteg jellemzését az *1. táblázat* mutatja be. A különböző daganatok előfordulási gyakorisága a következők szerint alakult: 48 beteget kezeltek rosszindulatú hematológiai daganattal, 14 beteget Ewing-szarkómával, 11 beteget központi idegrendszeri daganattal, 8 beteget csontsarcomával, 7 beteget a vázizomzatból kiinduló rosszindulatú daganattal (rhabdomyosarcoma), 21 beteget pedig egyéb rosszindulatú daganattal. A betegek közül 14 gyermeknek újult ki a betegsége.

A saját fejlesztésű szűrőmódszer összehasonlítása a már korábban validált SCAN-hez annak érdekében történt, hogy meg tudjuk állapítani a határ, vagyis a cut-off értéket. Legjobb eredményt az 1-es pontszám adott, mely 98%-os [95% CI: 90, 100] szenzitivitást, 62%-os [95% CI: 51, 71] specificitást, 58%-os pozitív prediktív értéket [95% CI: 47, 68] és 98%-os [95% CI: 91, 100] negatív prediktív értéket mutatott. 2-es pontszám esetén a szenzitivitás 86%-ra csökken [95% CI: 77, 93], míg a specificitás 77%-ra nő [95% CI: 65, 86]. Mivel elsősorban célunk az összes rizikós beteg kiszűrése volt, ezért a szenzitivitást részesítettük előnyben.

A SCAN AUC-értéke (görbe alatti terület) = 0,67 [95% CI: 0,58, 0,75] szignifikánsan alacsonyabb volt (Z = -2,46, p = 0,014), mint az NRS-PC esetében (AUC = 0,75 [95% CI: 0,67, 0,82]), jelezve, hogy az NRS-PC az egész beteg populációt tekintve jobb tulajdonságokkal rendelkezik az alacsonyabb izomtömegű gyermekek azonosítására (lásd *2. táblázat). A betegség különböző fázisaiban azonban nem találtunk szignifikáns különbséget.*

Annak érdekében, hogy az NRS-PC-t össze tudjuk vetni a bio-impedancia-analízissel mért izomtömeg értékeléshez két kategóriát állítottunk fel: alacsony izomtömegűt és normál vagy magas izomtömegűt. ROC görbét alkalmaztunk az izomtömeg-

1. táblázat: A bevont betegek jellemzése

Betegségszakasz	Esetszám (n=)	Férfi-nő arány	Átlagos életkor (évek) ±SD	Elveszített betegek (n=)	Visszaesés (n=)	SCAN pontszám	NRS-PC pontszám
Diagnózis	44	29:15	10,5±3,5	1	9	3,4±2,0	1,0±1,3
Aktív kezelés	36	22:14	14,5±3,5	4	1	3,4±1,6	1,2±1,3
Fenntartó kezelés	34	19:15	9,5±4,5	0	0	2,9±1,7	0,5±1,0
Kezelés vége	36	22:14	11,5±2,5	1	4	1,7±1,4	0,4±0,9

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2. táblázat: NRS-PC tápláltsági állapot szűrő módszer

Név: ..... Születési dátum: ..... Osztály:		
Testsúly: .....(kg) Életkor:..... Testmagasság: .....(cm) Diagnózis:.....		
BMI percentilis <10? Igen vagy Nem		
BMI percentilis <5? Igen vagy Nem		
Kérdések	IGEN	NEM
1. Panaszok óta legalább 1 kg-os súlycsökkenés		
2. Táplálkozási szokásváltozás: mennyiségben csökkent		
3. Táplálkozási szokásváltozás: alkalom kevés		
4. A megszokottnál gyakoribb vagy állagában változott széklet		
5. A korábbihoz képest fokozott hányás		
6. A korábbihoz képest csökkent fizikai aktivitás		
NRS-PC pontszám (az „Igen” válaszok száma):		
A szűrést végezte:..... Dátum:		

kategória és az NRS-PC különböző határértékei közötti kapcsolat értékelésére. Az érzékenységet, a specificitást, a negatív és pozitív prediktív értékeket minden határértékhez kiszámítottuk és a *3. táblázat* segítségével szemléltettük. Ideális esetben egy mérőeszköznek 100%-os érzékenységgel kell rendelkeznie, hogy azonosítson minden gyermeket, akinek alacsony az izomtömege. 1-es pontszám esetén az érzékenység 75%-os, a specificitás 60%-os értéket mutatott. Mintánkban ez azt jelenti, hogy a saját szűrőmódszerünk 13 gyermeket helytelenül a normál izomtömegűek csoportjába, míg 40 gyermeket helytelenül az alacsony izomtömegű csoportba sorolt volna.

BMI kategóriák tekintetében a két szűrőmódszer AUC értékeiben nem volt szignifikáns különbség, azonban az alacsony és normál BMI-csoportokban a DeLong teszt eredménye megközelítette a szignifikanciát (*4. táblázat*). Az alacsony BMI csoportban a SCAN jobb tulajdonságokkal rendelkezett, míg a normál BMI csoportban a saját szűrőmódszerünk bizonyult jobbnak. Ennek ellenére egyik teszt sem volt kellő érzékenységű az alacsony BMI-csoportban.

3. táblázat: Az NRS-PC validálása izomtömegre. 95%-os megbízhatósági intervallum

Határérték	Érzékenység		Specificitás		Negatív prediktív érték		Pozitív prediktív érték	
1	0,75	[0,62, 0,86]	0,6	[0,49, 0,69]	0,82	[0,71, 0,9]	0,5	[0,39, 0,61]
2	0,7	[0,59, 0,79]	0,71	[0,58, 0,81]	0,64	[0,52, 0,75]	0,76	[0,65, 0,85]
3	0,62	[0,53, 0,71]	0,82	[0,65, 0,93]	0,38	[0,26, 0,5]	0,92	[0,84, 0,97]
4	0,59	[0,5, 0,68]	0,9	[0,68, 0,99]	0,25	[0,16, 0,37]	0,97	[0,91, 1]
5	0,54	[0,45, 0,62]	1	[0,29, 1]	0,04	[0,01, 0,12]	1	[0,95, 1]

4. táblázat: A SCAN és az NRS-PC összehasonlítása a különböző BMI kategóriákban

BMI	Esetszám	NRS-PC AUC		SCAN-AUC		Z	p
Alacsony	27	0,5	[0,22 0,78]	0,62	[0,31 0,93]	-1,86	0,063
Normál	99	0,72	[0,61 0,81]	0,64	[0,54 0,75]	1,75	0,081
Magas	25	0,83	[0,54 1]	0,74	[0,22 1]	0,77	0,439

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Megbeszélés, következtetések

Közismert, hogy gyermek onkológiai betegek körében magas az alultápláltság előfordulási aránya (12, 13). Ezért a tápláltsági állapot szűrése, a rizikó felismerése és táplálás terápiát igénylő betegek azonosítása, valamint osztályozása hozzájárulhat a probléma megoldásához. Létfontosságú, hogy legyen egy gyors, jól használható és az ápoló személyzet által is könnyen alkalmazható tápláltsági állapot szűrőmódszer, mivel az onkológiai osztályokon dolgozó dietetikusok korlátozott kapacitással rendelkeznek, és egyes központokban előfordulhat, hogy táplálás terápiás munkacsoport sem áll rendelkezésre.

2012 előtt csak a fogyást tekintették az alultápláltság kockázati mutatójának, klinikánkon nem végeztek tápláltsági állapot felmérést. 2012-ben azonban megalakult a táplálás terápiás munkacsoport (angolul rövidítve: NST) és elkezdtük fejleszteni saját betegégspecifikus tápláltsági rizikó szűrőmódszerünket is. Daganatos gyermekek ellátása során ugyanis elengedhetetlen annak megállapítása, hogy kinek van szüksége további szűrővizsgálatra, táplálkozási tanácsadásra, szájon át történő táplálék kiegészítésre vagy bármilyen más táplálkozási beavatkozásra. Ebben a kutatásban arra törekedtünk, hogy felmérjük alkalmas-e az NRS-PC ezekre a célokra, és használható-e a betegség bármely szakaszában.

Eredményeink alapján a magas BMI indexű betegek szűrését először NRS-PC-vel javasoljuk. Alacsony BMI esetén azonban a bioimpedancia mérések pontosabb információkat szolgáltatnak az izomtömegről és a tápláltsági rizikó kockázatáról. További adatok szükségesek annak eldöntése érdekében, hogy az NRS-PC elég érzékeny-e a normál testtömeg indexű betegek esetében. Mivel a testösszetétel a daganat terápiás kezelés alatt is változik, ezért nyomon követéses vizsgálatot érdemes végezni annak tisztázása érdekében, hogy az NRS-PC szűrőmódszer önmagában is megbízható-e bioimpedancia alapú mérés nélkül.

Summary

Nutritional risk screening and screening algorithm in pediatric oncology patients

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Cancer is one of the leading causes of childhood deaths. In Hungary, 200-250 new cases are registered every year in the 0-18 age group. Many types of childhood tumors are associated with a high risk of malnutrition. The aim of our research was to present our self-developed nutritional risk screening method and to develop a screening algorithm that can be used in institutions for pediatric oncology cases. The nutritional status survey was conducted between 2017 and 2018 involving 109 patients. We compared our self-developed screening tool to already validated methods to determine the cut-off value. It was demonstrated that our self-developed screening method had better properties for identifying children with lower muscle mass.

KEYWORDS malnutrition, nutritional risk screening, risk screening tools, pediatric cancer, pediatric oncology

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Útravaló tudnivaló

- Daganatos gyermekek ellátása során foglalkozzunk a tápláltsági állapot felmérésével
- Magas BMI-vel rendelkező daganatos gyermek esetében használjuk az NRS-PC-t tápláltsági rizikószűrésre
- Alacsony BMI-jű betegek esetén alkalmazzunk bioimpedancia mérést pl. InBody készülékkel
- Tápláltsági rizikó vagy alultápláltság esetén konzultáljunk dietetikussal vagy kérjük a táplálás terápiás munkacsoport segítségét.

Tesztkérdések

1. Melyik állítás igaz?
a) A tápláltsági állapotnak nincs jelentősége dagantos gyermekek esetében
b) A tápláltsági állapot befolyásolja a túlélést és a betegség lefolyását
c) Daganatos gyermekekre nincsen kidolgozott tápláltsági állapotszűrő módszer
d) Dagantos gyermekekre csak külföldi tápláltási állapotszűrő módszer létezik

2. Mi az NRS-PC szűrőmódszer célja?
a) Megjósolni a túlélést
b) Meghatározni a dagnat ellenes kezelés módját
c) Táplálás terápiát biztosítani minden daganatos gyermek számára
d) Azonosítani a tápláltsági rizikóval rendelkező dagnatos gyermeke

Az egyszerű választásos tesztekre a megoldást a társaság honlapján kérjük megjelölni: www.gyermekorvostarsasag.hu.
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2021 évi tesztkitöltő verseny eredménye

A Gyermekgyógyászat folyóirat 8 pontos kredittel rendelkezik, tehát 8 gyermekgyógyászati kreditpontban részesülnek a helyes megoldásokat beküldők. Ehhez legalább 5 lapszám tesztjét szükséges kitölteni és összességében a kérdések minimum 70%-ára helyesen kell válaszolni (jelen esetben 82 helyes válasz). Az első helyezett a 8 kreditponton felül 100.000 Ft-os jutalomban részesül.

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I. helyezett lett Dr. Bach Ágnes, aki 118 kérdésből 118-ra válaszolt helyesen.
II. helyezett lett holtversenyben: Dr. Al Banna Ahmad és Dr. Orbán Katalin, akik 118 kérdésből 116-ra válaszoltak helyesen.
III. helyezett lett Dr. Erdős Fruzsina, aki 118 kérdésből 115-re válaszoltak helyesen.

A helyezést elért résztvevőknek gratulálunk, és minden tesztkitöltő kollégának köszönjük a részvételt!

Dr. Bach Ágnes

„Szekszárdon születtem, itt végeztem általános és középiskolai tanulmányaimat. Érettségi után az Szegedi Tudományegyetem Általános Orvostudományi Karán tanultam, majd 2006-ban szereztem általános orvosi diplomát. Csecsemő- és gyermekgyógyászatból 2011-ben tettem szakvizsgát. Orvosi munkámat a Csongrád-Csanád Megyei Egészségügyi Ellátóközpont Hódmezővásárhely-Makó (akkor még Erzsébet Kórház) hódmezővásárhelyi Gyermekosztályán kezdtem, és azóta is ott dolgozom. ”