NUTRITIONAL STATUS OF CHILDREN AT CANCER DIAGNOSIS AND DURING TREATMENT, WITH A FOCUS ON THE ASSOCIATION WITH THEIR CLINICAL OUTCOME

by
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Dissertation presented for the degree of
Doctor of Philosophy in the Department of Paediatrics and Child Health in the Faculty of Medicine and Health Sciences at Stellenbosch University

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December 2023

DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my original work, that I am the authorship owner, and that I have not previously submitted it in its entirety on part for obtaining any qualification.

This dissertation includes three original papers published in peer-reviewed journals and two unpublished papers. The development and writing of the papers *(published and unpublished*) were the principal responsibility of myself, and for each instance where this is not the case, a declaration is included in the dissertation, indicating the nature and extent of the contributions of co-authors.

PLAGIARISM DECLARATION

The chapters of this thesis have been submitted to the Turnitin module, and I confirm that my supervisors have seen my report and that any concerns revealed by such have been resolved with my supervisors.

Signature

December 2023

DEDICATION

To **Our Holy Father**, for allowing me to **find my purpose in life** early in my career
--- to be involved in the treatment of children with cancer - **what a privilege**!

To all my patients over the years
…. thank you for allowing me to be part of your cancer journey
…. for those I still see at the clinic…..
you bring so much **JOY TO MY LIFE** to see how you have grown
…. to those we lost along the way
……*until we meet again*.

To the best parents I could have asked for, **Lood & Annatjie Schoeman**,
for all their support throughout my life & encouragement towards this degree.
You are missed every single day.

"Not all of us can do great things,
but we can do **SMALL** things with great **LOVE."**
- Mother Teresa

THE NATURE AND SCOPE OF CONTRIBUTIONS

Judith Schoeman conceptualised the study, designed the study, developed the protocol, was the primary investigator, developed the Redcap database, chose the questionnaires, enrolled patients, collected data, and cleaned and analysed the data. The student drafted and finalised all manuscripts for publication in chapters 1-6.

Mariana Kruger conceptualised some parts of the study as indicated per the manuscript, assisted in the concept development of all studies, and critically reviewed and edited all manuscripts for chapters 1-6.

Elena Ladas and Paul Rogers supervised the study and contributed and critically reviewed the manuscripts of chapters 2-5.

Ilde-Marié Kellerman, Ronelle Uys, Gita Naidu, Biance Rowe, Jan du Plessis, Mariechen Herholdt, Karla Thomas, Barry Vanemmenes, Rema Mathews, Ané Büchner, Fareed Omar, David Reynders were investigators at the different sites, enrolled patients, collected data, and critically reviewed the manuscript. All co-authors agreed that they could be included in my PhD thesis. Chapters 2-5 Sandile Ndlovu (Chapters 3,5,6) and Carl Lombard (Chapters 2-5) were the statisticians who performed the data analysis and critically reviewed and edited all data-related reporting in the manuscripts.

SUMMARY (English)

Up to 50% of children diagnosed with cancer in low-middle-income countries are malnourished, while in paediatric oncology units (POUs) in Africa, less than half had a dedicated dietician, and only a third undertook routine nutritional assessment.

Newly diagnosed children with cancer were longitudinally assessed for nutritional status in South Africa, including micronutrient assessment at diagnosis. The majority of the 320 children were well-nourished at diagnosis, while less than 15% had either stunting (14.3%), underweight (11.6%), wasting (8.1%), while a quarter (24.3%) had moderate acute malnutrition (MAM). Girls were more prone to being underweight (12.2% versus 4.5%; $P = 0.027$), while children five years and older had a higher prevalence of MAM (33.5% versus 14.5%; $P < 0.001$), with significant improvement six months after diagnosis ($P < 0.001$). Stunting was significantly associated with poor overall survival one year after a cancer diagnosis (HR 1.9; 95% CI 1.1, 3.3; $P = 0.029$).

Nearly a third (27.8%) of patients had a high poverty risk that was significantly associated with stunting ($P = 0.009$), food insecurity ($P < 0.001$), and residential province ($P < 0.001$). Most children lived in households with a high risk of food insecurity (80%) and had an increased odds ratio for treatment abandonment (OR 4.5; 95% CI 1.0; 19.4; $P = 0.045$) and hazard for death (HR 3.2; 95% CI 1.02, 9.9; $P = 0.046$) compared to those with food security.

Of 261 patients assessed for micronutrient status in two POUs, half had iron deficiency (47.6%), a third Vit A (30.6%), Vit D (32.6%), or folate (29.7%) deficiencies. There were significant associations between MAM and low levels of Vit A (48.4%; $P = 0.005$), Vit B12 (29.6%; $P < 0.001$), and folate (47.3%; $P = 0.003$). Male patients (40.9%; $P = 0.004$) and those with wasting (63.6%;$P < 0.001$) are associated with Vit D deficiency. Folate deficiency is significantly associated with children five years and older (39.8%; $P = 0.002$), residing in provinces Mpumalanga (40.9%) and Gauteng (31.5%) ($P = 0.032$); food insecurity (46,3%; $P < 0.001$), or haematological malignancy (41.4%; $P = 0.004$).

The South African-adapted childhood cancer-specific nutritional algorithm was implemented in an intervention group versus a control group that received standard nutritional support protocol. The implementation of the algorithm led to a significant improvement in nutritional status for the malnourished patients in the intervention group, while it was insignificant for the control group.

Determining socio-economic status and micronutrients at childhood cancer diagnosis in South Africa is crucial to plan appropriate nutritional interventions. Of note, stunting is associated with a poor one-year overall survival. The South African-developed algorithm successfully managed children with malnutrition at cancer diagnosis.

OPSOMMING (Afrikaans)

Tot 50% van kinders in lae-middel-inkomste lande wat met kanker gediagnoseer is, is ondervoed. Minder as die helfte van Afrika se pediatriese onkologie-eenhede (POE's) het 'n toegewyde dieetkundige, terwyl slegs 'n derde van hierdie eenhede gereeld antropometrie assesserings doen.

Pas gediagnoseerde kinders met kanker in Suid Afrika is longitudinaal geassesseer vir voedingstatus terwyl mikronutrient status bepaal is by diagnose. Die meerderheid van die 320 kinders was goed gevoed by diagnose, terwyl minder as 15% óf te kort was (14.3%), ondergewig (11.6%) of te skraal (8.1%) was, en 'n kwart (24.3%) matige akute wanvoeding (MAW) gehad het. Meisies was meer geneig om ondergewig te wees (12,2% teenoor 4.5%; P = 0,027), terwyl kinders van vyf jaar en ouer 'n hoër voorkoms van MAW gehad het (33,5% teenoor 14.5%; P <0,001) met aansienlike verbetering ses maande na diagnose (P < 0.001). Lengte (kort) was betekenisvol geassosieer met swak algehele oorlewing een jaar na 'n kankerdiagnose (HR 1.9; 95% CI 1.1, 3.3; P = 0.029).

Byna 'n derde (27.8%) van pasiënte het 'n hoë risiko vir armoede wat betekenisvol geassosieer word met lengte (P = 0.009), voedselsekuriteit (P < 0.001) en residensiële provinsie (P < 0.001). Die meeste kinders het in huishoudings gewoon met 'n hoë risiko van voedselonsekerheid (80%) en het 'n verhoogde risiko gehad om behandeling te laat vaar (OR 4.5; 95% CI 1.0; 19.4; P = 0.045) en mortaliteit (HR 3.2; 95% CI 1,02, 9.9; P = 0.046) in vergelyking met dié met voedselsekerheid.

In twee POE is 261 pasiënte se mikronutrient status beoordeel, en het die helfte ystertekort (47.6%), 'n derde Vit A (30.6%), Vit D (32.6%) of folaat (29.7%) tekorte gehad. Daar was betekenisvolle assosiasies tussen MAW en lae vlakke van Vit A (48.4%; P = 0.005), Vit B12 (29.6%; P < 0.001) en folaat (47.3%; P = 0.003). Manlike pasiënte (40.9%; P = 0.004) en diegene met MAW (63.6%; P < 0.001) word geassosieer met Vit D-tekort. Folaattekort word betekenisvol geassosieer met kinders vyf jaar en ouer (39,8%; P = 0.002), of wat woon in Mpumalanga (40,9%)

en Gauteng (31,5%) (P = 0,032); voedselonsekerheid (463%; P < 0.001), of hematologiese maligniteit (41,4%; P = 0.004).

Die Suid-Afrikaans-aangepaste kinderkanker-spesifieke voedingsalgoritme is geïmplementeer in 'n intervensiegroep teenoor 'n kontrolegroep wat ‘n standaard voedings protokol ontvang het. Die implementering van die algoritme se resultate was 'n betekenisvolle verbetering in voedingstatus vir die ondervoede pasiënte in die intervensiegroep, terwyl dit nie betekenisvol was vir die kontrolegroep.

Die bepaling van sosio-ekonomiese status en mikronutrient vlakke met die diagnose van kinderkanker in Suid-Afrika is van kardinale belang om toepaslike voedingsintervensies te beplan. Let wel, lengte (belemmerde groei) word geassosieer met 'n swak algehele oorlewing een jaar na diagnose. Die Suid-Afrikaans-ontwikkelde algoritme het kinders met wanvoeding by kankerdiagnose se voedingstatus suksesvol verbeter.

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LIST OF ABBREVIATIONS

BMI	Body mass index
EFS	Event-free survival
	EFS is defined as time to one of the following events: relapse, death, and second malignant neoplasm.
H/A or HAZ	Height for age
HIC	High-income country
HM	Haematological malignancy
LIC	Low-income countries
LMIC	Low-middle-income-countries
MAM	Moderate acute malnutrition
MUAC	Mid-upper arm circumference
NGO	Non-profit organisations
OS	Overall survival: OS is defined as the time from the date of diagnosis till the present.
PODC	Paediatric Oncology in Developing Countries
POU	Paediatric Oncology Unit
POUs	Paediatric oncology units
SAM	Severe acute malnutrition
SANHANES-1	South African national health Nutrition Examination Survey
SD	Standard deviations
SGH	SIOP Global Health Network
SIOP	International Society for Paediatric Oncology
ST	Solid tumour
TPN	Total parenteral nutrition
TSF	Triceps skinfold thickness
UMIC	Upper-middle-income countries
UNICEF	United Nations Children Fund
W/A or WAZ	Weight for age
WHO	World Health Organization
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

Problem statement

Annually between 160,000[1] to 416 000[1,2] children are diagnosed with cancer. Most (80% - 85%) live in low- or middle-income countries (LMICs).[3–5] The cure rate is currently around 80% in high-income countries[3,6–9] due to early diagnosis and combination treatment of chemotherapy, radiotherapy, and surgery.[10] For children in LMIC, access to curative therapy may be limited due to resources[3,6] with a lower cure rate.[7,9] Malnutrition in childhood cancer varies between 6% and 65%, which can be a negative prognostic factor with a higher risk of relapse[11] or decreased survival. [5,7,12–14]

Malnutrition definition

Malnutrition is defined as under-or overnutrition.[15,16] Undernutrition is caused when energy, protein, and other micronutrients are deficient, leading to adverse effects on body tissue resulting in chronic undernutrition, known as stunting (low height-for-age (HAZ) z-score), underweight (low weight-for-age (WAZ) z-score) and wasting (body mass index (BMI) for age (BAZ) z-score.[17,18] According to the World Health Organisation (WHO), undernutrition is seen as severe acute Malnutrition (SAM) or moderate acute Malnutrition (MAM). [17] SAM is defined as BAZ three standard deviations below normal (<-3SD) with or without oedema, while MAM is two standard deviations (<-2 SD) below normal for the corresponding age and sex with no oedema.[17] Younger children (under five years of age) were classified as SAM if the mid-upper arm circumference (MUAC) measurement were below <115mm,[18] while in older children, it is less than the 5th percentile.[12] Visible severe wasting is age dependent and more associated with identifying SAM in older children,[19] while pitting oedema is an independent criterion of SAM in any age group.[20] Malnourished children need a full clinical assessment to confirm the diagnosis, including vitamin- and mineral deficiencies.[21,22]

A 2021 report indicates that sub-Saharan Africa is the region most affected by malnutrition, especially children younger than five, where 26% are classified as stunted, 21% as underweight, and 6% as wasted[23]. It remains one of the main factors associated with childhood morbidity and mortality,[2] contributing significantly to the global disease burden. [24] The prevalence in South Africa is relatively high, with 35.8% of children stunted, 20.5% underweight, and 17.2% wasted.[25] Causes of malnutrition include poverty with poor diet, food insecurity, poor sanitary conditions, destitute mother and child care, lack of adequate health services, and chronic diseases such as Human Immunodeficiency Virus (HIV) and tuberculosis.[15]

Aetiology of malnutrition in childhood cancer

SAM in children with cancer is multifactorial due to various factors[14] that include inflammation, increased metabolic rate, insufficient oral intake, and physical activity that differs as seen in Table 1.[26] In South Africa about five out of 10 children go to bed hungry that can increase the risk of malnutrition in children with cancer.[27]

Table 1: Factors Contributing to Cancer Cachexia in Pediatric Oncology Patients

Sources of energy imbalance	**Potential mechanisms**
Inflammation causing low energy intake and/or anorexia	Cytokines released by tumor, immune, and stromal cells alter central nervous system transmitters and affect appetite • Tumor necrosis factor alpha (TNF-a) and interleukin-1 (IL-1) may increase levels of corticotrophin-releasing peptide, a neurotransmitter that suppresses food intake Modulation of gastric motility and emptying • Direct effect on gastrointestinal system

Sources of energy imbalance	**Potential mechanisms**
	• Alteration of efferent signals regulating satiety; IL-1 blocks feeding stimulated by neuropeptide Y
Metabolic and endocrine alterations leading to increased catabolic drive	Carbohydrate metabolism • Increased fasting insulin levels • Increased glucose demand Protein metabolism • Loss of normal compensatory protein conservation mechanisms seen in starvation • Increased whole-body protein catabolism • Increased protein catabolism in muscle cells • Decreased regulators of muscle protein synthesis Fat metabolism • Accelerated lipolysis driven by inflammatory cytokine inhibition of lipoprotein • lipase; TNF-a and Il-6 implicated • Increased rate of fat oxidation and clearance • Decreased lipoprotein-lipase, may shift energy burden to lean body mass Disease burden • Metabolic demands of tumor in progressive disease

The metabolic effect of developing SAM in children with cancer due to the effect of cytokines produced by cancer, causing increased protein breakdown with decreased protein synthesis. The continuous release of tumour necrosing factor-alfa (TNFα), interleukin 1 (IL-a) and -6 (IL-6) cytokines leads to muscle store depletion, anorexia and increased turnover of protein, resulting in weight loss and poor muscle strength. Furthermore, cytokines also cause inflammation in the body and activation of macrophages, the immune system regulator of the child [28] that may differ per cancer diagnosis[29]. The increased protein turnover[28,30] weakens the immune system, and the decreased muscle strength of the heart and respiratory muscles ultimately causes heart and/or respiratory failure. Advanced stages of cancer have increased demand on the child, as an increased number of cytokines are released, causing increased protein turnover and decreased lean body stores.[28] TNFα also increase lipolysis[30,31], increase fatty acid turnover[31], with decreasing fat tissue,[30] and increasing weight loss. The combination of TNFα and IL-6 decreases glucose tolerance and increases insulin usage, which leads to increased gluconeogenesis and the need for glucose increase[28], as glucose is transformed to lactate by the tumour. The body requires glucose, so the lactate needs to be recycled to glucose,[30] leading to the use of diet-related amino acids and muscles via the Cori cycle to form glucose[28,30]. Glucose turnover increases, leading to adenosine triphosphate (ATP) loss and energy-wasting, causing SAM[28].

There is no clear answer regarding the effect of cancer on resting energy expenditure (REE) in a child. Studies have shown that children with haematological malignancy have no increase in REE, while children with a solid tumour have shown an increased REE. It is, therefore, a challenge to determine nutritional requirements in a child with cancer to prevent the worsening of potential existing malnutrition. [28]

Malnutrition at cancer diagnosis and during treatment

Worldwide there is a growing interest in supportive care's role in improving prognosis, especially nutrition.[10] Previous reports indicated that up to 50% of children diagnosed with cancer in LMIC were malnourished,[7,12–14] but the prevalence could be misleading due to the potential underestimation of undernutrition amongst this population.[32] Limited reports were available to review for Africa. In Ghana, 16.2% of the cancer patients were wasted, 11.5%

stunted, and 5.6% underweight, but according to MUAC, 54.1% were malnourished at diagnosis.[14] Nigerian and South African children diagnosed with cancer had similar results; about 20% and 25% were malnourished according to weight and height but this increased to 54.1% and 41.8% on MUAC measurements.[14,28] In the previously mentioned South African study group, patients diagnosed with a solid tumour had a higher prevalence of wasting than haematological malignancy but also had advanced disease, potentially indicating prolonged exposure to the catabolic effects of childhood cancer.[28] Arm anthropometry was considered more sensitive in assessing nutritional status in children with cancer; as the measurements are not influenced by a tumour mass,[3,7,32] and temporary gain in total body water,[33] therefore, MUAC should be included in the nutritional assessment [32,34,35]. The nutritional status could easily be measured by MUAC and indicator of protein- and musculature stores, [33,36] also known as lean body mass.[3,32]

Cancer patients classified as SAM in Nicaragua, an LMIC, had significantly lower EFS after two years post-diagnosis.[3] Nutritional status of cancer patients, therefore, has a prognostic effect on the outcome in LMIC. In LMIC, where a high percentage of patients are malnourished, supportive care is not accessible to all patients, as a 2012 survey for LMIC found that only 71% of participating hospitals had access to oral nutritional supplements, and the most significant barriers to nutritional services included finances, dietician availability, resources, and education of staff, meaning it was not available to every patient.[37]

Effect of malnutrition on the response to cancer treatment in children

Malnourished children respond differently to medical treatment than well-nourished children, with higher mortality risk, with or without complications.[22] Chemotherapy such as asparaginase and corticosteroids (to treat acute lymphoblastic leukaemia, acute myeloid leukaemia and non-Hodking's lymphoma) increase muscle breakdown or damage and/or protein catabolism leading to protein depletion and weakened muscle strength and immune system [28,29]. Malnourished cancer patients experience increased therapy-related toxicities, with an increased risk for infections[3,8,10,14] due to frequent episodes of severe neutropenia.[7,14] The reduced tolerance to therapy[3,8,10–12,14] may cause treatment delays[3,14] or dose adjustment for the chemotherapy.[8,14] In LMIC, malnutrition may be a negative prognostic factor in

children with cancer[14,38,39] that is often associated with increased hospital stay[10] morbidities[38,39] and increased treatment abandonment rate.[32] These children also have a higher incidence of relapse[11] and decreased survival.[3,8,10,12] Considerable benefits are seen in well-nourished cancer patients during cancer treatment,[812]

Food Insecurity, Poverty, and Micronutrient Deficiencies

UNICEF states that out of two households in LMIC experiences hunger[40,41] while about a quarter of the Sub-Sahara African population (23.3%) live in hunger [27] and 67% in poverty.[42] The majority of people globally living with food insecurity live in sub-Saharan Africa.[32] More than 56% of the South African population lives on less than US$5/day (R90/day),[43] even though it is an upper-middle-income country,[44] and most children live in chronic poverty leading to undernutrition and poor health.[45] Different tools are available to measure poverty; in South Africa, the Simple Poverty Scorecard® Poverty-Assessment Tool was tested and validated.[46] This tool can measure a family's risk of living in poverty (under US$ 2/day)[46], identifying vulnerable patients with cancer diagnoses needing referrals to social workers and support networks. UNICEF reports that one out of two households in South Africa experiences hunger,[40,41] and those worst affected live on commercial farms, rural areas, and informal urban areas.[41] It is estimated that 23.2% of the population experience hunger, and 40-50% of children go to bed hungry.[27] The Community Childhood Hunger Identification Project questionnaire-based measure can be used to measure household hunger; it is an excellent method to determine domestic hunger.[47] Household food security of all newly cancer-diagnosed children needs to be determined at pediatric oncology units (POU). Children go home between treatments and need to improve or maintain their nutritional status. A high percentage of the population in South Africa also suffers from "hidden hunger," meaning a person might not go to bed hungry. Still, the quality of their food intake may lack micronutrients (vitamins and minerals),[48] which leads to deficiencies.

The poorest people live in rural areas, where micronutrient deficiencies are common, especially vitamin A, iron, and zinc, indicating that food intake of animal origin, fruit, and vegetables is limited. [49] In the Middle East and Africa, the prevalence of Vitamin D

deficiency is current, even though these countries have high levels of sunlight exposure throughout the year, especially in summer and winter.[50] A 2015 report indicates that nearly a fifth of children ten years of age have had insufficient vitamin D levels, and 7% are deficient in South Africa.[50] South African children under five years have a 28.9% prevalence for anaemia and 21.4% for iron deficiency.[51] The risk for Vitamin A and folate deficiency in Sub-Sahara Africa was 42.4% and 12%, respectively.[52],[51] South African children diagnosed with cancer may be prone to micronutrient deficiencies and depleted concentrations, increasing therapy-related toxicities, [39] which should be addressed during nutritional supportive care during childhood cancer treatment.

Nutritional Support During Childhood Cancer Treatment

Nutritional support during childhood cancer treatment must ensure adequate nutrient – and anti-oxidant intake,[15] with improved nutritional status[36], age-appropriate growth and development,[8,53] and prevention or reversal of malnutrition[11,54] with improved well-being.[53] Supplementation may induce recovery from malnutrition, but nutritional education is essential as this contributes towards sustainability.[15] A lack of knowledge may be the leading cause of poor feeding practices and the development of nutritional deficiencies. Education programs may inspire parents and caregivers to change feeding behaviour to more appropriate diets and should be part of the nutritional support during childhood cancer treatment.[20]

Supportive care may decrease treatment-related mortality.[7] Nutritional support in the hospital and at home includes meals rich in energy and protein. Nutritional supplements or extra food may be needed to provide adequate macro-and micronutrients[7] due to the potential existing increased catabolism due to underlying cancer. [28] In Malawi, children received a fortified spread (50g) of maise/soya flour for 12 weeks, and both groups had a significant increase in weight with a decrease in stunting after one year.[55] Another Malawi study has provided energy-dense, lipid-based, ready-to-use supplements that have decreased wasting with the promotion of linear growth.[56] A retrospective study in Pretoria, South Africa, has indicated an improvement in BMI and arm anthropometry after three months in those patients who received adequate oral nutritional supplements.[57] A prospective nutritional

intervention study is therefore proposed to observe the effect on treatment-related mortality and outcomes for children at pre-defined time intervals. The conclusion will indicate which patients need nutritional support and must benefit from limited resources.[3]

Conceptual framework

The World Health Organization's Global Initiative to improve outcomes for children with cancer globally is currently the main focus in childhood cancer management globally[58]. As poor nutritional status might impact negatively on childhood cancer survival[58], this study is planned to investigate nutritional status' impact on early childhood cancer survival in South Africa with associations to current risk factors in the local context. The thesis is planned to undertake several studies simultaneously towards the PhD. The first study is a survey of what the status of nutritional support in Africa, as well as in South Africa. The other studies are investigating the associations between nutritional status at childhood cancer diagnosis with poverty, food insecurity, micronutrient deficiencies and early outcome, defined as the one-year post-cancer diagnosis in South Africa, as these variables are reported to be prevalent in South Africa[45]. These associations are chosen as South Africa faces major socio-economic which may impact on early outcome of a child with cancer.

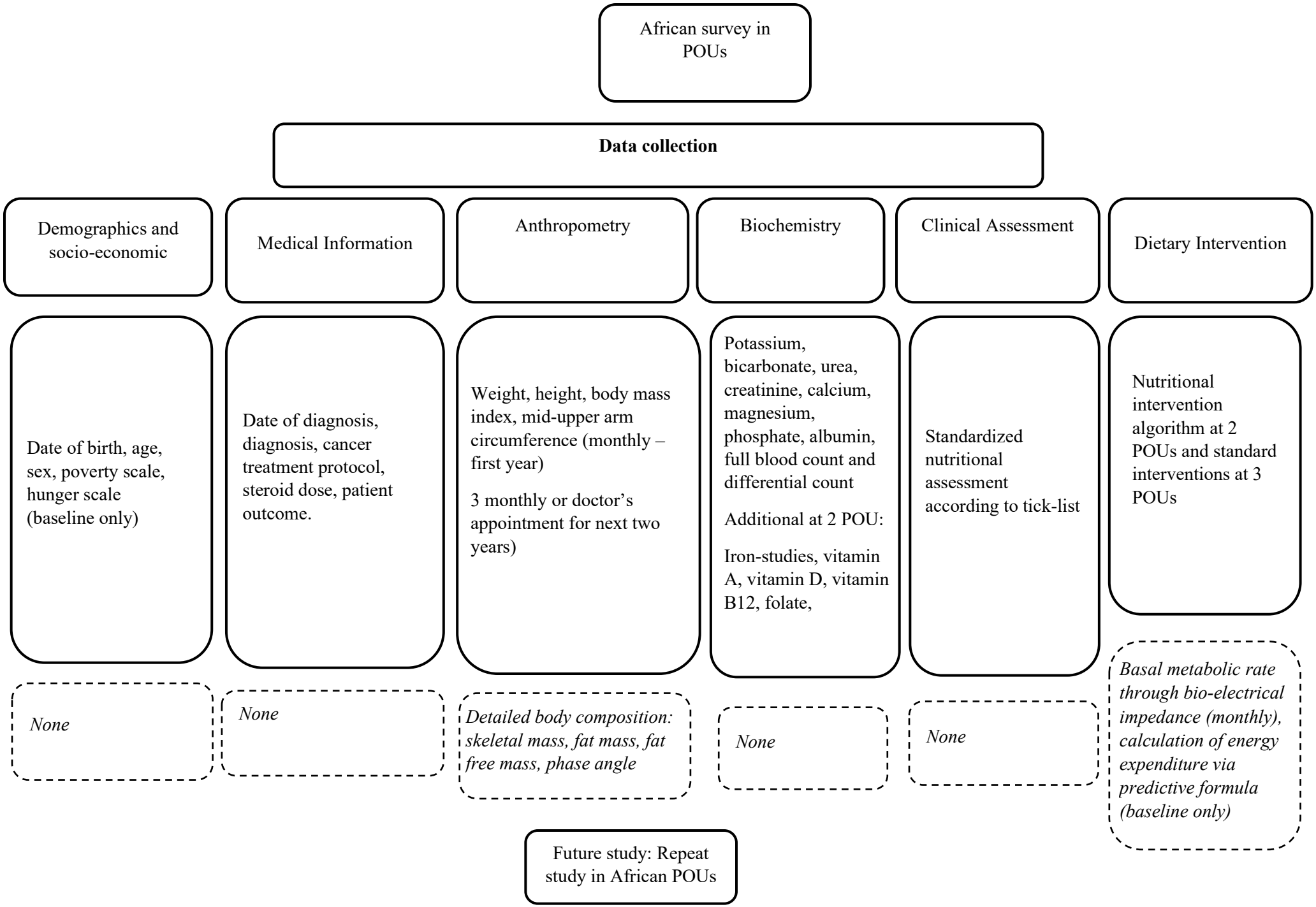
Conceptualisation of the PhD studies (Figure 1).

As Africa as a continent has limited access to supportive care for children treated for cancer and in line with the WHO's aim to improve childhood cancer survival,[58] the first study investigates the nutritional support and resources available in African POUs.[59]

This study has been completed prior to embarking on the other studies and the results have influenced the planning of these studies, especially the development of a Soth African specific nutritional support algorithm to be implemented in South Africa POUs if proven effective. The other studies involved the enrolment of newly diagnosed children with cancer and/or parenteral consent and children's assent. Data collection is discussed in the different chapters per study and have included demographic data (date of birth, age, sex, province of living), medical data (date of cancer diagnosis, cancer diagnosis, cancer stage or risk group, cancer

treatment protocol), socio-economic information (poverty – and hunger scale questionnaires) anthropometrical data (weight, height, BMI and MUAC), clinical assessment, nutritional interventions and outcome data one-year post-cancer diagnosis namely OS and EFS.

To determine the potential effect of poverty and food insecurity on nutritional status at diagnosis and one-year OS (see Chapter 3). To determine micronutrient status at diagnosis (Vit A, Vit D, Vit B1, folic acid and iron) and impact on nutrition status (see Chapter 4). To determine the prevalence of malnutrition at diagnosis and its effect on one-year OS and EFS (Chapter 5). The South African-specific nutritional support algorithm, developed for this PhD study, has been introduced in two of the South African POUs as proof of concept and have been compared to outcome with standard nutritional supportive care for children with cancer in the other three POUs (see Chapter 6). A nested masters' study with the title "*Changes in nutritional status, body composition and metabolic rate of paediatric cancer patients during initial onco-chemotherapy*" has been done at the Tygerberg hospital POU as they had access to a calibrated Body Impedance meter, which unfortunately none of the other South African POUs has. This study specifically investigates the use of BIA in the nutritional management of childhood cancers as this may be an improved method of nutritional assessment in children with cancer, Figure 1 illustrates the relationship between the PhD study (solid line) and the nested master's study investigations (dotted line) [previously reported in mentioned Master's thesis][60]



The research aims and objectives:

1. To determine the current status of nutritional support in POUs in Africa.
2. To determine the association between malnutrition at cancer diagnosis with poverty and/or food insecurity as well as with one-year overall survival (OS) and event-free survival (EFS).
3. To determine if vitamin and iron deficiency is common in children at cancer diagnosis at two POUs and whether there is an association between malnutrition at diagnosis and with one-year OS and EFS.
4. To determine the prevalence of malnutrition at childhood cancer diagnosis and associated with one-year OS and EFS.
5. To determine if the adapted South African nutritional intervention algorithm for children with cancer at time-set intervals has improved nutritional status in children treated in two POUs, compared with standard supportive nutritional care in the other POUs regarding one-year OS and EFS.

Patient recruitment

As discussed in the different studies in Chapters 2-6. Only patients with written consent and/or assent were included.

Statistics and Limitations of the different studies

As discussed in Chapters 2-6

Data Management

Data was collected and captured on the Redcap database server storage (Stellenbosch University) of which the principal investigator and supervisor that had access to the complete database. The co-investigators of each POU were able to load data on the database for their own unit, but after data was loaded it was locked to prevent -investigators changing data. The PhD student /principal investigators routinely checked the data to ensure all data was complete and to check for any outliers that needed to be verified by the co-investigators. On 31 December 2020 the data on Redcap was closed for adding any newly partipants. The investigators of each POU have access to upload follow-up assessments on Redcap database for all the patients' in their unit that's part of the study until the end of 31 December 2022.

Structure of the Dissertation

This thesis is in hybrid format, including three publications and two manuscripts still to be submitted for publication.

CHAPTER 2: Unmet Needs in Nutritional Care in African Paediatric Oncology Units

Africa continent: Paediatric Oncology Nutrition Study.
Ethics Reference #: N16/11/140.

The availability of nutritional services and- products in pediatric oncology units in Africa was unknown at the start of this research project. To understand this area of supportive care, an initiative between the International Society for Paediatric Oncology (SIOP) Global Health Network (GHN) Nutrition Workgroup (NWG) and SIOP Africa was formed to conduct a continental survey to identify barriers to nutritional care and institutional needs in POU in Africa. This survey intended to prioritise these needs and develop nutritional support programs to enhance OS in African children diagnosed with cancer and, in future, replicate this prospective study (chapters 3-6) in other African countries.

Hypothesis:

H0: POUs in Africa do not have barriers to nutritional care for childhood cancer patients.
Ha*:* POUs have barriers to nutritional care for childhood cancer patients

Objective:

An initiative between the SIOP GHN NWG and SIOP Africa was formed to conduct a continental survey to identify barriers to nutritional care and institutional needs in POU in Africa.

Method:

This study was an online survey adapted from a previously published survey in LMIC[61]. The Health Research Ethics Committee (HREC), Faculty of Medicine and Health Sciences, Stellenbosch University gave ethics approval. The survey collected information on respondents (e.g. discipline), the hospital's standard of nutritional- assessment and interventions, barriers to nutritional care, educational needs, and research interests. Participants were identified by the

SIOP GHN Nutrition Working Group, the SIOP GHN Supportive Group, Paediatric Oncology International Network for Training and Education website (POINTE) and SIOP Africa. The survey was conducted between December 2016 and June 2017 and administered through surveymonkey.com.

CHAPTER 3: Prevalence of Poverty and food insecurity at cancer diagnosis and Association with Malnutrition and overall survival in South Africa

South Africa is an upper-middle-income country,[44] but in 2015, more than 50% of the population lived on less than US$5/day (R90/day).[43] A high percentage of the population in South Africa also suffers from "hidden hunger," it can be explained that even though a person might not go to bed hungry, the quality of the food intake may lack vitamins and minerals, which leads to deficiencies and cause Malnutrition. South African children might have a high risk of living in poverty and hunger at cancer diagnosis, leading to Malnutrition.

Hypothesis:

H0: Children diagnosed with cancer, living in poverty, or experiencing household food insecurity are not prone to be undernourished at diagnosis and will have no association with 2-year OS and EFS.

Ha: Children diagnosed with cancer, living in poverty, or experiencing household food insecurity are prone to be undernourished at diagnosis and associated with a poor 2-year OS and EFS.

Objective:

To determine if there is an association between nutritional status at cancer diagnosis and poverty, as well as food insecurity and the potential impact on one-year OS and EFS.

Method

This was a structured interview based study in the five government/ state-funded POUs in South Africa. The recruitment of children diagnosed with cancer were done between 1 Oct. 2018 and 31 December 2020. The interview was conducted with the biological mother/father or legal guardian to obtain information regarding poverty and food security at home at the time of

diagnosis. Two questionnaires were completed during the interview [the questionnaires weres typed and added into the datasheet, to ensure all questions will be handled equally]

The household hunger scale (HHS) questionnaire with eight questions from the CHHIP was used. This questionnaire was and validated previously in South Africa (1999). Five (Yes) responses out of a maximum possible of eight were considered as "hungry". A score of one to four (Yes) responses out of eight indicated that the family was at "risk of hunger". A negative response (No) meant the family was food secure. 62 Thee questionnaire to determine poverty, namely the 'Simple Poverty Scorecard ® Poverty-Assessment Tool South Africa' with 12 questions was compiled, tested and validated in SA in 2017.46 Score of 0-35 indicated a high risk or ≥ 64.8% likelihood of living below poverty line (2$ per day); 36-50 indicated medium risk or ≥18.4% and 51-100 a low risk for living in poverty or ≤18.3% 63.

The interview was done within 72h after diagnosis and information used for possible association between food insecurity and poverty with malnutrition at cancer diagnosis, as well as one-year OS and EFS.

CHAPTER 4: Prevalence of vitamin and iron deficiency in newly diagnosed children in two POUs in South Africa and association with OS and EFS one year after cancer diagnosis

Vitamin and mineral deficiencies are a global public health problem, especially in regions where food insecurity and poor diet diversity are endemic.[64] In LMICs, micronutrient deficiencies are common,[65] and in sub-Sahara Africa[66-67] the prevalence in children ranges from 60% to 80% for vitamin A (Vit A), vitamin B12 (Vit B12), vitamin D (Vit D)[50,68,69] and iron deficiency.[66]

Hypothesis:

H0: Children diagnosed with cancer in South Africa are not vitamin and iron deficient and therefore not associated with poor OS and EFS

H1: Children diagnosed with cancer in South Africa are vitamin and iron deficient, and therefore associated with poor OS and EFS.

Objective:

To describe the prevalence of vitamin A, Vit D, Vit B12, folate, and iron deficiency in children at cancer diagnosis in two POUs and to determine if associated with a poor one-year OS and EFS.

Method:

This study was a prospective cohort study in two (Steve Biko Academic Hospital and Tygerberg Hospital) of the five government / state-funded POUs in South Africa with the recruitment of children diagnosed with cancer between 1 October 2018 and 31 December 2020. Standard blood tests [Full blood counts (FBC), electrolytes, and comprehensive metabolic panel (CMP) as required by the cancer diagnosis and management, were done at diagnosis. Additional tests done for the study at the 2 POUs included serum Vitamin A, vitamin D, vitamin B12, folate and iron studies within 72 hours after diagnosis. These micronutrients were documented as potential deficiencies in South Africa and tests were available at National Health Laboratory Services.

CHAPTER 5: Prevalence of Malnutrition in newly diagnosed children in five pediatric oncology units in South Africa and Association with overall survival one year after diagnosis

In LMIC, Malnutrition at cancer diagnosis is common, [7,12–14] but can be even higher due to the underestimation of undernutrition amongst this population.[32] Malnutrition is caused by increased catabolism and requirements to ensure growth and development; on the other hand, Malnutrition is a negative prognostic factor in children with cancer[14,38,39] that is often associated with increased hospital stay[10] morbidities[38,39] and increased treatment abandonment rate[32] and poor survival.

Hypothesis:

H0: There is a low percentage of children diagnosed with cancer with malnutrition at diagnosis, and therefore not associated with a poor OS, and EFS.

Ha: There is a high percentage of children diagnosed with cancer with malnourished at diagnosis, and therefore associated with a poor OS, and EFS

Objective:

To describe the prevalence and severity of Malnutrition in children at cancer diagnosis and to determine if Malnutrition, at cancer diagnosis, is associated with a poor one-year OS and one-year EFS.

Methods:

This study was a prospective cohort study in the five government / state-funded POUs in South Africa with the recruitment of children diagnosed with cancer between 1 October 2018 and 31 December 2020 with follow-up of patients from 1 August 2019 till 31 December 2023. This cohort study collected the anthropometric –and clinical data, (including cancer diagnosis), as well as demographic data (e.g. age, sex) on diagnosis. The data collected were analysed to determine the prevalence of malnutrition at cancer diagnosis and possible association with one year's OS and EFS. The sample group was also divided into the two major cancer disease groups, namely solid tumours versus haematological malignancies and a comparison between their nutritional status at diagnosis and their outcome after one-year investigated.

CHAPTER 6: Implemented nutritional intervention algorithm in pediatric oncology compared to standard nutritional supportive care outcomes in South Africa

The primary goal of nutritional support for patients diagnosed with cancer and during their treatment is to ensure adequate nutrient – and anti-oxidant intake,[15] improved nutritional status[36], age-appropriate growth[8,54], and development[8,53] and therefore prevent or reverse malnutrition[11,54] and improve well-being.[53] Supplementation may induce recovery from malnutrition

Hypothesis:

H0: Planned nutritional interventions at specific time points according to a specifically developed nutritional algorithm [at two POUs] for childhood cancer at specific time points will not improve nutritional status and one-year OS and EFS.

Ha: Planned nutritional interventions at specific time points according to a specifically developed nutritional algorithm (at two POUs) for childhood cancer will improve nutritional status and one-year OS and EFS.

Objective:

To determine if planned nutritional intervention at time-set intervals according to a specifically developed nutritional algorithm for childhood cancer will improve nutritional status in two POUs compared with standard supportive nutritional care/ protocols in the other POUs, as well as improve 2-year OS and EFS. This algorithm was developed specifically for this Ph.D. research project by the candidate.

Method:

This was an intervention, randomised prospective cohort study involving the study population recruited for the other studies between 1 Octpber 2018 and 31 December 2020. As only two paediatric oncology units had the ability to implement the nutritional intervention as they had dedicated dieticians to do so. These two POU were therefore selected as the intervention group. The children from the three other POUs acted as the control group with standard nutritional supportive care implemented. The nutritional interventions according to the specifically developed nutritional algorithm [compiled by PhD student – **chapter 6]** was Steve Biko Academic Hospital and Tygerberg Hospital, while the other POUs continued management according to the standard guidelines of supportive nutritional care from SIOP-GHN or POU guidelines. These guidelines include a high energy-high protein diet, additional supplements if needed and NG enteral nutrition for SAM patients as per discretion of the treating medical health care team. The interventions were captured on a REDCAP database prospectively. All assessments done at each visit to the POU clinic as per standard childhood cancer care; otherwise once a month until 1 year after diagnosis and thereafter once every 3 months (if medically indicated) during follow up visits at the paediatric oncology clinic as per standard of care until 31 December 2022. The data was analyzed and the two groups compared. The planned intervention group used the MUAC//Age Z-scores as an indicator of nutritional intervention.

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CHAPTER 2

Unmet Needs in Nutritional Care in African Paediatric Oncology Units

Ethics no: **#: N16/11/140**

Reference: Schoeman J, Ladas EJ, Rogers PC, Aryal S, Kruger M. Unmet Needs in Nutritional Care in African Paediatric Oncology Units. Journal of Tropical Pediatrics, 2018, 0, 1–8.
DOI: 10.1093/tropej/fmy068
(Impact factor 1.1)

This study determined the nutritional care, barriers and needs in Africa. The hypothesis was:

Ha*:* POUs in Africa have barriers to nutritional care for childhood cancer patients

H0: POUs in Africa do not have barriers to nutritional care for childhood cancer patients.

The International Society for Paediatric Oncology (SIOP) Global Health Network (GHN) Nutrition Working Group (previously PODC) and SIOP Africa conducted a continental survey to identify barriers to nutritional care and institutional needs in POU in Africa. This survey intended to prioritize these needs and develop nutritional support programs to improve overall survival in children with cancer in Africa.

More than 80% of the paediatric oncology units in low-income countries had no access to a full-time dietitian, but in South Africa, an upper-middle-income country, a third had allocated dieticians. Only half the newly diagnosed children admitted to the hospital underwent nutritional assessment, while a third at the outpatients' clinic, with no consensus on the parameters needed for assessment. The availability of nutritional supplements was a luxury and primarily used for inpatients.

Our study supported the hypothesis that African paediatric oncology units had multiple barriers to providing these patients with nutritional care. Non-profit organizations are essential in providing necessities to the units, meals, and/or nutritional support.

Journal of Tropical Pediatrics, 2018, 0, 1–8
doi: 10.1093/tropej/fmy068
Original paper

Unmet Needs in Nutritional Care in African Paediatric Oncology Units

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ABSTRACT

Background: Up to 50% of children diagnosed with cancer in low- and middle-income countries are malnourished, which likely affects survival.
Subjects and methods: An online survey to paediatric oncology units (POUs) in Africa was done regarding nutritional assessment and care.
Results: Sixty-six surveys were received from POUs in 31 countries. Only 44.4% had a dedicated dietician for nutritional assessment and support; 29.6% undertook routine nutritional assessment during treatment. None reported defined criteria for nutritional intervention. Total parenteral nutrition was not available for 42.6% of POUs, while 51.8% did not have access to commercial enteral nutrition for inpatients, and 25.9% of the hospitals could not supply any home-based nutritional supplements.
Conclusion: Nutritional assessment in POUs in Africa is neither routinely undertaken nor are there defined criteria to initiate nutritional interventions. Standardized guidelines for nutritional assessment and interventions are needed for African POUs to enable improved outcome.

KEYWORDS: survey, paediatric oncology, nutritional care, dieticians

INTRODUCTION

Globally >160 000 children are diagnosed with cancer each year, the majority (80–85%) live in low-income countries (LICs) and low- and middle-income countries (LMICs) [1–3]. The current cure rate for children with cancer in high-income countries is approximately 75–80% [1–6]. In LMICs, access to curative treatment is limited and poor survival rates have been reported [1, 2, 5–7]. Poor nutritional status, both under-and over-nutrition, range from 5% to 50% in paediatric cancer patients at diagnosis, with a higher prevalence of undernutrition in LMICs [6, 8–11]. The reasons for this are multifactorial [12] and influenced by the cancer diagnosis, stage of disease, co-morbidities, access to care and socio-demographic factors [11].

Poor nutritional status has an adverse effect on treatment-related toxicity and survival [1, 4, 9, 12, 13, 14, 15, 16]. Moreover, undernutrition has been associated with treatment delays [1, 4, 10, 11, 15, 16], dose adjustments [1, 4, 9, 11, 15, 16], increased hospital stay and abandonment of care [1]. Africa represents a large proportion of the global burden of undernourished children. This co-morbidity in children with cancer causes additional clinical challenges for paediatric oncologists. Up to 60% of children in Malawi were undernourished at diagnosis [6], and 25–50% in Ghana were wasted [11]. In Pretoria, South Africa, 21.6% of children were wasted and 24.3% underweight [17]. This prevalence of undernutrition highlights the need for nutritional resources so that necessary life-saving cancer therapy may be delivered.

Previous surveys have reported several barriers to the implementation of nutritional services in LICs [18, 19] but did not focus on the Africa continent or included hospitals that treat children with cancer with no paediatric oncologists. As part of a newly formed initiative between the International Society for Pediatric Oncology (SIOP) Paediatric Oncology in Developing Countries (PODC) Nutrition Working Group, SIOP Africa, and the International Initiative for Pediatrics and Nutrition Columbia University, we conducted a continental African survey.The intention of this survey was to identify the specific needs of paediatric oncology units (POUs) in Africa, develop nutritional support programmes to improve patient's nutritional status and overall survival. Nutritional support in other LIC POUs outside of Africa has resulted in improved outcomes [1, 9].

SUBJECTS AND METHODS

The online survey was adapted from a published survey [18] and conducted between December 2016 and June 2017 and administered through surveymonkey.com. Ethics approval was obtained from the Health Research Ethics Committee of Stellenbosch University.

The survey collected and collated information on the respondent's hospital's standard of care for nutritional assessment and interventions, barriers to nutritional care and educational needs. Participants were identified by the SIOP PODC Nutrition Working Group, the SIOP PODC Supportive Group, Paediatric Oncology International Network for Training and Education website and SIOP Africa.

Responses were categorized using the World Bank classification according to income in Africa, namely, LICs, LMICs and upper-middle-income countries (UMICs) as seen in Table 1 [20]. Incomplete surveys were removed from the study. Institutions that provided multiple responses were compared for consistency and institutions contacted for clarification. The countries of Swaziland, Lesotho, Mozambique, Eritrea and Sierra Leone were excluded from this survey, as they do not offer treatment for children with cancer. Results are presented as percent distribution of the institution's response by SPSS version 25.

RESULTS

In total, 66 (44.29%) of 149 surveys were received. Four surveys were incomplete and eight were removed as they were duplicates. The final results contained 54 surveys representing all income levels in Africa. Table 1 presents the responses by income group and region. The responses were, respectively, 35.2% ($n = 19$) for LICs, 33.3% ($n = 18$) for LMICs and 31.5% ($n = 17$) for UMICs.

Dietetic services

The majority (66.6%; $n = 36$) of the institutions had permanently appointed dieticians to consult on in- and outpatients, <45% ($n = 28$) had a dedicated dietician for their POU. It is observed that in LICs, 84.2% ($n = 16$ of 19) had no dedicated dietician in the POU, but the number decreased in UMICs with 33.3.7% (6 of 17) and LMICs with 35.3% (6 of 18).

Nutritional assessment

Nutritional assessment on all newly diagnosed children with cancer was performed at 51.9% of the hospitals in the inpatient setting ($n = 28$); only 33.3% attending outpatient clinics ($n = 18$) were assessed. Nutritional assessment for children during treatment was only performed when clinically indicated (61.1%) or if referred by the treating doctor (44.4%).

The parameters that are included in the nutritional assessment of children are presented in Table 2. Greater than 90% of POUs in all the different income groups relied on length/height and weight; >60% questioned on oral intake (82.4% in UMICs)

Table 1. Survey responses by country, income group and region

Economy	Region	Subregion of Africa	Income group	Number of sites responded
Benin	Sub-Saharan Africa	West	Low income	1
Burkina Faso	Sub-Saharan Africa	West	Low income	1
Chad	Sub-Saharan Africa	Central	Low income	1
Congo, Democratic Republic	Sub-Saharan Africa	Central	Low income	1
Ethiopia	Sub-Saharan Africa	East	Low income	1
Guinea	Sub-Saharan Africa	West	Low income	1
Madagascar	Sub-Saharan Africa	East	Low income	1
Malawi	Sub-Saharan Africa	East	Low income	3
Mali	Sub-Saharan Africa	West	Low income	1
Niger	Sub-Saharan Africa	West	Low income	1
Rwanda	Sub-Saharan Africa	East	Low income	1
Senegal	Sub-Saharan Africa	West	Low income	1
Tanzania	Sub-Saharan Africa	East	Low income	3
Uganda	Sub-Saharan Africa	East	Low income	1
Zimbabwe	Sub-Saharan Africa	East	Low income	1
Cameroon	Sub-Saharan Africa	Central	Lower middle income	2
Congo, Republic	Sub-Saharan Africa	Central	Lower middle income	1
Côte d'Ivoire	Sub-Saharan Africa	West	Lower middle income	1
Egypt, Arab Republic	Middle East and North Africa	North	Lower middle income	2
Ghana	Sub-Saharan Africa	West	Lower middle income	2
Kenya	Sub-Saharan Africa	East	Lower middle income	2
Morocco	Middle East and North Africa	North	Lower middle income	2
Nigeria	Sub-Saharan Africa	West	Lower middle income	3
Sudan	Sub-Saharan Africa	North	Lower middle income	1
Tunisia	Middle East and North Africa	North	Lower middle income	1
Zambia	Sub-Saharan Africa	East	Lower middle income	1
Angola	Sub-Saharan Africa	Central	Upper middle income	1
Algeria	Middle East and North Africa	North	Upper middle income	4
Botswana	Sub-Saharan Africa	South	Upper middle income	1
Namibia	Sub-Saharan Africa	South	Upper middle income	1
South Africa	Sub-Saharan Africa	South	Upper middle income	10

and nutritional symptoms (UMICs 76.5%). Greater than 55% included mid-upper arm circumference (MUAC) [68% in LIC] and laboratory indices [82.4% in UMIC]. There was a significant difference in MUAC as a parameter of nutritional status between LICs (68.1%), LMICs (61.1%) and UMICs (47.1%) ($p = 0.009$). Triceps skinfold thickness (TSF) and the use of complementary alternative medicine were reported in <25% of POUs.

Nutritional intervention

We did not observe a consensus on the parameters used to commence advanced nutritional intervention

Table 2. Indices used for routine nutritional assessment by units in income groups

Parameters of anthropometry	Income group						Total (*N*)	%
	Low income (*N*)	%	Lower middle income (*N*)	%	Upper middle income (*N*)	%		
Length/height	17	*89.5*	17	*94.4*	16	*94.1*	50	*92.6*
Weight	16	*84.2*	17	*94.4*	16	*94.1*	49	*90.7*
Symptoms/problems influence patient from eating	11	*57.9*	11	*61.1*	13	*76.5*	35	*64.8*
Oral diet/nutrient/food intake	10	*52.6*	10	*55.6*	14	*82.4*	34	*63.0*
MUAC	13	*68.4*	11	*61.1*	8	*47.1*	32	*59.3*
Laboratory indices (*e.g. albumin and pre-albumin, electrolytes*)	6	*31.6*	10	*55.6*	14	*82.4*	30	*55.6*
Head circumference	7	*36.8*	9	*50.0*	6	*35.3*	22	*40.7*
Complementary and alternative medicines (*i.e. vitamins and herbal products*)	5	*26.3*	4	*22.2*	5	*29.4*	14	*25.9*
TSF	4	*21.1*	6	*33.3*	3	*17.6*	13	*24.1*
Other	0	*0.0*	1	*5.6*	1	*5.9*	2	*3.7*

Table 3. Criteria for nutritional intervention

Parameters for intervention	Income group						Total (*N*)	% of 54 POUs
	Low income (*N*)	%	Lower middle income (*N*)	%	Upper middle income (*N*)	%		
Lost 10% weight	8	*42.1*	10	*55.6*	8	*47.1*	26	*48.1*
Change in MUAC	7	*36.8*	8	*44.4*	8	*47.1*	23	*42.6*
Oral food intake <80%	8	*42.1*	5	*27.8*	7	*41.2*	20	*37.0*
Change BMI *Z*-score or growth chart	7	*36.8*	5	*27.8*	7	*41.2*	19	*35.2*
Screening tool classify HR	8	*42.1*	7	*38.9*	4	*23.5*	19	*35.2*
Change in TSF	7	*36.8*	5	*27.8*	5	*29.4*	17	*31.5*
Change in BMI *Z*-score	1	*5.3*	3	*16.7*	3	*17.6*	7	*13.0*
No defined set criteria	4	*21.1*	1	*5.6*	2	*11.8*	7	*13.0*

Note: BMI, body mass index; HR, high risk.

(Table 3). More than 40% of the POU relied on weight loss and changes in MUAC. Less than 40% of POUs evaluated oral intake and used a screening tool or other anthropometric measurements.

Total 42% ($n = 23$) of the POUs did not have access to total parenteral nutrition (TPN): 68.4% in LICs ($n = 13$ of 19) and 44.4% in LMICs ($n = 8$ of 18). Enteral products were not available in 18.5% ($n = 10$) of POUs, with 26.3% ($n = 5$ of 19) in LICs, 17.6% in UMICs ($n = 3$ of 17) and 11.1% ($n = 2$ of 18) in LMICs.

Industrialized/commercial nutritional supplements were available at 48.2% ($n = 26$) of the POUs for inpatients, and 12.9% ($n = 7$) had no supplements available. LMICs were mostly affected with 22.2% having no access to supplements ($n = 4/18$); 10.5% LICs ($n = 2$ of 19) and 5.8% in UMICs ($n = 1$ of 11). In the ambulatory setting, 35.2% ($n = 19$) of

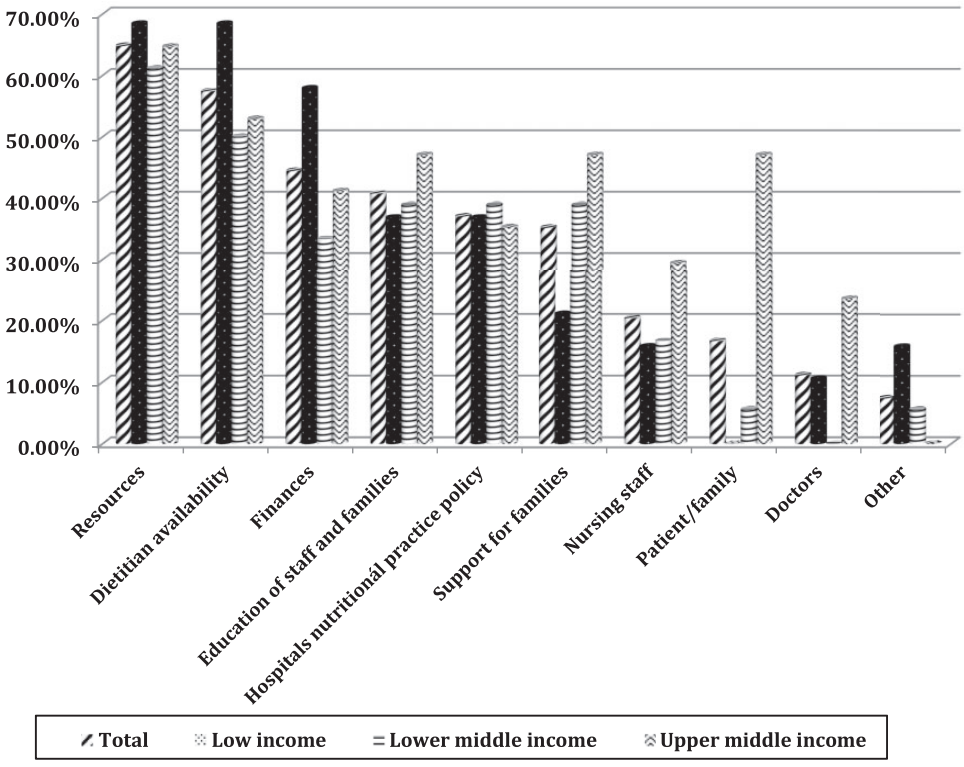

Fig 1. Barriers to preventing nutritional interventions.

POUs provided industrialized supplements home, and 25.9% ($n = 14$) gave no supplements. Total 44% of LMICs ($n = 8$ of 18), 21.05% of LICs ($n = 4$ of 19) and 11.7% of UMICs ($n = 2$ of 17) did not provide patients with homecare supplements. Home-made products were frequently relied on in LICs (21.1%) and LMICs (16.7%). The other products resembled World Health Organization (WHO) products, e.g. F100 for severe acute malnutrition (SAM) patients, but used in only 9.26% of POUs. The important nutritional barriers POUs experienced were lack of resources (64%); 57.1% claimed the availability of a dietician, and 44.4% had insufficient finances as seen in Figure 1. In LMICs, education of staff and families, as well as hospital nutritional policy were also factors (38.89%), and UMICs experienced lack of staff education and support to families (47.1%).

Nutritional education

Only 38.9% ($n = 21$) of POUs reported that nutrition education was provided to all patients and/or families. In LICs, 47.4% received advice ($n = 9$ of 19) with only 33.3% in LMICs ($n = 6$ of 18) and 35.3% in UMICs ($n = 6$ of 17). The barriers to the provision of nutritional education are presented in Figure 2. Total 40% did not have sufficient personnel ($n = 22$), 31.5% had time constraints ($n = 17$) and 29.6% did not have sufficient educational material to give to patients ($n = 16$). In UMICs 47.1% and LMICs 38.9% experienced lack of personnel, while 47.1% in UMICs and 22.2% in LMICs reported time constraints as the most significant barriers. In LICs, lack of educational material (42.1%) and financial resources (31.6%) was the primary barriers.

Non-profit organizations (NGO) play a major role in POUs at hospitals when all the children's treatment and supportive care needs cannot be met. The greatest need indicated by this survey in LICs was enteral products for both in- and outpatients; 31.5% ($n = 6$ of 19) and 21.1% (4 of 19), respectively, 27.7% of LMICs requested TPN ($n = 5$ of 18), while 35.3% in UMICs ($n = 6$ of 17)

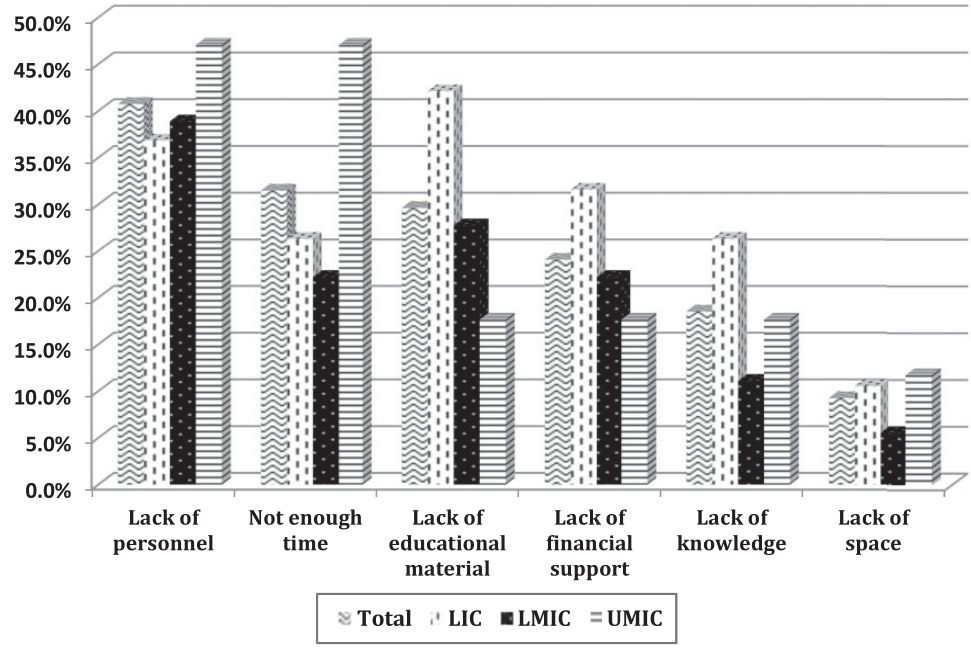

Fig 2. Barriers to nutritional education not given to patients.

considered that groceries for home would improve their patient's nutritional status.

DISCUSSION

The survey was representative of the different defined income groups in Africa. Less than half of the hospitals had a full-time dietician in the POU, which is lower than previously reported surveys that included sites in Africa [18, 21]. This can be because of the majority of the POUs responding were from LIC, which experience a lack of healthcare personnel because of limited resources. This likely explains our observation that newly diagnosed children with cancer are not uniformly nutritionally assessed and monitored during treatment. This is of great concern in light of the 2015 sub-Saharan Africa report: 21% of children <5 years of age were underweight, 39% stunted and 9% wasted [22].

The SIOP nutritional algorithm recommends the use of MUAC to classify the nutritional risk in children with cancer [23] because of its independence of tumour mass [1, 6, 12, 19], temporary gains in total body water [24] and ethnicity [1, 19]. In the survey most POUs still relied on weight and length/height as parameters. The use of MUAC for nutritional assessment is significantly higher than reported literature, 59.3% compared with 33% [18] with a significant difference between income groups. It is not sufficiently used as criteria for nutritional interventions. Our study confirms that there are no uniform standards of nutritional assessment and monitoring during treatment; parameters for initiating nutritional interventions such as weight loss were relied on in half of the institutions. This indicates the need for education on the importance of monitoring nutritional status during treatment.

Our survey identified several barriers to nutritional intervention. The majority of the POUs do not have access to the full range of TPN or commercial enteral nutritional products, which underlines the need for POU to use home-made products. Other approaches have been the provision of food products to patients and their families. In Cameroon, children were provided one egg, 200 ml of WHO F100 milk and families received the equivalent of US$1 per day to purchase food. This combined program (protein, nutritional supplement and money) led to increased MUAC and/or TSF in almost two-thirds of the children while on cancer treatment, and a suggestion of decreased treatment-related mortality [6].

The management of SAM patients remains a challenge for POUs, as studies have found that the SAM-WHO regime is not routinely available because of few hospital beds, lack of trained staff, costs of the WHO products and overall management thereof. For example, the cost of treatment of SAM is US$203 per child in Zambia and US$284 in Ethiopia [25]. Nutritional rehabilitation of children with SAM and access to F100 formula are mostly undertaken at small hospitals and clinics where the nursing staff are trained. In contrast, most nurses in POUs are not trained to treat SAM patients or POUs to receive WHO products. African POUs are in need of organizations, such as SIOP-Africa, to assist POUs in adopting models of care and increase their resources [19] to optimize nutritional care.

We observed that less than half of the POUs provide nutritional advice to families of patients, a figure aligned with a previous survey by the investigators [18]. This was explained by a lack of personnel and time, which is because of time spent on medical care of the patients and insufficient time with families. We found that majority in UMICs thought groceries for patients will improve their nutritional status, suggesting that food insecurity may impact nutritional care. Our survey highlights the need for collaborative initiatives with several stakeholders, especially NGOs to provide nutritional resources to support overall care in POUs.

In conclusion, our results provided important information on the relevant barriers to nutritional assessment, intervention and/or education at POUs in the different income groups within Africa. This information will be used to establish modifiable and adapted nutritional guidelines and education of all cancer healthcare staff in the different POUs. Once established, this will improve the understanding of the importance of nutrition in children and subsequently enable future research. We are planning a national nutrition study in South Africa and Cameroon to commence late in 2018 to evaluate in greater detail the nutritional status of patients at cancer diagnosis. Patients' nutritional status will be monitored longitudinally during treatment to determine the effect on clinic on clinical outcome. Nutritional studies in other Africa countries will follow.

LIMITATIONS

The limitations of the study are the identification of institutions caring for children with cancer using internet groups. As the survey was Internet-based that might affect the number of responses received because of limited availability thereof. An additional limitation is the inability to verify all of the information.

ACKNOWLEDGEMENTS

The authors would like to thank the SIOP PODC Nutrtiton Working Group and all the participants for their time in completing the survey and providing us with valuable information needed to plan future nutritional programs in Africa.

FUNDING

This research project was supported by The Tamarind Foundation (EJL) and Mullen Foundation (EJL).

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CHAPTER 3

Prevalence of Poverty and Hunger at Cancer Diagnosis and Its Association with Malnutrition and Overall Survival in South Africa

Reference: Judy Schoeman, Ilde-Marié Kellerman, Sandile Ndlovu, Elena J Ladas, Paul C Rogers, Carl J Lombard, Ané Büchner, David T Reynders, Gita Naidu, Biance Rowe, Jan du Plessis, Mariechen Herholdt, Karla Thomas, Barry Vanemmenes, Rema Mathews, Fareed Omar, Ronelle Uys & Mariana Kruger (2023): Prevalence of Poverty and Hunger at Cancer Diagnosis and Its Association with Malnutrition and Overall Survival in South Africa, Nutrition and Cancer, DOI: 10.1080/01635581.2023.2214970
https://doi.org/10.1080/01635581.2023.2214970
(Impact factor 2.816)

This study investigated the prevalence of poverty and food insecurity in the home of newly diagnosed children with cancer. The hypothesis was:

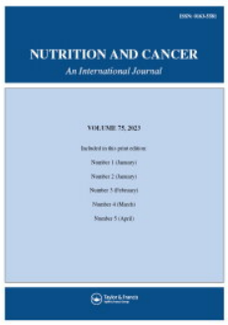
Ha: Children diagnosed with cancer, living in poverty, or experiencing household food insecurity are prone to be undernourished at diagnosis and associated with a poor 2-year OS

H0: Children diagnosed with cancer, living in poverty, or experiencing household food insecurity are not prone to be undernourished at diagnosis and will have no association with 2-year OS

South Africa is an upper-middle-income country, but poverty and food insecurity are prevalent. The Poverty Assessment Tool and the Household Hunger Scale questionnaire are validated in South Africa and therefore used in a structured interview with caregivers of children diagnosed with cancer to complete the two questionnaires.

About a third of the children were from families with a high risk of living in poverty (on less than 2US$ per day or R40 per day), even though more than half received the government child support grant. Eighty percent of the children had a high risk of food insecurity at home. Patients with food insecurity at home had a relatively high poverty risk and were significantly associated with both stunting and malnutrition at diagnosis, as well as treatment abandonment and poor OS.

The high poverty and food insecurity prevalence in the study population supports the hypothesis. Our study is the first to use the validated Poverty Assessment Tool and the Household Hunger Scale questionnaire to determine socio-economic circumstances at home in POUs in South Africa.



Nutrition and Cancer

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/hnuc20

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To cite this article: Judy Schoeman, Ilde-Marié Kellerman, Sandile Ndlovu, Elena J Ladas, Paul C Rogers, Carl J Lombard, Ané Büchner, David T Reynders, Gita Naidu, Biance Rowe, Jan du Plessis, Mariechen Herholdt, Karla Thomas, Barry Vanemmenes, Rema Mathews, Fareed Omar, Ronelle Uys & Mariana Kruger (2023): Prevalence of Poverty and Hunger at Cancer Diagnosis and Its Association with Malnutrition and Overall Survival in South Africa, Nutrition and Cancer, DOI: 10.1080/01635581.2023.2214970

To link to this article: https://doi.org/10.1080/01635581.2023.2214970

NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2023.2214970

Prevalence of Poverty and Hunger at Cancer Diagnosis and Its Association with Malnutrition and Overall Survival in South Africa

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ABSTRACT

Many South African children live in poverty and food insecurity; therefore, malnutrition within the context of childhood cancer should be examined. Parents/caregivers completed the Poverty-Assessment Tool (divided into poverty risk groups) and the Household Hunger Scale questionnaire in five pediatric oncology units. Height, weight, and mid-upper arm circumference assessments classified malnutrition. Regression analysis evaluated the association of poverty and food insecurity with nutritional status, abandonment of treatment, and one-year overall survival (OS). Nearly a third (27.8%) of 320 patients had a high poverty risk, associated significantly with stunting ($p=0.009$), food insecurity ($p<0.001$) and residential province ($p<0.001$) (multinomial regression). Stunting was independently and significantly associated with one-year OS on univariate analysis. The hunger scale was significant predictor of OS, as patients living with hunger at home had an increased odds ratio for treatment abandonment (OR 4.5; 95% CI 1.0; 19.4; $p=0.045$) and hazard for death (HR 3.2; 95% CI 1.02, 9.9; $p=0.046$) compared to those with food security. Evaluating sociodemographic factors such as poverty and food insecurity at diagnosis is essential among South African children to identify at-risk children and implement adequate nutritional support during cancer treatment.

List of Abbreviations: BMI: Body mass index; BMI/A or BAZ: Body mass index for age; CI: Confidence interval; CSG: Child Support Grant; HAZ: Height for age; MUAC: Mid-upper arm circumference; MUAC/A: Mid-upper arm circumference for age; OS: Overall survival; POUs: Pediatric oncology units; RRR: Relative risk ratio; US$: United States of America dollar unit

ARTICLE HISTORY
Received 18 January 2023
Accepted 11 May 2023

Introduction

'Absolute poverty' is described as "a condition characterized by severe deprivation of basic human needs, including food, safe drinking water, sanitation facilities, health, shelter, education, and information" (1). According to the South African census (2015), 30 million people live on less than R84.11 (US$5) per day (2) and 55% of South African children live below

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/01635581.2023.2214970.

Meeting abstract (poster viewing): The prevalence of household food insecurity in children diagnosed with cancer in two pediatric oncology units in South Africa. SIOP Congress, 23–25 October 2019, Lyon, France, Abstract no. 0227. https://onlinelibrary.wiley.com/doi/epdf/10.1002/pbc.27989

the ultra-poverty line (3) (R800/month or US$45.81/month) (4). Socioeconomic status has been associated with poor nutritional status in children with cancer (5–7) and poorer cancer outcomes. Malnutrition at diagnosis has been identified as a modifiable prognostic risk factor (5). Recognizing these factors, South Africa implemented the Child Support Grant (CSG) in 1998 to reduce child poverty by covering food costs (6). The CSG does not cover additional expenses incurred due to a life-threatening illness such as cancer (7).

Poor diet diversity is also strongly associated with low socioeconomic status (8). The effects of poor diet quality may be exacerbated among South African children, as poor diet quality is also linked to several micronutrient deficiencies (9) due to families relying on a small variety of foods, consuming less-expensive foods, and decreasing portion sizes (10–12). Recent literature has found that a high-quality diet may confer a protective effect against some treatment-related toxicities of cancer treatment (13). The effects of these factors within the context of a child undergoing cancer treatment in a low- and middle-income country have yet to be determined.

Identifying modifiable risk factors that lead to poor nutrition in childhood cancer is an understudied area, especially in low- and middle-income countries. It therefore is necessary to understand the scope of poverty and hunger, and their association with nutritional status among children undergoing cancer treatment. This knowledge will assist in efficiently allocating hospital resources and establishing support networks to ensure that the most vulnerable children are supported through proactive nutrition interventions while undergoing cancer treatment. As half of South Africans experience chronic poverty over time (14), food insecurity will be affected; we investigated the prevalence of poverty and food insecurity at cancer diagnosis, their association with malnutrition at the time of diagnosis, as well as the abandonment of treatment and overall survival (OS) at one year post-diagnosis.

Methods

Study Design

This cross-sectional study, nested in a prospective cohort study, recruited children newly diagnosed with cancer and aged between three months and 15 years in five of 13 pediatric oncology units (POUs) in South Africa from October 2018 to December 2020. Their parents' or caregivers' written consent was obtained prior to study enrollment, and assent was obtained from children older than seven years. The following institutions provided ethics approval: Stellenbosch University, Faculty of Medicine and Health Sciences (Health Research Ethics Committee [S18/04/050]), the University of Pretoria (Research Ethics Committee, [281/2018]), the University of the Witwatersrand (Human Research Ethics Committee [M190485]), the University of the Free State (Health Sciences Research Ethics Committee [UFS-HSD2019/0445/3007]) and Frere Hospital (Ethics Committee [CMHREC 001/19]). The national and provincial health departments gave approval for the study to be conducted in the public sector.

Study Instruments

A structured interview with the parent or legal guardian was held within 72 h of diagnosis in the language of their choice (e.g., English or native South African language). The Simple Poverty Scorecard® Poverty-Assessment Tool South Africa (15), a validated questionnaire consisting of 12 questions, was administered by an investigator to determine the risk of living in poverty. Participants selected answers from a series of multiple-choice questions that were allocated a score and then summed, creating a composite score for each participant. Scores were classified based on previously published data (15) and reflected the risk of living in poverty or below the poverty line of US$2/day. A score of 0 to 35 was classified as a high risk (≥ 64.8% risk) of living below the poverty line; a score of 36 to 50 indicated a medium risk (≥ 18.4% risk); and a score of 51 to 100 indicated a low risk (< 18.3%) of living below the poverty line (15). Additional information on household income was collected during the structured interview to determine the proportion of families receiving salaries or wages, and those who only received the CSG and therefore lived on less than US$2/day.

The Household Hunger Scale questionnaire (16) was also administered during the same interview and consisted of eight questions from the Community Childhood Hunger Identification Project (17) to determine food insecurity at home. Participants responded 'yes' or 'no' to eight questions and were classified into three groups: Group 1: Five to eight 'yes' responses, which indicated that food insecurity affected everyone in the household, with the classification 'hungry'; Group 2: One to four 'yes' responses, which indicated that the family was at 'risk of hunger'; and Group 3: All 'no' responses, which indicated food security in the household (16).

Clinical Data

Clinical data (diagnosis, stage or risk of disease, and chemotherapy protocol) was obtained from the medical files containing demographic data (age, sex and province of residence) and added to the study database. OS was defined as patients alive one year post-cancer diagnosis.

The nutritional anthropometric assessment was evaluated within 72 h after diagnosis, including weight, height and mid-upper arm circumference (MUAC). Children older than two years were weighed on a SECA column scale with a height meter (SECA 786 and SECA 220). Children younger than two years were weighed with a SECA electronic baby scale with a length meter attached (SECA 334). The length was measured while the child was lying flat on the scale. The UNICEF color band measured the MUAC of children under five (3), and a measuring tape (18) was used to obtain the MUAC in older children. All assessments were plotted on the WHO growth charts (19), and the WHO Anthro program was utilized to determine z-scores for height for age (HAZ), body mass index (BMI) for age (BAZ), and MUAC for age (MUAC/A) (20). The MUAC for children older than five was plotted on the Mramba et al. growth charts (21) and divided into categories. In this study, poor nutritional status was defined as stunting (HAZ < −2 SD) and malnutrition (BMI for age and/or MUAC/A < −2 SD) (22). (It is known that tumor weight and/or ascites can influence weight; therefore, we defined malnutrition according to BMI or MUAC.)

Statistical Analysis

Data was analyzed using STATA version 17.0 (STATA Corp. Texas, USA). Descriptive statistics (frequencies, percentages, means, medians and standard deviations) for demographics, anthropometrics, diagnosis, the results of the Poverty Assessment Tool, and the Household Hunger Scale variables were calculated. The total cutoff point of the scores from the Poverty Assessment Tool and the Household Hunger Scale was used. Proportions below and above the cut points were calculated, and the prevalence and Wilson 95% confidence intervals (CIs) were determined. The results were pooled over the five POUs, and chi-square tests were used to determine the association of sex, age, gestational age, disease group, diagnosis, anthropometric variables, and hunger risk with poverty risk. Relative risk ratios (RRR) and 95% CIs were calculated using a multinomial logistic regression analysis, using the low-poverty-risk group as the baseline comparison group. The Western Cape, one of the wealthiest provinces in South Africa (23), was used as the reference province for regression analysis regarding regional poverty assessment. An investigation was done to determine factors associated with the abandonment of therapy using a logistic regression analysis estimating odds ratios and 95% CIs. OS was investigated for the different poverty risk groups one year after diagnosis. The association between one-year OS, poverty risk, and food insecurity was assessed using log-rank tests and a Cox regression analysis, reporting hazard ratios and a 95% CI. For the Cox regression model, the baseline risk factors were adjusted for the stage or risk of disease at diagnosis. All non-correlating factors in the univariate analysis with a p-value < 1.0 were included in the regression analysis. A significance level of 5% or $p < 0.05$ was applied.

Results

Demographics

We enrolled 320 children and adolescents during the study period, with a male-to-female ratio of 1.1:1 and a median age of 5.3 years (range three months to 15 years). The majority were diagnosed with a solid tumor (55.9%), and 44.1% had a hematologic malignancy (Table 1). The most common diagnoses were acute lymphoblastic leukemia (23.1%), nephroblastoma (15.6%), and Hodgkin lymphoma (7.8%) (Supplementary Table S1).

Poverty

Nearly a third of the families (27.8%) had a high risk of living in poverty, a third (33.1%) had a medium risk, and 39.1% had a low risk (Table 2). More than a third of the children (35.9%) lived in households with more than six residents and reported no male head or spouse living with them (39.6%). Most female-headed households were proficient in English as a second language (70.9%) (Supplementary Table S2). Half of the families received a monthly salary (51.6%), 22.2% performed occasional informal work, and 10.6% had a household member receiving an older person's grant (namely, South African Social Security Agency pension for persons older than 60 years (24)). Most families received a CSG (58.2%) (Supplementary Table S3). The reported monthly median income was R3,000 (US$164.10) (IQR R1,280 to R5,600 or IQR US$70.02 to US$306.32), and 19% ($n = 61$) of the families lived on less than US$2/day. Nearly all families in the study owned essential and

Table 1. Demographics of the study population.

Demographics categories		N (Percentage)
Sex:	Males	168 (52.5%)
	Females	152 (47.5%)
Gestational age at birth:	Full term	259 (80.9%)
	Premature	61 (19.1%)
Age in years	Median (IQR)	5.3 (2.6 – 9.1)
	Mean (range)	6.14 (0.3 – 15.7)
Age groups	<5 years	154 (48.1%)
	≥5 years	166 (51.9%)
Hospital	Steve Biko Academic Hospital	154 (48.1%)
	Tygerberg Hospital	107 (33.4%)
	Chris Hani Baragwanath Hospital	29 (9.1%)
	Universitas Hospital	21 (6.6%)
	Frere Hospital	9 (2.8%)
Province of residence	Western Cape	106 (33.1%)
	Mpumalanga	92 (28.8%)
	Gauteng	82 (26.5%)
	Free State	19 (5.9%)
	Eastern Cape	10 (3.1%)
	Limpopo	4 (1.3%)
	North West	6 (1.9%)
	Northern Cape	1 (0.3%)
Disease group	Hematological malignancy	141 (44.1%)
	Solid tumor	179 (55.9%)

Abbreviations: IQR: Interquartile range.

Table 2. Results of the Simple Poverty Scorecard ® Poverty-Assessment Tool South Africa.

Total score for Poverty-Assessment Tool	The risk of living below the poverty line associated with the score *(column 1)* (US$2/day)	Group division	Group title	Percentage score for risk under the poverty line per group	N	%
0–20	95.9%	0–35	High poverty risk	≥ 64.8%	89	27.8
21-28	82.1%					
29–35	64.8%					
36–37	55.9%	36–50	Medium poverty risk	≥ 18.4%	106	33.1
38–40	50.8%					
41– 45	35.7%					
46–48	29.2%					
49–50	18.4%					
51–53	16%	51–100	Low poverty risk	< 18.3%	125	39.1
54–58	6.7%					
59–61	3.8%					
62–66	3.2%					
67–68	0.5%					
69–100	0%					

Abbreviations: US$2: United States of America dollar.

luxury items such as mobile phones (98.8%), fridges (85.6%), cooking stoves (88.1%), lounge suites (couches, 64.4%), and satellite television (56.9%) (Supplementary Table S2).

Hunger

Most children lived in households with a high risk of food insecurity (80%), with 37.2% living with hunger at home, 42.8% living with a risk of food insecurity, and a mere 20% living in households with food security (Supplementary Table S4). Most parents (71%) reported using a limited variety of foods to feed their children due to a lack of financial means. More than half (65.9%) of the households experienced a monthly shortage of funds for food, and most caregivers (56.6%) decreased their meal portions or skipped meals to be able to feed their families. Most parents (86.6%) ensured that their children never went to bed hungry, even though their financial means were limited. Of concern, however, is that most children (69.4%) experienced occasional hunger, and 68.4% of the parents also decreased the meal portions of their children due to a lack of funds. More than half of the parents (61%) indicated that their children ate less than they should due to inadequate financial means (Supplementary Table S5).

Demographic Associations with Poverty and Hunger

From the univariate analysis, the risk of poverty was significantly associated with the Household Hunger Scale score ($p < 0.001$) and the province of residence ($p < 0.001$), but not with age, sex, diagnosis, disease

group or stage/risk of disease (Table 3 and Supplementary Table S6). Hunger was significantly associated with age ($p = 0.035$) and the province of residence ($p < 0.001$), but not with sex, disease group or diagnosis (Supplementary Table S7). Patients who experienced hunger were most likely to be in the high-poverty-risk group (RRR 20.2, 95% CI 6.2, 66; $p < 0.001$) than in the low-poverty-risk group. The risk of hunger decreased as the risk of poverty decreased, as the medium-poverty-risk group had a lower risk of hunger than the high-poverty-risk group (RRR 9.7, 95% CI 3.8, 24.9, $p < 0.001$) in the multinomial regression analysis. Children living in Mpumalanga (RRR 14.6, 95% CI 4.4, 48.3; $p < 0.001$) were most likely to be in the high-poverty-risk group, followed by those living in the Free State (RRR 11.8, 95% CI 2.3, 59.3; $p = 0.003$) and the Eastern Cape (RRR 10.2, 95% CI 1.7, 62.9; $p = 0.012$), while patients from Gauteng had a non-significant lower risk for falling in the high-poverty-risk group (RRR 2.5, 95% CI 0.9, 6.9; $p = 0.073$) (Table 4).

Associations between Nutritional Status, Poverty and Hunger

In the univariate analysis, children with stunting ($p = 0.003$) and with malnutrition ($p = 0.001$) at diagnosis were significantly associated with the risk of living in poverty (Table 3). The score for the Household Hunger Scale ($p = 0.018$) was significantly associated with malnutrition, but not with stunting (Supplementary Table S7). In terms of the multiple regression analysis, children at high risk of living in poverty were more likely to be stunted (RRR 3.7, 95% CI 1.4, 10.0; $p = 0.009$), while children with malnutrition at diagnosis (RRR 3.6, 95% CI 1.4, 9.4; $p = 0.009$) were more likely to be in the medium-poverty-risk group than in the low-poverty-risk group (Table 4).

Abandonment of Treatment and Survival

The one-year post-cancer diagnosis outcome was available for all children who participated in the study ($n = 320$; 100%). The majority (77.5%; $n = 248$) were alive, 22.5% had died ($n = 72$), 8.8% had abandoned therapy ($n = 28$), and 3.4% had relapsed ($n = 11$). Most of the children who abandoned therapy were from the provinces of Mpumalanga (33%) and the Free State (15%), were older than five years of age (85.7%), and were well-nourished (52%). The univariate analysis indicated that the Household Hunger Scale score ($p = 0.031$) and the residential province score ($p = 0.025$) were significantly associated with treatment abandonment, but not with the poverty risk. In the multivariate analysis, children with food insecurity at home were 4.5 times more likely to abandon treatment (RRR 4.5, 95% CI 1.03, 19.4; $p = 0.045$). This was also the case for children from the Free State province, who had an increased risk of treatment abandonment (RRR 15.7, 95% CI 3.5, 70.6; $p < 0.001$) (Supplementary Table S8).

The one-year OS for the entire cohort was 77.5% (95% CI 72.5, 82.0). Stunting was independently and significantly associated with OS on univariate analysis.

Table 3. Association of demographics, Household Hunger Scale, and nutritional status with risk of living in poverty.

Category		High risk		Medium risk		Low risk		$N = 320$	p-value
		N	%	N	%	N	%		
Age	< 5 years	44	28.6	51	33.1	59	38.3	154	0.949
	≥ 5 years	45	27.1	55	33.1	66	39.8	166	
Sex	Male	43	25.6	64	38.1	61	36.3	168	0.139
	Female	46	30.3	42	27.6	64	42.1	152	
Gestational age	Term baby	80	30.9	87	33.6	92	35.5	259	0.011
	Premature	9	14.8	19	31.2	33	54.1	61	
Provinces	Eastern Cape	5	50.0	2	20.0	3	30.0	10	< 0.001
	Free State	10	52.6	4	26.3	5	26.3	19	
	Gauteng	20	24.4	24	29.3	38	46.3	82	
	Mpumalanga	40	43.5	37	40.2	15	16.3	92	
	Western Cape	12	11.3	35	33.0	59	55.7	106	
	Other	2	18.2	4	36.4	5	45.5	11	
Household Hunger Scale	No risk of hunger	6	9.4	11	17.2	47	73.4	64	< 0.001
	Risk of hunger	28	20.4	50	36.5	59	43.1	137	
	Food insecurity	55	46.2	45	37.8	19	16.0	119	
Length for age	Normal	67	24.5	91	33.3	115	42.1	273	0.003
	Stunted	22	46.8	15	31.9	10	21.3	47	
BMI for age	Normal	73	25.8	94	33.2	116	41.0	283	0.053
	Wasted	16	43.2	12	32.4	9	24.3	37	
MUAC for age	Normal	60	24.4	78	31.7	108	43.9	246	0.001
	Malnutrition	27	39.1	28	40.6	14	20.3	69	

Abbreviations: BMI: Body mass index; MUAC: Mid-upper arm circumference. A p-value of <0.05 was considered statistically significant.

Table 4. Multiple multinomial logistic regression of poverty risk on sociodemographic and anthropometry indicators at baseline with the low-poverty risk group as the reference group.

		High-poverty risk group		Medium-poverty risk group	
Variables	Parameters	*RRR (95% CI)	*p*-value	RRR (95% CI)	*p*-value
Province	Western Cape*	1		1	
	Free State	11.8 (2.3, 59.3)	0.003	2 (0.4, 10.2)	0.394
	Gauteng	2.5 (0.9, 6.9)	0.073	1.1 (0.5, 2.6)	0.752
	Mpumalanga	14.6 (4.4, 48.3)	< 0.001	5.3 (1.9, 14.3)	0.001
	Eastern Cape	10.2 (1.7, 62.8)	0.012	1.1 (0.1, 7.9)	0.945
	Other	1.1 (0.1, 9.4)	0.910	1.5 (0.3, 7.8)	0.625
Gestational age	Term*	1		1	
	Premature	0.6 (0.2, 1.5)	0.252	0.6 (0.3, 1.3)	0.193
Household Hunger Scale	No risk for hunger*	1		1	
	Risk of hunger	3.7 (1.2, 11.5)	0.023	3.5 (1.5, 8.1)	0.004
	Hunger	20.2 (6.2, 66)	< 0.001	9.7 (3.8, 24.9)	< 0.001
Length/Height for age	Normal	1		1	
	Stunted	3.7 (1.4, 10)	0.009	1.8 (0.7, 4.6)	0.219
BMI for age	Normal	1		1	
	Malnutrition	1 (0.3, 3.5)	0.941	0.5 (0.2, 1.8)	0.313
MUAC for age	Normal	1		1	
	Malnutrition	2.5 (0.9, 7)	0.086	3.6 (1.4, 9.4)	0.009

Abbreviations: *RRR: relative risk ratio; BMI: Body mass index; MUAC: mid-upper arm circumference. *A p*-value of <0.05 was considered statistically significant..

Children with normal length or height had an increased survival rate (79.5%, 95% CI 74.2, 84.1) compared to stunted children (65.9%; 95% CI 50.7, 79.1) ($p = 0.018$), but significance was not confirmed with Cox regression (Supplementary Table S9). There was no significant difference in OS between children with malnutrition, age groups, sex, province of living, or disease group on the log-rank test. From the Cox regression model, the hunger scale was a significant predictor of OS. Patients living with hunger at home at diagnosis had an increased risk of death (HR 3.2 (95% CI 1.0, 9.9; $p = 0.046$) compared to those with food security, adjusted for stage or risk of disease at diagnosis. Poverty risk at baseline, however, was not a significant predictor of OS.

Discussion

According to the World Bank poverty report on South Africa (2), children, in general, are at a high risk of living in poverty, hunger, and poor nutritional status (25). Aligned with this report, we found that a third of our population was in the high-poverty-risk group. At the same time, 80% lived with either food insecurity or a risk of food insecurity, which is strongly associated with abandoning treatment. Moreover, we found that the risk of poverty was significantly associated with stunting and malnutrition, potentially increasing the risk of treatment-related toxicities and poor outcomes. Nutritional intervention should be implemented from diagnosis to improve patients' nutritional status and survival (26). Our study identified that a large proportion of children with cancer experienced poverty and food insecurity at diagnosis, which may be exacerbated by the long duration of treatment for childhood cancer. Our study underscores the need for medical centers to enhance collaboration with organizations that provide financial and/or food aid support to families throughout treatment to enhance outcomes.

Although South Africa is classified as an upper-middle-income country, 26% of the population lives below the internationally defined poverty line of US$1/day (27), and 19% of the families in this study lived on less than US$2/day. The lower prevalence in our study may be because 50% of the participants received the CSG to supplement their household income. However, the CSG barely covers a child's basic needs (6), and a cancer diagnosis will likely strain families' finances (7). Future studies should evaluate how this fluctuates during treatment and examine the clinical repercussions of profound poverty on nutritional status and cancer outcomes among South African children progressing through treatment for cancer.

We found that the high-poverty-risk group was significantly associated with food insecurity at home, a finding that is similar to that of previous studies in Limpopo (12) and Mpumalanga, two of the nine South African provinces (16). Socioeconomic status was reported to affect nutritional status (28) and in this study, significantly more patients with stunting and malnutrition lived in the groups with a higher risk for poverty. Similar results were seen in healthy teenagers from medium and low socioeconomic status who suffered from wasting in Bloemfontein (Free

State province) (26). The authors also found that stunting was associated with household food security (28). This study illustrated that children with stunting and malnutrition at cancer diagnosis were more likely to live in poverty, thereby highlighting a group of children needing social services and support networks over and above the existing structures available to South African children with cancer.

Our study found that South African children with malnutrition at cancer diagnosis often experienced food insecurity at home, underscoring the need to address primary rather than secondary malnutrition due to underlying cancer. This observation was especially apparent among children from rural provinces. Many children in our study experienced high poverty and a food insecurity risk at diagnosis; thus, nutritional counseling targeting dietary intake in the home setting should be a priority for these patients. Future studies need to consider evaluating the impact of poverty and hunger on dietary intake during treatment, and to proactively prevent malnutrition or micronutrient deficiencies from developing. In turn, improved clinical outcomes may be observed.

A survey in Tanzania reported that poverty is one of the risk factors for stunting (28), demonstrated in this study by an association between stunting and the high-poverty-risk group. A recent study on healthy infants from Mpumalanga (a province in South Africa) found a significant association between stunting and maternal education, parental employment, and access to water at home. Stunting may also be due to poor maternal nutrition, late onset of complementary feeding practices for infants, lack of protein in the diet, or impaired nutrient absorption (29).

As an indicator of chronic malnutrition, stunting causes tissue damage and reduces the function of neurotransmitters (29). Stunting is also associated with reduced lung growth and function, which can influence the prevalence of pulmonary infections (31), affect morbidity, and increase the risk for mortality (30). Stunting affects cognitive development, with poorer academic achievement and economic productivity, which are fundamental aspects for the cured child with cancer (31).

Therefore, future studies should focus on the improvement of stunting in newly diagnosed children with cancer through planned interventions, as this is a modifiable risk factor to enhance OS and survivors' quality of life.

Although we have not observed a significant effect of poverty risk on OS, we have found that food insecurity increases the risk of treatment abandonment and decreases OS. This is a crucial finding, as previous studies have reported that increased counseling and resources for children at high risk of treatment abandonment reduce its prevalence (7). Several studies have also reported a positive association between sociodemographic factors and OS (32–34). In a previous South African study of children from families with higher socioeconomic status (household income of US$191/year or US$6/day) with germ cell tumors, it was found that they experienced significantly improved OS at five years ($p = 0.039$) (32). Indonesian children from low-income families diagnosed with acute lymphoblastic leukemia have also experienced significantly lower event-free survival two years or longer after diagnosis than those from higher-income families (33). Our study has documented that food insecurity can predict OS, but not poverty, indicating that the Hunger Scale is a better tool to use to identify at-risk children in South Africa. As hunger at home is significantly associated with increased risk for treatment abandonment and risk of death, the Hunger Scale should be completed at cancer diagnosis to plan nutritional and other supportive interventions to improve OS.

We recognize several limitations of this study of poverty and hunger. The South African POUs that participated in this study self-selected to participate and provided preliminary information on poverty and hunger. Our findings there are limited to the regions that participated. Our cohort consisted of a heterogenous sample with a variety of diagnoses and severity of the disease. Due to funding and personnel limitations, we did not evaluate diet history; thus, the impact of poverty, food insecurity, and poor nutritional status on dietary diversity is unknown.

A strength of our study is the use of validated questionnaires (15, 16) which could serve as comparison data in future studies. Future studies could also consider evaluating sociodemographic factors, especially the risk of hunger (16), along with nutritional assessment within a homogenous cohort to control for the heterogeneous variables in this study.

In conclusion, we found a high prevalence of poverty and hunger among South African children diagnosed with cancer. Food insecurity was associated with an increased risk of treatment abandonment and decreased risk of OS. A significant association was noted between the high-poverty-risk group and stunting, while stunting was associated with poorer OS. Our findings underscore the importance of incorporating an assessment of the risk of living in poverty and/or with food insecurity at diagnosis, and potentially throughout therapy, to ensure that families are referred to appropriate support networks.

Acknowledgements

The authors would like to acknowledge and thank the children and parents/caregivers who participated in the study, especially for their willingness to answer the two questionnaires and to disclose sensitive information. They would also like to thank the pediatric registrars, dieticians, and nursing staff of the POUs for their support in this study.

Conflict of Interest

The authors have no conflict of interest to report.

Contribution to the Manuscript

Judy Schoeman conceptualized the study. Judy Schoeman, a PhD student, designed the study, developed the Redcap database, chose the questionnaires, enrolled patients, collected data, cleaned the data, analyzed the data, and wrote the manuscript.

Mariana Kruger, Elena Ladas, and Paul Rogers assisted with the design of the study and critically reviewed the manuscript.

Ilde-Marié Kellerman, Ronelle Uys, Gita Naidu, Biance Rowe, Jan du Plessis, Mariechen Herholdt, Karla Thomas, Barry Vanemmenis, Rema Mathews, Ané Büchner, Fareed Omar and David Reynders were investigators at the different sites, enrolled patients, collected data and critically reviewed the manuscript.

Sandile Ndlovu assisted with this nested study's statistical design, analyzed the Poverty Assessment Tool data, and critically reviewed the manuscript. Carl Lombard did the statistical analysis of the hunger scale questionnaire and critically reviewed the manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, JS. The data are not publicly available due to data containing information that could compromise the privacy of research participants.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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CHAPTER 4

Prevalence of vitamin and iron deficiencies at cancer diagnosis at two pediatric oncology units in South Africa

Reference: Schoeman J, Kellerman I, Rogers PC, Ladas EJ, Lombard CJ, Uys R, Kruger M. Prevalence of vitamin and iron deficiencies at cancer diagnosis at two pediatric oncology units in South Africa. Pediatric Hematology and Oncology
https://doi.org/10.1080/08880018.2023.2188920
(Impact factor 1.17)

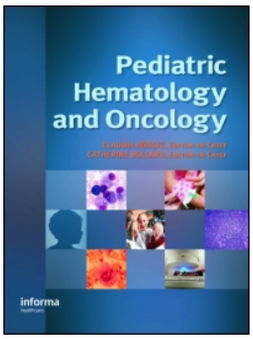
This study investigated the prevalence of vitamin and iron deficiency at cancer diagnosis at two paediatric oncology units in South Africa. The hypothesis was:

Ha: Children diagnosed with cancer in South Africa are not vitamin and iron deficient and therefore not associated with poor OS and EFS

H0: Children diagnosed with cancer in South Africa are vitamin and iron deficient, and therefore associated with poor OS and EFS

Nutritional and micronutrient status of Vit A, Vit B12, Vit D, folate, and iron levels were assessed at diagnosis. Nearly half had iron deficiency, while a third had Vit A, Vit D, or folate deficiency. There was a significant association between moderate acute malnutrition and Vit A, Vit B12, and folate deficiency, while Vit D deficiency was associated with children being underweight or wasted at diagnosis. Residential provinces, age groups, and food insecurity were associated with folate deficiency.

There were a few international studies with similar findings. This study was the first to document the need to assess micronutrient levels at cancer diagnosis in South African children, which should guide supportive nutritional care during childhood cancer treatment. The finding demonstrates a significant prevalence of micronutrient deficiency, and the hypothesis was supported.



Pediatric Hematology and Oncology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipho20

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To cite this article: Judy Schoeman, Ilde-Marié Kellerman, Paul C Rogers, Elena J Ladas, Carl J Lombard, Ronelle Uys & Mariana Kruger (2023): Prevalence of vitamin and iron deficiencies at cancer diagnosis at two pediatric oncology units in South Africa, Pediatric Hematology and Oncology, DOI: 10.1080/08880018.2023.2188920

To link to this article: https://doi.org/10.1080/08880018.2023.2188920

PEDIATRIC HEMATOLOGY AND ONCOLOGY
https://doi.org/10.1080/08880018.2023.2188920

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Prevalence of vitamin and iron deficiencies at cancer diagnosis at two pediatric oncology units in South Africa

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ABSTRACT

This study investigates the prevalence of vitamin and iron deficiencies at cancer diagnosis. Newly diagnosed children between October 2018 and December 2020 at two South African pediatric oncology units (POUs) were assessed for nutritional and micronutrient status (Vit A, Vit B12, Vit D, folate, and iron). A structured interview with caregivers provided information regarding hunger and poverty risks. There were 261 patients enrolled with a median age of 5.5 years and a male-to-female ratio of 1:0.8. Nearly half had iron deficiency (47.6%), while a third had either Vit A (30.6%), Vit D (32.6%), or folate (29.7%) deficiencies. Significant associations existed between moderate acute malnutrition (MAM) and low levels of Vit A (48.4%; $p = .005$), Vit B12 (29.6%; $p < .001$), and folate (47.3%; $p = .003$), while Vit D deficiency was associated with wasting (63.6%) ($p < .001$). Males had significantly lower Vit D levels (respectively, 40.9%; $p = .004$). Folate deficiency was significantly associated with patients born at full term (33.5%; $p = .017$), age older than five years (39.8%; $p = .002$), residing in provinces Mpumalanga (40.9%) and Gauteng (31.5%) ($P = .032$); as well as having food insecurity (46.3%; $p < .001$), or hematological malignancies (41.3%; $p = .004$). This study documents the high prevalence of Vit A, Vit D, Vit B12, folate, and iron deficiency in South African pediatric cancer patients, demonstrating the need to include micronutrient assessment at diagnosis to ensure optimal nutritional support for macro-and micronutrients.

ARTICLE HISTORY
Received 25 October 2022
Revised 2 March 2023
Accepted 4 March 2023

KEYWORDS
Cancer; Childhood cancer; nutritional status; iron deficiency; vitamin

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Supplemental data for this article is available online at https://doi.org/10.1080/08880018.2023.2188920

Introduction

Vitamin and mineral deficiencies are a global public health problem, especially in regions where food insecurity and poor diet diversity are endemic.[1] In low- and middle-income countries (LMICs), micronutrient deficiencies are common,[2] and in sub-Sahara Africa,[3,4] the prevalence in children ranges from 60 to 80% for vitamin A (Vit A), vitamin D (Vit D), vitamin B12 (Vit B12),[4–6] and iron deficiency.[3] The true prevalence of micronutrient deficiency in children with cancer in LMIC is limited (primarily data from India),[7] with prevalence in African countries largely unknown as the nutritional status, based on anthropometrics alone, of patients, is not a direct indicator of micronutrient status.[8] Studies done in pediatric oncology in high-income and upper-middle-income countries concluded micronutrient deficiencies in children range from 6 to 64%.[8,9]

Insufficient diet diversity is common in LMIC and South Africa due to diet composition consisting mainly of plant protein,[10–12] resulting in many South African children developing several micronutrient deficiencies.[13] The initiation of treatment for a pediatric malignancy is likely to exacerbate preexisting deficiencies, predisposing children to increased morbidity[14] and chemotherapy-related side effects.[15] To date, the prevalence of micronutrient deficiencies among children with cancer undergoing treatment in South Africa has not been thoroughly investigated.

The main aim of this study is to determine the prevalence of select vitamin and mineral deficiencies at cancer diagnosis in children treated at two pediatric oncology units (POUs) in South Africa and identify possible predictors of nutrient deficiencies to identify children at-risk and in need of advanced nutrition intervention at diagnosis.

Patients and methods

All newly diagnosed consecutive children and adolescents with cancer between October 2018 and December 2020 at two POUs in South Africa were enrolled if written consent and/or assent were obtained (ages between 3 months and 15 years). The POUs were in Steve Biko Academic Hospital in Gauteng Province (including patients from Mpumalanga and Limpopo) and Tygerberg Hospital in the Western Cape.

Demographic and clinical parameters

The patient`s sex, age at diagnosis, gestational age at birth, and the province of residence were included. The cancer diagnoses were classified as either hematological malignancy (all types of leukemia and lymphoma) or solid tumors (any solid tumor). The serum levels of Vit A, Vit B12, Vit D, folate, and iron were determined within 72 h of cancer diagnosis, using standard measurement procedures by the National Health Laboratory Services.[16]

Serum levels

The serum levels were determined as follows: (1) Serum Vit D (25-OH) 25-OH-vitamin D3 and 25-OH-vitamin D2 were measured using the Chromsystems reagent kit

MassChrom 25-OH vitamin D3/D2 (Part no. 62,000) and in plasma with HPLC-tandem mass spectrometry;[17] (2) Serum Vit A: After protein precipitation, retinol was extracted into hexane and centrifuged, and the organic layer was pipetted off and dried. Subsequently, the dried product was reconstituted and measured with an HPLC instrument;[18] (3) Serum Vit B12 was determined by the ARCHITECT B12 assay, a two-step assay with an automated sample pretreatment in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology;[19] (4) Serum Folate was measured using CMIA technology;[20] and (5) Serum iron was measured using Ferene-S* technology.[21]

The levels of the micronutrients evaluated were classified as decreased (less than normal range), normal levels (within normal range), and increased (above the normal range) (Supplementary Table 1) as per levels set forth by the National Health Laboratory Services South Africa.[16]

Anthropometry

Anthropometrical measurements were obtained within 72 h after diagnosis. The Z-scores for height-for-age (H/A), weight-for-age (W/A), and body mass index for-age (BAZ) were determined with WHO AntroPlus 2007.[22] Mid-upper arm circumference (MUAC) was measured, and the Z-score was determined with MUAC growth charts (<5 years WHO 2007[23] >5 years Mramba et al.).[24] Two standard deviations (< −2 SD) below normal defined malnutrition: stunting (< −2 SD H/A), underweight < −2 SD W/A), wasting (< −2 SD BMI/A), and moderate acute malnutrition (MAM) (< −2SD MUAC/A).

Parent interviews

A structured interview was completed with the parents/caregivers for the Hunger Scale Questionnaire[25] and the South African Poverty-Assessment tool.[26] The Hunger Scale Questionnaire consists of 8 'yes' or 'no' questions. The final score divides the population into groups: hunger (five or more 'yes' answers), the risk for hunger (equal to four 'yes' answers), and no risk (less than 4 'yes' answers).[25] The South African Poverty-Assessment Tool has 12 questions with points allocated to the answer. The total score was categorized to determine the risk of living under the poverty line in South Africa (R14.80/d or $0.92 US/d).[26] The final score of the Poverty Assessment-Tool points was categorized as those with more than a 50% risk of living in poverty and those with less than a 49% risk of living in poverty.[26]

Statistics

All data were analyzed using the Stata version 17 (StataCorp LLC, College Station, TX) software package. Descriptive statistics such as frequencies, percentages, means, standard deviations, and medians were calculated. The prevalence of decreased levels of Vit D, Vit A, Vit B12, folate, and iron was estimated with Wilson 95% confidence intervals. The Pearson chi-square test and Fisher's exact test were applied to evaluate associations between individual deficiencies of the micronutrients and sex, age group (younger or older than five years of age), disease group (hematological malignancy *vs.* solid tumor), specific diagnosis, province of residence, anthropometry (underweight,

stunting, wasting, or MAM), the Hunger Scale score, and risk for living in poverty. Logistic regression was used to model deficiency on the covariates hospitals, sex, age, poverty score, stunting, cancer diagnosis, hunger score, and pre-term birth. Odds ratios were estimated and reported with 95% confidence intervals. Province of residence and hospital were highly correlated, especially for Western Cape, where 99% of the children were from Tygerberg Hospital. Therefore, the latter was used in the multiple regression models. All deficiencies had missing values, and a complete case analysis was done under the assumption that data were missing completely randomly. Due to the number of covariates investigated, the logistic regression models consisted of main effects only, and no interactions were evaluated. Given this setup and the assumptions made, the results of the multiple regression should be considered exploratory. A p value of less than .05 was considered significant.

Ethics

The Health Research Ethics Committee, Faculty of Medicine and Health Sciences, Stellenbosch University (S18/04/050), and the Research Ethics Committee, University of Pretoria (281/2018) provided ethics approval. Parents/legal guardians provided written informed consent (with assent if children older than seven years) in the home language of the parent and/or child (English, Afrikaans, Zulu, Tsonga, Tswana, Sepedi, Xhosa).

Results

This nested prospective cohort study included 261 newly diagnosed children and adolescents at two POUs in South Africa with a median age of 5.5 years (Table 1). The three most common cancers were acute lymphoblastic leukemia (22.2%), nephroblastoma (14.2%), and Hodgkin Lymphoma (8.8%) (Supplementary Table 2). A third of the patients had one deficiency (31.8%, $n = 83$), 22.2% ($n = 58$) had two deficiencies, and 11.4% ($n = 30$) had three or more deficiencies.

Vitamin levels

Vit D levels were determined in 70.5% of the patients ($n = 184$), revealing a deficiency in 32.6% (Table 2). Significantly more males (40.9%) than females (21.5%) ($p = .004$) had Vit D deficiency, as well as children born prematurely (58.8%), compared to children born at term (26.3%) ($p < .001$) (Table 3). Wasted children (BAZ < -2) had significantly lower Vit D levels than non-wasted children (63.6 *vs.* 28.4%; $p < .001$), as did well-nourished children (W/A > -2 SD) compared to underweight children (W/A < -2 SD) (33.1 *vs.* 22.2%; $p < .001$) (Table 4). No other significant associations were observed (Tables 3 and 4).

Vit A levels were assessed in 60.2% of the study population ($n = 157$), and 30.6% had a deficiency (Table 2). A significant association was found with patients classified as MAM (48.8%; $p = .005$) (Table 4), but no association with sex, gestational age at birth, age group, disease groups, specific diagnosis, province of residence, other anthropometric measurements, Hunger Scale score, or risk of living in poverty (Tables 3 and 4).

Table 1. Demographic data.

Variable	Categories	Percentage (*n*) *N* = 261
Sex	Males	54.0 (141)
	Females	46.0 (120)
Gestational age at birth:	Full term	78.9 (206)
	Premature	21.1 (55)
Age in years	Median (IQR)	5.5 (2.6–9.9)
	Range (min-max)	0.3 – 15.7
	Mean	6.3
Diagnosis –consolidated	Hematological malignancy	44.4 (116)
	Solid tumors	55.5 (145)
Nutritional Status at diagnosis[a]	Stunted	15.3 (40)
	Underweight	8.6 (17/198)
	Wasted	11.9 (31)
	MAM	23.8 (62)
Hospital	Steve Biko Academic Hospital	59 (154)
	Tygerberg Children's Hospital	41 (107)
Province of residence	Western Cape	40.6 (106)
	Mpumalanga	35.2 (92)
	Gauteng	20.4 (53)
	North West	0.8 (2)
	Limpopo	1.5 (4)

[a]Stunted (HAZ < –2); Underweight (WAZ < –2); wasted (BAZ < –2); MAM (MUAC < –2).

Table 2. Prevalence of vitamin and iron levels with 95% confidence intervals.

Parameter	Decreased levels	Normal range	Increased levels	Total
Vitamin A	48 (30.6%) [23.9–38.2%]	91 (57.9%) [50.1–65.4%]	18 (11.5%) [7.48–17.4%]	157
Vitamin D	60 (32.6%) [26.3–39.7%]	121 (65.8%) [58.7–72.2%]	3 (1.6%) [0.6–4.7%]	184
Vitamin B12	28 (14%) [9.9–19.5%]	146 (73%) [66.5–78.7%]	26 (13%) [9.0–18.4%]	200
Folate	59 (29.7%) [23.7–36.3%]	138 (69.4%) [62.6–75.3%]	2 (1%) [0.3–3.6%]	199
Iron	100 (47.6%) [41.0–54.4%]	71 (33.8%) [27.8–40.5%]	39 (18.6%) [13.9–24.4%]	210

Vit B12 levels were available for 76.6% ($n = 200$) of the participants, and deficiency was found in 14% of the study population (Table 2). Children classified with MAM (29.6%) ($p < .001$) had a significantly higher prevalence of Vit B12 deficiency than well-nourished children (8.2%) (Table 4). Patients diagnosed with neuroblastoma (37.5%), carcinoma (25%), germ cell tumor (22.0%), nephroblastoma (20.8%), and acute lymphoblastic leukemia (20%) had significantly decreased Vit B12 levels compared to other diagnoses ($p = .038$) (Supplementary Table 4). No other variables showed significant prevalence differences between groups (Tables 3 and 4).

The multiple regression model confirmed that wasted patients had 8.5 times higher odds for a Vit D deficiency than non-wasted children (OR 8.5, 95% CI 2.8, 25.3, $p < .001$), similarly for patients born prematurely (OR 3.7, 95% CI 1.6, 9.0; $p = .003$). Females, compared to males, had lower odds for decreased Vit D levels (OR 0.3, 95% CI 0.2, 0.7, $p = .005$). Therefore, the univariate results are confirmed for Vit D but not other vitamins (Table 5).

Table 3. Association of demographic variables with decreased levels of vitamin and iron.

	Vit D (*N* = 184)			Vit A (*N* = 157)			Vit B12 (*N* = 200)			Folate (*N* = 199)			Iron (*N* = 210)		
	n	%	95% CI	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
Males	43	40.9	(32.0–50.5)	27	30.3	(21.8–40.5)	13	12	(7.2–19.5)	34	30.9	(23.0–40.1)	55	47	(38.2–56.0)
Female	17	21.5	(13.9–31.8)	21	30.9	(21.2–42.6)	15	16.3	(10.1–25.2)	25	28.1	(19.8–38.2)	45	48.4	(38.5–58.4)
p Value		.004			.665			.537			.904			.267	
<5 years	24	30.8	(21.6–41.7)	17	25.4	(16.5–36.9)	14	16.1	(9.8–25.2)	14	16.3	(9.9–25.5)	51	54.8	(44.7–64.6)
≥5 years	36	33.9	(25.7–43.40	31	34.4	(25.5–44.7)	14	12.4	(7.5–19.7)	45	39.8	(31.3–49.0)	49	41.9	(33.3–50.9)
p Value		.273			0.314			n/a			0.002			.131	
Term	40	26.7	(20.2–34.3)	40	31.1	(23.7–39.4)	26	15.9	(11.1–22.2)	56	33.5	(26.8–40.9)	87	51.2	(43.7–58.5)
Prem	20	58.8	(42.2–73.6)	8	28.6	(15.3–47.1)	2	5.6	(1.5–18.1)	3	9.4	(3.2–24.2)	13	32.5	(20.1–47.9)
p Value		<.001			.503			.028			.017			.076	
GP	9	19.6	(10.7–33.2)	14	31.1	(19.5–45.6)	10	18.9	(10.6–31.4)	17	31.5	(20.7–44.7)	31	58.5	(45.1–70.7)
LP	0	0	–	0	0	–	2	50.0	(15.0–85.0)	1	25	(4.6 – 69.9)	3	100	0
MP	24	30.4	(21.3–41.2)	23	30.7	(21.4–41.8)	14	16.1	(9.8–5.2)	36	40.9	(31.2 – 51.4)	44	51.2	(40.8–61.5)
NW	0	0	–	1	100	(20.7–100.0)	0	0	–	0	0	–	0	0	0
WC	27	49.1	(36.4–61.9)	10	30.3	(17.4–47.3)	2	3.6	(1.0–12.3)	5	9.6	(4.2–20.6)	22	32.8	(22.8–44.7)
p Value		.077			.810			.016			.032			.024	
HM	32	36.8	(27.4–47.3)	24	36.4	(25.8–48.4)	14	14.9	(9.1–23.5)	38	41.3	(31.8–51.5)	26	25.2	(17.8–34.4)
ST	28	28.9	(29.8–38.6)	24	26.4	(18.4 – 36.3)	14	13.2	(8.0–20.9)	21	19.6	(13.2–28.2)	74	69.2	(59.9–77.1)
p Value		.383			.407			.106		.004			<.001		

Term = Patients born at term; prem = Patient born prematurely; GP = Gauteng province; LP = Limpopo province; MP = Mpumalanga province; NW = North West Province; WC = Western Cape Province; HM = Hematological malignancy; ST = Solid tumor

Table 4. Association of anthropometric variables with decreased levels of vitamins and iron.

	Vit D (*N* = 184)			Vit A (*N* = 157)			Vit B12 (*N* = 200)			Folate (*N* = 199)			Iron (*N* = 210)		
	n	%	95% CI	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
Stunted	8	27.6	(14.7–45.7)	7	29.2	(14.9–49.2)	6	18.8	(8.9– 35.3)	9	29.0	(16.1–46.6)	20	60.6	(43.7–75.3)
Normal length	52	33.6	(26.6–41.3)	41	30.8	(23.6– 39.1)	22	13.3	(8.81–19.03)	50	29.8	(23.4–37.1)	80	45.2	(38.1–52.6)
p Value		.589			.835			.699			.824			.260	
Underweight	2	22.2	(6.3–54.7)	2	33.3	(9.7–70.0)	1	11.1	(1.9–43.5)	4	44.4	(18.9–73.3)	3	27.3	(9.8–56.6)
Normal weight	58	33.1	(26.6–40.4)	46	30.5	(23.7–38.2)	27	14.1	(9.9–19.8)	55	28.9	(22.9–35.8)	97	48.7	(41.9–55.7)
p Value		<.001			.891			.448			.592			.378	
Wasted	14	63.6	(42.9–80.3)	5	33.3	(15.2–58.3)	3	12	(4.2–29.9)	8	29.6	(15.9–48.5)	14	53.9	(35.5–71.2)
Normal	46	28.4	(22.0–35.8)	43	30.3	(23.3–38.3)	25	14.3	(9.9–20.2)	51	29.7	(23.3–36.9)	86	46.7	(39.7–53.9)
p Value		<.001			.340			.868			.853			.717	
MAM	18	36.0	(24.1–49.9)	20	48.4	(34.3–63.5)	16	29.6	(19.1–42.8)	26	47.3	(34.7–60.2)	33	61.1	(47.8–72.9)
Well-nourished	42	31.3	(24.1–39.6)	28	24.1	(17.3–32.7)	12	8.2	(4.8–13.8)	33	22.9	(16.8–30.4)	67	42.9	(35.4–50.8)
p Value		.228			.005			<.001			.003			.057	

Legend: Stunted (HAZ<-2); Underweight (WAZ<-2); wasted (BAZ <-2); MAM (MUAC<-2).

Table 5. Multiple logistic regression analysis of micronutrient deficiencies on selected covariates at diagnosis.

		Decreased Vit D levels		Decreased Vit A levels		Decreased Vit B12 levels		Decreased folate levels		Decreased iron levels	
Variable	Parameters	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Hospitals for regions	Steve Biko	1		1		1		1		1	
	Tygerberg	1.9 (0.9, 4.3)	.096	0.9 (0.4, 2.5)	.996	0.2 (0.04, 1.0)	.052	0.2 (0.1, 0.5)	.002	0.6 (0.3, 1.1)	.110
Sex	Males	1		1		1		1		1	
	Females	0.33 (0.2, 0.7)	.005	1.1 (0.6, 2.3)	.752	1.7 (0.7, 4.04)	.217	1.4 (0.6, 2.8)	.420	1.0 (0.5, 1.9)	.949
Gestational age	Term	1		1		1		1		1	
	Premature	3.7 (1.5, 9.0)	.003	0.9 (0.3, 2.3)	.752	0.6 (0.1, 2.7)	.476	0.3 (0.1, 1.3)	.106	0.6 (0.2, 1.3)	.200
Age	<5 years	1		1		1		1		1	
	≥5 years	0.9 (0.4, 1.9)	.725	1.7 (0.8, 3.6)	.198	0.8 (0.3, 2.1)	.627	3.6 (1.6, 8.3)	.002	1.0 (0.5, 1.9)	.923
Hunger Scale	No risk	1		1		1		1		1	
	Hunger	1.0 (0.9, 1.2)	.829	0.9 (0.4, 2.0)	.404	1.2 (0.9, 1.4)	.136	1.2 (1.1, 1.5)	.007	0.9 (0.9, 1.1)	.938
Disease group	ST	1		1		1		1		1	
	HM	0.6 (0.3 1.3)	.281	0.7 (0.3 1.5)	.363	0.7 (0.3 1.7)	.381	0.4 (0.2, 0.8)	.007	6.4 (3.3, 12.2)	<.001
Wasting	BAZ >−2	1		1		1		1		1	
	BAZ <−2	8.5 (2.8, 25.3)	<.001	1.1 (0.3, 3.7)	.866	0.8 (0.2, 2.9)	.715	0.7 (0.2, 2.0)	.513	1.2 (0.4, 2.90)	.771

OR = Odds ratio; CI = Confidence interval; ST = Solid tumor; HM = Hematological malignancy; BAZ = Body mass index for age.
OR of reference values has been reported as 1.

Folate levels

Twenty-nine percent (29%; $n = 100$) of those who had folate levels measured were classified as folate deficient ($n = 199$) (Table 2). Participants older than five years of age (39.8%) had an increased prevalence of folate deficiency compared to those under five years of age (16.3%) ($p = .002$). Participants living in the provinces of Mpumalanga (40.9%) and Gauteng (31.5%) had significantly more folate deficiency in comparison to those residing in the Western Cape (9.7%) ($p = .032$) (Table 3). Furthermore, MAM (47.3%) and hematological malignancy (41.3%) were significantly associated with folate deficiency (respectively, $p = .003$ and $p = .004$) (Tables 3 and 4). The participants in the hunger group were more prone to folate deficiency (46.3%) than the children in the other categories: risk for hunger (17.1%) or the food security group (22.6%) ($p < .001$) (Supplementary Table 3). No other significant parameter associations were found (Tables 3 and 4). Multiple regression analysis confirmed these results as patients from Tygerberg Hospital (Western Cape province) had lower odds of folate deficiency than those from other provinces treated in Steve Biko Hospital (Gauteng, Mpumalanga, Limpopo) (OR 1.8; 95% CI 0.0.06, 0.53, $p = .002$). Patients older than five years of age also had higher odds of suffering from folate deficiency (OR 3.6 95%, 95% CI 1.69, 8.3; $p = .002$) (Table 5).

Iron levels

Iron levels were obtained in most children; (80.4%; $n = 210$), and 47.6% were classified with iron deficiency (Table 2). Children residing in Gauteng and Mpumalanga had significantly lower iron levels (58.5 and 51.2%, respectively) compared to children living in the Western Cape (32.8%) ($p = .024$) (Table 3). Significantly more patients diagnosed with solid tumors (69.2%) experienced iron deficiency compared to hematological malignancy (25.2%) ($p < .001$) (Table 3). Patients diagnosed with nasopharynx carcinoma (100%), nephroblastoma (90.9%), germ cell tumor (88.8%), Ewing sarcoma (80%), and neuroblastoma (75%) had significantly decreased iron levels at diagnosis compared to other diagnoses ($p < .001$ (Supplementary Table 4). There was no significant prevalence difference for other parameters. In the multiple regression analysis, the univariate analysis was not confirmed as hematological malignancy had 6.3 times higher odds for lower iron levels than the solid tumor patients (OR 6.3, 95% CI 3.3, 12.2, $p < .000$) at diagnosis, indicating hematological malignancies dominating the signal from the rest of the factors (Table 5).

Discussion

Our study found that micronutrient deficiencies are prevalent among children diagnosed with cancer in South Africa. Only one previous report documented the micronutrient status of children with cancer in South Africa and found that 57.1% had Vit A deficiency at diagnosis[27] compared to 30.6% in our study. Recent studies in children with cancer from high-income and upper-middle-income countries found that 64% of childhood cancer patients had Vit D deficiency,[28] 9% Vit A deficiency, and 6% had Vit B12 deficiency;[29] while a study performed in Turkey, an upper middle-income country

similar to South Africa, indicated 79% had Vit D deficiency, 26% had Vit B12 deficiency, and 10% folate deficiency.[9] Taken together, these studies suggest that micronutrient deficiencies are not uncommon among children with cancer and may need to be a part of the initial work-up, particularly among children undergoing treatment in an LMIC.

Children with cancer have a high risk of becoming more deficient due to the cancer treatment and may be especially vulnerable to poor bone health.[30] A study of healthy South African children under eight years of age found that 15.4% had Vit D deficiency.[31] Our study documented a higher prevalence; 32.6% were vitamin D deficient, higher among boys and children categorized as wasted. Our findings were supported by a Hungarian study.[32] In contrast, a study performed in India among children with acute lymphoblastic leukemia found that girls had significantly lower Vit D levels than boys; the authors believed this was attributed to cultural beliefs, where males are allowed to play outside more often than females, *vs.* the treatment itself.[33] A possible explanation for the higher prevalence of Vit D deficiency in cancer children may be due to decreased physical activity, less sunlight exposure, and/or poor nutritional intake.[9,30] It is distinct in our study compared to the previous report of healthy South African children[31] that our population was more Vit D deficient. Our findings suggest that additional research is warranted, and preventative interventions may be necessitated to either replete or prevent further depletion of Vit D among South African children undergoing treatment for cancer.

Vit A deficiency among South African children is common, with 62% of children older than five years of age and 58% of those under five years of age classified as deficient.[34] A previous report in children with cancer also reported a high prevalence of Vit A deficiency, with 57% deficient at diagnosis.[27] Vit A deficiency in children with cancer was associated with increased complications,[8] such as an increased risk for stomatitis and infections.[27] The prevalence in this study was lower (30.6%) than the previous South African report, which was probably due to the South African Vit A supplementation program, which began in 2002 for children younger than five years of age.[35] Nevertheless, our study suggests that a large proportion of children diagnosed with cancer experience low Vit A levels, which may have an adverse effect on treatment-related toxicities.

An important finding was that nearly a third of this study population had folate deficiency (29.7%) associated with families experiencing food insecurity. This was much higher than the reported prevalence of 10% in children with cancer in Hungary but may be partly explained by the finding that more than 50% of South African school children in 2014 were not meeting the estimated average requirement for folate, even though fortified cereals, bread, and other grain products were available.[9,34–36] Deficiencies were associated with the geographical regions in South Africa as children living in Mpumalanga and Gauteng had significantly lower folate-, vit B12-, and iron levels at diagnosis compared to other provinces. Of note, these provinces also had a significant number of families experiencing hunger and poverty. Poor food knowledge can also affect families' ability to make healthy food choices within the budget.[37]

Despite the limitations of serum folate, the observed sociodemographic factors may identify children who are especially vulnerable to folate depletion. Future studies should explore sociodemographic factors in tandem with red blood cell folate to ascertain the role, if any, of folate depletion in children with cancer.

Finally, our study identified several potential predictors of individual micronutrient depletion; however, no single sociodemographic predictor indicated depletion in all nutrients. Nutritional status, gestational age at birth of patients, and type of cancer diagnosis were all associated with deficiencies in several micronutrients. It is well-established that children with under nutrition are predisposed to nutrient deficiencies,[38] and clinicians should prioritize these patients for nutritional intervention. In the event routine laboratory assessments are not available, our evidence suggests that the administration of commercial nutritional supplements providing macro- and micronutrients, especially in patients with food insecurity at home, may benefit the children without imparting the risk of excess intake.[39] The associations with a diagnosis need to be interpreted with caution as deficiencies in hematological malignancies may be solely due to the malignant hematopoietic cell's increased use of folate,[40] or in solid tumor with advanced abdominal tumors that are associated with decreased oral intake,[39] which was also observed in an Indian childhood cancer study (2014).[8] Our study establishes hypothesis-generating pilot work that is worthy of follow-up in a homogenous cohort of children.

Our study was a pilot study in South Africa POUs and represents one of the few studies to systematically evaluate micronutrient deficiencies among children with cancer. However, the data collected must be interpreted considering several limitations. We were unable to collect vitamin and mineral levels for all study participants, as some blood samples were lost or did not have adequate volume for the necessary tests. We were also limited to the analysis of plasma folate rather than red blood cell folate, which indicates long-term folate status and is less impacted by the malignancy itself. Due to personnel limitations, dietary intake was not collected, precluding us from confirming that deficiencies were due to poor dietary intake, the disease itself, or a combination of both. Finally, only the main effects of multiple regression models were used in multivariate analysis due to a large number of covariates.

In conclusion, we found a high prevalence of Vit D, Vit A, and Vit B12, folate, and iron deficiency on diagnosis at two POUs in South Africa; this article adds to the literature on micronutrient status at diagnosis and some clinical correlations in this pediatric cancer population. Our findings suggest indications for individual clinical care and nutritional supplementation, as well as pave the way for prospective studies to be performed in a larger cohort of children, as the topic of when to supplement in the absence of clinical evidence of micronutrient deficiency is controversial. There is a need for further studies correlating overall cancer outcomes, including how micronutrient deficiency may affect chemotherapy toxicity.

Acknowledgments

The authors acknowledge the children and parents/caregivers who participated in the study. They want to thank the pediatric registrars, dieticians, and nursing staff of the POU at Steve Biko Academic Hospital and Tygerberg Children's Hospital for supporting this study.

Special thanks to the Pediatric Hematology-Oncology team at Steve Biko Academic Hospital, especially Ané Büchner, Fareed Omar, and David Reynders, for identifying patients for the study and their support toward the study.

Conflict of interest

None.

Contribution to the manuscript

Judy Schoeman and Mariana Kruger conceptualized the study. Judy Schoeman, a Ph.D. student, designed the study, developed the Redcap database, enrolled patients, collected, cleaned, analyzed, and wrote the manuscript. Mariana Kruger, Elena Ladas, and Paul Rogers assisted with the design of the study and critically reviewed the manuscript. Ilde-Marié Kellerman and Ronelle Uys enrolled patients, collected the data, and reviewed the manuscript. Carl Lombard conducted the statistical analysis of the data and reviewed the manuscript.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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Data availability statement

The data supporting this study's findings are available on request from the corresponding authors. The data are not publicly available due to ethical restrictions.

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CHAPTER 5

Prevalence of malnutrition in newly diagnosed children in five paediatric oncology units in South Africa and association with overall survival one year after diagnosis

The manuscript is publication-ready and will be submitted to Pediatric Blood and Cancer for publication (Impact factor 3.83)

(Text is US English as journal requirements)

https://onlinelibrary.wiley.com/journal/15455017

This study investigated the prevalence and severity of malnutrition at cancer diagnosis in South Africa. The hypothesis was:

Ha: There is a high percentage of children diagnosed with cancer with malnourished at diagnosis, and therefore associated with a poor OS, and EFS

H0: There is a low percentage of children diagnosed with cancer with malnutrition at diagnosis, and therefore not associated with a poor OS, and EFS.

Less than 15% of the children in the cohort were stunted, underweight, or wasted. However, mid-upper arm circumference measurements identified 24.3% with moderate acute malnutrition (MAM). Girls were more prone to being underweight than boys, while five years and older children were more likely to be classified as MAM. Children with undernutrition improved significantly six months after diagnosis. However, children stunted at diagnosis had significantly poorer overall survival (OS) one year after a cancer diagnosis (HR 1.9; 95% Ci 1.1, 3.3; $P = 0.029$). Malnutrition at childhood cancer diagnosis might be expected in low-middle-income countries and is associated with poor OS, but the impact in South Africa is unknown. Malnutrition at cancer diagnosis was less than 15%, and the hypothesis was not supported.

PREVALENCE OF MALNUTRITION AND ASSOCIATION WITH OVERALL ONE-YEAR SURVIVAL IN NEWLY DIAGNOSED CHILDREN WITH CANCER IN SOUTH AFRICA

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Contribution to the manuscript

Judy Schoeman and Mariana Kruger conceptualized the study. Judy Schoeman, a Ph.D. student, designed the study, developed the Redcap database, enrolled patients, collected data, cleaned-, transferred data to the World Health Organization Anthro and Pedi-Tools programs to calculate Z-scores, analyzed the data, and wrote the manuscript.

Mariana Kruger, Elena Ladas, and Paul Rogers supervised the study, conducted an extensive critical review, and approved the manuscript.

Ilde-Marié Kellerman, Ronelle Uys, Gita Naidu, Biance Rowe, Jan du Plessis, Mariechen Herholdt, Karla Thomas, Barry Vanemmenes, Rema Mathews, Ané Büchner, Fareed Omar, and David Reynders were investigators at the different sites, enrolled patients, collected data, and critically reviewed the manuscript.

Sandile Ndlovu, Etienne Nel, and Carl Lombard did the statistical analysis and critically reviewed the manuscript.

Word count:

a) Abstract: 230
b) Main text (exl tables and figures): 3017

The number of tables: 2

The number of figures: 3

The number of supporting files: Supplementary tables:5

The number of supporting files: Supplementary figures:3

Short running title: Malnutrition at childhood cancer diagnosis

Keywords: Nutritional status, malnutrition, childhood cancer, overall survival

List of abbreviations

Abbreviation	Term
BAZ	Body mass index for age
BMI	Body mass index
CI	Confidence interval
EFS	Event free survival
HAZ	Height/lenght for age
HR	Hazard ration

Abbreviation	Term
LMIC	Low- and middle- income country
MUAC	Mid-upper arm circumference
MUAC/A	Mid-upper arm circumference for age
OR	Odds ratio
POU	Pediatric oncology unit
OS	Overall survival
MAM	Moderate acute malnutrition
SD	Standard deviation
UNICEF	United Nations Children's Fund
WAZ	Weight for age
WHO	World Health Orhanazation

Abstract

Introduction:

This study investigated the prevalence of malnutrition at childhood cancer diagnosis in South Africa and the association with one-year post-diagnosis overall survival (OS)

Method:

Nutritional status was prospectively assessed for newly diagnosed children with cancer. Malnutrition was defined as two standard deviations (SDs) or more below zero for height/length-for -age (HAZ), weight -for -age (WAZ), body mass index for age (BAZ), and mid-upper arm circumference for age (MUAC/A). The association between the nutritional status at diagnosis and age, sex, disease group, and one-year post-diagnosis OS was analyzed with Cox regression and hazard ratios (HRs).

Results:

Less than 15% were stunted (14.3%), underweight (11.6%), or wasted (8.1%), but 24.3% had moderate acute malnutrition (MAM) for the cohort of 320 patients at cancer diagnosis. More females than males were underweight (12.2% versus 4.5%; $P = 0.027$). Children five years of age and older had a higher prevalence of MAM than children under five years of age (33.5% versus 14.5%) ($P < 0.001$), with significant improvement six months after diagnosis ($P < 0.001$). Stunting was significantly associated with poorer OS one year after a cancer diagnosis (HR 1.9; 95% CI 1.1, 3.3; $P = 0.029$).

Conclusion:

MUAC/A identified more children with malnutrition than other nutritional parameters. Stunting was significantly associated with poorer OS one year after a cancer diagnosis. Optimal nutritional support should be provided for South African children, especially those with stunting, to improve OS.

Introduction

Childhood cancer treatment aims to cure children and ensure that survivors experience normal growth and development.[1] The estimated incidence of cancer in children and adolescents in 2020 was about 413 000, with the majority (80 - 90%) living in low- and middle- income countries (LMICs). [2] LMICs also have the highest prevalence of stunting and wasting in children,[3] which a cancer diagnosis may exacerbate.[4] In Africa, an estimated 61.4 million children are stunted, 15.1 million are wasted, and 10.6 million are overweight, according to the United Nations Children's Fund (UNICEF), the World Health Organization (WHO), and the World Bank Group (2020).[5] In South Africa, an upper-middle-income country, the prevalence of stunting in children is 23.2%, while 12.9% are overweight. [6] A third of all hospital deaths in children in South Africa are still associated with severe – or moderate acute malnutrition (MAM).[7]

Nutritional anthropometric assessment in childhood cancer is crucial for early diagnosis of malnutrition with planned appropriate nutritional intervention to improve nutritional status [8] and decrease mortality.[5] A survey of African pediatric oncology units (POUs) reported that only 52% of newly diagnosed children with cancer were nutritionally assessed as in-patients and even fewer in ambulatory clinics (33%), most often due to limited resources.[9] This is of major concern as malnutrition in childhood increases treatment-related toxicity,[10,11] prolongs hospital stay, delays wound healing, decreases the quality of life,[12] and increases delays in treatment with a potentially negative effect on overall survival (OS) and event-free survival (EFS).[10,13]

Limited data exist about the influence of cancer and cancer treatment on the nutritional status of children, especially in South Africa, as no data has been published.[14] This study investigated the prevalence of malnutrition in newly diagnosed children with cancer in South Africa and, its association with one-year OS and EFS, and with longitudinal growth during the first six months of cancer treatment.

METHODS

Study design

This prospective cohort study recruited newly diagnosed children with cancer between three months and 15 years of age in five POUs in South Africa from October 2018 through December 2020.

Clinical data

Clinical and demographic data (diagnosis, stage or risk of disease, chemotherapy protocol, age, sex, and province of residence) was prospectively collected into a REDCAP database. The patient diagnoses were either hematological malignancy (leukemia and lymphomas) or solid tumors.

Anthropometry

Anthropometry (weight, height, and mid-upper arm circumference [MUAC]) was assessed within 72 hours after cancer diagnosis while children were barefoot and wearing light clothing. Body weight and height (older children) were measured with a calibrated column SECA weight scale with an attached height meter (the SECA 786 and SECA 220 model). Weight was recorded to the nearest 100 g and length to the nearest 0.1 cm. Children stood straight, facing forward with their backs against the height meter. A calibrated SECA electronic baby scale with a length meter was used to assess children younger than two years (SECA 334 model). The UNICEF color band was used to measure MUAC in children under five,[15] and the MUAC circumference measuring band was used to measure MUAC in children five years of age and older. [16] To measure MUAC, the child's arm was flexed toward the chest at a 90° angle. The investigator determined the midpoint of the arm, between the acromion and olecranon, the arm was relaxed, and the palm was facing towards the body; the MUAC was measured at the midpoint.[17]

All measurements were repeated once a month until six months after diagnosis. The WHO Anthro program was used to determine the z-scores for height/length for age (HAZ), weight for age (WAZ), body mass index (BMI), BMI for age (BAZ), and MUAC for age (MUAC/A).[18] Pedi-Tools[19] was used to determine MUAC/A z-score for older children based on the Mramba et al. growth charts,[20] and this was added to the database. Malnutrition for this study was defined as measurements of two standard deviations (SDs) below normal: for stunting as HAZ SD < -2; underweight as WAZ SD <-2, wasting as BAZ SD < -2, and MAM as MUAC/A SD < -2.

Outcome at year post cancer diagnosis

The study endpoint was defined as outcome at one- year post- cancer diagnosis. Abandonment was described as patients not returning for treatment. OS was defined as alive after one- year post- cancer diagnosis, and EFS as the time that these patients remained event free, without any death, relapse, or disease progression up to one- year post- cancer diagnosis.

Statistical analysis

All data were analyzed using STATA version 20 (STATA Corp. Texas, USA). Descriptive statistics for frequencies, percentages, means, standard deviations, and medians were calculated. Complete case analysis was done with frequencies on all parameters with the associated confidence intervals (CI); the Chi- square test and the Fisher's test were used for comparisons between anthropometry at diagnosis and sex, age group (younger than five years of age or five years and older), disease group (hematological malignancy versus solid tumor), specific diagnosis and the province of residence. Limpopo, North West, and the Northern Cape were grouped togerher for analysis due to the small number of participants per province for analysis. All factors that had a *P*-value of < 0.1 in the univariate analysis were added to logistic regression modes, and odds ratios (Ors) and their 95% CIs were estimated. The mean z-scores with their 95% CI were calculated, and the t-test was used to compare means between two groups, while the one-way ANOVA was used to compare the means of more than two groups. A multilevel mixed-effects regression analysis was done to show the differences in mean z-scores over six months, and factors influencing the z-scores over time were investigated. Predicted margins were plotted using marginsplot. Descriptive statistics for frequencies, percentages, means, standard deviations, and medians were calculated for the first six months of treatment. Log-rank tests were used to identify risk factors associated with one- year OS and EFS. All risk factors with a *P*- value < 0.05 were included in a Cox proportional hazard model, and hazard ratios (HRs), 95% CIs, and Kaplan-Meier curves were presented. A *P*-value <0.05 was considered statistically significant.

Ethics approval

Parents or caregivers' gave written consent prior to study enrolment, and children gave assent if older than seven years. The following institutions provided ethics approval: Stellenbosch University (Health Research Ethics Committee, Faculty of Medicine and Health Sciences [S18/04/050]), University of Pretoria (Research Ethics Committee, [281/2018]), University of the Witwatersrand (Human Research Ethics Committee [M190485]), University of the Free state (Health Sciences Research Ethics Committee [UFS-HSD2019/0445/3007]), and Frere Hospital (Ethics Committee [CMHREC 001/19]). The national and provincial health departments approved the conduct of the study in the public sector.

RESULTS

Demographics and nutritional status at diagnosis

We enrolled 320 patients from five POUs in South Africa. The median age was 5.3 years, and the male-to-female ratio was 1:0.9 (Table 1). A total of 55.9% (n = 179) presented with solid tumors and 44% (n = 141) with hematological malignancies. The five most common childhood cancer diagnoses were acute lymphoblastic leukemia (23.1%), nephroblastoma (15.6%), Hodgkin lymphoma (7.8%), rhabdomyosarcoma (7.2%), and retinoblastoma (6.3%) (Supplementary Table S1).

Table 1: Demographics of the study population

Patients enrolled	320	Percentage (n)
Sex	Males	52.5% (168)
	Females	47.5% (152)
	Males: Females	Ratio 1:0.9
Age	Median	5.3 years
	Range	0.3 -15.7 years
	Mean	6.1 years.
Hospital	Steve Biko Academic Hospital	154 (48.1%)
	Tygerberg Children Hospital	107 (33.4%)
	Chris Hani Baragwanath Academic Hospital	29 (9.1%)
	Universitas Hospital	21 (6.6%)
	Frere Hospital	9 (2.8%)
Province of residence	Western Cape	33.1% (106)
	Mpumalanga	28.7% (92)
	Gauteng	25.9% (83)
	Free State	5.9% (19)
	Limpopo	1.3% (4)
	North West	1.9% (6)
	Eastern Cape	3.1% (10)

Stunting, wasting, and being underweight at cancer diagnosis were observed in 14.7%, 11.6%, and 8.1% of patients, respectively, while the majority were well- nourished at diagnosis (89.5% had normal weight; 81.8% had normal length/height and 81.9% had normal BMI). The minority were overweight (6.6% according to BMI, 2.4% according to WAZ, and 2.8% according to MUAC/A).

Utilizing MUAC, however, identified that 24.3% of the children had MAM (26.3% with solid tumors and 21.7% with hematological malignancy).

Associations between malnutrition and selected variables

In the univariate analysis, children under five years of age had a significantly higher prevalence of being stunted (20.8%; n = 32) compared to children five years and older (9%; n = 15) ($P = 0.004$). More girls (12.2%; n = 14) than boys (4.5%; n=6; $P = 0.027$) were underweight at diagnosis.

Table 2: Associations of nutritional status according to demographics

CATEGORY		HAZ (N = 320)		WAZ (N = 248)		BAZ (n = 320)		MUAC/A <5 yrs* (N =152)		MUAC ≥5 yrs** (N =161)		MUAC/A Z-scores all ages (N=313)	
		Stunted	Mean (range)	Underweight	Mean(range)	Wasted	Mean (range)	MAM	Mean (range)	MAM	Mean (range)	MAM	Mean (range)
		% (N)		% (N)		% (N)		% (N)		% (N)		% (N)	
Sex	Male	14.3 (24)	-0.8 (-4.6, 3.9)	4.5 (6)	-0.4 (-3.2, 2.8)	11.9 (20)	-0.2 (-5.5, 4.6)	13 (10)	-0.4 (-3.3, 3.1)	33.3 (29)	-1.5 (-8.2, 2.2)	23.8 (39)	-1.0 (-8.2, 3.1)
	Female	15.1 (23)	-0.7 (-4.9, 3.5)	12.2 (14)	-0.6 (-3.8, 2.8)	11.2 (17)	-0.3 (-4.0, 3.4)	14.7 (11)	-0.5 (-5.3, 3.2)	35.1 (26)	-1.2 (-7.3, 3.6)	24.8 (37)	-0.8 (-7.3, 3.6)
	P- value	0.831	0.754	0.027	0.111	0.840	0.662	0.764	0.946	0.810	0.278	0.828	0.344
Age	<5 years	20.8 (32)	-1.0 (-4.6, 2.6)	6.5 (10)	-0.4 (-3.8, 2.8)	3.9 (6)	-0.3 (-3.7, 4.6)					14.5 (22)	-0.5 (-5.3, 3.2)
	≥5 years	9 (15)	-0.5 (-4.9, 3.9)	10.6 (10)	-0.6 (-3.2, 2.3)	18.7 (31)	-0.7 (-5.5, 3.3)					33.5 (54)	-1.4 (-8.2, 3.6)
	P-value	0.003	0.004	0.245	0.168	< 0.001	< 0.001					< 0.001	< 0.001
Province	FS	15.8 (3)	-0.8 (-2.7, 1.3)	12.5 (2)	-0.5 (-3.2, 1.7)	10.5 (2)	0.0 (-3.9, 4.6)	10 (1)	-0.7 (-3.2, 1.0)	14.3 (1)	-0.8 (-3.1, 0.7)	11.8 (2)	-0.7 (-3.2, 1.0)
	GP	14.6 (12)	-0.9 (-4.6, 2.0)	6.9 (5)	-0.7 (-2.7, 1.8)	7.3 (6)	-0.1 (-4.0, 3.2)	21.4 (9)	-0.7 (-5.3, 1.9)	38.5 (15)	-1.3 (-7.1, 3.6)	29.6 (24)	-1.0 (-7.1, 3.6)
	MP	18.5 (17)	-0.8 (-4,9, 2.6)	6.2 (4)	-0.5 (-3.8, 2.8)	15.2 (14)	-0.4 (-5.5, 3.4)	17.5 (7)	-0.7 (-5.0, 3.2)	46 (23)	-2.0 (-7.3, 2.2)	33.3 (30)	-1.4 (-7.3, 3.2)
	EC	0 (0)	-0.4 (-1.6, 1.7)	0 (0)	0.4 (-0.8, 2.8)	10 (1)	0.6 (-2.0, 2.7)	0	0.3 (-2.0, 3.1)	50 (1)	-2.1 (-2.7, -1.5)	10 (1)	-0.2 (-2.7, 3.1)
	WC	12.3 (13)	-0.5 (-4.6, 3.9)	11.4 (9)	-0.4 (-3.7, 2.3)	11.3 (12)	-0.2 (-4.4, 3.3)	6.1 (3)	-0.1 (-2.7, 2.2)	21.4 (12)	-0.9 (-8.2, 2.1)	14.3 (15)	-0.5 (-8.2, 2.2)
	Other ***	18.2 (2)	-0.8 (-2.4, 1.4)	0	-0.5 (-1.6, 0.7)	18.2 (2)	-1.0 (-3.1, -0.2)	33.3 (1)	-1.8 (-2.4, -1.4)	42.9 (3)	-1.7 (-3.1, -0.1	40 (4)	-1.7 (-3.1, -0.1)
	P value	0.639	0.092	0.631	0.032	0.674	0.075	0.199	0.161	0.103	0.003	0.011	0.003

*WHO anthro software; ** Mramba et al. with Peditools; *** Other provinces are Limpopo, Northern West, and Northern Cape.

Abbreviations: HAZ: height for age; WAZ: weight for age; BAZ= body mass index for age; MUAC: mid-upper arm circumference; FS: Free state province; GP: Gauteng province; MP: Mpumalanga province; EC: Eastern Cape province; WC: Western Cape province. A p-value of 0.05 is considered significant.

A higher percentage of children five years and older (18.7%; n = 31) were wasted compared to children under five years: (3.9%; n = 6; $P < 0.001$), and classified with MAM (MUAC/A) (33.5%; n = 54 vs. 14.5%; n = 22); $P < 0.001$) (Table 2).

More children younger than five years of age diagnosed with a solid tumor were classified with MAM (18.7%; n = 20) than those with hematological malignancy (2.2%; n = 1; $P = 0.007$). (Supplementary table S2). Province of residence was significantly associated with children classified with MAM. Mpumalanga (33.3%; n = 30), Gauteng (29.6%; n = 24), and the three grouped- together provinces (Limpopo, Northern West, and the Northern Cape) (40% (n = 4) had the most children classified with MAM compared to the Western Cape, Free State and Eastern Cape ($P = 0.011$) (Table 2). No significant associations with other parameters were found (Table 2 and Supplementary Table S2).

In the univariate analysis, age group was the only factor associated with stunting, with children under five years having an increased risk of being stunted compared to children five years and older (OR 2.6, 95% CI 1.4, 5.1; $P = 0.004$). Girls showed the same trend, with higher odds of being underweight compared to boys (OR 2.9; 95% CI 1.1, 7.9; $P = 0.033$). Children five years and older had higher odds of being classified as wasted compared to those younger than five years (OR 5.7, 95% CI 2.3, 14.0; $P < 0.001$) and being diagnosed with MAM compared to the younger children (OR 2.9, CI: 95% 1.7, 5.2; $P < 0.001$). Children living in Gauteng and Mpumalanga had increased odds of being classified with MAM compared to the Western Cape as reference (Gauteng: OR 2.7, 95% CI 1.2, 5.7; $P = 0.012$) and (Mpumalanga: OR 2.8, 95% CI 1.3, 5.9; $P = 0.007$) (Supplementary Table S3).

Nutritional status during the first six months of treatment

The prevalence of children classified with stunting varied over the initial six- months of treatment, with the mean z-score worst in month four (HAZ -0.96) (Figure 1 and Supplementary Table S4), while those classified as underweight worsened in month two (13.6%; mean WAZ -0.67). The prevalence of children with wasting fluctuated over time, the worst being the first month after diagnosis (13.3%; mean z-score for BAZ -0.33) (Figure 1 and Supplementary Table S4). The prevalence of children with MAM was the highest at diagnosis for children five years and older (33.9%, mean MUAC /A z-score -1.48) (Figure 1 and Supplementary Table S4), while the younger than five years old had the highest prevalence in month one after diagnosis (16.4%, mean MUAC/A z-score -0.55) (Figure 2 and Supplementary Table S4).

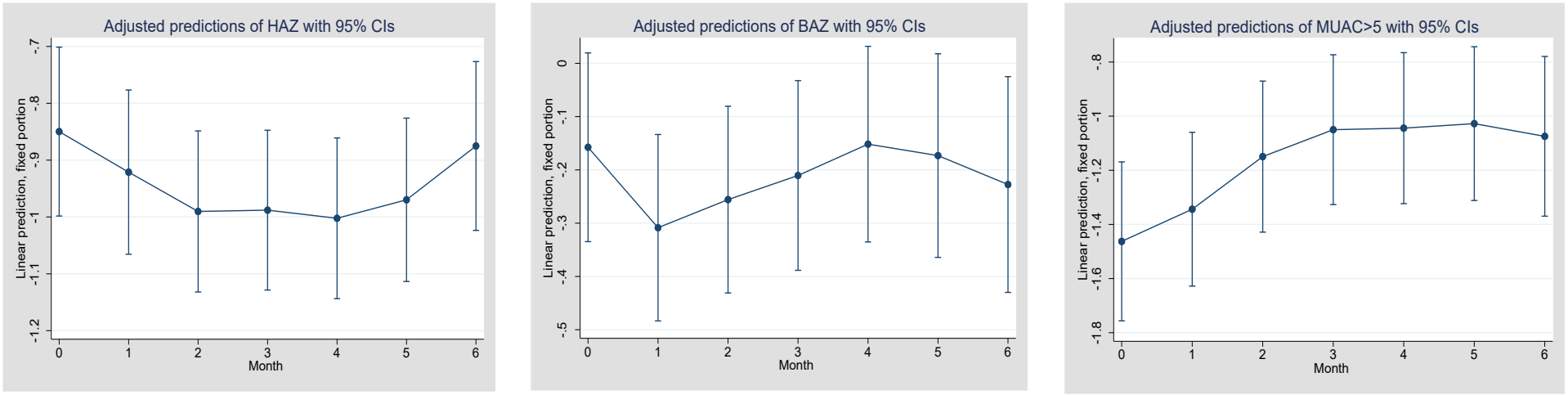

Figure 1: Adjusted predictions of stunting (HAZ), wasting (BAZ), MAM (MUAC) with mean Z-scores as parameters during treatment.

Abbreviations; HAZ: Height/length for age; BAZ; BMI for age; MAM: moderate acute malnutrition, MUAC: id-upper arm circumference P-value <0.05 statistically significant

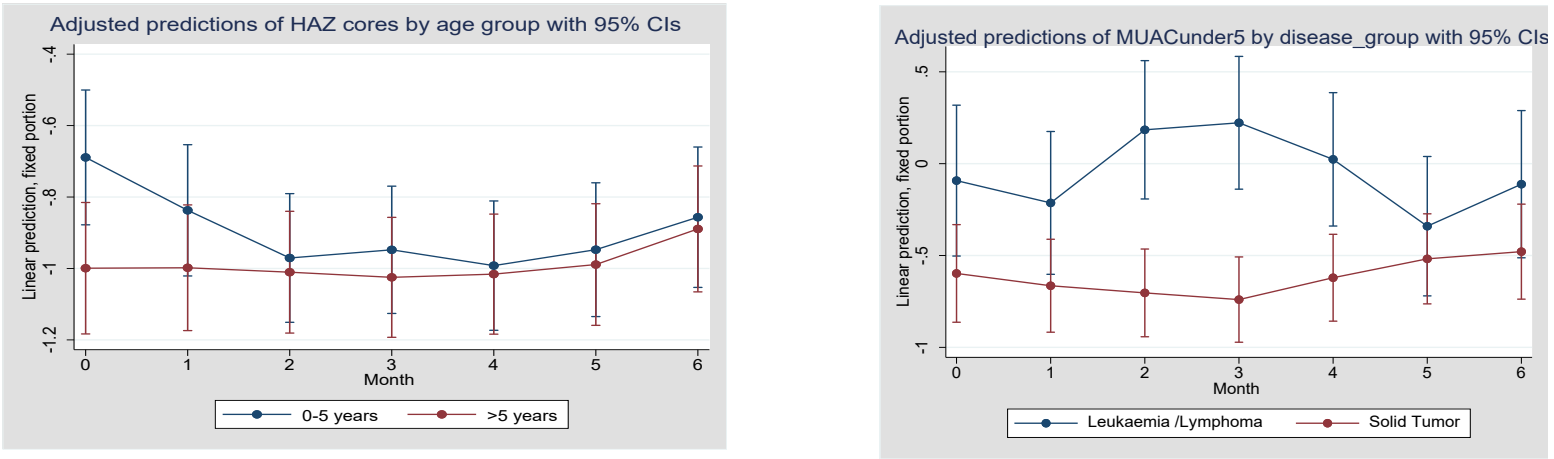

Figure 2: Adjusted predictions of stunting (HAZ) and MAM with z-scores by age or disease group with 95% CI during the treatment.

Abbreviations; HAZ: Height/length for age; MAM: moderate acute malnutrition P-value <0.05 statistically significant

Although the prevalence of children younger than five years of age with stunting was higher in the logistic regression analysis, children five years and older had significantly worse mean z-scores from month one (HAZ coefficient 0.15; 95% CI 0.02, 0.27; $P = 0.020$) to month six (HAZ coefficient 0.28; 95% CI 0.05, 0.50; $P = 0.015$) after diagnosis compared to children under five years (Figure 2 and Supplementary Table S5). Older children were affected worse by being underweight, with the lowest mean z-scores observed at month two (WAZ coefficient 0.33; 95% CI 0.14, 0.52; $P < 0.001$) to month four (WAZ coefficient 0.28; 95% CI 0.1, 0.5; $P = 0.012$) after diagnosis compared to younger children, even though there was no significant difference in the prevalence of underweight in the two age groups. No significant differences in the number of children with wasting were identified (Supplementary Table 5S).

Underweight children diagnosed with a solid tumor worsened from month one (WAZ coefficient -0.31; 95% CI -0.5, -0.1; $P = 0.001$) to month four, and in month six (WAZ coefficient -0.29; 95% CI -0.6, -0.0; $P = 0.027$) compared to children diagnosed with hematological malignancy (Figure 2 and Supplementary Table S5). Similar results were seen for solid tumor patients with wasting in months one to six of treatment (month one: BAZ coefficient -0.27; 95% CI -0.5, -0.1; $P = 0.015$; month six: BAZ coefficient -0.46; 95% CI -0.8, -0.1; $P = 0.010$) compared to patients with hematological malignancies. Children diagnosed with a solid tumor and MAM worsened significantly; younger children between months two and three after diagnosis (month two: MUAC coefficient -0.38; 95% CI -0.7, -0.3; $P = 0.032$; month three: MUAC coefficient -0.45; 95% CI -0.8, -0.1; $P = 0.0320$) than those diagnosed with hematological malignancies. In contrast, older children worsened from month one to month four of treatment (month one: MUAC coefficient -0.32 95% CI -0.6, -0.3; $P = 0.008$; month four: MUAC coefficient -0.38; 95% CI -0.7, -0.3; $P = 0.034$) than those diagnosed with hematological malignancy (Supplementary Table S5).

Province of residence was only significant for the children under five, with those living in Mpumalanga and diagnosed with MAM improving from month one to month four post- diagnosis (month one: MUAC coefficient 0.32; 95% CI 0.03, 0.6; $P = 0.032$; month four: MUAC coefficient 0.42; 95% CI 0.01, 0.8; $P = 0.046$) (Supplementary Table S5). No other significant factors were seen.

One year post diagnosis overall survival

The OS rate was 77.5% (95% CI 72.5, 82.9) at one- year post- cancer diagnosis (Supplemental Figure 1). There were 22.5% deaths (n = 72), while 3.4% had a relapse of the disease (n = 11). Causes of death were as follows: 47.2% had progression of disease (n = 34), 25% had neutropenic sepsis (n = 20), 8.3% had relapses (n = 6), 6.4% had other treatment-related toxicity (excluding sepsis) (n = 5);

6.4% had non-cancer related caused of death (pneumonia, drowning or gastroenteritis) (n = 5), and 2.8% had an unknown cause of death (n = 2). Most deaths occurred within the first month of treatment (22.2%; n = 16), followed by 15.3% in month five (n = 11), 12.5% in month three (n = 9), and 11.1% respectively in months six and eight (n = 8) while less than 8% died during the other months post-diagnosis (n = 6).

A minority of the children abandoned therapy (8.8%, n = 28). Children residing in the Free State had an 8.8- times higher risk of treatment abandonment than those living in the other provinces (OR 8.8, 95% CI 2.0, 38.2*; P* = 0.004).

The log-rank test identified stunting as significantly associated with both OS and EFS. Children classified as stunted at diagnosis had an increased risk for shorter OS one-year post-diagnosis (HR 1.9; 95% CI 1.1, 3.3; *P* = 0.029) (Figure 3), and shorter EFS (HR 2.1; 95% CI 1.2, 3.5; *P* = 0.007) from the Cox regression analysis (Supplementary Table S6 and supplementary figure 3). EFS was 76.3% (95% CI 71.2, 80.8) (Supplementary Figure 2). Children who were underweight and wasted with MAM had shorter OS, but this was not significant. In conclusion, MUAC identified more children with MAM while only stunting at diagnosis was significantly associated with poor one-year OS and EFS (Supplementary Figure S3).

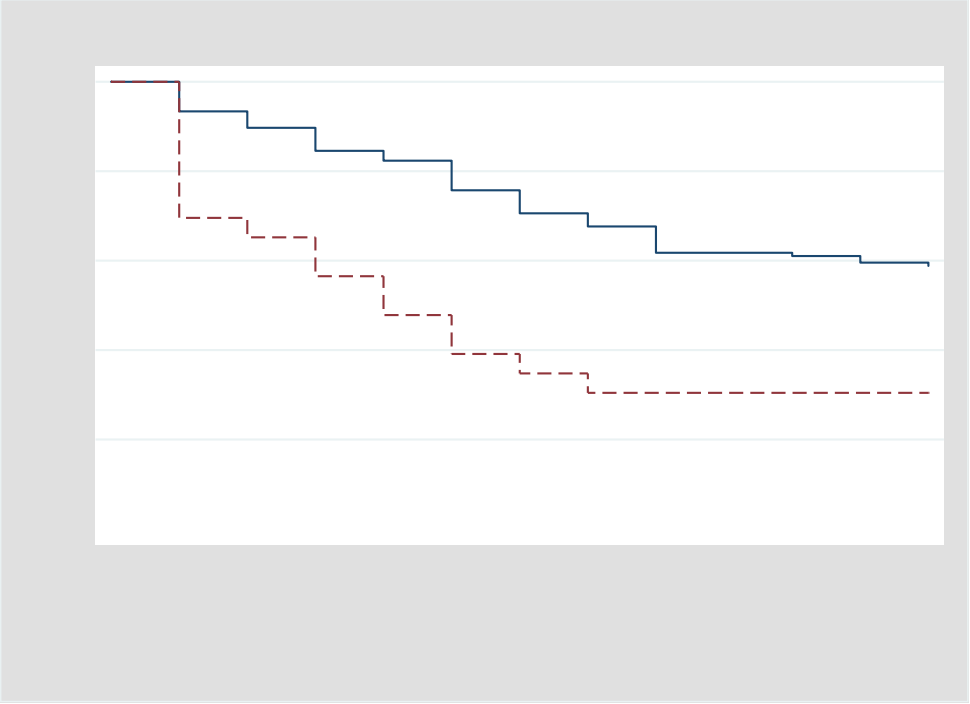

FIGURE 3: Kaplan Meier survival curves for overall survival concerning length ((*P* = 0.014)

DISCUSSION

A recent sub-Saharan African study (2020) found stunting in 26% of otherwise healthy children, while 21% were underweight and 5% were wasted.[21] This was not the case for this study cohort, as less than 15% of newly diagnosed cancer patients were classified as stunted, underweight, or wasted at diagnosis. A 2015 South African report regarding healthy children found more stunting among children younger than five years of age, while older children were more prone to being wasted,[22] findings that were confirmed in this study. However, in this study, more girls than boys were underweight, which differed from the 2015 South African report.[22] MAM was more prominent in older children in this study, as confirmed by studies in India [23] and Malawi,[24] regarding children with cancer.

A Scotland study reported that linear growth stagnated during the first months of treatment,[14] with similar results seen in this study. The Scottish children had a significant increase in their BMI, especially those children diagnosed with hematological malignancy during the first months of treatment,[14] in contrast with a Switzerland study in which BMI decreased,[24] while in this study, BMI fluctuated (seen in the z-scores for BAZ). MUAC increased in the Scotland study,[14] similar to our study, probably due to the nutritional interventions in South African POUs (study to be submitted). [25] No undernutrition was found six months after diagnosis in children with a solid tumor in the Scotland study,[14] while in our study, there were children with solid tumors still classified as underweight (WAZ), as wasted (BAZ), and with MAM (MUAC/A) six months after diagnosis. (Supplementary Table S4).

Well-nourished children with a cancer diagnosis have a better prognosis.[26] Malnutrition of both obesity and underweight is identified as an independent but potentially modifiable adverse prognostic factor.[27] Reports from Central America and Nicaragua documented the significantly decreased EFS of malnourished children versus well-nourished children with cancer,[10,31] a finding not demonstrated in an Indian study. [23] Our study documented the significant association between stunting and poorer OS and EFS one- year post- cancer diagnosis, which was not significant in well-nourished children.

The International Society of Paediatric Oncology Global Health Network Nutrition Working Group suggests that nutritional assessments should be done according to the feasible levels of care.[4] This study assessed height/length, weight, and MUAC. Triceps skinfold thickness was not included as not all POUs had access to a skinfold caliber, and the assessment was time-consuming. The procedure requires strict adherence to the standard procedure, which can be difficult for inexperienced investigators. The recommendation to use MUAC as part of the standard assessment in children with

cancer was proven in this study, as many children were diagnosed with malnutrition that was missed by other nutritional parameters.

The limitations of this study were that not all South African POUs could participate due to limited human resources. Still, seven provinces which provided valuable information on South African children diagnosed with cancer were represented. There might have been subtle differences in anthropometry measurement techniques among investigators, but training was repeated during the study to prevent these differences from being significant.

In conclusion, this South Africa multicenter study confirms, as previously reported, that MUAC assessment should be included in measurements in children with cancer to ensure that malnutrition that can be masked by factors such as edema or a tumor mass is identified.[11] Stunting is prevalent during the first six months of treatment, while MAM decreased. Our study also identified stunting at diagnosis as significantly associated with poor OS and EFS one year after a cancer diagnosis. Optimal nutritional support is needed for children diagnosed with malnutrition to improve early outcomes after a cancer diagnosis.

Acknowledgements

The authors want to acknowledge and thank the children and their parents/caregivers who participated in the study and the pediatric registrars, dieticians, and nursing staff of the POUs for their support.

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Supplementary Table S1: Diagnosis of the study population

Diagnosis	Percentage (n)
ALL	23.1% (74)
Nephroblastoma	15,6% (50)
Hodgkin's lymphoma	7.8% (25)
Rhabdomyosarcoma	7.2% (23)
Retinoblastoma	6.3% (20)
AML	5.3% (17)
Neuroblastoma	4.7% (15)
Non-Hodgkin lymphoma	4.7% (15_
Hepatoblastoma	4.1% (13)
Osteosarcoma	4.1% (13)
Brain tumour	3.8% (12)
Germ cell tumour	3.4% (11)
Burkitt Lymphoma	2.8% (9)
Other	2.5% (8)
Ewing's sarcoma	1.6% (5)
Carcinoma	1.3% (4)
Nasopharyngeal carcinoma	0.9% (3)
Sarcoma	0.6% (2)
CML	0.3% (1)
Total	320

Supplementary Table S2: Prevalence and correlation of undernutrition per diagnosis with mean scores and range

Parameter	HAZ (n = 320)		WAZ (n =248)		BAZ (n =320)		MUAC < 5 yr (n =152)		MUAC ≥5 yrs (n =161)		MUAC all ages Z-scores (n=313)	
	Stunted	Mean (range)	Underweight	Mean (range)	Wasted	Mean (range)	MAM	Mean (range)	MAM	Mean (range)	MAM	Mean (range)
Disease group	% (N)		% (N)		% (N)		% (N)		% (N)		% (N)	% (N)
HM	11.4 (16)	-0.7 (-4.5, 2.8)	6.1 (6)	-0.5 (-3.5, 2.8)	10.6 (15)	-0.3 (-4.6, 3.4)	2.2 (1)	-0.1 (-2.7, 2.0)	31.2 (29)	-1.3 (-8.2, 2.3)	21.7 (30)	-0.9 (-8.2, 2.3)
ST	17.4 (31)	-0.8 (-4.9, 3.9)	9.3 (14)	-0.5 (-3.8, 2.8)	12.3 (22)	-0.2 (-5.5, 4.6)	18.7 (20)	-0.6 (-5.3, 3.2)	38.2 (26)	-1.4 (-7.3, 3.6)	26.3 (46)	-0.9 (-7.3, 3.6)
P-value	0.134	0.633	0.364	0.927	0.646	0.745	0.007	0.057	0.351	0.719	0.352	0.996
Leukaemia	6.5 (6)	-0.5 (-2.7, 2.8)	4.6 (3)	-0.3 (-3, 2.8)	8.7 (8)	-0.2 (-4.6, 3.4)	0	0.1 (-1.9, 2.0)	25.9 (15)	-1.3 (-6.7, 2.0)	16.7 (15)	-0.8 (-6.7, 2.0)
Brain tumor	25 (3)	-0.9 (-2.8, 0.8)	36.4 (4)	-0.9 (-3.2, 1.9)	25 (3)	-0.4 (-3.9, 2.8)	14.3 (1)	0.5 (-2.6, 3.2)	25 (1)	-1.2 (-2.9,-0.2)	18.2 (2)	-0.1 (-2.9, 3.2)
Lymphoma	18.4 (9)	-1.0 (-4.5, 1.3)	6.1 (2)	-0.7 (-2.7, 0.9)	14.3 (7)	-0.3 (-4.4, 2.8)	8.3 (1)	-0.5 (-2.7, 1.8)	38.9 (14)	-1.5 (-8.2, 2.3)	15 (31.3)	-1.2 (-8.2, 2.3)
Germ cell tumor	27.3 (3)	-1.5 (-4.4, 0.1)	10 (1)	-0.7 (-3.8, 1.7)	18.2 (2)	0.2 (-3.7, 4.6)	28.6 (2)	-1.4 (-5.0, 0.4)	0	-0.6 (-1.6, 1.5)	18.2 (2)	-1.1 (-5.0, 1.5)
Nephroblastoma	14 (7)	-0.8 (-3.2, 2.3)	4.3 (2)	-0.4 (-2.7, 2.1)	4 (2)	0.1 (-3.4, 2.7)	23.5 (8)	-1.2 (-3.6, 1.0)	46.7 (7)	-1.3 (-4.0, 1.6)	30.6 (15)	-1.2 (-4.0, 1.6)
Hepatoblastoma	46.2 (6)	-1.7 (-3.0, 0.4)	15.4 (2)	-0.8 (-2.3, 0.6)	0	0.3 (-0.9, 1.6)	23.1 (3)	-0.3 (-2.3, 1.5)	0	-	23.1 (3)	-0.3 (-2.3, 1.5)
Neuroblastoma	20 (3)	-0.7 (-3.6, 2.6)	6.7 (1)	-0.2 (-2.0, 1.8)	0	0.3 (-1.7, 3.2)	33.3 (3)	-1.8 (-5.3, 0.9)	40 (2)	-1.6 (-4.7, 0.3)	35.7 (5)	-1.7 (-5.3, 0.9)
Osteosarcoma	15.4 (2)	-0.1 (-2.4, 3.9)	0	-1.2 (-1.9,-0.3)	46.2 (6)	-2.0 (-4.0, 1.3)	100 (1)	-2.6 (-2.5, -2.6)-	27.3 (3)	-1.1 (-3.4, 0.9)	33.3 (4)	-1.2 (-3.4, 0.9)
Retinoblastoma	10 (2)	-0.6 (-4.6, 2.2)	5 (1)	-0.5 (-2.1, 2.8)	10 (2)	-0.2 (-2.3, 2.5)	0	0.3 (-1.9, 3.1)	100 (1)	-3.3(-3.3, -3.3)	5 (1)	0.1 (-3.3, 3.1)
Rhabdomyosarcoma	8.7 (2)	-0.4 (-3.2, 2.2)	10.5 (2)	-0.3 (-2.5, 1.5)	8.7 (2)	.0.0(-2.6, 2.7)	0	0.7 (-1.5, 1.6)	41.7 (5)	-1.5 (-7.1, 3.6)	21.7 (5)	-0.5 (-7.1, 3.6)
Other	18.2 (4)	-1.1 (-4.9, 3.5)	16.7 (2)	-0.9 (-3.7, 2.3)	22.7 (5)	-1.0 (-5.5, 2.2)	28.6 (2)	-1.2 (-3.0, 0.4)	46.7 (7)	-2.0 (-7.3, 2.1)	40.9 (9)	-1.7 (-7.3, 2.1)
P-value	0.032	*0*.092	0.076	0.059	0.002	0.020	0.004	0.199	0.439	0.068	0.148	0.019

Abbreviations: HAZ: height for age; WAZ: weight for age; BAZ= body mass index for age; MUAC: mid-upper arm circumference; HM: hematological malignancy; ST: solid tumor;

A *P*-value of 0.05 is considered significant

Supplementary Tabe S3: Regression logistic analysis of nutritional status at diagnosis with associations and 95% CI

Variables	**Category**	**OR (95% CI)**	***P* -value**
Stunting	≥5 years*	1	
	<5 years	2.6 (1.4, 5.1)	0.004
Underweight	Males*	1	
	Females	2.9 (1.1, 7.9)	0.033
Wasted	<5 yr*	1	
	≥5 years	5.7 (2.3, 13.9)	< 0.001
MAM for all ages	<5 years*	1	
	≥ 5 years	2.9 (1.7, 5.2)	< 0.001
Age group	< 5 years*	1	
	≥ 5 years	2.9 (1.7, 5.2)	< 0.001
Province	Western Cape*	1	
	Free State	0.9 (0.2, 4.30	0.851
	Gauteng	2.7 (1.2, 5.7)	0.012
	Mpumalanga	2.8 (1.3, 5.9)	0.007
	Eastern Cape	0.9 (0.1, 8.0)	0.926
	Other	3.3 (0.8, 13.9)	0.101

Abbreviations: OR: Odds rati**o;** MAM = moderate acute malnutrition according to MUAC

Supplementary Table S4: Prevalence of undernutrition during treatment with means Z-score per month

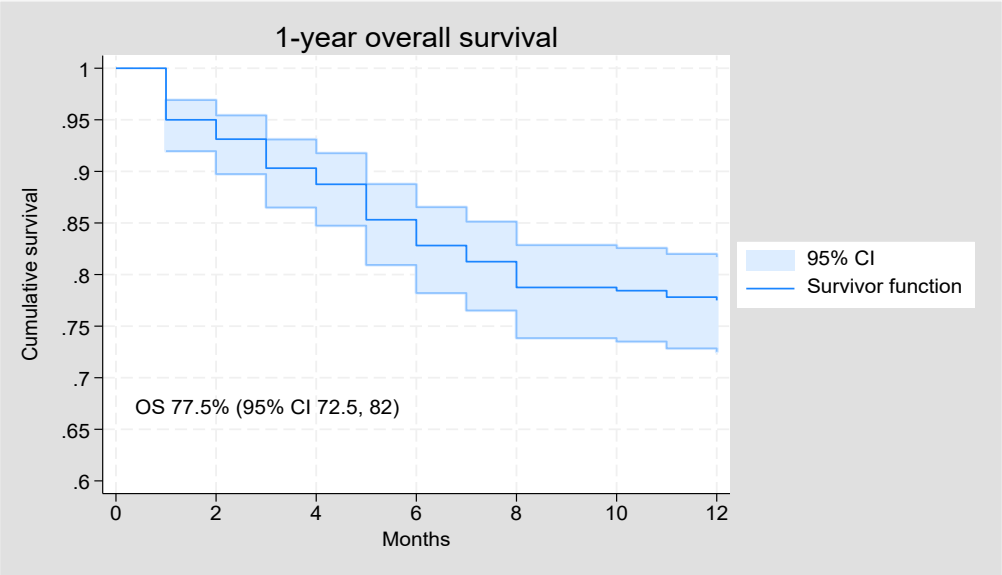
	Admission (n=319)		**Month 1 (n=313)**		**Month 2 (n=286)**		**Month 3 (n=271)**		**Month 4 (n=254)**		**Month 5 (n=245)**		**Month 6 (n=224)**	
	% (N)	Mean (range)	% (N)	Mean (range)	% (N)	Mean (range)	% (N)	Mean (range)	% (N)	Mean (range)	% (N)	Mean (range)	% (N)	Mean (range)
Stunting (HAZ)	15.7 (50)	-0.85 (-4.91, 3.87)	17.2 (52)	-0.91 (-4.94; 3.77)	16.4 (47)	-0.94 (-4.49; 3.66)	15.9 (43)	-0.94 (-5.49; 3.6)	15.8 (40)	-0.96 (-5.49; 2.64)	15.5 (38)	-0.93 (-5.73; 2.64)	14.7 (33)	-0.80 (-5.39; 2.54)
Underweight (WAZ)	8.1 (20)	-0.5 (-3.76, 2.78)	12.2 (28)	-0.62 (-4.03, 3.04)	13.6 (30)	-0.67 (-4.60, 2.87)	9.4 (20)	-0.63 (-3.92, 2.52)	10.2 (20)	-0.62 (-3.86, 2.72)	5.4 (10)	-0.56 (-3.92, 2.71)	7.1 (12)	-0.50 (-4.1, 2.86)
Wasting (BAZ)	10.7 (34)	-0,16 (-5.52, 4.56)	13.5 (41)	-0.33 (-5.98, 6.71)	11.5 (33)	-0.27 (-5.67, 3.97)	10.7 (29)	-0.19 (-6.65, 3.3)	11.0 (28)	-0.12 (-4.96, 3.16)	9.4 (23)	-0.09 (-7.19, 3.86)	11.6 (26)	-0.13 (-6.93, 3.7)
MAM (*MUAC <5y)r	13.8 (21)	-0.45 (-5.33, 3.16)	16.4 (21)	-0.55 (-4.00, 2.44)	12.8 (15)	-0.45 (-3.28, 2.98)	9.1 (10)	-0.50 (-4.58, 1.96)	7.3 (7)	-0.43 (-3.05, 2.06)	4.6 (4)	-0.51 (-4.11, 1.89)	5.9 (5)	-0.34 (-2.91, 1.85)
MAM (**MUAC ≥5yr)	33.9 (55)	-1.48 (-13.89, 2.31)	28.8 (46)	-1.35 (-13.96, 2.15)	28.9 (42)	-1.03 (-6.37, 2.75) _	26.1 (36)	-0.88 (-6.39, 2.13)	21.1 (27)	-0.92 (-6.17, 2.14)	24.1 (30)	-0.87 (-8.19, 2.25)	25.2 (28)	-0.93 (-8.58, 2.33)

*WHO anthro software; ** Mramba et al. with Peditools; Abbreviations: HAZ: height for age; WAZ: weight for age; BAZ= body mass index for age; MAM: moderate acute malnutrition; MUAC: mid-upper arm circumference. A p-value of 0.05 is considered significant.

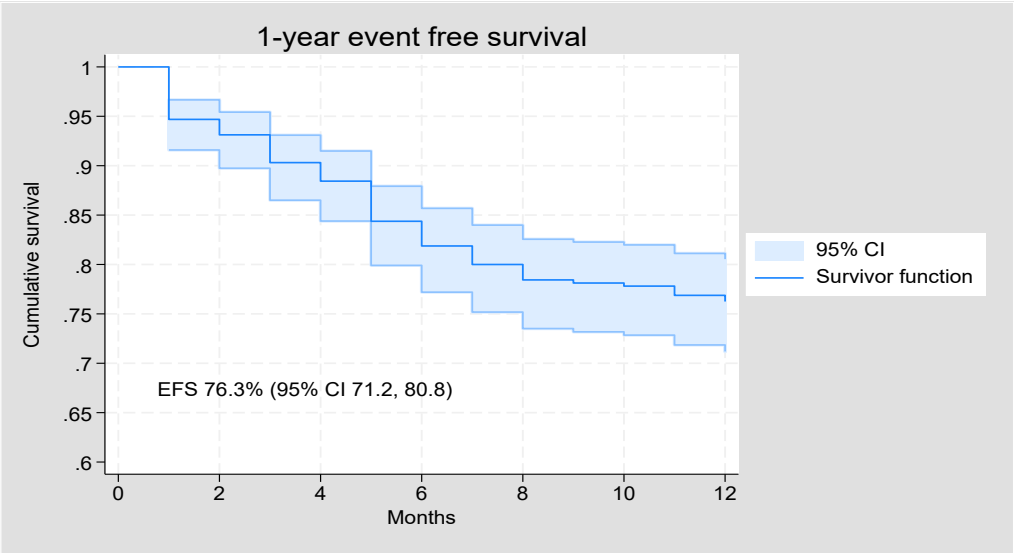
Supplementary Table S5: Factors affecting fluctuating z-scores over months of treatment from diagnosis

Variables	Parameters	Coefficient (95% CI)	*p*-value
Stunting	<5 years*	Ref	
	≥5 yr month 1	0.15 (0.02, 0.27)	0.020
	≥5 yr month 2	0.27 (0.13,0.41)	< 0.001
	≥5 yr month 3	0.23 (0.08, 0.39)	0.003
	≥5 yr month 4	0.29 (0.11, 0.46)	0.001
	≥5 yr month 5	0.27 (0.07, 0.47)	0.008
	≥5 yr month 6	0.28 (0.05, 0.50)	0.015
Underweight	<5 years*	Ref	
	≥5 yr month 1	0.12 (-06, 0.30)	0.178
	≥5 yr month 2	0.33 (0.14, 0.52)	< 0.001
	≥5 yr month 3	0.24 (0.04, 0.44)	0.019
	≥5 yr month 4	0.28 (0.062, 0.51)	0.012
	≥5 yr month 5	0.11 (-0.13, 0.35)	0.381
	≥5 yr month 6	0.15 (-0.12, 0.41)	0.280
Underweight	Hematological malignancy*	Ref	
	Solid tumor month 1	-0.31 (-0.49, -0.13)	0.001
	Solid tumor month 2	-0.49 (-0.67, -0.31)	< 0.0001
	Solid tumor month 3	-0.49 (-0.69, -0.29)	< 0.0001
	Solid tumor month 4	-0.39 (-0.60, -0.17)	< 0.0001
	Solid tumor month 5	-0.18 (-0.43, 0.05)	0.123
	Solid tumor month 6	-0.29 (-0.56, -0.03)	0.027
Wasting	Hematological malignancy*	Ref	
	Solid tumor month 1	1-0.27 (-0.48, -0.05)	0.015
	Solid tumor month 2	-0.48 (-0.71, -0.25)	< 0.0001
	Solid tumor month 3	-0.55 (-0.80, -0.30)	< 0.0001
	Solid tumor month 4	-0.43 (-0.71, -0.16)	0.002
	Solid tumor month 5	-0.28 (-0.59, 0.2)	0.070
	Solid tumor month 6	-0.46 (-0.80, -0.11)	0.010
MUAC <5yr	Hematological malignancy*	Ref	
	Solid tumor month 1	0.05 (-0.26, 0.37)	0.734
	Solid tumor month 2	-0.38 (-0.73, -0.33)	0.032
	Solid tumor month 3	-0.45 (-0.84, -0.07)	0.020l

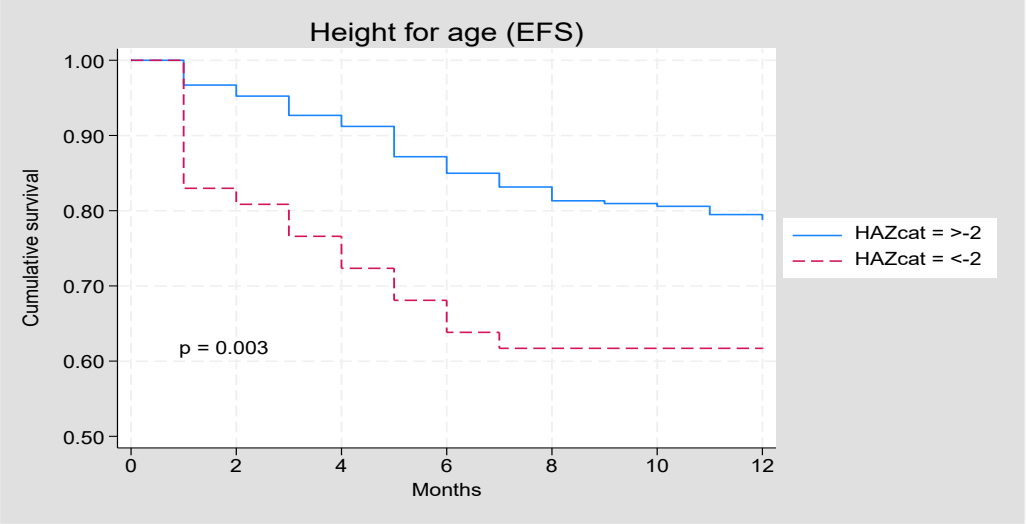
Variables	Parameters	Coefficient (95% CI)	*p*-value
	Solid tumor month 4	-0.14 (-0.57, 0.29)	0.532
	Solid tumor month 5	0.32 (-0.17, 0.82)	0.195
	Solid tumor month 6	0.14 (-0.42, 0.69)	0.626
MUAC <5yr	Western Cape*	Ref	
	Mpumalanga month 1	0.31 (0.03, 0.59)	0.032
	Mpumalanga month 2	0.62 (0.30, 0.94)	< 0.001
	Mpumalanga month 3	0.57 (0.21, 0.92)	0.002
	Mpumalanga month 4	0.42 (0.01, 0.83)	0.046
	Mpumalanga month 5	0.35 (-0.12, 0.82)	0.144
	Mpumalanga month 6	0.47 (-0.07, 1.01)	0.087
MUAC ≥5 yr	Hematological malignancy*	Ref	
	Solid tumor month 1	-0.32 (-0.56, -0.09)	0.008
	Solid tumor month 2	-0.53 (-0.79, -0.26)	< 0.0001
	Solid tumor month 3	-0.38 (-0.68, -0.07)	0.016
	Solid tumor month 4	-0.38 (-0.73, -0.29)	0.034
	Solid tumor month 5	-0.33 (-0.74, 0.08)	0.112
	Solid tumor month 6	-0.31 (-0.77, 0.16)	0.196



Supplementary FIGURE S1: Kaplan-Meier Survival curve for OS for all the patients one year after diagnosis (died n=72)



Supplementary Figure S2: Kaplan Meier's event EFS survival curves for all patients one year after diagnosis



Supplementary Figure S3: Kaplan Meier survival curves for EFS concerning length indicating stunting (*P* = 0.003)

CHAPTER 6

Implemented nutritional intervention algorithm in pediatric oncology compared to standard nutritional supportive care outcomes in South Africa

The manuscript is publication-ready and will be submitted to Clinical Nutrition for publication (Impact factor 7.6)

(Text is US English as journal requirements)

https://www.clinicalnutritionjournal.com/

This study determined if planned nutritional intervention at time-set intervals according to a specifically South African-developed nutritional algorithm for childhood cancer will improve nutritional status in two paediatric oncology units (POUs) compared with standard supportive nutritional care/ protocols in the other POUs.

The Hypothesis was:

Ha: Planned nutritional interventions at specific time points according to a specifically developed nutritional algorithm (at two POUs) for childhood cancer will improve nutritional status and one-year OS and EFS.

H0: Planned nutritional interventions at specific time points according to a specifically developed nutritional algorithm [at two POUs] for childhood cancer at specific time points will not improve nutritional status and one-year OS and EFS.

Malnutrition in children diagnosed with cancer is common, and the effect on poor overall survival is known. The goal is to improve their nutritional status during cancer treatment and potentially decrease treatment toxicity with improved OS. The study implemented a South African-adapted childhood cancer-specific nutritional algorithm for interventions based on the z-score for MUAC for age at time-set intervals at two POU (intervention group) and compared to the results of standard nutritional care protocol in three POUs in South Africa (control group).

The intervention group patients with malnutrition at diagnosis significantly improved their nutritional status six months after diagnosis. The control group patients also showed an improvement in the nutritional status from admission to six months, but this was not significant for the cohort. Only moderate acute malnutrition in younger than five years of age improved significantly. The differences

between the two groups were not significant at six months post-cancer diagnosis.

This South African nutritional algorithm did improve the nutritional status of those children with malnutrition at diagnosis, supporting the hypotheses. However, that standard care in the other South African POUs (control group) was also adequate; however, the improvement in nutritional status was not significant, except for those under five years of age with moderate acute malnutrition.

IMPLEMENTED NUTRITIONAL INTERVENTION ALGORITHM IN PEDIATRIC ONCOLOGY COMPARED TO STANDARD NUTRITIONAL SUPPORTIVE CARE OUTCOMES IN SOUTH AFRICA.

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Word count: Abstract: 267

Word count: Main text (exl tables etc.) 3271

Number of Tables: 2

Number of Supplementary Tables: 2

Number of Figures: 2

Number of Supplementary Figures: 5

Keywords: Algorithm, nutritional interventions, nutritional status, malnutrition, childhood cancer, nutritional supplements.

List of abbreviations

Abbreviation	**Word**
BAZ	Body mass index for age
CI	Confidence interval
GHN NWG	Global Health Network Nutrition Working Group
HAZ	Height for age
LMIC	Low and middle-income country
MAM	Moderate acute malnutrition
MUAC	Mid-upper arm circumference
MUAC/A	Mid-upper arm circumference for age
NG	Nasogastric
POU	Pediatric oncology unit
SAM	Severe acute malnutrition
SD	Standard deviation
SIOP	International Society of Paediatric Oncology
WAZ	Weight for age

Contribution to the manuscript

Judy Schoeman and Marianna Kruger conceptualized the study; Judy Schoeman, as a Ph.D. student, designed the study, adjusted the SIOP SGH NWG nutritional algorithm and REDcap database,

enrolled patients, collected and managed data, transferred data to the World Health Organization Anthro plus program to calculate Z-scores and wrote the manuscript.
Mariana Kruger, Elena Ladas, and Paul Rogers supervised the study, conducted an extensive review, and contributed to and approved the manuscript.
Ilde-Marié Kellerman, Ronelle Uys, Gita Naidu, Biance Rowe, Jan du Plessis, Mariechen Herholdt, Karla Thomas, Barry Vanemmenes, Rema Mathews, Ané Büchner, Fareed E Omar and David T Reynders enrolled patients at different sites, collected data, and critically reviewed the manuscript.
Sandile Ndlovu analyzed the data statistically and critically reviewed the manuscript.

ABSTRACT

Aim: To implement a childhood cancer-specific nutritional algorithm adapted for the South African context for interventions at time-set intervals to evaluate differences in the nutritional status of newly diagnosed children with cancer.

Method: Children with newly diagnosed cancer were assessed for stunting, underweight, wasting, and moderate to severe malnutrition (MUAC < -2SD and < - 3 SD) between October 2018 and December 2020 in a longitudinal nutritional assessment study with monthly assessments. Two pediatric oncology units (POUs) served as the intervention group that implemented the nutritional algorithm-directed intervention and three other POUs formed the control group that implemented standard supportive nutritional care.

Results: A total of 320 patients were enrolled with a median age of 6.1 years (range three months to 15.3 years) and a male-to-female ratio of 1.1:1. The malnourished patients in the intervention group showed significant improvement at six months after diagnosis for stunting (P =0.028), underweight ($P < 0.001$), and wasting until month five ($P = 0.014$). The improvements in the control group were not significant. Moderate acute malnutrition (MAM) significantly improved over the first six months of cancer treatment in the intervention group (P <0.001), while MAM improvement was only significant in the control group for the children under five years of age ($P = 0.004$). The difference in mean z-scores over time for the nutritional parameters between the intervention and control groups was insignificant.

Conclusion: We established that the nutritional algorithm adapted for South Africa as an intervention tool for childhood cancer assisted in optimizing nutritional interventions and improved nutritional outcomes over the first six months of cancer treatment.

Introduction

The primary goal of nutritional support for children with cancer is to ensure an optimal nutritional status,[1] which is crucial in low- and middle- income countries (LMICs), as malnutrition at childhood cancer diagnosis is common and can affect the disease outcome. [2] Dietary counseling and appropriate intervention should ensure adequate macronutrient and micronutrient intake,[3] to promote age-appropriate growth -and development,[3,4] remediate and prevent the development of malnutrition or worsening thereof and potentially improve cancer outcomes.[3,5]

The severity of treatment-related toxicity, and mortality, and treatment abandonment is higher among malnourished children than well-nourished children.[6] There is documented improved five-year overall survival for children with acute lymphoblastic leukemia whose nutritional status is improved during treatment.[7]

Algorithms are developed as a tool to improve decision- making and are used in the clinical setting as a cancer- screening tool.[8] In Canada, a pediatric intensive unit a multidisciplinary- developed algorithm improved patient's nutritional support.[9] The utilization of a decision-aid algorithm or timely nutritional interventions is recommended.[6] The International Society of Paediatric Oncology (SIOP) and the Global Health Network (GHN) Nutrition Working Group (NWG) have developed such a consensus-derived nutritional intervention algorithm for LMICs in the context of the resource limitations in the LMIC setting (Supplementary Figure 1). The goal is to harmonize care among pediatric oncology units (POUs) in an LMIC and to provide a guide for proactive nutritional care.[10] This algorithm has been validated in children with cancer in India (2019); improved nutritional status resulted from using the algorithm for a six-month period.[11] The SIOP GHN NWG algorithm was therefore adapted for the South African context, with specific nutritional guidelines based on the standard deviation (SD) of the mid-upper arm circumference (MUAC) for age (MUAC/A). Our algorithm included common nutritional interventions utilized in South Africa, such as industrialized supplements, enteral nutrition, and total parenteral nutrition in both the hospital and home settings.

This study investigated the efficacy of implementing the nutritional algorithm adapted for South Africa in newly diagnosed children with cancer to improve the nutritional status among undernourished children and maintain the nutritional status of well-nourished children undergoing treatment in South Africa. This algorithm was implemented in two POUs (intervention group) and compared to the standard nutritional supportive care provided at three other POUs (control group) during the first six months of cancer treatment.

METHODS

Study design

This longitudinal comparative cohort study was performed between October 2018 and December 2020 at five POUs in South Africa. Two POUs (Steve Biko Academic Hospital in Gauteng and Tygerberg Hospital in the Western Cape) implemented the nutritional algorithm as the intervention group. The other three participating POUs (Chris Hani Baragwanath Hospital in Gauteng, Universitas Academic Hospital in the Free State, and Frere Hospital in the Eastern Cape) served as the control group using standard nutritional care practices. Nutritional assessments occurred monthly from diagnosis to the sixth month of treatment.

Clinical data

Prospective data collection included the clinical data (disease group and diagnosis) and demographic data (patient's sex, age, and province of residence) obtained from the medical charts and entered into the study database monthly. Children were grouped according to age; younger children were under five, years while older children were defined as five years and older.

Anthropometry (weight, height, and MUAC) was assessed within 72 hours after cancer diagnosis; whilst children were barefoot and wearing light clothing. Body weight and height (older children) were measured with a calibrated column SECA weight scale with an attached height meter (the SECA 786 and SECA 220 model). Weight was recorded to the nearest 100g and length to the nearest 0.1 cm. Children stood up straight, facing forward with their backs against the height meter. A calibrated SECA electronic baby scale with a length meter was used to assess children younger than two years (SECA 334 model). The UNICEF color band was used to measure MUAC in children under five, [12] and the MUAC measuring band was used to measure MUAC in older children. [13] To measure MUAC, the child's arm was flexed toward the chest at a 90° angle. The investigator determined the midpoint of the arm, between the acromion and olecranon, the arm was relaxed, and the palm was facing towards the body; the MUAC was measured at the midpoint.[14]

The WHO Anthro program was utilized to determine z-scores for height for age (HAZ), weight for age (WAZ), body mass index for age (BAZ), and MUAC/A for children younger than five years.[15] MUAC for children older than five was plotted on the Mramba *et al.* growth charts;[16] the absolute z-scores for MUAC/A were determined on Peditools [17] and divided into categories. Undernutrition was defined as severe if stunting was HAZ < -3 SD; underweight as WAZ < - 3 SD, wasting as BAZ < -3 SD, whilst stunting was HAZ < -2 SD, underweight as WAZ < -2 SD and wasting as BAZ < -2 SD.

[18] Severe acute malnutrition (SAM) as MUAC/A <-3 SD; moderate acute malnutrition (MAM) was defined as MUAC/A < -2 SD.[12]

Nutritional algorithm

Based on the SIOP GHN NWG algorithm (Supplementary Figure 1) the South African nutritional intervention algorithm was adjusted considering the standard nutritional supportive care for children diagnosed with and treated for cancer (Figure 1). The MUAC/A z-score was used to identify which children should receive nutritional supplements for home care with guidelines on the content and amount. The algorithm intervention depended on the MUAC/A z-score; it also included specific guidelines regarding the percentage provision of energy and/or protein requirements (in the form of the percentage of the requirements) according to the patient's MUAC/A z-score with industrialized supplements, enteral nutrition, and /or total parenteral nutrition in the hospital.

All patients received the standardized high-energy, high-protein hospital diet according to age; additional nutritional supplementation was received if indicated. The nutritional interventions in the intervention group were implemented according to the MUAC/A z-score at the time of assessment, as follows (Figure 1):

1. Children with MUAC for age < -3 SD were admitted to the POU, and 24-hour nasogastric (NG) enteral feeds were initiated to reach the goal of feeds providing 70-100% of protein requirements. If the patient's caregivers refused an NG tube, oral supplementation was provided with a syringe.
2. Children with MUAC/A < -2 SD were admitted to the POU if medically indicated, and overnight NG enteral feeds (12-14 hour feeds) were initiated to reach the goal of 40-60% of the protein requirements. Oral intake was actively encouraged, but if patients did not reach 100% of the requirements with oral intake, the enteral feeds were increased to 100% of the patient's requirements. If not admitted, patients received supplements to take home to reach 50% of the protein requirements, plus a take-home meal plan to reach 100% of the requirements.
3. Children with MUAC/A < -1 SD did not receive nutritional supplements at the POU or at home. Still, if specific criteria were applicable according to the algorithm, as seen in Figure 1, patients did receive supplementation.

The control group's nutritional support included the existing nutritional protocol of the control POUs, including nutritional supplements and NG enteral feeds given in the hospital or at home. In both

intervention group POUs, parenteral nutrition was administered if necessary (e.g., in case of neutropenic enterocolitis or pancreatitis or post-abdominal surgery).

All parents or caregivers received continuous nutritional education regarding healthy meals and food choices. The education was based on the My Plate model, whereby the food groups were explained in the form of a plate to visualize a healthy meal.[19] Nutritional advice sheets were given to take home. The interventions and anthropometric data were captured monthly on a REDCAP database.

Statistical analysis

All data were analyzed using STATA version 17 (STATA Corp. Texas, USA). A repeated nutritional assessment measures analysis was done monthly using a multilevel mixed-effects regression model comparing mean Z-scores in the two intervention group POUs for the first six months after diagnosis according to the classification of malnutrition based on z-scores for stunting, underweight, wasting, SAM, and MAM. Descriptive statistics such as: frequencies, percentages, means, standard deviations, and medians were calculated for each month by intervention or control group depending on the z-score at diagnosis. Chi-square tests determined the association between sex, the age groups, and disease groups at diagnosis. At the same time, a t-test was used to compare the mean age between the intervention and control groups. The severe to moderately malnourished children (< -3 and < -2 SD) were grouped together as the malnourished group for the time trend in the mixed-effects regression analysis. Margins plot graphs were used to visualize the improvement trend over time in the two groups if the z-score at diagnosis was < -2 SD for stunting (HAZ), underweight (WAZ), wasting (BAZ), and MAM (MUAC/A) over time. A significance level of $P < 0.05$ was applied.

Ethics approval

Parents/legal guardians provided written informed consent for each child before enrolment in the study in the language of their choice (one of the following: English, Afrikaans, Zulu, Tsonga, Tswana, Sotho, Sepedi or Xhosa). Written assent was elicited if the child was older than seven years. The following institutions provided ethics approval: Stellenbosch University (Health Research Ethics Committee, Faculty of Medicine and Health Sciences [S18/04/050]), University of Pretoria (Research Ethics Committee, [281/2018]), University of the Witwatersrand (Human Research Ethics Committee [M190485]), University of the Free State (Health Sciences Research Ethics Committee [UFS-HSD2019/0445/3007]), and Frere Hospital (Ethics Committee [CMHREC 001/19]). The national and provincial health departments approved the conduct of the study in the public sector.

RESULTS

Demographics

A total of 320 children were prospectively enrolled between October 2018 and December 2020. The intervention group recruited 72% (n = 229) versus 28% in the control group (n = 91). The two groups had no significant differences in demographics or diagnosis. More than half of the children had been diagnosed with a solid tumor in both groups, 55.5% in the intervention group and 57.1% in the control group. The prevalence of hematological malignancies was 44.5% in the intervention group compared to 42.9% in the control group (Table 1).

Table 1: Demographics of the total population

Patients enrolled (n = 320)		Intervention group % (N)	Control group % (N)	*P* - value
Total		71.6 (229)	28.4 (91)	
Sex	Males Females	54.2 (124) 45.9 (105)	48.4 (44) 51.7 (47)	0.349
Age in years	Median (IQR) Mean (Range)	5.3 (2.6 -10) 6.3 (0.3 – 15.7)	5.1 (2.4 - 8.4) 5.6 (0.3 -14.9)	0.444
Age groups	< 5 yr ≥ 5 yr	47.6 (109) 52.4 (120)	49.5 (45) 50.5 (46)	0.765
Disease group	Hematological malignancy Solid tumor	44.5 (102) 55.5 (127)	42.9 (39) 57.1 (52)	0.784
Undernourished patients (<-2 SD)	Stunted Underweight (n=248) Wasted MAM under five (n=152) MAM five years and older (n=162)	17.1 (39) 8.1 (14/173) 11.4 (26) 13.8 (15/109) 37 (44/119)	12.1 (11) 8.0 (6/75) 8.8 (8) 14 (6/43) 23.3 (10/43)	0.266 0.980 0.495 0.975 0.102

MAM = moderate acute malnourished (according to MUAC)

Nutritional status at diagnosis

The children in the intervention group had a higher prevalence of undernutrition (stunting 17%, underweight 8%, and wasting 11%) compared to the control group (stunting 12%, underweight 8%,

and wasting 9%), although the difference was not significant ($P = 0.266$, $P = 0.980$, and $P = 0.495$, respectively). The intervention group had more children with MAM in both age groups, namely children younger than five and those five years and older (14% and 37%) compared to the control group (14% and 23%); which was not significant (Table 1).

Nutritional interventions

During the first six months of cancer treatment, the patients in the intervention group were more likely to receive NG enteral feeds as 12% (n = 28/229) received 24-hour continuous feeds compared to 1% (n = 1/91) in the control group, which was not significant ($P = 0.850$). A further 33% (n = 75/229) received 12-14 hour continuous overnight feeds in the intervention group compared to 15% (n = 14/91) in the control group ($P = 0.456$). More children (125%; n = 288/229) in the intervention group received oral commercial and/or additional supplements during their hospital stay compared to the control group (65%; n = 14/91), which was significant ($P < 0.001$). A minority received parenteral nutrition over the first six months of cancer treatment, only 12% (n = 28/229) in the intervention group and 2% (n = 1/91) in the control group ($P = 0.735$).

The prevalence of severe- and moderate malnutrition during the first six months of treatment

In the intervention group, the number of children with severe stunting had decreased from 5% (n = 12) to 2% (n = 4) at six months post-diagnosis, with a similar trend observed for patients who were severely underweight and wasted. The prevalence of SAM in patients (five years and older) had decreased from 6% (n = 7) to 1% (n = 1), while the prevalence of SAM in children (under five years) had decreased from 6% (n = 6) to zero at six months post-diagnosis. (Supplementary Table S1).

In contrast, in the control group, there were two children with severe stunting, which had decreased to only one after six months of treatment. Similar results were seen for patients with severe underweight and wasting. Arm anthropometry indicated only two patients with SAM, and both improved during the six months (Supplementary Table S1).

The number of patients classified as stunted in the intervention group (6%; n = 14) decreased to 1% (n = 1) at six months post-diagnosis. The number of underweight children (6%; n = 14) decreased to 1% (n = 1), as had the children with wasting, from 11% (n = 26) to 5% (n = 10). The number of children five years and older with MAM had decreased from 6% (n = 15) to 2% (n = 2), while the number of younger children with MAM had decreased from 14% (n = 15) to only 2% (n = 2) at six months post diagnosis (Supplementary Table S2).

Table 2: The differences in nutritional status of malnourished patients (SD <-2) over time trend for the two groups from admission to six months post-diagnosis

	Intervention group			**Control group**		
Time period	**Coefficient**	**95% CI**	***p*-value**	**Coefficient**	**95% CI**	***p*-value**
Length (HAZ)						
Admission month	Ref			Ref		
Month 1	0.012	[-0.201; 0.224]	0.913	0.138	[-0.134; 0.410]	0.319
Month 2	-0.019	[-0.268; 0.229]	0.878	0.131	[-0.147; 0.408]	0.355
Month 3	0.097	[-0.182; 0.376]	0.496	0.083	[-0.230; 0.397}	0.602
Month 4	0.130	[-0.194; 0.455]	0.433	0.306	[-0.018; 0.631]	0.064
Month 5	0.369	[-0.003; 0.741]	0.052	0.272	[-0.065; 0.610]	0.114
Month 6	0.477	[0.052; 0.902]	0.028	0.172	[-0.205; 0.549]	0.372
Weight (WAZ)						
Admission month	Ref			Ref		
Month 1	0.428	[-0.030; 0.885]	0.067	-0.361	[-0.729; 0.008]	0.055
Month 2	0.289	[-0.206; 0.784]	0.252	0.137	[-0.301; 0.574]	0.541
Month 3	0.686	[0.157; 1.216]	0.011	0.367	[-0.163; 0.899]	0.174
Month 4	0.586	[0.029; 1.143]	0.039	0.431	[-0.208; 1.071]	0.186
Month 5	1.117	[0.513; 1.721]	<0.001	0.698	[-0.097; 1.492]	0.085
Month 6	1.281	[0.539; 2.024]	<0.001	0.598	[-0.280; 1.477]	0.182
Wasting (BAZ)						
Admission month	Ref			Ref		
Month 1	0.293	[-0.045; 0.631]	0.089	-0.068	[-0.800; 0.664]	0.856
Month 2	0.764	[0.349; 1.177]	<0.001	0.558	[-0.198; 1.313]	0.148
Month 3	1.099	[0.594; 1.604]	<0.001	0.841	[-0.062; 1.745]	0.068
Month 4	0.941	[0.330; 1.552]	0.003	0.938	[-0.074; 1.950]	0.069
Month 5	0.908	[0.183; 1.633]	0.014	1.225	[-0.002; 2.451]	0.050
Month 6	0.778	[-0.074; 1.663]	0.074	0.856	[-0.419; 2.132]	0.188
MAM for children under five years, according to MAUC						
Admission month	Ref			Ref		
Month 1	0.796	[0.356; 1.235]	<0.001	-0.114	[-0.818; 0.589]	0.750
Month 2	1.175	[0.690; 1.659]	<0.001	0.735	[-0.007; 1.477]	0.052

	Intervention group			Control group		
Time period	**Coefficient**	**95% CI**	***p*-value**	**Coefficient**	**95% CI**	***p*-value**
Month 3	1.448	[0.908; 1.987]	<0.001	1.167	[0.355; 1.979]	0.005
Month 4	1.848	[1.205; 2.490]	<0.001	1.175	[0.077; 2.273]	0.036
Month 5	1.904	[1.165; 2.643]	<0.001	0.845	[-0.643; 2.333]	0.266
Month 6	1.993	[1.161; 2.825]	<0.001	1.739	[0.561; 2.917]	0.004
MAM for children five years and older, according to MAUC						
Admission month	Ref			Ref		
Month 1	0.450	[0.171; 0.729]	0.002	0.567	[0.004;1.129]	0.048
Month 2	1.093	[0.776; 1.410]	<0.001	0.375	[-0.462; 1.212]	0.380
Month 3	1.304	[0.941; 1.666]	<0.001	0.736	[-0.455; 1.927]	0.226
Month 4	1.213	[0.798; 1.628]	<0.001	0.405	[-1.256; 2.064]	0.633
Month 5	1.151	[0.676; 1.626]	<0.001	0.785	[-1.256; 2.826]	0.451
Month 6	1.115	[0.567; 1.663]	<0.001	1.031	[-1.338; 3.399]	0.394

MAM = moderate acute malnourished (according to MUAC)

The number of patients with stunting in the control group had decreased from 12% (n = 11) to 6% (n = 5) at six- months post- diagnosis, with a similar trend observed for the number of children who were underweight (7%; n = 6 vs. 3%; n = 2) and wasted (9%; n = 8 vs. 3%; n = 2). The number of children five years and older with MAM had decreased from 13% (n = 6) to 2% (n = 1), while the prevalence of MAM in younger children (under five years) was the same at the end of six months of treatment (Supplementary Table S2).

The difference in nutritional status of malnourished children with time trend during the first six months after diagnosis in the two intervention groups compared to the admission diagnosis data.

The intervention group had improved nutritional status as children with stunting decreased significantly till six months post-diagnosis (HAZ coefficient 0.5; 95% CI 0.1, 0.9; $P = 0.028$). Patients' weight improved over time as patients with underweight decreased till month six of treatment (WAZ coefficient 1.3 (95% CI 0.5, 2.0; $P < 0.001$), and BMI improved until five months of treatment (BAZ coefficient 0.9; 95% CI 0.2, 1.6; $P = 0.014$) (Table 2). Children with MAM also improved significantly after six months post-diagnosis for both age groups, namely for the under five years of age (MUAC coefficient 1.9; 95% CI 1.2, 2.8; $P <0.001$) and for the children five years and older (MAUC coefficient 1.1; 95% CI 0.6, 1.7; $P <0.001$) (Table 2).

In the control group, the difference in the mean z-scores from diagnosis to six months post-diagnosis improved, but not significantly: stunting (HAZ coefficient 0.2; 95% CI -0.2, 0.5; P = 0.372), underweight (WAZ coefficient 0.6; 95% CI -0.3, 1.5; P = 0.182), or wasting (BAZ coefficient 0.9; 95% CI -0.4, 2.1; P = 0.1828. The children younger than five years of age with MAM did improve significantly (MUAC coefficient 1.7; 95% CI 0.6, 2.9; P = 0.004), while the children five years and older was not significant (MUAC coefficient 1.0; 95% CI -1.3, 3.4; P = 0.394 (Table 2).

Predicted margins for undernourished patients (≤ -2 SD) during the first six months of treatment

Figures 2 and 3 display the difference in the time trend effect of the intervention- and control group separately according to the age groups using marginsplot graphs of the predicted margins of the mean z-scores with their 95% CI for comparison between the groups. Children from both age groups (under five and five and older) classified with MAM (MUAC/A <-2) in the intervention group showed significant improvement at six- months post- diagnosis (respectively $P < 0.001$) (Figures 2 and 3 and Table 2). Stunting (HAZ < -2SD) for the intervention group had decreased significantly at six months post- diagnosis (P = 0.028) (Supplementary Figure S2).

Figure 1: Adjusted predictions of children younger than five years of age with MAM (MUAC <-2) with 95% CI based on mean Z-scores during the first six months of treatment in the two groups.

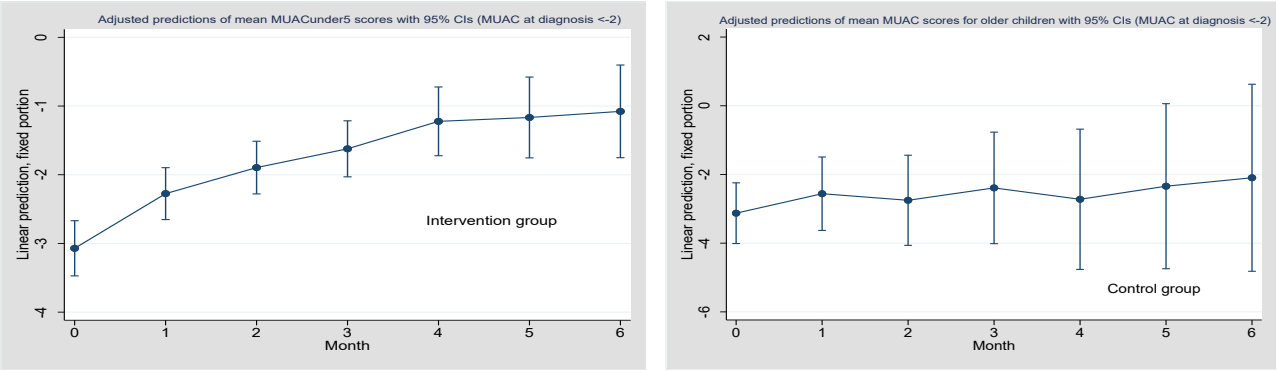
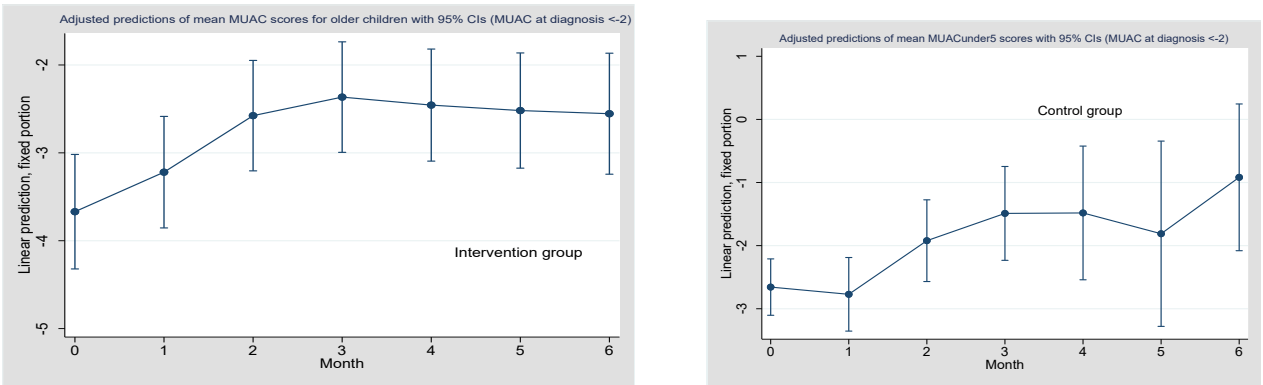


Figure 2: Adjusted predictions of older children with MAM with 95% CI based on mean Z-scores during the first six months of treatment.



In the control group, children under five years of age classified with MAM (MUAC/a < -2) showed significant improvement in MUAC measurements six- months post- diagnosis ($P = 0.004$) (Figure 2 and Table 2). The predicted margins for stunting showed a reduction that was not significant *(P* = 0.356) (Supplementary Figure 2 and Table 2). No other significant results were reported. (Figures 2 and 3).

The multilevel mixed- effect model compared the difference between the intervention and control groups for the difference in the mean z-scores for stunting, underweight, and wasting for the two groups at six months post- diagnosis, and this was insignificant. The same was seen for MAM in both age groups (Supplementary Figure S5).

Our study demonstrated an improved nutritional status as the severity of children with stunting, wasting, and MAM improved significantly in the intervention group but not in the control group, proving the algorithm's success as a nutrition intervention tool.

DISCUSSION

Nutritional interventions during cancer treatment aim to improve nutritional status and survival.
Our study has proven that the nutritional algorithm adapted for South Africa improved nutritional status among malnourished children with cancer undergoing treatment.

Nutritional support during cancer treatment

Deterioration of children's nutritional status during cancer treatment commonly occurs in LMIC, [20] and malnutrition at cancer diagnosis and during cancer treatment is a modifiable prognostic variable,[21] as was seen in the intervention group in our study. Nutritional support should include a diet rich in energy and protein in the hospital and at home. In LMICs, additional foods or supplements may be needed to provide sufficient calories, protein, and micronutrients [22] to improve nutritional status.[6]

Patients with Burkitt lymphoma from a Cameroon study (2011) received additional oral supplements with a protein portion despite their age for the first 28 days of treatment, which decreased MAM from 16% to 10% on day 28 of the study,[23] while our intervention group received a percentage of a child's protein needs. In severely malnourished children in Guatemala receiving nutritional intervention (education, oral- or enteral supplements, or parenteral nutrition)

nutritional status was improved to a well-nourished state six months after diagnosis.[7] Similar findings were seen in a retrospective study in Pretoria, South Africa (2008), with improved BMI and arm anthropometry after three months of oral nutritional supplements high in protein and/or calories.[8] Children older than 10 diagnosed with cancer in Nicaragua (2017) received a hypercaloric supplement with balanced macronutrients for a maximum of two months, decreasing severe malnutrition from 65.4% to 45.3%.[2]

Algerian children who received a fortified diet for six months showed significant linear growth improvement after three months.[24] A study in Malawi gave children an energy-dense, lipid-based, ready-to-use supplement, resulting in catch-up and linear growth in wasted children.[7] The nutritional supplementation of the adapted intervention algorithm given in this study significantly improved nutritional status, as stunting, underweight, and wasting significantly decreased six months after diagnosis. The control groups' nutritional status did improve, but not significantly.

Nutrtioanal intervention algortihm

A nutritional intervention study in India (n = 50; 2019) investigated the application of the SIOP GHN NW (previously the SIOP-PODC) nutritional algorithm for children under 12 years of age with a control group by using MUAC as an indicator. The children in the algorithm group showed significant improvement in their MUAC increments after three months (P = 0.020). Similar results were observed in this study, as the prevalence of MAM significantly decreased in the intervention group over the first six months of cancer treatment, highlighting the need for validated clinical nutritional intervention algorithms.

Using appropriate nutritional algorithms in LMICs for nutritional assessment and nutritional intervention aids in enhancing the clinical care of pediatric cancer patients. This study showed a decrease in the number of children with wasting, underweight, and MAM, which was significant in the intervention group. Even though some of the outcomes were not significant, all POUs participating in our study made appropriate nutritional interventions due to recognizing that malnutrition requires nutritional interventions to improve outcomes. These reports all justify the importance of longitudinally assessing nutritional status and nutritional intervention when required. Using an evidence-based clinical algorithm improves decision-making and outcomes.

Limitations of the study

The intervention and control groups were not equally divided, which could have influenced the results, but the groups were similar as no significant difference in demographics or disease was

observed between them. There may have been a difference between the two intervention groups POUs' adherence to the algorithm. The enteral products used depend on availability at the different POUs; therefore, the variability could have affected results.

Conclusion

Nutritional algorithms are helpful for the nutritional management [25] of children with cancer, not only for identifying malnutrition but also for optimizing nutritional intervention, [11,25] improving nutritional outcomes,[26] and potentially improving cancer outcomes. Nutritional support in LMICs is challenging due to low resources but is essential for children treated for cancer to improve clinical outcomes.[2] Our findings concur with those of previous studies as our intervention group's nutritional status improved significantly during the period with nutritional interventions implemented according to the developed South African nutritional algorithm. MUAC is the best indicator of malnutrition and MAM in children with cancer. The nutritional algorithm in the intervention group significantly decreased the prevalence of MAM in both age groups.

ACKNOWLEDGEMENT

The authors want to acknowledge and thank the children and parents/caregivers who participated in the study, especially those with a more extended hospital stay, for improving their nutritional status. They want to thank the pediatric registrars, dieticians, and nursing staff of the POUs for their support in this study.

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Supplementary Table S1: Descriptive data of severely undernourished patients at diagnosis (SD≤-3) according to mean Z-score during the first six months of treatment on nutritional intervention

Parameter	Time trend	Intervention group		Control group	
		% (n) malnourished	Mean (range)	% (n) malnourished	Mean (range)
Severely stunted (HAZ)	Admission	5.2 (12/229)	-4.04 [-4.91, -3.04]	2.2 (2/91)	-3.37 [-3.57, -3.17]
	Month 1	3.9 (9/227)	-4.00 [-4.94, -3.23]	1.1 (1/91)	-3.64 [-4.34, -2.93]
	Month 2	2.7 (6/221)	-3.83 [-4.30, -3.37]	2.2 (2/89)	-3.72 [-4.34, -3.09]
	Month 3	2.8 (6/212)	-3.85 [-5.49, -2.45]	50 (1/87)	-3.68 [-3.68, -3.68]
	Month 4	1.9 (4/208)	-3.69 [-5.49, -1.51]	1.1 (0/83)	-2.36 [-2.62, -2.10]
	Month 5	2.4 (5/206)	-3.57 [-5.73, -1.51]	0 (0/82)	-2.78 [-2.83, -2.72]
	Month 6	1.9 (4/202)	-3.29 [-5.39, -0.83]	1.3 (1/79)	-3.10 [-3.26, -2.94]
Underweight (WAZ)	Admission	0.9 (2/229)	-3.67 [-3.76, -3.53]	3.3 (3/91)	-3.13 [-3.19, -3.07]
	Month 1	0.9 (2/227)	-3.63 [-4.03, -3.13]	3.3 (3/91)	-3.07 [-3.08, -3.06]
	Month 2	0.9 (2/221)	-3.53 [-4.60, -2.08]	2.2 (2/89)	-3.17 [-3.17, -3.16]
	Month 3	0.9 (2/212)	-2.86 [-3.92, -1.80]	1.1 (1/87)	-3.11 [-3.11, -3.10]
	Month 4	0.5 (1/208)	-2.86 [-3.86, -1.86]	1.2 (1/83)	-2.82 [-3.57, -2.06]
	Month 5	0 (0/206)	-2.56 [-3.92, -1.20]	1.2 (1/82)	-1.83 [-1.83, -1.83]
	Month 6	0.5 (1/202)	-4.10 [-4.10, -4.10]	1.3 (1/79)	-2.82 [-3.85, -1.79]
Wasted (BAZ)	Admission	6.1 (14/229)	-3.98 [-5.52; -3.04]	4.3 (4/91)	-3.66 [-4.04; -3.32]
	Month 1	4.4 (10/227)	-3.91 [-5.98; -1.22]	2.2 (2/91)	-2.66 [-3.68; -1.18]
	Month 2	3.6 (8/221)	-3.33 [-5.67; -1.05]	2.2 (2/89)	-2.31 [-3.77; -0.35]
	Month 3	1.9 (4/212)	-3.02 [-6.65; -0.86]	1.1 (1/87)	-2.12 [-3.56; -0.73]
	Month 4	0.9 (2/208)	-2.41 [-4.96; -0.71]	1.2 (1/83)	-2.09 [-3.73, -1.13]
	Month 5	1.9 (4/206)	-2.55 [-5.64; -0.02]	0 (0/82)	-1.32 [-1.35, -1.28]
	Month 6	1.9 (4/202)	-3.26 [-6.93; -0.61]	1.3 (1/79)	-2.00 [-3.93; -1.20]
Patients under 5 years with SAM (MUAC < -3)	Admission	5.6 (6/107)	-4.00 [-5.33; -3.08]	2.3 (1/44)	-3.2 [-3.2; -3.2]
	Month 1	0.9 (1/106)	-2.36 [-4.00; -1.11]	-	-
	Month 2	-	-1.96 [-2.96; -1.46]	-	-2.76 [-2.76; -2.76]
	Month 3	-	-1.73 [-2.50; -1.16]	-	-1.28 [-1.28; -1.28]
	Month 4	-	-1.73 [-2.73; -0.46]	-	-1.34 [-1.34; -1.34]

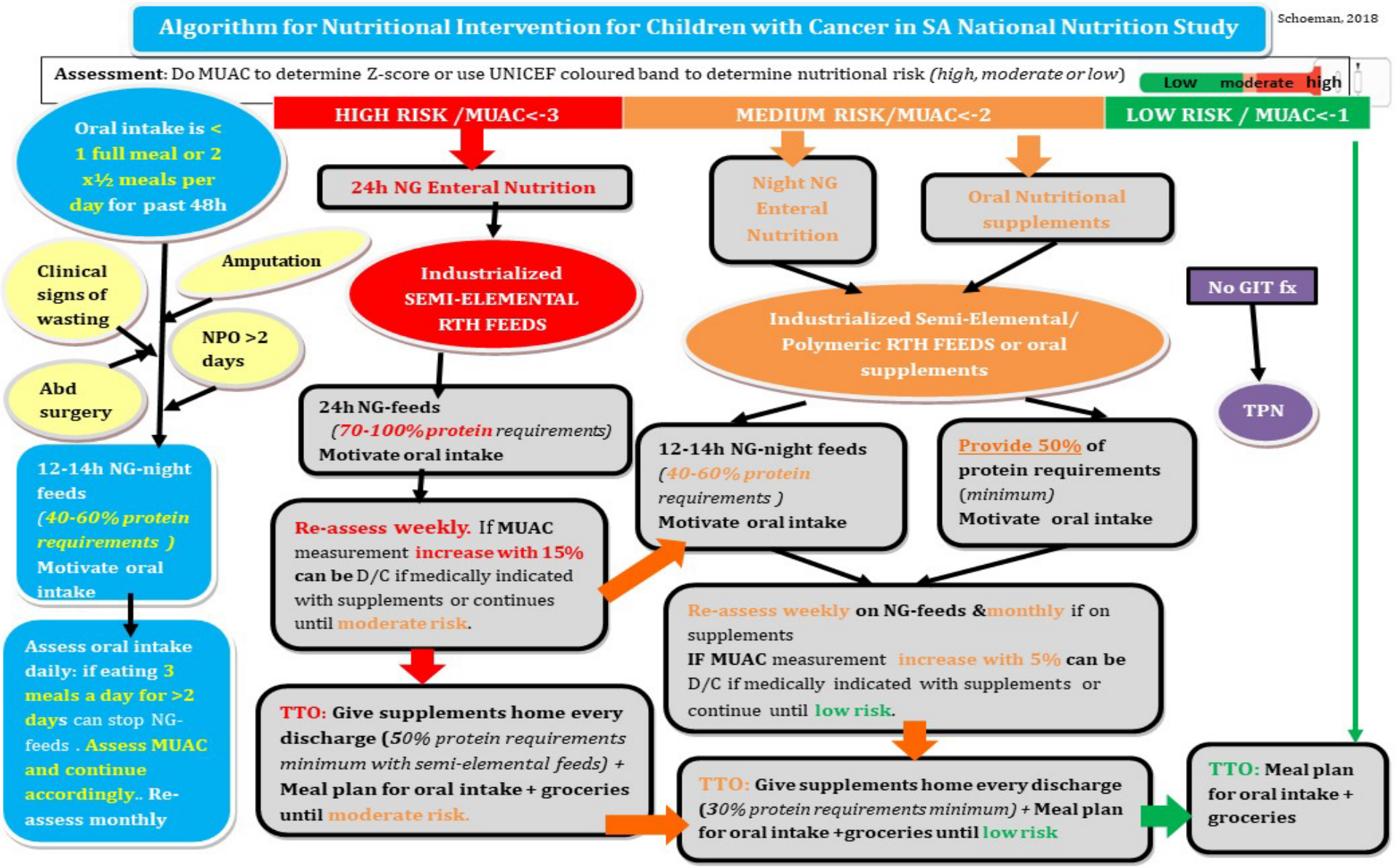
Parameter	Time trend	Intervention group		Control group	
		% (n) malnourished	Mean (range)	% (n) malnourished	Mean (range)
	Month 5	-	-1.36 [-2.06; -0.67]	-	-
	Month 6	-	-1.98 [-2.57; -1.63]	-	-2.55 [-2.55; -2.55]
Patients ≥ 5 years with SAM (MUAC < -3)	Admission	5.7 (7/122)	-4.94 [-13.89, -3.04]	2.1 (1/47)	-4.54 (-7.08, -3.11]
	Month 1	4.9 (6/121)	-4.37 [-13.96, -1.57]	-	-4.19 (-7.15, -2.49]
	Month 2	0.8 (1/121)	-2.94 [-6.37, -0.34]	-	-2.29 [-2.29; -2.29]
	Month 3	0.9 (1/116)	-2.76 [-6.39, -0.64]	-	-
	Month 4	1.7 (2/116)	-2.98 [-6.17, -0.79]	-	-
	Month 5	0.9 (1/115)	-2.85 [-8.19, -1.16]	-	-2.73 [-2.73; -2.73]
	Month 6	0.9 (1/114)	-3.21 [-8.58, -1.19)	-	-

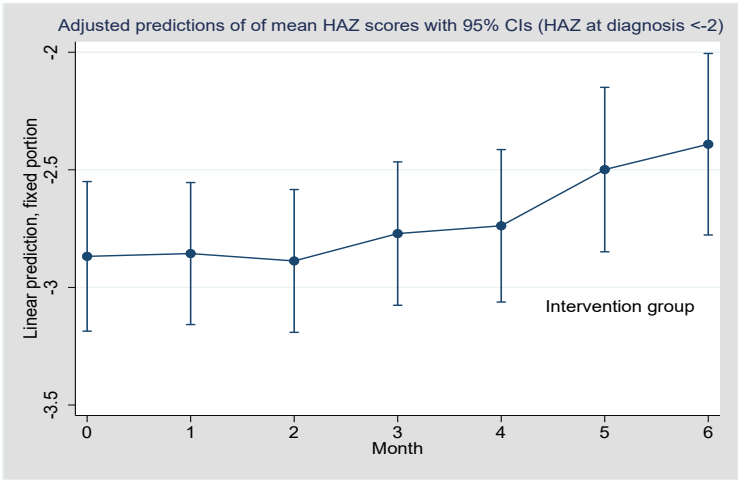
Supplementary Table S2: Descriptive data of moderate malnourished patients at diagnosis (< -2 >-3SD) according to mean Z-score changes during the first six months of treatment on nutritional intervention

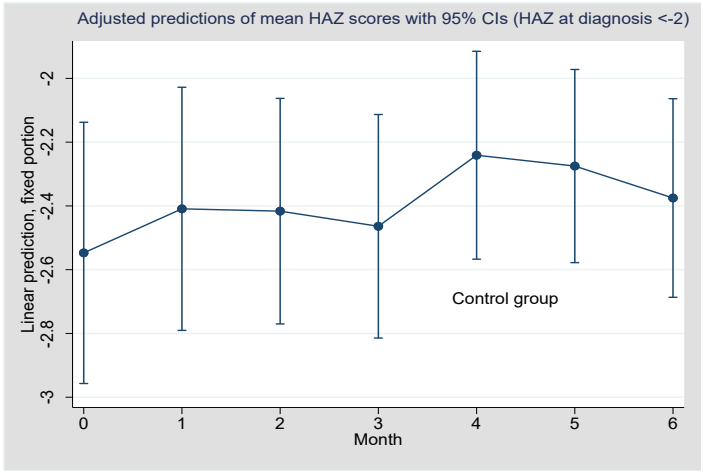
Parameter	Time trend	Intervention group		Control group	
		% (n) malnourished	Mean (range)	% (n) malnourished	Mean (range)
Stunted (HAZ)	Admission	21.8 (50/229)	-2.87 [-4.91, -2.01]	12.1 (11/91)	-2.54 [-3.57, -2.03]
	Month 1	18.1 (41/227)	-2.78 [-4.94, -0.52]	9.8 (9/91)	-2.41 [-4.34, -1.32]
	Month 2	15.3 (34/221)	-2.73 [-4.49, -1.87]	8.9 (8/89)	-2.42 [-4.34, -1.35]
	Month 3	14.6 (31/212)	-2.67 [-5.49, -0.83]	6.8 (6/87)	-2.38 [-3.68, -1.84]
	Month 4	13.9 (29/208)	-2.61 [-5.49, -1.09]	7.2 (6/83)	-2.24 [-2.65, -1.93]
	Month 5	12.6 (26/206)	-2.43 [-5.73, -0.79]	7.3 (6/82)	-2.28 [-2.83, -1.74]
	Month 6	11.9 (24/202)	-2.38 [-5.39, -0.39]	6.3 (5/79)	-2.45 [-3.26, -1.66]
Underweight (WAZ)	Admission	6.1 (14/229)	-2.70 [-3.76, -2.03]	6.5 (6/91)	-2.71 [-3.19, -2.28]
	Month 1	3.5 (8/227)	-2.28 [-4.03, -0.42]	3.3 (5/91)	-3.10 [-3.53, -2.53]
	Month 2	4.1 (9/221)	-2.50 [-4.60, -0.42]	4.5 (4/89)	-2.64 [-3.17, -1.84]
	Month 3	1.9 (4/212)	-1.98 [-3.92, -0.19]	3.4 (3/87)	-2.43 [-3.11, -1.53]
	Month 4	2.9 (6/208)	-2.08 [-3.86, -0.26]	3.6 (3/83)	-2.38 [-3.57, -1.75]
	Month 5	0.9 (2/206)	-1.58 [-3.92, -0.33]	1.2 (1/82)	-1.97 [-2.73, -1.34]
	Month 6	0.5 (1/202)	-1.69 [-4.10, -0.04]	2.5 (2/79)	-2.24 [-3.85, -1.28]
Wasted (BAZ)	Admission	11.3 (26/229)	-3.25 [-5.52, -2.02]	8.8 (8/91)	-2.99 [-4.04, -2.04]
	Month 1	7.9 (18/227)	-2.96 [-5.98, -0.86]	6.5 (6/91)	-3.09 [-4.12, -1.18]
	Month 2	4.9 (11/221)	-2.52 [-5.67, 0.34]	5.6 (5/89)	-2.44 [-3.77, -0.35]
	Month 3	4.7 (10/212)	-2.12 [-6.65, 0.94]	3.4 (3/87)	-2.09 [-3.56, -0.73]
	Month 4	5.2 (11/208)	-2.06 [-4.96, -0.02]	2.4 (2/83)	-1.96 [-3.73, -0.76]
	Month 5	4.4 (9/206)	-2.01 [-5.63, 1.10]	1.2 (1/82)	-1.47 [-3.01, -0.24]
	Month 6	4.9 (10/202)	-2.27 [-6.93, 1.67]	2.5 (2/79)	-1.97 [-3.93, -0.58]
Children <5 yr with MAM (MUAC < -2)	Admission	14.1 (15/107)	-3.07 [-5.33; -2.02]	2.3 (1/44)	-2.66 [-3.20; -2.01]
	Month 1	9.4 (10/106)	-2.27 [-4.00; -1.11]	2.3 (1/44)	-2.71 [-3.02; -2.48]
	Month 2	6.0 (6/100)	-1.91 [-3.28; -0.45]	2.4 (1/42)	-1.92 [-3.06; -0.49]
	Month 3	5.2 (5/96)	-1.63 [-2.50; -0.32]	2.4 (1/42)	-1.37 [-2.33; -0.45]
	Month 4	3.2 (3/92)	-1.32 [-2.73; 0.40]	2.5 (1/40)	-1.83 [-2.31; -1.34]

Parameter	Time trend	Intervention group		Control group	
		% (n) malnourished	Mean (range)	% (n) malnourished	Mean (range)
	Month 5	2.2 (2/91)	-1.33 [-2.42; -0.09]	0 (0/39)	-1.96 [-1.96; -1.96]
	Month 6	2.3 (2/88)	-1.18 [-2.91; 0.53]	2.7 (1/36)	-0.77 [-2.55; -0.55]
	Admission	6.6 (8/122)	-3.67 [-13.89; -2.02]	12.7 (6/47)	-3.13 [-7.08; -2.11]
Children ≥5 yr with MAM (MUAC < -2)	Month 1	5.7 (7/121)	-3.29 [-13.96; -0.30]	8.5 (4/47)	-2.79 [-7.15; -0.71]
	Month 2	3.3 (4/121)	-2.31 [-6.37; 0.78]	4.3 (2/47)	-2.26 [-2.89; -0.73]
	Month 3	5.2 (6/116)	-2.07 [-6.39; 0.99]	2.2 (1/45)	-1.78 [-2.79; 1.49]
	Month 4	4.3 (5/116)	-2.16 [-6.17; 0.47]	2.2 (1/45)	-2.78 [-3.58; -1.98]
	Month 5	4.3 (5/115)	-2.25 [-9.19; 0.62]	0 (0/45)	-2.36 [-2.58; -2.13]
	Month 6	3.5 (4/114)	-2.43 [-8.58; 0.41]	2.3 (1/43)	-2.35 [-2.59; -2.02]

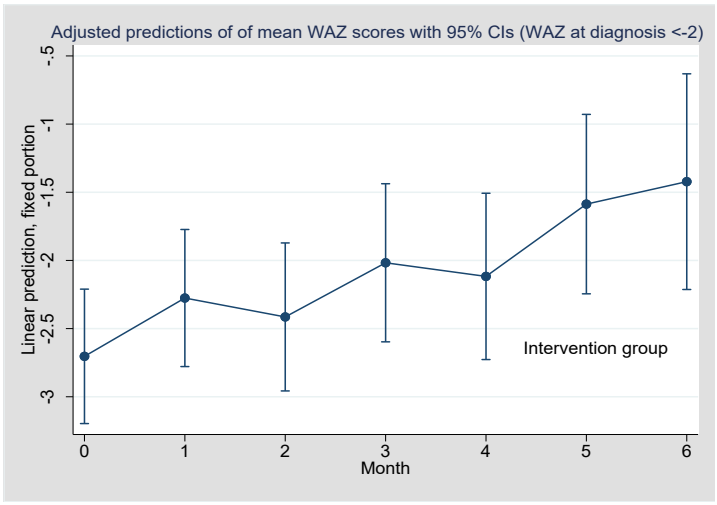
Supplementary Figure S1: Nutritional algorithm for study group according to mid-upper arm circumference

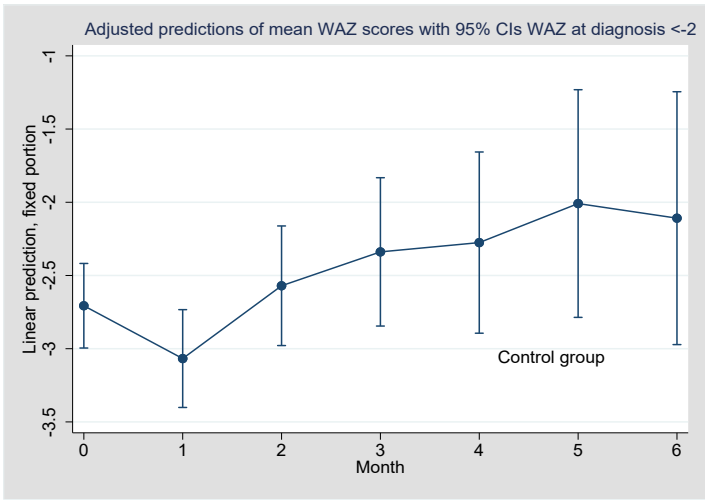




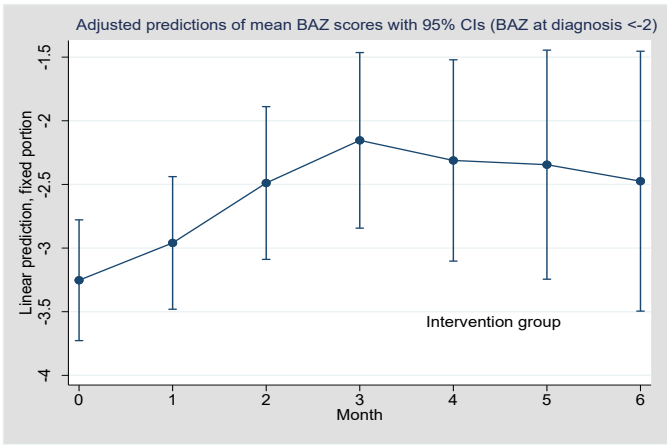


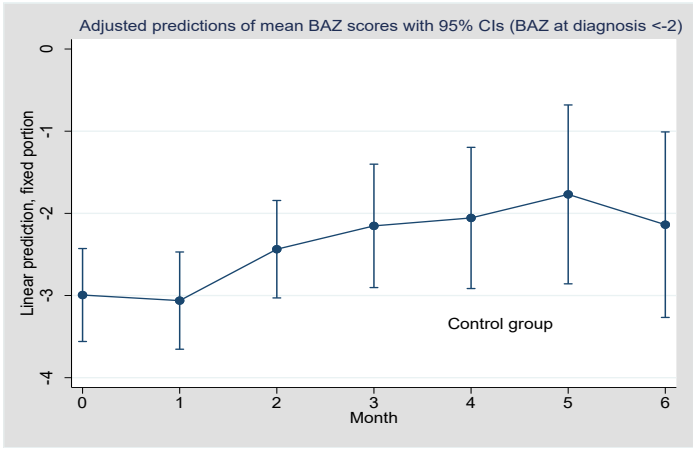
Supplementary Figure S2: Adjusted stunting (HAZ<-2) predictions based on mean Z-scores during the first six months of treatment.





Supplementary Figure S3: Adjusted predictions of underweight based on mean Z-scores (WAZ <-2) during the first six months of treatment





Supplementary Figure S4: Adjusted predictions of wasting (BAZ <-2) with 95% CI based on mean Z-scores during the first six months of treatment

CHAPTER 7

Discussion, conclusion, and recommendations

The local context is vital to consider and although South Africa is classified as an upper middle-income country, the 2019 poverty report indicates that more than half the population lives in poverty [1] (living on less than US$5.00 or R98.00 per day).[2] The country also experiences a significant challenge with a high disease burden, [2] and more than 80% of South Africans rely on the public government healthcare systems that struggle with service delivery to meet the increased demand.[1,2] Nutritional status is a crucial aspect of health, [3] and this study investigated several associations between the nutritional status of children with cancer and significant variables that might impact their health.

The World Health Organization (WHO) initiated the Global Initiative in 2018 with the aim of improving childhood cancer survival globally to more than 60% by 2030. [4] It is therefore important to investigate nutritional-supportive cancer care, which is crucial for the survival of children with cancer. At the initiation of the study, limited data was available regarding the impact of nutritional status at childhood cancer diagnosis on overall survival (OS) in South Africa or Africa, as well as potential associated risk factors. This study was undertaken especially to investigate the role of nutritional status at childhood cancer diagnosis in OS.

Discussion

The main aim of childhood cancer treatment is to cure children and ensure normal growth and development during cancer treatment and thereafter. [5] As mentioned earlier, childhood cancer is very curable, with approximately 75–80% OS in high-income countries, although this is not yet the case for low- or middle-income countries (LMICs) with reported poor OS rates,[6] namely 25- 52%.[7] At the start of this study, the available data regarding nutritional status in paediatric oncology patients at diagnosis indicated both under- and over-nutrition, ranging from 5 to 50%, with a higher prevalence of undernutrition in LMICs.[8]

The study on a topic not previously investigated in paediatric oncology units (POUs) in South Africa was undertaken to determine the current status of nutritional support for children with cancer in Africa. As stated in Chapter 2, there are barriers to nutritional care and intervention in POUs in Africa, with limited nutritional assessment done on these patients and limited access

to commercial nutritional supplements or parenteral nutrition. It was found that most of the POUs experienced personnel shortages that included dieticians or nutritionists, staff also lacked the necessary knowledge of nutrition.[8,9] Non-profit organisations (NGOs) can play a major role in providing nutritional care in Africa by providing essential nutritional products for hospitals and home care. [8] The International Initiative for Pediatrics and Nutrition (IIPAN) was established in 2016 with the aim to train nutritionists in LMICs and collaborate with NGOs by building capacity to develop protocols and nutritional guidelines.[10] The importance of the role of NGOs in a POU was seen in the twinning programme between Stellenbosch University and Cameroon Baptist Health Services started in 2003 for patients with Burkitt lymphoma. The patients received free medical care, food items, and financial aid to provide meals for their families. The one-year post-treatment OS rate had increased to 58.1% by 2011. [7]

Socioeconomic status (income, education, and occupation) impacts nutritional status,[11] and living with food insecurity results in stunting in children, known as chronic undernutrition, Poverty also contributes to poor health outcomes[1] as children from low-income families only have access to the already overloaded public healthcare facilities.[1] The low economic growth in South Africa leads to increased unemployment and high consumer prices which cause a decrease in households' living standards. In 2019, the population living below the poverty rate was 44.8%, representing 26.3 million.[12] UNICEF reported in 2021 that in LMIC, two-thirds of children under five years of age lived with food insecurity.[13] Poorer nations have limited access to a sufficient variety or amount of food, leading to inadequate nutrition. [9] Factors such as food insecurity, poor diet, disease, poor sanitary conditions, lack of inadequate health services, and poor education increase the risk of malnutrition development. [11,14] Undernutrition due to a deficiency of energy, protein, and other micronutrients leads to quantifiable adverse effects in the body.[12] Several studies have shown that socioeconomic status is a predictor of nutritional status [1115] and the course of a disease,[16] in this case cancer,

South Africa implemented the Child Support Grant (CSG) in 1998 in an attempt to reduce child poverty by covering food costs.[17] In 2022 about 10.3 million families received the CSG;[18] however, the CSG does not cover additional expenses incurred due to a life-threatening illness such as cancer.[19] In the context of the poor socio-economic status of many families in South Africa, it is of concern that a third of the children diagnosed with cancer in South Africa live in poverty, and 80% live with either food insecurity or the risk of food insecurity (Chapter 3). These factors may impact many aspects of childhood cancer management ranging from

treatment abandonment to poor OS. The crucial findings regarding the associations of poverty with hunger, childhood stunting, and the province of residence at cancer diagnosis, as well as children living in a family with food insecurity, showed an increased risk of abandonment of treatment and decreased OS.[15]

These findings have indicated the importance of assessing the poverty risk groups and food insecurity at childhood cancer diagnosis to assist with planning adequate supportive care and refer these children to NGOs for assistance. Certain NGOs in South Africa, namely the Childhood Cancer Foundation South Africa (CHOC), [20] the Cancer Associations of South Africa- Touch Living with Cancer (CANSA-TLC),[21] and the Rainbow and Smiles Foundation, [22] support POUs with transport for families to hospitals,[20,22] food parcels,[20,21,22] basic supplies (e.g. toiletries), [20,22] and accommodation for parents and/or caregivers.[20,21]

Vitamin and mineral deficiencies are a global public health problem, especially in regions with food insecurity and poor diet diversity.[1] Malnourished South African children may develop several micronutrient deficiencies due to poor diet quality.[23] These deficiencies may be due to poor diet diversity as the daily South African diet consists mainly of plant protein,[24–26] and poor food knowledge that affects families' ability to make healthy food choices within their budget.[27] The common deficiencies that South African children experience include Vitamin A (Vit A),[28] vitamin D (Vit D),[29] and Vitamin B12 (Vit B12),[30] and iron deficiency.[28] Micronutrient deficiencies such as iron and zinc deficiency cause stunting, (chronic undernutrition), impaired cognitive ability, increased risk of infection- and increased mortality.[5,6] Other micronutrient deficiencies existing in malnourished children are often referred to as hidden hunger.[7]

A recent study from Scotland (2020) found that 9% of childhood cancer patients had vit A deficiency and 6% had Vit B12 deficiency.[28] The prevalence of micronutrient deficiencies among children with cancer undergoing treatment in South Africa has not been thoroughly investigated. Our study illustrated a high prevalence of Vit D, Vit A, Vit B12, folate, and iron deficiency on diagnosis at two POUs in South Africa,[16] and also showed that these deficiencies were associated with the geographical regions in South Africa as children living in Mpumalanga and Gauteng had significantly lower folate-, Vit B12-, and iron levels at diagnosis compared to other provinces. The same provinces had a high prevalence of families living with food insecurity and poverty.[16]

African studies indicated that 17.2% of Malawian children[29] and 9.6% of Nigerian children were wasted at diagnosis.[30] Undernutrition in South African children diagnosed with cancer is less prevalent than in other LMICs [31] as less than 15% of newly diagnosed cancer patients were stunted, underweight, or wasted at diagnosis (Chapter 5). However, the crucial findings of a significant association of stunting with poor one- year post- cancer diagnosis OS and event-free survival (EFS) necessitate immediate identification and intensive nutritional management to improve OS.

The American Society for Parenteral and Enteral Nutrition accepts MUAC as a single screening tool to determine malnutrition; [32] therefore, the International Society for Paediatric Oncology (SIOP) Global Health Network (GHN) Nutrition Working Group (NWG) suggested that MUAC should be included in nutritional assessment in a child with cancer as a screening tool, especially in resource-constrained settings.[33]

Measuring MUAC and assessing children for the presence of moderate acute malnutrition (MAM) are more reliable and much more straightforward than measuring weight and height, and the measurement is inexpensive and quick. [34] Measuring MUAC offers a cheap, rapid, and easy assessment of a child's nutritional status, that is sensitive to measuring musculature and available protein stores [33,35] or lean body mass; [29,30,33,36,37] independent of tumour mass, [6,29,33,37,38] or temporary gains in total body water. [33,39] Risk groups for undernutrition identified in this study included children younger than five years of age for stunting, girls for underweight and children five and older for MAM.

A Scotland study reported that linear growth stagnated during the first months of treatment.[40] The Scottish children had a significant increase in their BMI during the first months of treatment, especially those children diagnosed with haematological malignancy,[40] in contrast with a Switzerland study in which the BMI decreased.[41] MUAC increased in the Scotland study.[40] There was no undernutrition six months after diagnosis in children with a solid tumour in the Scotland study.[40] In contrast, in our study, the prevalence of children in the cohort classified as being underweight and having a low BMI varied, such that wasting decreased but was still present; the solid tumour was a significant factor affecting the z-scores for both underweight and wasting after six months of treatment. In this study, the MUAC measurements improved till six months in the longitudinal part of the study.

Body composition can be measured by bioelectrical impedance analysis (BIA) that determines the rate of electric currents through the body in response to body composition to determine the fat mass (FM) and fat-free mass (FFM).[42] In a nested master's study at Tygerberg Hospital (Junie 2019 until April 2020), body composition was assessed by FM, FFM, skeletal muscle mass, and phase angle. In these 43 patients, moderate malnutrition was seen: 7% was stunted, 11% was underweight, and 13.7% was wasted, while MUAC indicated 13.7% with MAM. Body composition indicated that 41.8% had low skeletal muscle mass, 11.6% had low FFM, and 44.2% had low FM. This study suggests that anthropometric assessment alone cannot identify body depletion in cancer patients, which can result in loss of functional tissue, loss of muscle strength, and weakened immune system, all factors that can influence a child's response to cancer treatment. [43]

Nutritional algorithms are helpful for the nutritional management[44] of children with cancer, not only for identifying malnutrition but also for optimising nutritional intervention[44,45] and improving nutritional outcomes.[46] The results from the intervention part of the retrospective study in South Africa (2008) were used [47] to adjust the SIOP GHN NWG nutrition algorithm [48] for this study to improve the nutritional status of children with undernutrition. The intervention group showed improved nutritional status of undernourished children, with the severity significantly decreased, while in the control group, only MAM in children younger than five years decreased significantly.

Conclusion

In 2023, IIPAN nutritionists have been appointed at POUs in five African countries: Cameroon, [9] Tanzania, Kenya, Uganda, and Ethiopia, and are soon to be appointed in Zimbabwe.[10] Many children diagnosed with cancer in South Africa experience poverty, and the majority live with food insecurity. Our study observed that food insecurity increased the risk of treatment abandonment, especially in the deep- rural areas of our country, decreasing OS.[15] This is a crucial finding, as previous studies have reported that increased counselling and resources for children at high risk of treatment abandonment reduce its prevalence. [19]

Children diagnosed with cancer have a high prevalence of Vit D, Vit A, Vit B12, folate, and iron deficiency. Nutritional status, food insecurity, and province of residence are associated

with these deficiencies, emphasising the need to assess cancer diagnosis for additional supportive care.[16] This study paves the way for prospective studies to be performed in a larger cohort and correlating overall cancer outcomes, including how micronutrient deficiency may affect chemotherapy toxicity.

Undernutrition in South African children diagnosed with cancer is less prevalent than in other LMICs as less than 15% of newly diagnosed cancer patients were stunted, underweight, or wasted at diagnosis. MUAC assessment is a sensitive measurement to determine MAM as suggested by the SIOP GHN NWG and should be included in nutritional assessment.[33] The body composition study indicated that although MUAC measurements indicated a higher percentage of children with MAM, than the other anthropometric measures, it was still not an accurate indicator of the body depletion that patients suffered.[43] Risk groups identified in this study included children younger than five years of age for stunting, girls for underweight and children five years and older for MAM. The prevalence of wasting fluctuated during the initial six months of cancer treatment, as the BMI varied during the period, while the MUAC measurements improved till six months in the longitudinal part of the study. An important finding is a significant association of stunting with poor one-year post-cancer diagnosis OS and EFS.

The nutritional algorithm adapted for the South African context that was used during the first six months of treatment significantly improved the nutritional status of undernourished children, while in the control group, improvement was not significant. This proves that nutritional algorithms are helpful for the nutritional management [44] of children with cancer.

Recommendations

With more funding, IIPAN can increase training and assist more POUs in Africa countries and LMICs. Access to nutritional products is still a challenge, and this is where organisations such as World Child Cancer, and local NGOs or cancer foundations can assist POUs with nutritional care products. The IIPAN nutritionists can also evaluate/improve the recipes of homemade supplements to ensure that they are nutritionally balanced.

We recommend that each POU in South Africa use the Simple Poverty Scorecard Poverty-Assessment Tool and the Household Hunger Scale questionnaires as part of the initial

assessment to identify children living in families at high risk of food insecurity and poverty. These families may have a higher risk of micronutrient deficiencies and cancer treatment abandonment. Additional nutritional and financial support should be sought from NGOs since the current South African CSG will not cover the extra expenses that a cancer diagnosis will likely cause with the cost of treatment and supportive care straining the families' finances.[19]

Micronutrient status needs to be part of the initial work-up at cancer diagnosis. The topic of when to supplement without clinical evidence of micronutrient deficiency is controversial. Our evidence indicates that commercial nutritional supplements providing macro- and micronutrients, especially in patients with food insecurity at home, may benefit children treated for cancer. As micronutrient deficiencies are identified, further investigation is needed to determine the impact on complications during cancer treatment and provide the necessary information to optimise supportive care to families.

The best indication of body composition is obtained through a body composition analyser. We recommend that it be used in high-income countries to assess children,[43] Our study indicated that in LMIC, MUAC assessment should be part of the nutritional assessment of children treated for cancer to determine malnutrition that can be masked by other factors, such as massive tumours and/or oedema.[33]

We strongly suggest that POUs use the nutritional algorithm adapted for the South African context based on the MUAC measurement during nutritional assessment to improve nutritional status during cancer treatment. Children classified as severely acute malnourished or MAM at diagnosis would significantly improve following the nutritional algorithm during the first six months of treatment.

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ACKNOWLEDGEMENTS

I want to thank the following people and departments from the bottom of my heart for their contribution to completing this thesis:

My family: Thinus, Pieter, Lizl-Louise, Rohan, Danielle, Aunt Pop, Judy & Rüza and my 'chosen family': Elmarie, Jacoline, Madeleine, Jaques, Hannes, Roeline, Hildegard & Maria for supporting me during the worst time of my life, losing my mom and dad; your continued motivation and support throughout this study, late night phone calls & making sure I take time for myself. You are the best!

My supervisor, Prof Mariana Kruger, for always believing that nutrition can make a difference in a child's life, for believing in me since 2001 & encouraging me to further my studies. Her support during difficult times in my life and throughout this study, her guidance and mentorship will forever impact my life.

My co-supervisors, prof Paul C Rodgers and Elena J Ladas. Paul for believing I had potential, for his continued support in my career, for encouraging me to take the PhD road, and for his lifelong contribution toward nutrition in paediatric oncology. Elena, for encouraging me to do a research study, for guidance throughout this study, and for making a dream come true – becoming part of IIPAN and working in Africa.

My Paediatric Oncology family at Steve Biko Academic Hospital, for your support and encouragement during my career, for agreeing to be part of my study, for the neverending discussions with mothers and for believing nutrition makes a difference, especially Ané Büchner, Poppy Ncube and Ansie van Nel.

The co-authors and study co-investigators of each site for continuing this research study during difficult circumstances, Covid 19 and personnel shortages.

The extensive analysing of data, Prof Carl Lombard and Sandile Ndlovu, Biostatisticians at Stellenboch University. Thanks to Sandile for her wisdom and for walking the extra mile with me to turn my vision into reality; you have a bright future ahead!

The Head of Dietitics: Steve Biko Academic Hospital, Ida Heyneke, for her support and for allowing me to take leave when I was overwhelmed.

The language editing of consent forms, articles, and chapters in this thesis was done by the Stellenbosch University Language.

Lastly, Anita Fourie, Stellenbosch University, for her support, guidance, and endless patience..… you made a mountain, a small hill to climb.

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APPENDICES:

Appendix A: Ph. D committee clearance

Every breath counts

9 April 2018.

Dear Prof Kruger

PhD proposal Ms Judy Schoeman

Thank you for the submission of the revised PhD proposal of Ms Judy Schoeman.

The committee members have reviewed the revised proposal and would like to make the following comments:

1) The members of the committee would like to thank the candidate for the changes made to the proposal, and would like to thank the supervisor for overseeing these changes.

2) The committee members agree unanimously that the candidate has addressed the points of major concern and has made the necessary corrections in the proposal.

3) The committee recommends that the candidate can now accept the changes in the document, read it one last time for small corrections to still be made, and then submit the PhD proposal and register as a PhD student.

4) The committee hopes that the candidate found the suggestions made of value and that she has learnt a small bit from the comments and suggestions made.

5) The committee wishes the candidate well in the next steps of the PhD journey.

Kind regards

Nulda Beyers
Committee chair on behalf of the rest of the evaluation committee

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Fakulteit Geneeskunde en Gesondheidswetenskappe ⌗ Faculty of Medicine and Health Sciences
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Direkteur ⌗ Director: Prof Anneke Hesseling (annekeh@sun.ac.za)

Appendix B: Ethical Clearances

UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Health Research Ethics Committee (HREC)

Approval Notice

New Application

16/08/2018

Project ID :6733

HREC Reference #: S18/04/050

Title: Nutritional status of children at cancer diagnosis and during treatment, with a focus on the association with their clinical outcome

Dear Ms Judy Schoeman,

The **Response to Modifications** received on 20/06/2018 11:09 was reviewed by members of **Health Research Ethics Committee 2 (HREC2)** via **expedited** review procedures on 16/08/2018 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: **This project has approval for 12 months from the date of this letter.**

Please remember to use your **Project ID [6733]** on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Translation of the informed consent document(s) to the language(s) applicable to your study participants should now be submitted to the HREC.

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Departement of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-research-approval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website https://applyethics.sun.ac.za/ProjectView/Index/6733

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Mr. Francis Masiye ,

HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number: IRB0005240 (HREC1)·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects;the South African Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition); as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

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Approved with Stipulations

Response to Modifications- (New Application)

13-Dec-2016
Schoeman, Judith J
Private Bag 19063
Matieland
Stellenbosch, WC

Ethics Reference #: N16/11/140

Title: **AFRICA CONTINENT: PAEDIATRIC ONCOLOGY NUTRITION SURVEY (A Survey to determine the availability of Nutritional care and Interventions in Hospitals trea**

Dear Ms Judith Schoeman,

The **Response to Modifications -** ***(New Application)*** received on **09-Dec-2016**, was reviewed by members of **Health Research Ethics Committee 1** via Expedited review procedures on **12-Dec-2016**.

Please note the following information about your approved research protocol:

Protocol Approval Period: **13-Dec-2016 -12-Dec-2017**

The Stipulations of your ethics approval are as follows:
Remove the sentence referring to consent waiver in the introduction to the survey. By continuing to the survey participants are consenting to participation.

Please remember to use your **protocol number** (**N16/11/140**) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States

Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at .

Included Documents:

JS - Email- Cover letter SIOP Africa Nutrion Survey.31 Oct 2016 doc.doc
20161212 MOD Email- Cover letter SIOP Africa Nutrion Survey.doc
JS - SIOP AFRICA NUTRION SURVEY PROTOCOL - 31 OCT 2016.doc
CV P Rogers.doc
Checklist(Eng)_V2.1 April 2016.doc
Declaration J Schoeman.pdf
Js - Survey - AFRICA CONTINENT - PAEDS ONC NUTRITON SURVEY.pdf
CV M Kruger.docx
Declaration E Ladas.pdf
Application form signature page.pdf
Application form.doc
20161212 MOD HREC Modifications Required.pdf
Declaration P Rogers.pdf
CV E Ladas.pdf
20161212 MOD Cover letter.pdf
Barsdorf N Dr Expedited Review.pdf
JS - SIOP AFRICA NUTRION SURVEY PROTOCOL Synopsis - 5 Nov 2016.doc
20161212 MOD Protocol.doc
CV J Schoeman.pdf
Declaration M Kruger.pdf

Sincerely,

Franklin Weber
HREC Coordinator
Health Research Ethics Committee 1

Investigator Responsibilities

Protection of Human Research Participants

Some of the responsibilities investigators have when conducting research involving human participants are listed below:

1.Conducting the Research. You are responsible for making sure that the research is conducted according to the HREC approved research protocol. You are also responsible for the actions of all your co-investigators and research staff involved with this research.

2.Participant Enrolment. You may not recruit or enrol participants prior to the HREC approval date or after the expiration date of HREC approval. All recruitment materials for any form of media must be approved by the HREC prior to their use. If you need to recruit more participants than was noted in your HREC approval letter, you must submit an amendment requesting an increase in the number of participants.

3.Informed Consent. You are responsible for obtaining and documenting effective informed consent using **only** the HREC-approved consent documents, and for ensuring that no human participants are involved in research prior to obtaining their informed consent. Please give all participants copies of the signed informed consent documents. Keep the originals in your secured research files for at least fifteen (15) years.

4.Continuing Review. The HREC must review and approve all HREC-approved research protocols at intervals appropriate to the degree of risk but not less than once per year. There is **no grace period.** Prior to the date on which the HREC approval of the research expires, **it is your responsibility to submit the continuing review report in a timely fashion to ensure a lapse in HREC approval does not occur.** If HREC approval of your research lapses, you must stop new participant enrolment, and contact the HREC office immediately.

5.Amendments and Changes. If you wish to amend or change any aspect of your research (such as research design, interventions or procedures, number of participants, participant population, informed consent document, instruments, surveys or recruiting material), you must submit the amendment to the HREC for review using the current Amendment Form. You **may not initiate** any amendments or changes to your research without first obtaining written HREC review and approval. The **only exception** is when it is necessary to eliminate apparent immediate hazards to participants and the HREC should be immediately informed of this necessity.

6.Adverse or Unanticipated Events. Any serious adverse events, participant complaints, and all unanticipated problems that involve risks to participants or others, as well as any research-related injuries, occurring at this institution or at other performance sites must be reported to the HREC within **five (5) days** of discovery of the incident. You must also report any instances of serious or continuing problems, or non-compliance with the HRECs requirements for protecting human research participants. The only exception to this policy is that the death of a research participant must be reported in accordance with the Stellenbosch Universtiy Health Research Ethics Committee Standard Operating Procedures www.sun025.sun.ac.za/portal /page/portal/Health_Sciences/English/Centres%20and%20Institutions/Research_Development_Support/Ethics/Application_package All reportable events should be submitted to the HREC using the Serious Adverse Event Report Form.

7.Research Record Keeping. You must keep the following research-related records, at a minimum, in a secure location for a minimum of fifteen years: the HREC approved research protocol and all amendments; all informed consent documents; recruiting materials; continuing review reports; adverse or unanticipated events; and all correspondence from the HREC

8.Reports to the MCC and Sponsor. When you submit the required annual report to the MCC or you submit required reports to your sponsor, you must provide a copy of that report to the HREC. You may submit the report at the time of continuing HREC review.

9.Provision of Emergency Medical Care. When a physician provides emergency medical care to a participant without prior HREC review and approval, to the extent permitted by law, such activities will not be recognised as research nor will the data obtained by any such activities should it be used in support of research.

10.Final reports. When you have completed (no further participant enrolment, interactions, interventions or data analysis) or stopped work on your research, you must submit a Final Report to the HREC.

11.On-Site Evaluations, MCC Inspections, or Audits. If you are notified that your research will be reviewed or audited by the MCC, the sponsor, any other external agency or any internal group, you must inform the HREC immediately of the impending audit/evaluation.

Appendix C: Ethical clearance for nested study: MSc study

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Approval Letter
Amendment

10/04/2019

Project ID: 6733

Ethics Reference #: S18/04/050

Title: Nutritional status of children at cancer diagnosis and during treatment, with a focus on the association with their clinical outcome

Dear Prof Mariana Kruger,

Your amendment request dated 15 March 2019 and the response to modifications received on 26 March 2019 refer.

The Health Research Ethics Committee (HREC) reviewed and approved the amended documentation through an expedited review process.

The following amendments were reviewed and approved:

1. Revised protocol version 3 dated 24 March 2019
2. Revised consent form for the Nutritional Intervention version 3 dated 24 March 2019
3. Revised assent form for 7 - 12 year children for the SA Nutritional Study version 2 dated 15 March 2019
4. Revised assent for for 12 - 15 year children for the SA Paeds Onc Nutritional Study version 2 dated 15 March 2019
5. Appendix 13: Calculations used to determine BMR as standard practice of care version 1 dated 15 March 2019
6. Addition of Prof Renee Blaauw as a supervisor/co-study leader to the study
7. Addition of Ilde-Marie Kellerman as a co-investigator to the study.

Where to submit any documentation

Kindly note that the HREC uses an electronic ethics review management system, *Infonetica*, to manage ethics applications and ethics review process. To submit any documentation to HREC, please click on the following link: https://applyethics.sun.ac.za.

Please remember to use your **Project ID [6733]** and ethics reference number **[S18/04/050]** on any documents or correspondence with the HREC concerning your research protocol.

Yours sincerely,

Mr. Francis Masiye,

HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1)·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board (IRB) Number:
IRB0005240 (HREC1)·IRB0005239 (HREC2)

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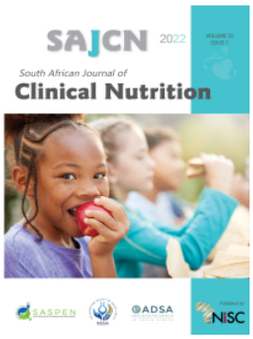

South African Journal of Clinical Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ojcn20

Agreement between measured energy expenditure and predictive energy equations in paediatric oncology

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To cite this article: I Kellerman, M Kruger, J Schoeman & R Blaauw (2023): Agreement between measured energy expenditure and predictive energy equations in paediatric oncology, South African Journal of Clinical Nutrition, DOI: 10.1080/16070658.2023.2220270

To link to this article: https://doi.org/10.1080/16070658.2023.2220270

Published online: 04 Jul 2023.

South African Journal of Clinical Nutrition 2023: 1–7
https://doi.org/10.1080/16070658.2023.2220270

SAJCN
ISSN 1607-0658 EISSN 2221-1268

RESEARCH ARTICLE

Agreement between measured energy expenditure and predictive energy equations in paediatric oncology

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[b]*Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa*
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Purpose: Optimal nutritional support in childhood cancer relies on the adequate provision of energy. This study investigated the impact of chemotherapy on resting energy expenditure (REE) during the first six months of treatment and the accuracy of predictive equations in calculating said requirements of newly diagnosed children with cancer.
Methods: REE was measured at diagnosis utilising a validated bioelectrical impedance analysis (BIA) mobile unit and compared with three predictive equations (Schofield 1985, World Health Organization [WHO] 1985 and the Recommended Dietary Allowance [RDA] 1989). Agreement and accuracy of these equations were tested by determining bias and agreement rates and displayed using the Bland–Altman plot. Baseline values were plotted against monthly follow-up measurements over time. Statistical significance was 5% and a priori limits of agreement set between 90% and 110% of measured REE.
Results: Forty-three newly diagnosed children with median age 4 years (IQR 2.0–7.6) were measured prior to chemotherapy initiation. Compared with measured REE (mean ± SD) 719.53 ± 206.29 kcal/day, all predictive equations significantly overestimated REE: WHO 1985 (889.75 ± 323.31 kcal/day; 23% overestimation), Schofield 1985 (899.62 ± 336.10 kcal/day; 25% overestimation) and RDA (1647.67 ± 481.06 kcal/day; 129% overestimation) ($p < 0.001$). Despite significant proportionate bias in all three equations ($p < 0.001$), the intra-class consistency coefficient showed good reliability for the Schofield 1985 (0.864) and WHO 1985 (0.849) equations. Though statistically significant (chi-square = 23.11, $p < 0.003$), the overall 1 kcal/kg (1.3%) increase for all cancer types at six months may not be clinically significant.
Conclusion: Existing predictive equations are unable to calculate REE accurately at childhood cancer diagnosis, highlighting the need for future investigations into the development of cancer-specific equations.

Keywords paediatric nutrition, paediatric oncology, predictive equations, resting energy expenditure

Introduction

Energy imbalance is common in paediatric disease states, leading to either malnutrition or excessive weight gain.[1] The adequate provision of energy and protein requirements in children is therefore essential to sustain rapid growth and development during the first phases of the life cycle.[2,3] In the child with cancer, both over- and underfeeding may have severely detrimental effects on health-related quality of life and survival,[4] hence the most important focus of care is arguably the emphasis on the promotion of optimal nutritional support during therapy.[3,5] The accurate determination of energy requirements as a basis for such nutritional interventions may facilitate a positive energy and nitrogen balance, aiding optimal growth and development despite the presence of cancer, its treatment and their related side effects.[3,5–7]

Metabolic changes in the cancer population may include variations in energy expenditure, with the widespread belief that all cancer patients are hypermetabolic.[8] For this reason indirect calorimetry (IC) is regarded as the gold standard for determining resting energy expenditure (REE) by measuring oxygen and carbon dioxide concentrations during respiratory gas exchange and recommended for use in patient populations at risk for hypo- or hypermetabolism such as children with cancer.[9,10] However, the practicality of implementing the test, as well as the costs involved, limits its use in the paediatric setting.[6,11] In the absence of IC, a child's total daily energy requirements may be determined by adding estimated REE to energy associated with physical activity, thermogenesis and growth.[7] Several practical predictive equations have consequently been derived from healthy populations utilising variables including age, gender, weight and height for the calculation of REE.[8] Popular predictive equations, namely the Schofield (weight, height),[12] World Health Organization (WHO) 1985[13] and recommended dietary allowance (RDA) 1989,[14] are used regularly to calculate the energy requirements for both healthy and sick patients. Speculation regarding the accuracy of their predictive values has been on the forefront of research enquiries in recent years, especially in light of the child with chronic illness.[9,11,15,16] However, scant information is available regarding this topic in the child with cancer.[6,7]

This study investigated the impact of chemotherapy exposure on the REE of children newly diagnosed with cancer during the first six months of intensive chemotherapy and whether predictive equations are able to accurately estimate such requirements at diagnosis as a basis for nutritional interventions.

Methods

Study design

Newly diagnosed participants presenting at the paediatric oncology unit at Tygerberg Hospital, Cape Town for the period April 2019–January 2020 were recruited after obtaining written consent and assent from all caregivers and participants

aged seven years and older. Those requiring exclusive radiotherapy or surgical interventions were excluded. Enrolled participants were followed up monthly from diagnosis for the remainder of their individual intensive therapy regimens up to a maximum of six months. This prospective, descriptive cohort study was performed in line with the principles of the Declaration of Helsinki and approved by the University of Stellenbosch`s Health and Research Ethics Committee (S18/04/050).

Data collection

Demographic data (date of birth, age, sex), cancer diagnosis and each participant`s respective chemotherapy regimens were collected at diagnosis. Baseline anthropometrical status, body composition and REE were measured within 72 hours of diagnosis prior to the initiation of chemotherapy, utilising standardised protocols and the validated S10 InBody bio-electrical impedance (BIA) mobile unit (InBody Co Ltd, Korea).[17,18] During the same reading to determine body composition, the BIA equipment simultaneously determined REE (pre-programmed with the Cunningham equation 1991).[19] Measured REE was expressed in kcal/day and compared with calculated energy requirements from other age- and sex-based paediatric predictive formulae at baseline only: Schofield 1985 (weight, height)[12] equation, WHO 1985[13] equation and the recommended dietary allowance (RDA) 1989 equations[14] (Table 1). Predicted values between 90% and 110% of measured values were considered clinically acceptable.[7,16] Patterns of change over time were assessed by comparing monthly follow-up measurements with baseline values.

Data analysis

REE at diagnosis, as well as changes and associations between baseline and follow-up measurements, were identified utilising both inferential and basic descriptive statistics. Baseline data and trends in change over time were expressed in absolute values (kcal/day) and reported according to median (interquartile range [IQR]), mean ± standard deviation (SD) and percentage change where appropriate. The Friedman rank test (non-parametric) compared median variable values between diagnosis and the end of follow-up (month five) and per cancer group (haematological malignancies and solid tumours). Bootstrap multiple comparisons furthermore addressed the small sample size and the non-normality of the data distribution and compared interaction means from the RMANOVA between months (each month) and cancer groups. Intra-class correlations for agreement and consistency, as well as Bland–Altman plots, were used to investigate the agreement and accuracy of predictive equations when compared with the measured baseline REE.[20,21] Statistical significance for the agreement analysis was 5% and a priori levels of the clinically accepted limits of agreement were set at 10%.[7,16] Data were analysed using the STATISTICA (version 13, TIBCO Software Inc.) data analysis software system.

Results

Forty-three participants aged 3 months to 15 years (median age 4 years; IQR 2.0–7.6) with a variety of haematological malignancies (53%) and solid tumours (47%) participated in the study (Table 2). The male:female ratio was 1:09.

REE at diagnosis and the accuracy of predictive equations

Measured REE for all cancer types at baseline included a median of 650 kcal/day (IQR 579–804 kcal/day) and a mean ± SD of 719.53 ± 206.29 kcal/day within a wide range of 476–1387 kcal/day. As summarised in Table 3, a large difference was seen when comparing measured REE with predicted values, despite the strong correlation between them ($p < 0.001$). All three equations overestimated REE with the WHO (23.6%) faring the best and the RDA (129.0%) the worst. Although intra-class agreement was moderate to poor for all equations, the intra-class consistency coefficient showed good reliability for the Schofield 1985 (0.864) and WHO 1985 (0.849) equations.

The Bland–Altman plots (Figures 1–3) depict the significant differences and proportionate bias between measured REE (mean ± SD), WHO 1985, Schofield 1985 and RDA 1989 ($p < 0.001$ respectively). The proportionate bias of the WHO 1985 equation (−170.2 ± 149.0 kcal/day) (Figure 1) was lower than both the Schofield 1985 (−180.1 ± 145.7 kcal/day) (Figure 2) and RDA (−928.1 ± 324.8 kcal/day) (Figure 3) equations. Coupled with the large variance between measured and predicted REE all three equations exceeded the 90–110% limits of minimal clinically accepted agreements, rendering these predictive equations inaccurate for use in the clinical setting. Only nine (Schofield 1985, WHO 1985) and three (RDA 1989) participants respectively fell within the 90–110% clinically accepted limits of agreement.

Table 1: Calculations used to determine resting energy expenditure[12–14,19]

Equation	Age (years)	Male (kcal/day)	Female (kcal/day)
Cunningham	–	370 + 21.6(FFM)	370 + 21.6(FFM)
Schofield (weight, height)	< 3	0.167(W) + 15.174(H)−617.6	16.525(W) + 10.232(H)−413.5
	3–10	19.59(W) + 1.303(H) + 414.9	16.969(W) + 1.618(H) + 371.2
	10–18	16.25(W) + 1.372(H) + 515.5	8.365(W) + 4.65(H) + 200.0
WHO	< 3	60.9(W)−51	61(W)−51
	3–10	22.7(W) + 495	22.5(W) + 499
	10–18	17.5(W) + 651	12.2(W) + 746
Recommended dietary allowance	0.0–0.5	650	650
	0.5–1.0	850	850
	1–3	1 300	1300
	4–6	1 800	1800
	7–10	2 000	2000
	11–14	2 500	2200
	15–18	3 000	2200

kcal/day: kilocalories per day, FFM: fat free mass, W: weight, H: height, WHO: World Health Organization.

Table 2: General patient characteristics

Demographics	Total study population	Type of cancer	
		Haematological malignancies	Solid tumour
Total number of participants (*n*, %)	43 (100)	23 (53)	20 (47)
Sex:			
• Male (*n*, %)	22 (51)	12 (52)	10 (50)
• Female (*n*, %)	21 (49)	11 (48)	10 (50)
Age in years (mean ± SD)	5.4 ± 4.2	5.6 ± 4.3	5.2 ± 4.1
Age in years (median, Q1-Q3)	4 (2.0–7.6)	4.2 (2.0–8.8)	3.9 (2.0–7.1)
Cancer diagnosis (*n*, %):			
• Acute lymphoblastic leukaemia	13 (30.2)	13 (56.5)	
• Acute myeloid leukaemia	3 (7.0)	3 (13.0)	
• Langerhans cell histiocytosis	2 (4.7)	2 (8.8)	
• Lymphoma	5 (11.6)	5 (21.7)	
• Ewing sarcoma	1 (2.3)		1 (5.0)
• Hepatoblastoma	2 (4.7)		2 (10.0)
• Medulloblastoma	1 (2.3)		1 (5.0)
• Nephroblastoma	5 (11.6)		5 (25.0)
• Neuroblastoma	1 (2.3)		1 (5.0)
• Osteosarcoma	3 (7.0)		3 (15.0)
• Retinoblastoma	2 (4.7)		2 (10.0)
• Rhabdoid sarcoma	1 (2.3)		1 (5.0)
• Rhabdomyosarcoma	3 (7.0)		3 (15.0)
• Yolk sac tumour	1 (2.3)		1 (5.0)

SD: standard deviation; Q1: 25th centile; Q3: 75th centile.

Table 3: Variance and agreement between measured and predicted REE values at diagnosis

Resting energy expenditure (kcal/day)	Mean ± SD	% Variance from measured REE	Intra-class correlation	Intra-class agreement (95% CI)	Intra-class consistency (95% CI)	*p*-value
Measured REE	719.53 ± 206.29					
Schofield 1985	899.62 ± 336.10	25.0	0.97	0.716 (0.006,0.901)	0.864 (0.762,0.924)	< 0.001
WHO 1985	889.75 ± 323.31	23.6	0.95	0.71 (0.043,0.894)	0.849 (0.738,0.915)	< 0.001
RDA 1989	1647.67 ± 481.06	129.0	0.91	0.149 (−0.050,0.458)	0.615 (0.389,0.771)	< 0.001

kcal/day: kilocalories per day; SD: standard deviation; %: percentage; REE: resting energy expenditure; CI: confidence interval; WHO: World Health Organization; RDA: recommended dietary allowances.

Changes in REE over time

The study population experienced several changes in measured REE over time (Table 4). A 20 kcal/day (3%) decrease in median REE was seen during the first two months of treatment for all cancer types, which increased during month three and five to end with a significant increase of 16 kcal/day (2.5%) at month five (chi-square = 23.11, $p < 0.003$). When converted to kcal/kg in relation to the participant`s diagnosis weights, these trends translate to a 1.3 kcal/kg (3.2%) decrease and 1 kcal/kg (2.4%) increase respectively, which is not clinically significant during the calculation of energy requirements. Patterns of change varied among cancer diagnosis and the haematological malignancy group, despite their 64 kcal/day (9.4%) lower baseline REE, experienced a gradual monthly increase ending in a significant overall 33 kcal/day (5.3%) increase by month five (chi-square = 11.79, $p = 0.038$). In contrast, the solid tumours experienced an initial decrease in median REE of 45 kcal/day (6.6%) followed by a rapid 64 kcal/day (10%) increase during month three to end in an excess of 15 kcal/day (2%) of baseline values (chi-aquare = 14.23, $p = 0.014$). Despite the variation in trends over time, bootstrap multiple comparisons confirmed there was no significant monthly difference in measured REE between cancer types (data not shown).

Discussion

Our findings illustrate the inability of commonly used predictive equations to calculate REE at childhood cancer diagnosis. Though an overall overestimation, significant bias and moderate to poor agreement was present for all three equations; both the WHO 1985 and Schofield 1985 (weight, height) proved more reliable for resting energy calculations than the RDA 1989 equation. Changes in REE were observed after chemotherapy initiation for all cancer types, which, albeit statistically significant, may be deemed negligible during energy calculations. No significant monthly difference was found between cancer types despite the varied response to treatment over time.

The debate regarding the potential for increased resting metabolic rate in children with cancer remains ongoing. Den Broeder *et al*. showed that the Schofield (weight) equation underestimated REE as measured by IC by 3–21% at

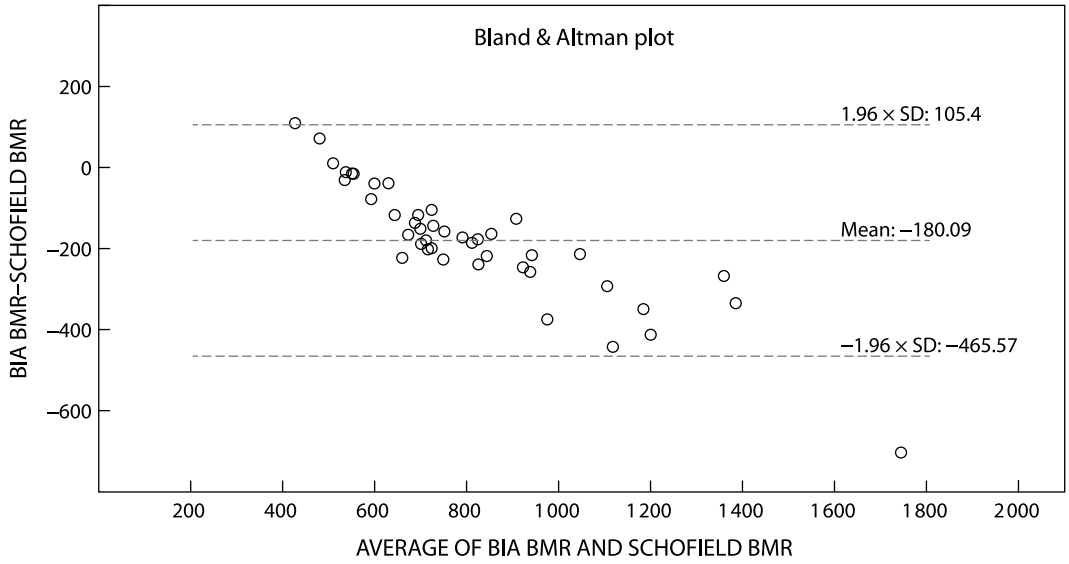

Figure 1: Agreement between measured basal metabolic rate and the Schofield 1985 equation. BIA: bioelectrical impedance analysis; BMR: basal metabolic rate.

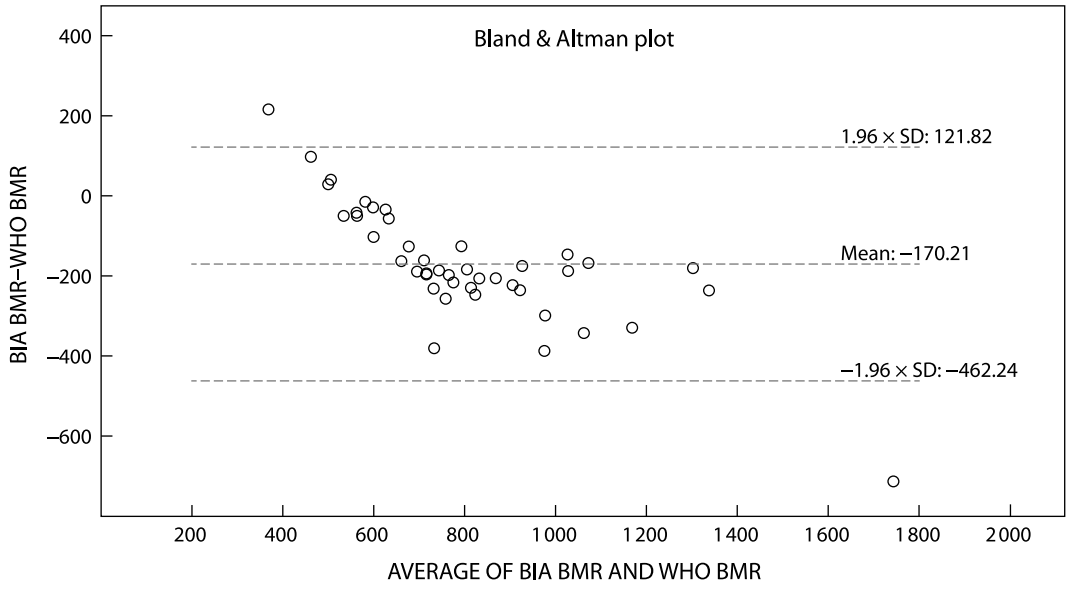

Figure 2: Agreement between measured basal metabolic rate and the WHO 1985 equation. BIA: bioelectrical impedance analysis; BMR: basal metabolic rate; WHO: World Health Organization.

diagnosis, proposing the addition of a factor of 1.0–1.2 during the first two courses of chemotherapy to compensate for the suggested increased energy demand from the tumour during this time.[7] In contrast, Galati *et al*. found no difference in REE as measured by IC between their oncology patient groups (solid tumour, non-solid tumour and all cancer types) and their healthy age- and sex-matched controls. Their study population was therefore not considered to be hyper-metabolic and there was no need to adjust requirements for the presence of cancer.[6] Our results, however, concur with those of Brinksma *et al*. by reiterating that the RDA severely overestimated the REE in their mixed cancer population and was not applicable to REE calculations due to their lower activity levels and poor appetite.[2] Although originally developed to include an activity factor of 1.7 for healthy, ambulant children,[14] it may be better suited for catch-up growth than resting energy requirements.

Our findings furthermore demonstrate a mere 1–1.3 kcal/kg fluctuation in REE over the six-month period, which may in turn influence the accuracy of energy calculations based on static predictive equations. When compared with existing short methods for bedside calculations in healthy infants (100–120 kcal/kg),[22] these changes may appear small, especially in younger children, and may be deemed negligible. Previous studies also reported changes in REE, describing brief increases in acute lymphoblastic leukaemia (with high-risk disease) for the first 14–30 days, after which REE returned to baseline values.[9,23] Similarly, Den Broeder *et al*. found that their solid tumour population also demonstrated an initial increase in REE followed by a prompt reduction after two to four courses of chemotherapy to match those predicted by Schofield (weight).[7] Because cancer patients have lower levels of activity, an increased resting energy metabolic rate might not necessarily equate to a higher total energy expenditure and may indeed be negated

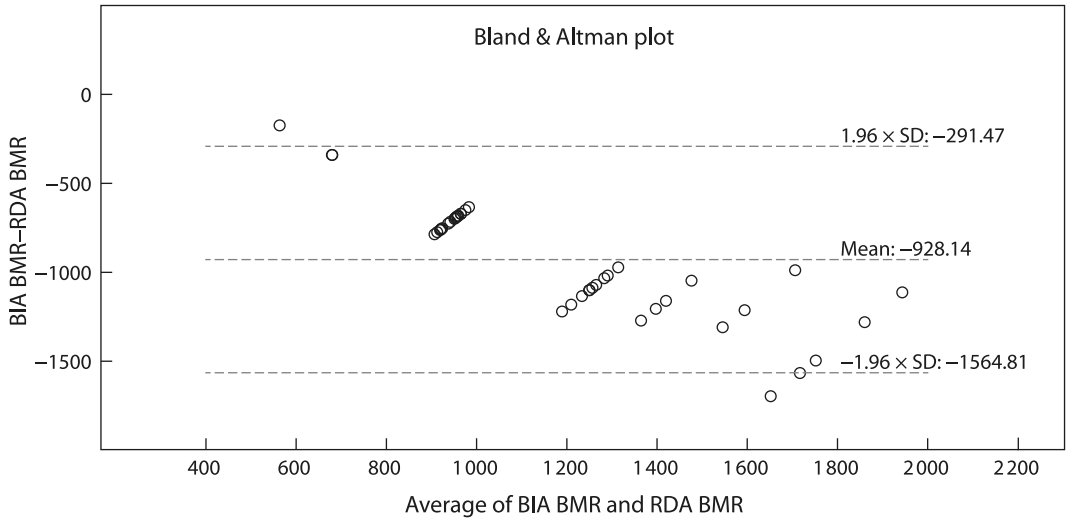

Figure 3: Agreement between measured basal metabolic rate and the RDA 1989 equation. BIA: bioelectrical impedance analysis; BMR: basal metabolic rate; RDA: recommended dietary allowance.

Table 4: Changes in median resting energy expenditure over time

REE (kcal/day)	Monthly changes in REE (kcal/day) over time in median (Q1, Q3)						
	Diagnosis *n* = 43	Month 1 *n* = 42	Month 2 *n* = 41	Month 3 *n* = 39	Month 4 *n* = 37	Month 5 *n* = 32	*Chi-square (*p*-value)
All cancer types	650 (579, 804)	630 (572, 782)	632 (576, 800)	662 (608, 822)	637 (614, 839)	666 (620, 877)	23.11 (< 0.003)
Cancer group							
Haemato-logical malignancies	619 (574, 794)	627 (566, 782)	632 (584, 811)	648 (592, 822)	635 (608, 919)	652 (595, 941)	11.79 (0.038)
Solid tumours	683 (603, 804)	638 (594, 794)	632 (563, 800)	696 (618, 812)	696 (620, 838)	698 (642, 818)	14.23 (0.014)

*The chi-squares and *p*-values given in the last column result from the Friedman test, which compared the median REE from diagnosis with month five.
REE: resting energy expenditure; kcal/day: kilocalories per day; Q1: 25th centile; Q3: 75th centile.

with lower activity levels.[7,24] Galati *et al*. did not report changes in REE over time, but their results included randomly selected patients of all cancer types regardless of the phase of treatment.[6] Their findings could be relevant to our current investigation as they inadvertently demonstrated no change in REE at any given time point after treatment was commenced.[6]

The illustrated deviations between measured REE and predicted values among our study populations may result from the various methodologies, technical differences in experimental conditions and predictive equations used.[6,7,11] Additionally, the metabolic turnover of the child with cancer is influenced by a host of factors such as age, sex, altered body compartments, ethnicity, hormones, the environment (temperature) and levels of physical activity.[5,6,11,15] Of these factors, age, sex and nutritional status at diagnosis may cause the greatest variation in measured REE.[5,6,11] However, the proportionate bias found in our study population showed that the equations consistently misjudged measured REE at the same rate despite large age gaps in our sample. Varied patterns of change in REE may also be linked to cancer diagnosis, stage of cancer and accompanying treatment regimen,[7] yet no statistical difference was found among our cancer groups. Rather, our initial decrease as exhibited by the solid tumours may be directly linked to their increased risk for malnutrition and functional losses as established by adult and paediatric findings.[6,8] This concurs with the deduction of Sanner *et al*. that the dynamic development of energy requirements is related to changes in anthropometric and body composition status.[5]

As REE, the largest component of total energy expenditure, is mainly influenced by metabolically active organ tissues contained within fat free mass (FFM),[3,9,25] changes in REE reflect a close association with changes in weight, body composition and energy imbalance.[26] This may affect the metabolic rate of children with cancer, who are particularly vulnerable to FFM depletion during the first three months of treatment.[24] Similarly, the degree of sarcopenia found in children with anorexia nervosa and the extent of muscle loss in children with cerebral palsy was also correlated with variations in REE and inaccurate energy predictions as supplied by predictive equations.[9] Anthropometric variables (weight, height) employed by commonly used equations do not reflect underlying body composition, thereby limiting their accuracy and predictability.[9] For this reason it is suggested that energy calculations instead be based on lean size rather than weight, as relatively normal weight may conceal underlying changes in body composition.[1] The accurate measure of body composition and FFM is therefore crucial to detect metabolic changes in ill patients when determining energy expenditure in resting conditions.[27]

Changes in REE are consequently best interpreted in conjunction with changes in body composition, whilst affording clinicians additional insights into the equally important timing of nutritional interventions from as early as diagnosis. For this purpose, a mobile device such as BIA is ideal as it is child-friendly, cost-effective and yields rapid bedside results. The InBodyS10 employs the Cunningham equation, which utilises FFM to derive REE,[19] limiting the generalisability of our result

interpretation as we were unable to compare our findings with IC. Despite such limitations, the use of BIA and the Cunningham equation and their ability to incorporate patterns of change in functional tissues may be preferred over weight-based formulas.[25] Energy intake should match a patient's energy requirements[24] to attain a positive energy balance to sustain growth despite their chronic disease state.[6] The use of IC remains ideal, yet practical challenges with regard to its use in children, coupled with poor access to such devices, leads to the continued use of predictive equations despite their reported inaccuracy.[6,9] Some have endeavoured to formulate new population and disease-specific equations,[10,27] but there is no alternative for paediatric cancer as yet. Limited by our small sample, this study highlights the need for further investigations within a larger sample size that allow for stratification of age, sex and cancer type to find suitable equations for children with cancer.

However, in the absence of IC, such predictive formulae may be used as a starting point from which to calculate requirements.[15] In our sample the WHO and Schofield (weight, height) proved more reliable for baseline REE calculations, with no need to adjust for activity or cancer-specific stress factors. The RDA could therefore rather be considered for the calculation of catch-up growth requirements. Energy requirements may then be titrated over time according to each child`s clinical progress in conjunction with monthly anthropometric and body composition assessments from which to anticipate fluctuations in resting energy needs.

Conclusion

A clear need exists for future investigations into the development of paediatric cancer-specific energy equations, as current existing predictive equations may not accurately calculate REE at childhood cancer diagnosis.

Acknowledgements – The authors would like to offer a special note of thanks for the invaluable statistical insights of Prof. D G Nel and the unwavering support from doctor R Uys during the period of data collection.

Disclosure statement – No potential conflict of interest was reported by the authors.

Funding – The author(s) reported there is no funding associated with the work featured in this article.

Author contribution – I Kellerman, M Kruger and R Blaauw conceptualised the study. I Kellerman developed the protocol, collected the data, analysed the data, and wrote the manuscript. M Kruger and R Blaauw critically reviewed the manuscript and contributed to the data analysis. J Schoeman critically reviewed the manuscript.

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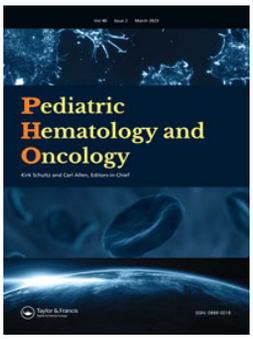
Received: 9-02-2023 Accepted: 22-05-2023



Pediatric Hematology and Oncology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipho20

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To cite this article: I. Kellerman, R. Blaauw, J. Schoeman & M. Kruger (2023): Changes in anthropometrical status and body composition in children with cancer during initial chemotherapy, Pediatric Hematology and Oncology, DOI: 10.1080/08880018.2023.2201299

To link to this article: https://doi.org/10.1080/08880018.2023.2201299

PEDIATRIC HEMATOLOGY AND ONCOLOGY
https://doi.org/10.1080/08880018.2023.2201299

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Changes in anthropometrical status and body composition in children with cancer during initial chemotherapy

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ABSTRACT

Children with cancer require adequate nutritional support to prevent malnutrition. This study investigated the impact of chemotherapy on anthropometrical status and body composition during the first six months of treatment. Anthropometrical status and body composition were measured at diagnosis, utilizing standardized protocols and validated S10 InBody bio-electrical impedance (BIA) measurements and compared to subsequent consecutive monthly follow-up measurements to plot changes over time during the first six months. Statistical significance was defined as $p < 0.05$. Forty-three newly diagnosed children (median age 4 years, IQR: 2.0-7.6; male-female ratio 1:0.9; 53% haematological malignancies and 47% solid tumors) were included. Prevalence of malnutrition varied, with under-nutrition 14% (mid-upper arm circumference (MUAC)/body mass index (BMI)), over-nutrition 9.3% (BMI) and stunting 7% at diagnosis. MUAC (14%) identified fewer participants with underlying muscle store depletion than BIA (41.8%). Chemotherapy exposure acutely exacerbated existing nutritional depletion during the first two months after diagnosis for all variables except fat mass (FM), with contrary effects on cancer type. Haematological malignancies had rapid increases in weight, BMI and FM. All patients had an acute loss of skeletal muscle mass. Nutritional improvement experienced by all cancer types during month two to three of treatment resulted in catch-up growth, with a significant increase in weight ($chi^2=40.43$, $p < 0.001$), height ($chi^2=53.79$, $p < 0.001$), BMI ($chi^2=16.32$, $p < 0.005$), fat free mass ($chi^2=23.69$, $p < 0.003$) and skeletal muscle mass ($chi^2=24.19$, $p < 0.001$) after six months. Monthly nutritional assessments, including advanced body composition measurements, are essential to provide timely nutritional interventions to overcome the acute decline in nutritional reserves observed during the first two months of chemotherapy exposure.

ARTICLE HISTORY
Received 11 November 2022
Revised 27 February 2023
Accepted 9 March 2023

KEYWORDS
Pediatric cancer; pediatric nutrition; anthropometrical status; body composition; change over time

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/08880018.2023.2201299.
Meeting Abstract: 54th SIOP congress, 28/9 – 1/10/2022, Barcelona, Spain.

Introduction

Children with cancer are faced with many nutritional challenges along their treatment journey that may result in the development of malnutrition, whose profound negative impact on their quality of life, growth and development and clinical outcomes from as early as diagnosis has been well established.[1–3] The importance of maintaining an optimal nutritional status through timely nutritional interventions has recently been highlighted with a positive correlation demonstrated between the patient's health related quality of life (HRQL) and 5-year survival and their ability to overcome malnourished states during the first year of treatment.[2,3] The prevalence and degree of malnutrition has traditionally been quantified by anthropometrical status. However, such assessments are merely indicators of body size and not body composition, failing to distinguish between fat and functional tissue (fat free mass).[2,4,5] Although alterations in nutritional status frequently occur during the initial months of treatment, little is known about the exact timing and degree of impact on nutritional status and body composition since it cannot be identified by conventional anthropometrical assessments alone.[5,6]

It is pertinent to investigate interactions between cancer drugs and the alteration of said body compartments,[7] as alterations of the metabolically active fat free mass may lead to changes in drug metabolism (volume of distribution, drug absorption, protein binding, decreased oxidative metabolism and glomerular filtration) with detrimental effects on HRQL and chemotoxicity throughout treatment.[2,8–10] The understanding and interpretation of the effects of cancer-driven mechanisms and treatments on body composition through detailed, advanced body composition analysis used in conjunction with anthropometrical assessments[2,8] is thus essential to help navigate and implement prompt, patient specific nutritional interventions that will ensure the best outcome in these patients - throughout all stages of treatment.[2,6–8,11] This study investigated the impact of initial chemotherapy on anthropometrical status and body composition and its subsequent pattern of change during the first six months of treatment to determine when this patient population is most vulnerable for nutritional depletion during this time frame.

Materials and methods

Study design

This prospective, descriptive, cohort study was conducted at the Pediatric Oncology Unit (POU) at Tygerberg Hospital, Stellenbosch University, Cape Town, South Africa according to the principles of the Declaration of Helsinki, after obtaining ethical approval from the University of Stellenbosch`s Health and Research Ethics Committee (S18/04/050). Written consent and assent were provided by all caregivers and children older than seven years. Recruited patients were followed up from diagnosis for a maximum of six consecutive monthly visits during the study period from April 2019 until June 2020.

Data collection

Medical information and demographic data were collected at diagnosis. Baseline assessments were performed within 72 hours of diagnosis prior to the initiation of

chemotherapy and compared to subsequent monthly visits to plot change over time. Anthropometrical measurements included weight measured to nearest 0.1 kg (0.01 kg for infants; baby scale, Seca 354 and 874), height measured to the nearest 0.1 cm (stadiometer, Seca217) and mid-upper arm circumference (MUAC) using a non-stretchable tape to the nearest 0.1 cm at the mid-point of the upper-arm. Recumbent length was used in children <2 years or those unable to stand. Body compartments assessed included fat mass (FM), fat free mass (FFM), skeletal muscle mass (SMM) and phase angle (PA), measured by a single, calibrated, multi-frequency portable segmental body composition analyzer (Inbody S10, InBody Co Ltd, Korea). The device is validated against dual energy x-ray absorptiometry (Dexa), has proven sensitivity for detecting fluid status in the clinical setting and suitable for pediatric use.[12–14] Four touch-type electrodes (sticky-adhesive type electrodes in infants) were placed on both hands and feet and patients were required to remain static in supine position for two minutes without jewelry or metal-containing clothing. This was performed prior to the initiation of hyper-hydration as a precaution to eliminate the potential confounding impact of fluid balance on its readings. Individualized nutritional support (counselling, oral supplements, tube feeds and total parenteral nutrition) was implemented from diagnosis for both in- and out-patients according to the dietician's existing nutrition support protocols.

Data analysis

Anthropometrical status was defined according to age and gender specific World Health Organization (WHO) and Mramba et al. (MUAC for children older than 5 years) classifications[15,16] as under-nutrition (weight-for-age <-2 z-score, body mass index (BMI)-for-age or weight-for-length <-2 z-score, MUAC-for-age <-2 z-score), over-nutrition (weight-for-age >+2 z-score, BMI-for-age >+2 z-score) and stunting (height-for-age <-2 z-score). A z-score <-3 and >+3 was considered severe. Body stores were categorized as high or low according to the pre-programmed InBody S10 specifications as no population standards for healthy children exist in South Africa. In the absence of such 'normal' values for comparative purposes, the monitoring and description of changes over time in relation to baseline values were considered relevant and most appropriate. The absolute values of all continuous variables were used to assess and describe trends in actual monthly measurements. This allowed for insights into underlying body compartment modifications in relation to changes in absolute anthropometrical values over time.

Anthropometrical status and body composition at baseline, as well as changes and associations between baseline and follow-up measurements, were identified utilizing both inferential and basic descriptive statistics. Trends in change over time were expressed in absolute values (median; IQR), percentage changes and the appropriate classification for anthropometrical and body composition status as per z-scores and bio-electrical impedance analysis (BIA). The Friedman rank test (non-parametric) compared median variable values between diagnosis and the end of follow-up and per cancer group. Data were analyzed using the STATISTICA (version 13, TIBCO Software Inc. (2018)) data analysis software system. $p < 0.05$ indicated statistical significance for all variables.

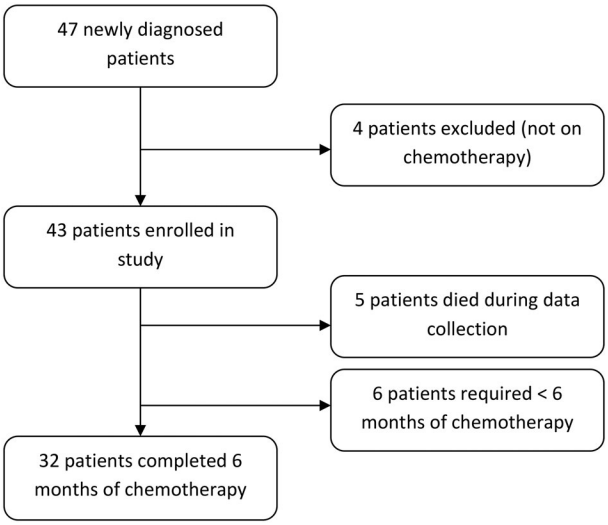

Figure 1. Flow diagram describing study participation.

Results

Forty-three of the forty-seven consecutive newly diagnosed patients aged three months to 15 years with haematological malignancies and solid tumors were recruited and received chemotherapy (Figure 1). Four patients requiring exclusive radiotherapy or surgical interventions were excluded. Patients who died (n = 5) during the first six months or who required less than six months of chemotherapy (n = 6) were included in the study up to the last of their respective measurements. The male-female ratio was 1:0.9 with a median age 4 years (IQR: 2.0-7.6) (Table 1). The most common haematological malignancy (n = 23, 53%) was acute lymphoblastic leukemia (n = 13, 56.5%) and nephroblastoma (n = 5, 25%) was the most frequent solid tumor (n = 20, 47%).

Results at diagnosis

At baseline, the degree of malnutrition and the duration thereof (acute or chronic) varied among anthropometrical variables, translating to a rate of acute malnutrition (under-nutrition) between 11.67 (weight) – 14% (MUAC/BMI), over-nutrition of between 4.67 (weight) – 9.3% (BMI) and chronic malnutrition (stunting) of 7% at diagnosis (Table 2). The prevalence of wasting, including severe wasting, ranged between 11.67% (weight) – 14% (BMI). Using MUAC to classify acuity of malnutrition, two (4.67%) patients had severe acute malnutrition, and four (9.3%) moderate acute malnutrition. One patient (2.33%) was severely stunted and two (4.67%) stunted, all belonging to the haematological group.

Derangements in body composition affected a larger proportion of patients, of which the alteration in fat (44.2% low and 18.6% high), and skeletal muscle (41.8% low and 9.3% high) were most notable (Table 3). MUAC (14%) and FFM (11.6%) identified lower levels of SMM depletion as measured by BIA (41.8%). No population standards exist for the classification of the median phase angle of 4.20° (IQR:3.4-4.7°) as low,

Table 1. General patient characteristics in relation to cancer type.

Demographics	Total study population (n = 43)	Type of cancer: Haematological malignancies (n = 23)	Type of cancer: Solid tumors (n = 20)
Total number of participants (n, %)	43 (100)	23 (53)	20 (47)
Sex			
Male (n, %)	22 (51)	12 (52)	10 (50)
Female (n, %)	21 (49)	11 (48)	10 (50)
Age in years (mean ± SD)	5.4 ± 4.2	5.6 ± 4.3	5.2 ± 4.1
Age in years (median, Q1-Q3)	4 (2.0-7.6)	4.2 (2.0-8.8)	3.9 (2.0-7.1)
Cancer diagnosis (n, %)			
Acute lymphoblastic leukemia (ALL)	13 (30.2)	13 (56.5)	
Acute myeloid leukemia (AML)	3 (7.0)	3 (13.0)	
Langerhans cell histiocytosis	2 (4.7)	2 (8.8)	
Lymphoma	5 (11.6)	5 (21.7)	
Ewing sarcoma	1 (2.3)		1 (5.0)
Hepatoblastoma	2 (4.7)		2 (10.0)
Medulloblastoma	1 (2.3)		1 (5.0)
Nephroblastoma	5 (11.6)		5 (25.0)
Neuroblastoma	1 (2.3)		1 (5.0)
Osteosarcoma	3 (7.0)		3 (15.0)
Retinoblastoma	2 (4.7)		2 (10.0)
Rhabdoid Sarcoma	1 (2.3)		1 (5.0)
Rhabdomyosarcoma	3 (7.0)		3 (15.0)
Yolk sac tumor	1 (2.3)		1 (5.0)

Abbreviations used: SD: standard deviation; Q1: 25th centile; Q3: 75th centile.

Table 2. Classification of anthropometrical status at diagnosis for all cancer types ($n = 43$).

Type of malnutrition			Chronic n (%): Height-for-age	Acute n (%): Weight-for-age	Acute n (%): BMI-for-age/ weight-for length*	Acute n (%): MUAC-for-age
z-score classification**	Over	> +3	–	1 (2.3)	–	–
		> +2 and < +3	–	1 (2.3)	4 (9.3)	–
	Normal	< +2 and > −2	40 (93)	36 (83.7)	33 (76.7)	37 (86)
	Under	< −2 to > −3	2 (4.7)	2 (4.7)	4 (9.3)	4 (9.3)
		< −3	1 (2.3)	3 (7)	2 (4.7)	2 (4.7)

*Weight-for length used in children < 2 years.
**Classified according to WHO z-scores.
Abbreviations used: BMI: body mass index; MUAC: mid-upper arm circumference.

Table 3. Classification of anthropometrical status and body composition at diagnosis.

Variable (n = 43)	All cancer types median (Q1, Q3)	Classification* Low (n, %)	Classification * Normal (n, %)	Classification* High (n, %)
Weight (kg)	15.5 (11.4,23.0)	5 (11.6)	36 (83.7)	2 (4.7)
Height (cm)	100.0 (84.5,127)	3 (7)	40 (93)	–
BMI (kg/m^2)**	15.7 (14.1,17.6)	6 (14)	33 (76.7)	4 (9.3)
MUAC (cm)	16.0 (14.9,17.4)	6 (14)	37 (86)	–
Fat mass (kg)	2.5 (1.3,4.1)	19 (44.2)	16 (37.2)	8 (18.6)
Fat free mass (kg)	13.0 (9.7,20.1)	5 (11.6)	32 (74.4)	6 (14)
Skeletal muscle mass (kg)	5.6 (3.8,9.9)	18 (41.8)	21 (48.9)	4 (9.3)
Phase angle (degrees)	4.2 (3.4,4.7)	–	–	–

*Classification based on z-scores and S10-Inbody pre-programmed interpretation. Anthropometrical status was classified as WHO z-scores Low: <-2, Normal: < +2 and >-2, High: > +2.
**Weight-for length used in children < 2 years.
Abbreviations used: Q1: 25th centile; Q3: 75th centile; kg: kilograms, cm: centimeters, kg/m^2: kilograms per meter squared; BMI: body mass index; MUAC: mid-upper arm circumference.

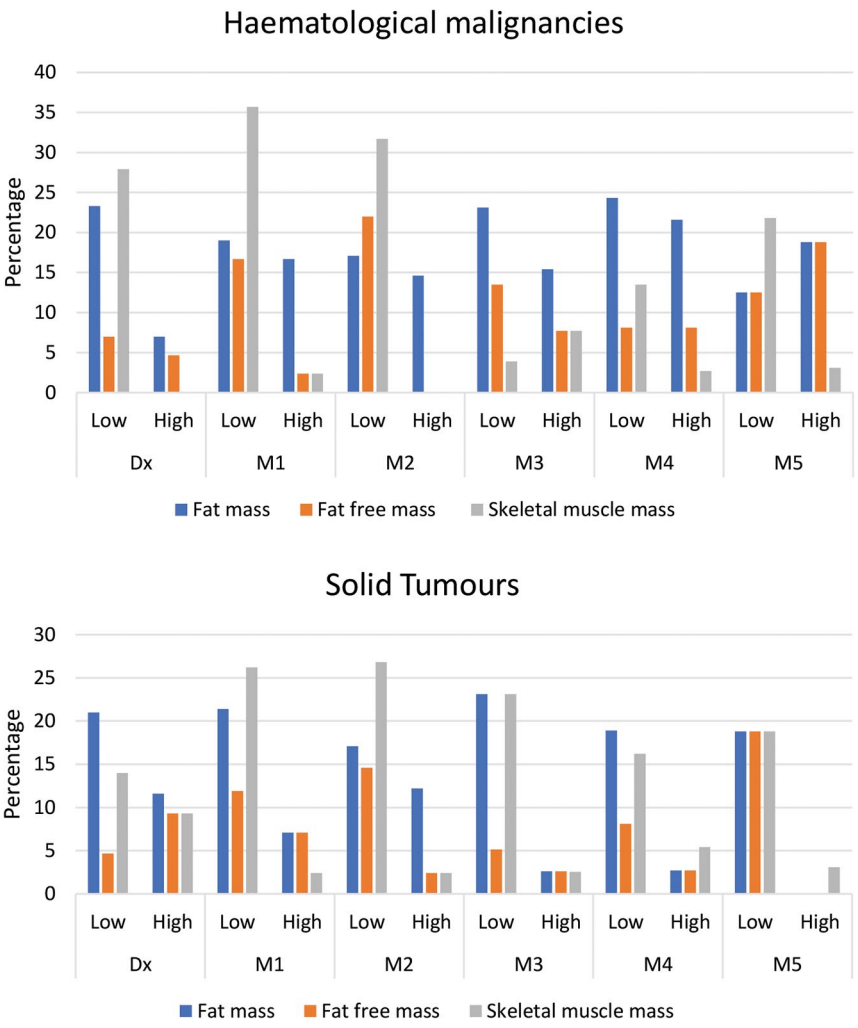

Figure 2. Change in classification of body composition variables over time.
Classifications based on S10-Inbody pre-programmed interpretation.

normal or high. Haematological malignancies (n = 10, 23.3%) had an almost equal prevalence of low FM than the solid tumor group (n = 9, 21%), but double the rate of muscle depletion (n = 12, 27.9%) when compared to the solid tumors (n = 6, 14%) (Figure 2, Supplementary Table S1).

Trends in change over time

Several changes occurred for all anthropometrical variables over time of which the acute decrease of median weight (300 g, 2%), BMI (0.4 kg/m^2, 2.6%) and MUAC (0.7 cm, 4.4%) for all cancer types during the first month after chemotherapy was the most notable (Table 4). Height remained static during this period. This acute decline improved during months two and three to surpass baseline values for all

variables except MUAC, resulting in a significant increase in weight (chi^2=40.43, $p < 0.001$), height (chi^2=53.79, $p < 0.001$) and BMI (chi^2=16.32, $p < 0.005$) between diagnosis and month five. An improvement in severe wasting, stunting, muscle depletion and overweight was seen by month five, but the number of wasted patients remained the same as at diagnosis and obesity doubled. Cancer sub-groups responded differently to chemotherapy: The solid tumor group experienced an acute decline in month one in weight (800 g, 4.8%), BMI (0.5 kg/m^2, 3.1%) and MUAC (0.5 cm, 3.2%) in contrast to the gradual monthly increase in weight (100-500 g) and height (0.5-1.5 cm) seen in the haematological malignancy group. Over time the solid tumor group experienced a significant increase in both weight (800 g, 4.8%, chi^2=14.93, $p < 0.01$) and height (6 cm, 5.9%, chi^2=27.46, $p < 0.001$) between diagnosis and month five. The haematological malignancy group experienced a significant increase in weight double that of the solid tumors (1.6 kg, 11%, chi^2=28.39, $p < 0.001$), height (4.5 cm, 4.5%, chi^2=26.67, $p < 0.001$) and BMI (1.3 kg/m^2, 8.5%, chi^2=15.4, $p < 0.009$) by the end of follow-up.

Body compartment depletion was most profound during the first two months after treatment initiation, resulting in a decrease in FFM (1 kg, 7.7%), SMM (700 g, 12.5%) and PA (0.35 degrees, 8.3%) for all cancer types (Table 4). The initial decrease in low muscle levels involved 62% of the study population after the first month of treatment, affecting both cancer groups. Body store repletion only improved from month three onwards with a subsequent significant increase from baseline values in FFM (700 g, 5.4%; chi^2=23.69, $p < 0.003$) and SMM (300 g, 5.5%; chi^2=24.19, $p < 0.001$) for all cancer types by the end of follow-up. At the end of the study, 13 (40.6%) of the remaining 32 patients still had a low SMM, of whom seven had a haematological malignancy and six a solid tumor (Figure 2, Supplementary Table S1).The initial decrease in median SMM (1.35 kg, 20.6%) and PA (0.3 degrees, 6.9%) was more pronounced in the solid tumor group, but only the haematological malignancies showed an overall improvement in phase angle (0.4 degrees, 10.8%) and significant increase in SMM (650 g, 13.3%); chi^2=11.32, $p = 0.045$) by month five. In contrast to the significant decrease in FM (350 g, 11.5%, chi^2=0.79, $p = 0.98$) for the solid tumor group, the steady increase in FM for all cancer types (600 g, 24%, chi^2=2.17, $p = 0.82$) and haematological malignancies (1.2 kg, 48%, chi^2=5.01, $p = 0.41$) was not statistically significant when compared to baseline values (Table 4). All the patients with a high FM at the end of follow-up had haematological malignancies (Figure 2, Supplementary Table S1).

Discussion

Our findings demonstrate that anthropometrical status could not identify the extent of underlying body store depletion from diagnosis throughout follow-up. Chemotherapy exposure furthermore acutely exacerbated the existing malnutrition and body store depletion during the first two months of treatment with contrary effects on cancer groups. The haematological group was prone to a continuous gain in weight, fat mass and over-nutrition, ending with a significant increase in weight, height, FFM, SMM and BMI by the end of the study. The solid tumor group by contrast experienced a rapid decline in all measured variables during the first two months of chemotherapy to end

Table 4. Median change in variables over time.

Variable	Monthly change over time in median (Q1, Q3)						
	Diagnosis n = 43	Month 1 n = 42	Month 2 n = 41	Month 3 n = 39	Month 4 n = 37	Month 5 n = 32	Chi-sq* (p-value)
All cancer types (total)							
Weight (kg)	15.5 (11.4,23.0)	15.2 (11.9,26.0)	15.8 (12.0,26.0)	15.9 (12.4,27.3)	16.5 (12.8,28.4)	16.65 (13.7,27.3)	40.43 (< 0.001)
Height (cm)	100.0 (84.5,127.0)	100.5 (89.4,129.5)	101.0 (89.5,131.5)	104.0 (92.0,135.0)	104.0 (92.5,135.3)	104.0 (95.3,135.8)	53.79 (<0.001)
BMI (kg/m^2)	15.7 (14.1,17.6)	15.3 (13.9,17.6)	16.1 (14.3,17.0)	15.6 (14.5,17.2)	15.7 (14.6,17.7)	16.1 (14.7,17.4)	16.32 (<0.005)
MUAC (cm)	16.0 (14.9,17.4)	15.3 (14.5,17.3)	16.0 (14.6,16.9)	16.2 (14.6,18.3)	16.2 (14.8,18.5)	16.0 (14.8,19.3)	6.9 (0.23)
Fat mass (kg)	2.50 (1.3,4.1)	2.80 (1.7,4.4)	2.50 (2.0,6.1)	3.10 (1.7,4.4)	2.70 (1.9,4.5)	3.10 (2.1,5.3)	2.17 (0.82)
Fat free mass (kg)	13.00 (9.7,20.1)	12.00 (9.3,19.1)	12.10 (9.5,19.9)	13.50 (11.0,20.9)	12.30 (11.3,21.7)	13.70 (11.5,23.5)	23.69 (<0.003)
Skeletal muscle mass (kg)	5.60 (3.8,9.9)	4.90 (3.6,9.15)	5.10 (3.6,9.6)	5.70 (4.4,10.2)	5.30 (4.45,11.7)	5.90 (4.7,12.4)	24.19 (< 0.001)
Phase angle (degrees)	4.20 (3.4,4.7)	3.85 (3.3.,4.5)	3.90 (3.5,4.7)	4.00 (3.5,4.6)	4.10 (3.5,5.0)	4.10 (3.7,5.0)	10.04 (0.074)
Haematological malignancies							
Weight (kg)	15.00 (10.8,23.0)	15.1 (12.0,24.1)	15.60 (12.5,25.6)	15.8 (12.2,27.3)	16.50 (12.5,28.9)	16.6 (12.9,31.0)	28.39 (< 0.001)
Height (cm)	99.0 (87.5,134.0)	100.0 (90.0,134.0)	101.0 (91.0,135.0)	102.5 (91.0,135.0)	103.0 (92.0,135.5)	103.5 (94.0,136.0)	26.67 (<0.001)
BMI (kg/m^2)	15.2 (14.1,17.2)	15.0 (13.9,17.9)	16.3 (14.3,18.2)	15.7 (15.0,18.6)	15.7 (15.3,19.1)	16.5 (15.1,19.7)	15.40 (<0.009)
MUAC (cm)	15.7 (14.6,17.4)	15.2 (14.3,17.0)	16.0 (14.7,17.6)	16.2 (15.0,18.0)	16.5 (15.1,17.8)	16.2 (14.5,19.5)	6.48 (0.26)
Fat mass (kg)	2.50 (1.1,3.4)	2.90 (1.8,4.9)	2.50 (2.5,7.3)	2.50 (1.7,4.5)	3.20 (2.0,4.5)	3.70 (2.1,6.0)	5.01 (0.41)
Fat free mass (kg)	11.50 (9.5,19.6)	11.85 (9.1,19.1)	12.10 (9.9,2.4)	12.90 (10.3,20.9)	12.20 (11.0,25.4)	13.00 (10.4,26.4)	12.78 (0.026)
Skeletal muscle mass (kg)	4.90 (6.5,9.9)	4.75 (3.4,8.9)	5.10 (4.0,9.6)	5.30 (4.0,9.9)	5.00 (4.4,12.6)	5.55 (4.2,13.4)	11.32 (0.045)
Phase angle (degrees)	3.70 (2.6,4.5)	3.50 (3.0,4.5)	3.50 (3.3,4.3)	3.90 (3.4,4.3)	4.00 (3.4,4.9)	4.10 (3.7,5.1)	8.43 (0.134)
Solid tumors							
Weight (kg)	16.60 (12.4,24.9)	15.8 (12.0,26.4)	16.00 (12.1,26.2)	17.2(13.0,26.0)	17.4 (13.9,27.5)	17.4 (14.6,27.0)	14.93 (0.01)
Height (cm)	101.5 (87.3,125.3)	101.5 (87.3,125.8)	101.5 (87.3,125.8)	107.0 (92.0,128.0)	107.5 (95.5,131.5)	107.5 (96.0,135.0)	27.46 (<0.001)
BMI (kg/m^2)	16.1 (14.5,17.8)	15.6 (13.8,16.9)	16.0 (14.2,16.7)	15.4 (13.5,16.8)	15.7 (14.4,16.6)	15.4 (14.6,16.7)	3.70 (0.59)
MUAC (cm)	16.2 (15.1,18.0)	15.7 (14.7,17.9)	16.1 (14.5,16.8)	16.2 (14.5,18.4)	16.1 (14.4,18.8)	15.9 (14.8,19.3)	6.89 (0.59)
Fat mass (kg)	3.05 (1.55,4.35)	2.80 (1.4,4.2)	2.85 (1.8,5.4)	3.10 (1.7,3.7)	2.55 (1.7,4.6)	2.70 (2.1,3.3)	0.79 (0.98)
Fat free mass (kg)	14.45 (10.8,20.1)	12.35 (10.4,19.6)	12.15 (8.9,19.85)	15.10 (11.5,20.5)	15.05 (11.6,21.7)	15.20 (12.6,20.7)	13.78 (0.017)
Skeletal muscle mass (kg)	6.55 (4.6,9.7)	5.20 (4.15,9.3)	5.10 (3.3,9.4)	6.85 (4.8,10.2)	6.80 (4.8,10.6)	6.95 (5.3,10.2)	14.26 (0.14)
Phase angle (degrees)	4.35 (4.05,5.45)	4.05 (3.7,4.55)	4.25 (3.7,5.0)	4.10 (3.6,4.8)	4.15 (3.65,5.15)	4.25 (3.7,5.0)	6.39 (0.270)

*The chi-squares and p-values given in the last column result from the Friedman test which compared the median from diagnosis to month five.

Abbreviations used: Q1: 25th centile; Q3: 75th centile; Dx: diagnosis; M1: month one; M2: Month two; M3: month three; M4: month four; M5: month five; kg: kilograms; cm: centimeters; BMI: body mass index; kg/m^2: kilograms per meter squared; MUAC: mid-upper arm circumference.

with a significant increase in weight, height and FFM alone. The only similar trend over time between groups was the initial loss of functional tissues (MUAC, SMM, PA) during the first two months of treatment, albeit to varying degrees of severity.

Compared to the national South African rate of malnutrition for stunting (< 5 yr: 27.4%, 5-19 yr: 12.9%), wasting (< 5 yr: 2.5%, 5-19 yr: 5%), severe wasting (< 5 yr: 1%) and overweight (< 5 yrs: 13.3%, 5-19 yr: 25%), only the level of baseline wasting (including severe wasting) was worse in our participants than the national prevalence.[17–19] These findings are in contrast with higher diagnosis prevalence rates of malnutrition (12-65%) as reported in recent South African publications regarding newly diagnosed children with nephroblastoma,[20–22] which may be attributed to probable advanced disease in these studies or the various cancer diagnoses included in our study. Late presentation at healthcare centers with advanced disease were also a cited reason for a higher prevalence and severity of malnutrition in those with solid tumors living in low-middle income countries (LMIC).[3,23,24] We did however find comparative rates of under- and over-nutrition as reported by various LMIC and high income countries studies despite their use of weight and BMI z-scores alone.[2,23–26]

A much larger proportion of patients suffered from decreased fat and muscle stores at diagnosis, which may be attributed to the low levels of physical activity and appetite reported upon initial presentation at POUs[2,27] or the onset of the disease itself.[24] The early identification of depleted muscle stores prior to treatment initiation is essential since it results in a loss of functional tissues, strength, immune- and pulmonary function[4,5] and may serve as a poor prognostic marker.[28,29] Our findings concur with those of Yaprak et al. since MUAC and BMI identified more acute malnutrition than weight alone.[24] However, the inability of these variables to identify the severity of muscle depletion in our study highlights the need for incorporating advanced body composition analysis as part of routine assessments to avoid overlooking underlying body store depletion from as early as diagnosis.[4,5,28]

Examining trends in change over time revealed an acute decline of nutritional stores during the first two months after diagnosis. Similar longitudinal studies investigating changes in anthropometrical status and body composition over time employed larger, follow-up assessment intervals (usually three monthly) and a variety of methods for body composition measurements that include BIA, deuterium solutions and Dexa.[5,28,30–32] Despite differing methodologies, the current study findings also describe the first three months of chemotherapy as the period that presented with the worst impact on anthropometrical status[28,31,33] and body compartments.[5,28,32] Severe acute changes in anthropometry (weight loss >5% or BMI z-score <1.5) during the first three months of initial chemotherapy may affect between 46-63.7% of children with cancer, resulting in profoundly detrimental effects on HRQL, overall patient survival and infectious outcomes in a variety of malignancies.[2,28,33,34] The acute weight loss seen in our population during the first month of treatment fell short of the 5% cutoff proposed by the American Society for Parenteral and Enteral Nutrition for severe acute weight loss,[35] but the large difference seen in patterns of change among cancer types might have diluted the severity of the overall effect. This illustrated contrast between cancer groups is consistent with reported findings describing those with solid tumors as prone to develop acute malnutrition upon initial chemotherapy, whilst the haematological group remained most affected by chronic malnutrition (stunting) and over-nutrition.[26,28,31]

Contrary to the results presented by Brinksma et al.[28] the rapid increase in weight and BMI did not translate to an equally rapid increase in the overweight classification of our participants. Rather, current findings illustrate the value of monitoring both absolute values and z-score classifications in relation to baseline measurements to anticipate nutritional derangements, as a large variance in absolute values (≥10%) was required before a change in z-score classification was seen.

The most critical acute change in body compartments during the first two months after diagnosis impacts stores (SMM, FFM, PA) related to functionality, quality of life and prognosis,[2,9,28,36] affecting both cancer groups albeit to varying degrees of severity. The simultaneous increase in FFM and decrease in SMM may be explained by the haematological malignancy group's exposure to steroids rather than hyper-hydration,[37] whilst the initial decrease in FFM as experienced by the solid tumor group might be attributed to an overall loss of weight or inflammatory processes associated with tumor activity.[28] The profound loss of functional tissues may furthermore be obscured by the large cumulative increase in weight and FM as demonstrated in our study. Similar trends (high FM and the low FFM and SMM) within the haematological group have been well described and may be induced by the use of steroid therapy and its resulting increased appetite, increased levels of reported fatigue with lower activity levels than those of their peers, diminished height velocity during active treatment, active tube feeding and taste changes.[2,5,20,28,32]

As a measure of cell integrity and functionality, PA values may change in line with a patient`s response to treatment, the presence of malnutrition or infection.[38–40] The varied degree of malnutrition among cancer type may thus explain the difference noted in PÀs patterns of change among our cancer sub-groups.[39,40] The lack of pediatric-specific PA reference values makes the interpretation of results challenging. A range between 4.5°- 5.6° has been linked to an improved prognosis in adults with a variety of cancer diagnoses,[39,40] whilst a range below 2.8° and above 5.1° indicated either increased or improved morbidity and mortality in critically ill pediatric and adults patients respectively.[38,41] More studies are therefore needed to establish a threshold value for the use of PA as a proxy for functional capacity within the pediatric cancer population. Until such time, the patterns of change from diagnosis may be a valuable measure of growth and the patient's response to nutritional interventions.[42]

The limited sample size secondary to the relative rarity of the underlying cancer diagnosis prevented effective stratification of the research population's response to chemotherapy according to age group, sex, and disease-risk categories. Future research within a larger study population will assist healthcare practitioners to better understand the impact of these factors on the child with cancer`s response to chemotherapy. Our interpretation of catch-up growth was also limited as we did not investigate the relationship between changes in nutritional stores and overall survival due to the short time span (six months) of the study period. We furthermore acknowledge that the pre-programmed BIA classifications utilized within this study are not validated for all populations. Results should therefore be interpreted with caution in conjunction with patterns of change over time according to the individual`s response to treatment.

This study adds to the growing body of knowledge describing the negative impact of chemotherapy exposure on nutritional reserves from as early as diagnosis. The consequent acute changes in anthropometrical status and body composition for all

cancer types should therefore be assessed by differentiating between body size and body composition in pursuit of a more thorough representation of the child's overall growth patterns and the body's nutritional reserves.[4,28] Additionally, we illustrated a trend toward nutritional store improvement from as early as two (anthropometrical status) and three months (body composition) post chemotherapy initiation, therefore minimum monthly assessments are warranted to avoid such severe, acute changes requiring immediate nutritional support. This study utilized BIA due to the lack of access to Dexa or computerized tomography scans as an accessible, child-friendly alternative[9,28,43] with demonstrated improved accuracy in the estimation of hydration status than single frequency devices.[36] Our findings regarding nutritional repletion attest to implementing prompt nutritional interventions at the patient's bedside the moment nutritional derangements become apparent, as facilitated by our mobile BIA device. However, MUAC`s ability to mimic the patterns of change in functional tissues over time demonstrates its value for use in the absence of advanced body composition assessments, especially in resource constraint settings. Small changes in trends over time should be carefully considered and interpreted as they may represent larger underlying changes in functional tissues requiring immediate intervention. We therefore conclude that frequent follow-up assessments based on an evaluation of patterns of change in comparison to the patient's unique baseline results may be more appropriate to determine outcomes than large assessment intervals based on z-score and pre-programmed classifications alone.

Conclusion

Children with cancer requiring initial chemotherapy are most vulnerable for nutritional depletion during the first two months of treatment, with a demonstrated contrary effect between haematological and solid malignancies. Anthropometrical status, including MUAC, failed to identify the extent of underlying body store depletion and should accompany advanced body composition techniques to thoroughly assess nutritional reserves. Early identification of malnutrition through a minimum of monthly assessments from diagnosis may result in timely nutritional interventions and nutritional repletion. The first two months of treatment exposure therefore becomes the window of opportunity to serve as basis for timely nutritional interventions that preempt, rather than react to the presence of malnutrition in order to pave the way for improved HRQL throughout their cancer journey onto survival.

Acknowledgements

A special note of thanks for the invaluable statistical insights of Prof DG Nel and the unwavering support from doctor R Uys during the period of data collection.

Author contribution

Ilde-Marié Kellerman and Mariana Kruger conceptualized the study. Ilde-Marié Kellerman developed the protocol, collected the data, analyzed the data, and wrote the manuscript. Mariana

Kruger and Renee Blaauw critically reviewed the manuscript and contributed to the data analysis. Judy Schoeman critically reviewed the manuscript.

Disclosure of interest

The authors report no conflict of interest.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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Data availability statement

Data will be made available on request and subject to intellectual property rights.

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Conference report on the 14th International Society of Paediatric Oncology African Continental Meeting, 16–18 March 2022, Kampala, Uganda

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Conference Report

Abstract

Together with the Africa Continental Branch of the International Society of Paediatric Oncology (SIOP Africa), the Uganda Cancer Institute, a tertiary governmental institution for specialised cancer care services, research and training, hosted the 14th continental meeting of SIOP Africa from the 16–18 March 2022. Under the conference theme, 'Innovate for Africa', the hybrid conference brought together close to 400 international delegates to discuss innovations and experiences, as well as share the latest research in the field of paediatric oncology. The World Health Organisation 2030 Global Initiative for Childhood Cancer provided the main starting point for the conference with a comprehensive pre-conference workshop programme, from multiple stakeholders and organisations and the themes for the plenaries towards improving survival to the main breakout sessions. Delegates discussed various ways of improving outcomes in Africa, despite the challenges faced individually and collectively ranging from education, management systems and treatment guidelines to future governmental and NGO involvement in African cancer care. The main achievements of the conference were various commitments for collaboration, investing in junior investigators, development of registries and systems for improved childhood care on the African continent, while working towards greater access to advanced management options such as targeted therapies and bone marrow transplant services.

Keywords: *SIOP, Africa, Uganda, children, conference, workshops, WHO, six index cancers, innovation*

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ecancer 2022, **16**:1423
https://doi.org/10.3332/ecancer.2022.1423

Published: 07/07/2022
Received: 11/04/2022

Introduction

In March 2022, International Society of Paediatric Oncology (SIOP) Africa held the continental SIOP conference in Kampala, Uganda. The highly successful event, delayed for a year due to the COVID-19 pandemic, brought together colleagues and friends from 33 countries and 3 continents, confirming the desire for the paediatric oncology community to engage in-person. The conference was organised by the Uganda Cancer Institute (UCI), supported by the Ugandan Cancer Society, the Palliative Care Association of Uganda, the Uganda Child Cancer Foundation and the Uganda Paediatric Association. Colleagues from South Africa, Egypt and the USA supported the scientific committee and the organisers of the pre-conference workshops.

Since the 2018 launch of the World Health Organisation (WHO) Global Initiative on Childhood Cancer (GICC) aimed at reaching at least a 60% survival rate for children with cancer by 2030 [1], efforts on the African continent have been coordinated to reach these goals. The theme for the conference 'Innovating for Africa' was closely aligned with the WHO 2030 GICC agenda [2], and the scientific programme focused on practising paediatric oncology in African circumstances, advanced care on the continent, multidisciplinary and multinational collaboration.

In keeping with the theme of innovation, this SIOP Africa was the first hybrid meeting to facilitate access to delegates to participate regardless of their location, allowing international experts to share their expertise. A record number of pre- and post-conference workshops were held by colleagues from fields including medical, surgical, radiation oncology, allied health services and civil society. In line with SIOP International and SIOP Africa strategies, many of the educational programmes were aimed at improving content for junior investigators [3]. Echoing the WHO GICC guidelines, the conference was supported by the national government, backed by the Uganda Ministry of Health, and included plenaries with a focus on organisational and governmental structures to advance management in Africa.

Conference statistics

The scientific committee received 140 abstracts from more than 35 countries. The in-person component attracted close to 400 participants from 33 countries, with the majority coming from Uganda, South Africa, Ghana, Ethiopia and Tanzania. Disciplines represented were paediatric oncology, paediatric surgery and neurosurgery, nursing, dietetics, pharmacy, rehabilitation, pathology, social work and psychology. Scholarships were awarded to 123 medical and nursing delegates. The virtual component, generously sponsored by St Jude Global and run by Cvent, attracted 55 viewers.

Main scientific conference

Opening address

SIOP Africa President Joyce Balagadde-Kambugu referred to the WHO GICC goals in the context of multiple challenges on the African continent, requiring locally relevant and innovative solutions and hence the theme 'Innovate for Africa'. SIOP Africa is dedicated to developing systems and opportunities in Africa to achieve these goals, including engagement with governments. These innovations should improve access to diagnosis, treatment, supportive and palliative care for children with cancer and ensure the gains made are not lost.

SIOP President Kathy Pritchard-Jones commended the paediatric oncology community on their response to the COVID-19 challenges, continuing to apply best practice standards of care with necessary adaptations and collaborating on clinical research studies that improve access to treatment. The topics of the pre-conference workshop, in particular, the adapted treatment regimens, provided an opportunity to discuss the realities of implementing the WHO's GICC. Good infrastructure and multidisciplinary care are prerequisites for tackling the unmet needs for cancer control, including childhood cancer control. The SIOP President-elect Guillermo Chantada praised SIOP Africa in leading the way in adapting therapies to local resources, addressing specific regional needs and adapting innovations for the advancement of paediatric oncology.

The WHO representative to Uganda Yonas Tegegn Woldemariam commented on the difficulty in contextualising African paediatric oncology cases in the 400,000 annual global childhood cancers, because the burden of childhood cancers in Africa is underestimated due to poor coverage of population-based cancer registries. The inadequate capacity for early detection of cancers, including childhood cancers, compounded with limited treatment capacity, are the main drivers of low cancer survival rates in Africa. Reliable and accurate epidemiological cancer data to inform cancer control services delivery with adequate human resource capacity were central to improving national cancer control.

The keynote address, 'The history of cancer in Uganda', was presented by Charles Olweny, UCI Board Chair, detailing how paediatric cancer services began as lymphoma treatment centres at the Mulago National Referral Hospital where Dennis Burkitt first described Burkitt lymphoma. This centre grew to become the present UCI. The concept of essential oncology drugs in Africa, started in Uganda, has demonstrated that we can improve access to essential cancer drugs in Africa. The concept originated from the essential drugs list, where utilising a limited number of medications, most diseases could be treated effectively. The same principle was applied to chemotherapy drugs such as vincristine, doxorubicin, cyclophosphamide etc. [4]. By ensuring the availability of these essential chemotherapy drugs for the six index childhood cancers in all African countries, the GICC goals become more reachable.

Jackson Orem, Executive Director of UCI, reflected on the successes of the Uganda Cancer Institute which was mandated by an act of parliament to establish four regional cancer centres and has completed the development of a national cancer control plan. His reflections brought home the importance of government support in the establishment of training programmes for cancer specialists, including paediatric oncologists. UCI, which receives 7,000 new cancer cases, 10% of whom are children, continues to strive to improve clinical and scientific services with the Integrated Electronic Medical Record System, a fully automated radiology unit and laboratory auto-analysers. Jane Ruth Aceng, Minister of Health for Uganda, emphasised the importance of the government in fighting childhood cancer on a continent with low survival rates of less than 30% in many countries. She attributed Uganda's survival rate of approximately 50% to leveraging resources for cancer control with truly mutually supportive partnership focusing on similar goals.

Plenaries

WHO Global Initiative for Childhood Cancer (GICC)

Childhood cancer mortality reflects global disparities in health outcomes. Avoidable deaths from childhood cancers in low- and middle-income countries (LMIC) result from, among others, failure to prioritise early detection, misdiagnoses, lack of access to care, treatment abandonment and treatment delays. Inequities in quality care outcomes for paediatric cancer in LMICs demand urgent engagement of national and regional government structures to accelerate improvement in paediatric cancer continuum of care. The WHO GICC lays out policy advocacy, including childhood cancer policy and plans, for improved childhood cancer care outcomes. The WHO's proposed technical 'CureAll package', includes the creation of centres of excellence; universal health coverage; regimens and roadmaps for diagnosis, treatment, evaluation and monitoring; and a sufficient competent workforce. The three cross-cutting enablers are advocacy, leveraged financing and linked policies/governance. SIOP President Kathy Pritchard-Jones noted that even with the establishment of multiple Paediatric oncology units (POUs) in large countries, all can deliver quality care. She recommended the term 'Centres of Expertise' rather than 'Centres of Excellence' to avoid discouraging those who have not been classified as 'Centres of Excellence', to encourage development of specialist centres, but not to distinguish on the basis of the quality of care rather the level of care.

'Not without us'—Advocacy for access by patients, survivors and parents—Focus on Uganda

Limited financing for cancer control and early detection remains a bottleneck in LMICs like Uganda. Uganda developed their first Uganda National Cancer Plan (UNCCP), through a wide consultative process coupled with active participation and involvement of various stakeholders. In this UNCCP, a section is dedicated to childhood cancer control, with the main goal to achieve an overall survival of 60% for children with cancer by 2026. Advocacy for cancer control is required in all resource settings, but should be a consolidated effort to avoid fragmented approaches. Stigma towards people with cancer should be addressed as a human rights issue. This may be achieved by involving people with

cancer and survivors in cancer control advocacy towards improving advocacy and service delivery. An example of efforts to increase awareness and decrease stigma is the 3C club (Children Caring about Cancer), a peer-to-peer network.

Targeted therapy

Alaa Elhaddad (Egypt) focused on the international application of precision medicine. Opening those increased efforts was needed to develop this modality on the African continent. The challenges of targeted therapy in clinical practice in Africa include high cost, long turnaround time, failure to obtain adequate tumour material, defining pathogenic variants in paediatrics and ethical issues surrounding genetic material. Paediatric malignancies have a relative paucity of targeted mutations and distinct molecular alterations compared to adult cancers, and rational combinations of targeted therapies are required in the universalisation of practice.

Jennifer Geel (South Africa) described increasing crowdfunding efforts to afford targeted therapies for individuals in South Africa, suggesting that potential funders be informed of the expected poor prognosis of many of these patients. Pharma-sponsored clinical trials for targeted cancer therapy for children in South Africa may increase access, but care should be taken to protect vulnerable populations and patients.

Suzanne Turner (UK) highlighted Africa's role in the development of targeted therapy for conditions such as lymphomas. The potential unique genetics and biology of lymphoma in Africa are under study in collaborative projects, and efforts are underway to identify existing efficacious drugs with fewer side effects with patient surrogate mouse models. Turner stressed that targeted therapies must be adapted to the environment in which they are administered.

Mahmoud Hammad (Egypt) presented chimeric antigen receptor (CAR) T-cells therapy as a viable treatment option in Egypt for children and young adults to achieve remission in relapsed/refractory B-ALL. Barriers to CAR T-cell therapy include resource constraints such as cost, expertise and infrastructure. Modified protocol development and twinning are required to support Africa in the development and implementation of CAR T-cell therapy. Support should be given to this therapeutic modality while financing and developing infrastructure.

The panel discussion concluded with the recommendation that more bone marrow transplant specialists should be trained, with the Children's Cancer Hospital (Egypt) being a viable option as a centre with high volumes [5].

Childhood cancer in special circumstances (refugees, internally displaced persons and other humanitarian crises)

Ugandan WHO Country Representative Yonas Tegegn Woldemariam focused on poor healthcare systems which influence childhood cancer survival. Disasters disrupt healthcare for both patients and healthcare workers. There is a need to advance universal health coverage, address health emergencies and increase government investment, continental cooperation and global partnership for technology transfer and capacity building. The African continent should accelerate the adoption and implementation of childhood cancer initiatives and related tools.

Francine Kouya (Cameroon) shared her experience in a conflict zone, stressing the importance of patient follow-up programmes, strengthening multidisciplinary teams and the value of communication for patient safety. In times of crisis, psychosocial support has increased importance to parents, children and healthcare workers involved in childhood cancer care.

Access to basic palliative care is still lacking for refugees according to Eddie Mwebesa (Uganda) and a palliative care policy should be implemented to improve the management of refugees with cancer. Provision of food, shelter and education often takes priority over healthcare in refugee settlements, with a negative impact on the survival of children with cancer.

Julius Ecuru explored ethical considerations in the management of these vulnerable children, whose treatment may be interrupted or delayed due to visa and working permit applications and lack of resources to pay for medical services. Potential solutions would be for host countries to anticipate special circumstances, prepare for their management, embrace humanitarian holistic care for these children and use technology to help in hard-to-reach areas for the provision of health services.

Conference presentations

Medical tracks

Margaret Lubwama (Uganda) reported high rates of multidrug-resistant bacteria, the main cause of bacteraemia in paediatric haematologic cancer patients with febrile neutropaenia, while Youssef Madney reported that Echinocandin-resistant *Candida* infections were a source of high mortality in haematological malignancies in Egypt [6]. El-Mahallawy reported that rapid molecular detection of organisms with real-time multiplex PCR detection during sepsis could improve outcomes by guiding more targeted antimicrobial use. Use of this modality, which detects 21 different bacterial pathogens, resulted in a significantly shortened time to detection of bacterial pathogens with rapid change to appropriate antimicrobials.

Christin Edan (France) described the successful initiation of a 3-year palliative care programme integrated into POUs in 15 Francophone countries under the auspices of the French-African Paediatric Oncology Group (GFAOP).

Both Lily Gloria Tagoe (Ghana) and Mapule Kholong (South Africa) reported low rates of COVID-19 in children with cancer, although Tagoe reported 2 deaths in a cohort of 10 infected patients, while Kholong reported minimal clinical impact on 432 patients tested. Rose Nankinga (Uganda) described the increased rate of late presentations due to the pandemic, threatening to reverse gains made in overall survival, and Karim Assani from the AMCC group indicated that the pandemic increased the difficulties of implementing programmes aimed at improving the survival of patients with retinoblastoma.

In Tanzania, pupillary dilatation, high intraocular pressure, shallow anterior chamber and extensively necrotic tumours were associated with histopathological high-risk features in retinoblastoma, according to Neema Moshi, and Nicholaus Benedicto found that Tanzanian parents or caregivers refused enucleation because of their perception towards the appearance of the child after enucleation, low level of education, traditional and religious beliefs and poor socio-economic status.

Ernestina Schandorf reported a 5-year OS for nephroblastoma in Ghana for stages 1 through to 4 were 100%, 87.7%, 71.1% and 52.4%, respectively. Sahmima Namugerwa (Uganda) linked higher survival in nephroblastoma to improved pathology reporting, increased intensity treatment and improved access to surgery and radiotherapy.

On behalf of the South African Neuroblastoma Working Group, Jaques van Heerden reported that less than half of the patients with high-risk neuroblastoma (HR-NB) are operated on, mostly determined by post-induction metastatic remission rate, with non-standard surgical practices, leading to variable OS. A greater rate of primary tumour resection in HR-NB is advocated to improve survival. Robyn Charlton (South Africa) found that socio-economic factors were not significantly associated with neuroblastoma survival, suggesting that tumour biology exerts an overriding influence on prognosis. Irene Nanyanga (Uganda) demonstrated that palliative metronomic CADo led to longer median survival time.

Brenda Mallon for the GFAOP group showed the feasibility of staging and estimating outcomes for Burkitt lymphoma, retinoblastoma and nephroblastoma, according to the Toronto Paediatric Cancer Staging guidelines, in seven hospital-based cancer registries.

Richard Nyeko (Uganda) demonstrated the importance of multidisciplinary team meetings in the improvement of brain tumour care in Uganda, while Mwebe Katasi described the capacity to improve the early detection, referral, diagnosis and comprehensive care for children with brain tumours in low-resource settings through innovative collaborations.

Chemotherapy utilisation (reliable supply chain, safe chemotherapy preparation, administration and disposal) is suboptimal in LMICs such as Ethiopia. Atalay Mulu Fentie identified gaps and designed interventional strategies at POUs to improve safety. In Ghana, most antineoplastic medicines surveyed were found in the private pharmacies; however, the mean availability across all studied pharmacies was below the WHO target of 80%. Kofi Boamah Mensah concluded that the low availability of medicines at public pharmacies indicates the need for government interventions. Furthermore, Ghanaian community pharmacists play an essential role in the provision of cancer health promotion services. Shauna Aroa (Uganda) audited the UCI chemotherapy safety programme, leading to the establishment of a multidisciplinary team

with pharmacist involvement. This allowed formalisation of chemotherapy prescribing and administration, which highlighted the value of paediatric pharmacy input for safety, standardisation and education of staff and patients.

SIOP global mapping programme

A comprehensive overview of paediatric oncology care in Africa from the SIOP Global Mapping Programme emphasised marked disparities between countries. Some countries have highly specialised services, while no paediatric oncology services are present in certain countries, including Mauritius, until recently a high-income country [7]. A long-term strategy to eliminate disparities in African paediatric cancer care should be aligned with the WHO GICC aims and facilitated by SIOP Africa. Patrick Makupe (Malawi) reported that only 36 of 47 reporting countries had physiotherapy services available to children, with higher availability in upper-middle-income countries. As survival rates improve in LMICs, it is vital to increase the awareness of paediatric oncology rehabilitation needs and attract/retain rehabilitation professionals. Mawethu Bell (South Africa) stated that the majority of reporting African POUs have access to social workers, while a minority access other professionals involved in psychosocial care, placing a disproportionate burden of responsibility on social workers. Investment in all components of psychosocial care is strongly recommended to contribute to improvements in childhood cancer care and survival in Africa. The SIOP Global Mapping Programme data also confirmed that the number of population-based registries remains stable at only 6 in Africa, while only 17 countries reported hospital-based registries. Responses from nine countries indicated that they had a national cancer registry, a paediatric oncology registry and a national paediatric oncology association, suggesting that the minority have the organisational infrastructure to coordinate strategic efforts in childhood cancer care. Nursing data confirmed gross understaffing and priority research and training topics were identified, including professional practice, psychosocial support, chemotherapy administration and side effects, psychosocial support, palliative care, infection prevention and control. The theme that emerged from the Global Mapping Programme presentations was that coordinated efforts are both required and possible to introduce low-cost and high-impact interventions to achieve WHO GICC goals.

Nursing track

The nursing track comprised 2 full days of free paper sessions attended by over 80 nurses from more than 30 countries. Nursing training was highlighted by Elianeth Kiteni (Tanzania) due to the heterogeneous training nursing staff receive in paediatric oncology. The SIOP Nursing baseline standards have been introduced in an effort to formalise paediatric oncology nursing training. Joan Nakabiri (Uganda) and Tadala Mulemba (Malawi) presented the Global HOPE nursing education programme as an example of continued professional education for nurses. Wendy Eyiah-Mensah described the initiation of a specialist paediatric oncology nursing programme in Ghana, a collaboration between partners in the UK, USA and Ghana, resulting in 17 graduates in the first year.

Glenn Afungchwi (Cameroon) described 57 topic areas identified for inclusion in a foundation course, including a general introduction to cancer and treatment modalities; chemotherapy administration and side effects; psychosocial support, palliative care and infection prevention; and control. Nurses were involved in the development of five (23.8%) national cancer control plans with specific recommendations for nurses. During the COVID-19 pandemic, nurses were forced to adapt to online training. The 'Fundamentals in Paediatric Oncology' programme, developed by the GFAOP nursing group in 2013, evolved into an e-learning format with 10 modules. Continuous weekly nursing education sessions at UCI have improved nurses' knowledge and attitudes, are sustainable, cost-effective and further multidisciplinary team integration. The Global HOPE programme continues to develop nurse leaders from Botswana, Malawi and Uganda in a year-long programme. Modules include essential nursing leadership skills, high-performance teams, diplomatic communication, strategic management and practice models, and nursing quality care. Paediatric palliative care training of healthcare providers in resource-poor settings has been prioritised, with 52 graduates of an online course run in collaboration with Global HOPE.

Invited speaker Marilyn Hockenberry emphasised the use of protective gear as well as the important role played by nurses in cross-checking and confirming prescriptions prior to chemotherapy administration to minimise treatment errors. Enyo Bosumprah described a teaching tool to empower nurses to educate parents on discharge on important issues such as response to fever, take-home medication and treatment side effects. The tool resulted in marked increases in test scores, which may translate to improved patient outcomes.

Civil society track

This track successfully incorporated the presentations from various members of the multidisciplinary team, fostering goodwill and networking. Glenn Afungchwi reported that effective training of healthcare workers on early warning signs of childhood cancer required understanding cultural beliefs and values. Both Nchasi *et al* and Gategetse *et al* reported that in-person on-site training was effective for increased awareness on early warning signs of childhood cancer. The Awareness for Burkitt Lymphoma Eradication programme (ABLE+) in Northern Uganda is an example of a successful intervention to increase detection and referral, resulting in a marked increase in referrals of children with Burkitt lymphoma.

Treatment abandonment remains an obstacle to cure in sub-Saharan Africa, where cost is an overriding reason for abandonment. George Chagaluka (Malawi) described a comprehensive package to enable parents to complete treatment. Results from a World Child Cancer (WCC) survey indicated that in Ghana, the majority of respondents felt that they would not have been able to access treatment for their child without NGO support, and the most important type of support included financial support for drugs and diagnostic tests.

Claire Namulwa (Uganda) reported that sustained psycho-social support retained children in cancer care during the COVID-19 lockdown and ensured completion of treatment, highlighting the importance of psychosocial care in adherence and raising survival rates. A study of rural Ugandan adolescents reported fear of death which felt inevitable, fear of dependency and lack of privacy, and fear of being a burden. They expressed the desire to be given the opportunity to make decisions relating to their own care, despite parental opinions that they are incapable. Depression and isolation were common feelings, exacerbated by isolation from peers and mutilating surgeries such as amputations. Adolescents reported that peers questioned their ability to function as sexual beings, and they reported stress due to fear of infertility. A Kenyan study on gaming technology as a method of non-pharmacological pain relief noted that in 75% of the cases, cooperation during procedures was improved. Other outcomes included more engagement with peers and improved coping skills. Chagira *et al* suggested that children's hospitals should incorporate a variety of gaming technology as tools within greater play-based oncology programmes to improve overall coping and psychosocial care for children with cancer. From a study of nurses' well-being, four interventions were highlighted as areas where nurses need greater support: access to a psychologist, case study meetings to discuss emotional impact of work, greater support and recognition from management and more training in emotional well-being and resilience.

Conference awards

Lifetime and academic awards awarded after the conference can be seen in Table 1.

Table 1. SIOP Africa 2022 awards [6].

Award	Recipient
Friend of SIOP Africa	Prof Catherine Patte (France) for her contributions to the continent through her work with the GFAOP.
Lifetime Achievement Award: Medical	Prof Elhamy Rifky (Egypt) for his dedication to improving services in Egypt and support of African and Middle Eastern colleagues.
Lifetime Achievement Award: Nursing	Sr Enyo Bosumprah (Ghana) for mentoring and educating nurses in Ghana, and her many contributions to local and international paediatric oncology organisations.
Best oral presentation	'Association between high-risk histopathological and clinical features of primary enucleated eyes at Muhimbili National Hospital'. N. Moshi, Muhimbili University of Health and Allied Services, Dar es Salaam, Tanzania.
Best poster presentation	'Combatting treatment dropout in paediatric cancer'. R. Kabore, Yalgado Ouedraogo University Hospital, Ouagadougou, Burkina-Faso
Most innovative presentation	'Integrating a palliative approach into the healthcare provided by paediatric oncology units. Insights from a 3-year training programme'. C. Edan, GFAOP - Gustave Roussy, Villejuif, France

Table 2. SIOP Africa 2022 various meetings and proceedings [6].

Pre-conference days			Conference days		Post-conference day
Day 1	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 1**
AMCC Retinoblastoma workshop Day 1	AMCC retinoblastoma workshop Day 2	Civil Society and Parents Symposium	**OPENING REMARKS**	**PLENARY SESSION** Targeted therapy	Nutrition workshop
Wilms' tumour workshop Day 1	Wilms' tumour workshop Day 2	Nurses children's palliative care workshop	**PLENARY SESSION** WHO GICC	**PARALLEL SESSIONS** Presentation of abstracts	
	Radiation oncology workshop	Paediatric oncology pharmacy workshop	**CONFERENCE OPENING**	**NURSES BUSINESS** *Meeting*	
	Young SIOP educational day	IPSO Surgical Symposium	WCC workshop	SIOP AFRICA **ANNUAL BUSINESS** *Meeting*	
	GFAOP *Meeting*	The ARIA-adapted management guidelines workshop	**PARALLEL SESSIONS** Presentation of abstracts	**PARALLEL SESSIONS** Presentation of Abstracts	
			PLENARY SESSION Advocacy for access	**PLENARY SESSION** Childhood cancer in special circumstances	

The pre- and post-conference workshops and symposia

An overview of the workshops and symposia can be seen in Table 2.

1. Alliance Mondiale Contre le Cancer (AMCC) Retinoblastoma Workshop Day

The 'Alliance Mondiale Contre le Cancer' (AMCC) is an NGO mainly focused on women's and children's cancer in LMICs through training, education and research [8]. The AMCC retinoblastoma workshop was designed to support multidisciplinary teams managing retinoblastoma to achieve early diagnosis, access to treatments, rehabilitation and follow-up of children in sub-Saharan Africa. The aim of strengthening networks between teams treating retinoblastoma in English-speaking and Portuguese-speaking sub-Saharan Africa was successful as 105 delegates shared experiences of achieving early diagnosis, discussing aspects of patient care, data collection and research. The group of professionals included 36 ophthalmologists, 11 ocularists, 26 paediatric oncologists, 10 pathologists and 20 ophthalmic officers/nurses from 14 countries.

Guillermo Chantada (Argentina) discussed different therapeutic approaches according to settings [9]. Didi Fabian (Israel) spoke about disparities in treatment outcomes, based on large global retinoblastoma data sets [10, 11]. Laurence Desjardins (France) provided baseline data on retinoblastoma management and outcomes in Anglophone Africa. Presenters from Uganda, Rwanda, Ghana, Nigeria, Tanzania, Kenya, Ethiopia and Mozambique shared local experiences, providing rich material for discussion in both plenary and breakaway sessions. Emphasis was placed on the importance of ocularists providing prostheses to enhance cosmesis and quality of life, thus limiting stigmatisation while improving adherence and survival [12].

The workshop compiled an early diagnosis multi-year plan with the agreement of the Ugandan Ministry of Health. Aims included that 1) all teams in attendance develop multidisciplinary care of children with retinoblastoma and organise at least one referral centre per country for conservative treatments to preserve eye and vision in bilateral cases; 2) all teams collect data on a common basis for all cases of

retinoblastoma in their respective countries; and 3) all teams advocate for the reduction of the cost for retinoblastoma care because no child should die of a highly curable malignancy, such as retinoblastoma, because of financial barriers.

The workshop concluded with an invitation to all teams to participate in the regular webinar every 2 weeks to discuss challenging cases.

2. Civil Society and Parents Symposium

The Civil Society and Parents Symposium attracted 57 professionals and individuals across the continuum of childhood cancer care to discuss initiatives to benefit children's treatment experiences. Emphasis was placed on patients as the primary reason for discussion of improvements in childhood cancer care, rehabilitation and reintegration of survivors. The theme 'Nothing for us without us' sent a strong message that patients and caregivers should be integral to the decision-making and planning of childhood cancer services. Some of the key talking points included getting feedback from families that are taking care of cancer patients, psychosocial issues experienced by adolescents, treatment abandonment, retention in care, psychosocial support for vulnerable children with cancer during COVID-19 lockdown, need for educating healthcare workers on the early warning signs of childhood cancer and national paediatric oncology registries in Africa.

The symposium acknowledged the position that childhood cancer care may not succeed without parents and caregivers supporting and providing for the children during the process of receiving care. Attendees from diverse backgrounds were encouraged to address specific gaps according to their skill sets, expertise and passion. As many civil society organisations were formed as a result of individuals and groups who have lived through the experiences of childhood cancer itself, their particular experiences were acknowledged as vital to quality care for children and adolescents with cancer.

Recommendations included the need for increased advocacy for budget increment by governments, increased efforts directed at developing or creating an enabling policy environment for childhood cancer care and management and public-private partnerships to accelerate access to care. Suggestions included increased patient involvement, especially cancer survivors, in advocacy efforts and involvement of schools.

3. IPSO Surgical Symposium

The International Society of Paediatric Surgical Oncology (IPSO) [13] hosted its first meeting as part of the SIOP Africa conference, its first truly hybrid meeting. Presentations focused on surgical principles and challenges in various paediatric solid tumours treated in African centres, sparking robust discussion and engagement [14]. An inspiring talk entitled 'Paediatric surgical oncology in practice in Uganda: A journey of 20 years', by Arlene Muzira and John Sekabira, highlighted both the growth of the paediatric oncology service in the country and the current limitations of local resources. Sharon Cox discussed vascular access including appropriate line choice and modifications in techniques applicable to LMIC settings.

Nasser Kakembo (Uganda) highlighted the adaptation of resources to achieve optimal outcomes in surgical management of nephroblastoma. Derek Harrison's presentation on bilateral nephroblastoma recommended neoadjuvant chemotherapy for at least 6 weeks, or 12 weeks in cases of suboptimal response, followed by bilateral nephron-sparing surgery, if possible, or unilateral nephrectomy with nephron-sparing surgery in the least affected kidney. In cases of nephroblastoma with inferior vena cava extension, the recommendation is to administer neoadjuvant chemotherapy for a maximum of 6 weeks, following which infrahepatic thrombus may be removed safely, while suprahepatic disease requires cardiopulmonary bypass on standby while thrombus is removed from the right atrium.

Hafeez Abdelhafeez (USA), a surgeon with experience in both low- and high-income settings, stated that the optimal setup for safe hepatoblastoma surgery is feasible across different settings. Peri-operative optimisation, inflow and outflow control, a parenchymal transection strategy, haemostasis and biliostasis are key steps in mitigation of complications.

Hafeez discussed the principles of sarcoma staging, biopsy and management and sound tumour biopsy strategy. Understanding the role of multimodality therapy and neoadjuvant therapy based on tumour biology and anatomy and complete surgical resection with preservation of form and function are key factors to improving sarcoma outcomes.

Jed Nuchternon spoke on the principles of neuroblastoma staging and management, emphasising multimodality therapy, indications for resection, extent of resection and operative considerations.

A 'tumour board' interactive panel discussion took place where the management of five patients was debated. This interactive session proved to be the highlight of the meeting with the principles from the previous talks being put into practice, creating lively debate. The day was very well attended with delegates from many continents and many African countries and allowed old and new friends a chance to catch up and share their experiences, be it anecdotal but valuable experiences or sharing new cutting-edge practices based on latest protocols and guidelines. Due to the unprecedented success of this inaugural meeting, IPSO plans this to be the first of many African continental meetings going forward, and we all look forward to meeting up again in the near future.

4. Nurses Children's Palliative Care Workshop

A one-day workshop on children's palliative care was coordinated by the International Children's Palliative Care Network (ICPCN) [15], with experienced facilitators from ICPCN, the Palliative Care Education and Research Consortium [16] and WCC [17]. The interactive day provided opportunities for discussion and sharing of experiences. The workshop introduced participants to the principles and practice of palliative care and its integration into the management of children with cancer. Topics included pain assessment and management, communication, managing other symptoms, advanced care planning, end of life care, the nurse's role and caring for ourselves. Eighty nurses attended the conference from a range of countries, including Uganda, Rwanda, Zambia, Tanzania, Kenya, South Africa, Ghana, Malawi, Egypt, Sudan, Nigeria, Cameroon, Zimbabwe, UK and Sweden. Key messages included 1) that palliative care is an integral part of the care of children with cancer; 2) that we can manage pain and symptoms effectively; 3) that communication is key, as is how we discuss diagnosis and prognosis with children and their parents; 4) nurses have a key role in the provision of palliative care for children with cancer; and 5) that in order to provide palliative care for children with cancer, we need to care for ourselves and be committed to developing our resilience. The workshop was made possible through funding from the Burdett Trust for Nursing.

5. Nutrition Workshop

Approximately 46% of the children with cancer in Africa are malnourished at diagnosis [18]. Malnutrition in children with cancer is associated with increased infection, toxicity, decreased survival and increased abandonment of care [19]. Through collaboration with the International Initiative for Paediatrics and Nutrition (IIPAN), significant advances have been made in improving the education and clinical capacity of nutrition services in Africa, closing the gap on several unmet needs reported by paediatric oncology units in Africa [20]. To further expand on this regional initiative, a post-conference nutrition workshop was held with the aim to improve knowledge on the delivery of care and management of nutritional complications among children with cancer. This workshop reviewed fundamentals of nutrition assessment and intervention, providing instruction on the management of nutritional conditions common in childhood cancer, which may be particularly challenging in LMICs. Attended by approximately 50 participants (live and virtual) the audience included dieticians, nutritionists, nurses, physicians, parent groups and non-governmental organisations.

Elena Ladas (USA) provided an overview of IIPAN activities in Africa and Judy Schoeman (South Africa) described the objectives of the SIOP Global Health Nutrition Workgroup such as advocating for nutrition as an essential member of the management team, increasing nutritional education on the African continent and increasing dieticians and nutritionists in LMICs. IIPAN nutritionists from Cameroon, Tanzania, Uganda and Kenya presented cases relevant to local settings and optimal delivery of nutritional care with limited resources, while paediatric oncologists presented the management of severe acute malnutrition, mechanisms of liver impairment and nutritional management of enterocolitis/pancreatitis. Happiness Ndifon (Cameroon) discussed the role IIPAN played in establishing food supply during COVID-19 lockdown in 2019–2020. In summary, the workshop highlighted important nutrition-related management challenges that need increased attention in the African setting in parallel to building the capacity of nutritionists and dieticians on the continent.

6. Paediatric Oncology Pharmacy Workshop

True multidisciplinary care for children with cancer includes a pharmacist for safe preparation, administration and rational use of anticancer and supportive care medications. In LMICs, frequent stock-outs require precise pharmacy prognostication, ordering and tracking of

medications. Pharmacists are critical for safe handling and disposal of medications and educating the medical team about new medications. However, the highly specialised field of Paediatric Oncology Pharmacy is poorly represented in most LMICs [21].

The aim of the inaugural SIOP Africa pharmacy workshop was to increase the involvement of pharmacists in the African paediatric oncology community. The workshop was attended by 31 people including survivors, herbalists, clinical pharmacists, paediatric oncology pharmacists, a clinical pharmacist with bone marrow transplant experience and paediatric oncology nurses. The pharmacy workshop explored the issues of mentoring, continuous professional development, specialisation, involvement in a multidisciplinary team and imparted skills in pharmaceutical care plans, safe chemotherapy administration and research [22].

Talks were given on paediatric pharmacy, off-licence and off-label use of drugs, clinical trials, nutrition, herbal medicines and cancer registries [23]. Friendships and collaborations with pharmacists, nurses and oncologists from Egypt, Ethiopia, Tanzania, Zimbabwe, Cameroon and South Africa were part of the successes of the workshop. Discussion of potential projects resulted in analysing the inclusion of pharmacists in paediatric oncology units across Africa, developing neutropaenic guidelines and regular education sessions to discuss a particular disease area, medicines involved and the role of the pharmacist.

Pharmacists have a vital role to play in the day-to-day management of cancer in children. The workshop was a call that united pharmacists from all over the continent, with the same goal to provide quality care to children with cancer. It is hoped that the momentum from this meeting will grow to have an important impact on childhood cancer survival rates in Africa.

7. Radiation Oncology Workshop

A one-day, online radiotherapy workshop was arranged by the SIOP Africa radiotherapy EXCO representatives, endorsed and supported by the International Paediatric Radiation Oncology Society (PROS) [24]. Registration for the workshop was free, allowing more participants to attend.

Twelve practical talks were aimed at radiation oncologists in Africa who are currently treating children. These included general considerations for treating children, modifications required to treat children in a busy adult radiotherapy centre, how to understand and incorporate paediatric disease-specific protocols, the role/interplay of the paediatric oncologist when treating children with radiotherapy in LMIC, imaging, anaesthesia for radiotherapy, best practice contouring, late effects and disease-specific guidelines for nephroblastoma, medulloblastoma, rhabdomyosarcoma and palliative care. International faculty from PROS and CCLG, based in the United Kingdom and the United States, assisted African faculty with practical talks.

The workshop proceeded seamlessly with 46 attendees from not only Africa, but globally. Informal feedback suggested that current challenges were addressed. This is just one example of how COVID-19 has facilitated improved online communication, with additional exposure to a relatively rare sub-speciality.

8. The Adapted Management Guidelines Workshop

The resources to develop AMG in Africa are not fully developed [25]. The AMG workshop was organised by SIOP Africa and St Jude Global as an interactive activity led by African and international experts who have developed resource-based management guidelines and protocols in their own settings. Participants were guided in the development process, stimulating problem-solving to develop locally relevant guidelines and protocols. A practical approach was used to initiate the development of treatment approaches for the multidisciplinary team, independent of tumour type or resource setting. The experiences of the attendees were used as the starting point to demonstrate that African healthcare workers are resourceful and can solve childhood cancer problems on the African continent that collaborative partnerships can advance knowledge and create insight for more innovative solutions and that interregional collaboration is of great value.

The 62 participants and 14 facilitators were from 22 African countries, 5 European countries and the USA, representing 58 institutions. The disciplines represented (paediatric oncology, paediatric surgery, ophthalmology, pharmacy, policy and nursing) were an example of the multidisciplinary collaboration required to successfully formulate AMGs, and participants left the energetic meeting with renewed vigour

to continue this important work on their return home. The participants were equipped with the basic tools to identify available resources, assemble a multidisciplinary team and initiate discussion for the development of tumour-based protocols and clinical research questions.

9. Wilms' Tumour Group/CANCaRe AFRICA Workshop

The Collaborative African Network for Childhood Cancer Care (CANCaRe Africa) is an active multidisciplinary regional network in sub-Saharan Africa [26–28]. It functions as a platform to improve outcomes of children with cancer in Africa through research, capacity-building and clinical care. The mission is to improve survival for children with common and curable cancers in sub-Saharan Africa by reducing treatment abandonment and death during treatment to less than 10% and by developing, implementing and evaluating locally appropriate treatment guidelines. The 13 participating centres are from Cameroon, Ghana, Malawi, Uganda, Kenya, Zimbabwe, Tanzania and Ethiopia.

At the workshop, the specific goals for the current projects were articulated: the Wilms' tumour Africa project, 'SUCCOUR – Supportive Care for Children with Cancer in Africa' and 'Zero Abandonment from Start to Finish'. The workshop was attended by site leads and steering committee members of CANCaRe Africa and facilitated by advisory committee members. Goals were articulated in the areas of research and data collection, teaching and education, advocacy, partnerships and capacity building. The goals include were to have over 95% complete data, to have a multidisciplinary symposium on a relevant supportive care topic every year, to strengthen the global alliance for the prevention of treatment abandonment with a focus on out-of-pocket costs for families and to continue to build local capacity with a focus on creating leadership roles for junior faculty. The intent is to publish the goals on the CANCaRe Africa website once finalised and approved by all site leads.

The Wilms Africa Phase II study started in January 2020 and is evaluating a revised and comprehensive adapted treatment guideline. In Phase I, end of treatment survival increased from 52% to 69% (p = 0.002) and treatment abandonment decreased from 23% to 12% (P < 0.001) [29].

The SUCCOUR Phase II study includes a clinical research and nursing component which aims to improve supportive care and the management of fever and neutropenia by implementing and evaluating a local care pathway. SUCCOUR Phase I reported on treatment-related mortality and demonstrated a high mortality of fever and neutropenia episodes and late start of empiric antibiotics, often without obtaining a blood culture [30, 31].

The 'Zero abandonment from Start to Finish' study aims to reduce treatment abandonment to less than 10%. The study includes a clinical research, advocacy and fundraising component to reduce out of pocket costs for families of children with cancer. Previous work supported the significance of preventing treatment abandonment to improve survival and the importance of reducing costs for families to enable them to complete the treatment of their child [32].

10. World Child Cancer Workshop

The WCC [17] workshop highlighted efforts to improve childhood cancer management in sub-Saharan Africa. The discussions focused on the main challenges, successes, lessons learned and plans for the future.

Sumit Gupta (Canada) demonstrated the case for cost-effectiveness of childhood cancer interventions in Ghana. This model, developed by the Policy and Economics Research in Childhood Cancer [33] unit, shows the cost of treatment per patient compared to daily-adjusted life year saved and compares this to the gross national income (GNI) per person where the cost per DALY is less than the GNI per capita; the treatment is cost-effective, as was demonstrated in Ghana [34]. Spending a little more money might improve outcomes and further increase the cost-effectiveness of the interventions.

Lily Gloria Tagoe provided a Ghanaian perspective on childhood cancer management. She shared the history and major achievements since 2010, including (1) an increase in the number of trained medical, nursing and pharmacy specialists; (2) the development of national treatment guidelines and improvements in supportive care, leading to improved survival of children with some of the GICC-focus tumours; and (3) initiatives to decrease treatment abandonment, such as the establishment of funded family accommodation near the paediatric oncology units. Before the launch of the Ghanaian National Childhood Cancer Strategy, the Ministry of Health announced that drugs for four common childhood cancers would be purchased by the government.

WCC efforts to improve outcomes in childhood cancer and the patient experience through strengthening paediatric oncology nursing were presented by WCC board members Rachel Hollis, Glenn Mbah and Ayire Emmanuel Adongo. They detailed components of the nursing education programme from the foundation phase through to training the trainers. A critical achievement was to obtain a commitment by the Ghana College of Nurses and Midwives (GCNM) to establish an accredited specialist programme in paediatric oncology nursing, resulting in the graduation of 17 nurse specialists in paediatric oncology in 2021.

11. Young SIOP Educational day

Systematic development, implementation and evaluation of standardised care practices are essential prerequisites to building a foundation for multicentre clinical research and incorporating these research discoveries into routine care. The recognition that African research is poorly represented on the international stage led the hosts of the first Young SIOP Education Day at the SIOP Africa conference to target emerging researchers on the continent. The event was held in hybrid format, hosted by the University of the Witwatersrand and Texas Children's Hospital Global HOPE Programme. The theme 'Standardisation of care as a foundation for paediatric cancer cooperative group research in Africa' reflected the position that clinical research is a critical driver of quality care, novel therapies and quality of care to cure childhood cancer. Subject experts provided comprehensive reviews of the six GICC index cancers, building on historical overviews of developments in each cancer, with critical insights into latest trends in both high and LMIC settings. An afternoon session covered major points in research methods, with a particularly African flavour, such as 'Approaches and strategies to integrate clinical research into busy clinical workflows', which stressed persistent hard work to achieve success in research, and 'Writing abstracts for presentations and publications', which emphasised the importance of following simple rules to increase the chances of abstract acceptance at international conferences.

12. Francophone-African Group of Paediatric Oncology **(GFAOP) meeting**

The GFAOP was founded in 2000 by African and French doctors as a medical association bringing together a network of childhood cancer specialists from 18 countries of the Maghreb and sub-Saharan Africa with a vision that children with cancer in Africa can and should be treated locally by trained staff.

The GFAOP workshop entitled 'Decision-making in the treatment of childhood cancer' was attended by 14 participants from 8 Francophone countries: Burkina Faso, France, Ivory Coast, Mauritania, Morocco, Niger and Senegal. The objective was to provide skills to assist healthcare workers to decide when to use palliative or curative protocols for patients. This was based on the findings that in Francophone Africa most patients present with late-stage disease. Advanced disease complicates management, leaving limited options for treatment which may render diagnostics and treatment impossible in resource-limited settings.

Discussion points included the clarification of the definition of 'advanced stage' and 'late stage' since it is not related to standardised international staging systems, but can relate to a combination of factors such as tumour volume, metabolic or nutritional status and the degree of tolerance of toxic treatment.

Possible solutions included:

1. To differentiate between three categories of patients:

   a. Category 1: patients presenting with a known poor prognosis or patients with a very poor or no chance of survival (DIPG, metastatic alveolar RMS, osteosarcoma with bone metastases, etc.);

   b. Category 2: patients presenting with a disease where outcomes have been improved by cellular therapies, targeted therapies or innovative therapies (metastatic neuroblastoma);

   c. Category 3: curable diseases focusing on the WHO GICC index cancers.

2. Upon admission each patient should be classified in one of these categories and the treatment tailored accordingly:

   a. Category 1: managed with a palliative strategy
   b. Category 2: If possible, refer to a local or international centre where therapies are available. If this is not possible, then category 1 treatment (palliative strategy ± metronomic chemotherapy) should be started;
   c. Category 3: adapted management guidelines and regimens or standard therapies should be started.

3. Ethical issues raised by inequality of access to care worldwide and how to communicate with families regarding limited resources were discussed.

The final discussions related to the importance of palliative care in LMICs. The number of patients requiring palliative care in LMICs exceeds those in HICs and therefore teams treating childhood malignancies should as a first step set up a palliative care programme parallel to curative strategies. Once management teams gain experience, the number of patients undergoing curative treatment is expected to increase progressively. This strategy should be modulated according to the local setting and the context of resources available in the setting. At the end of the workshop, all the participants acknowledged the importance of a robust classification system to prevent waste of resources that are already limited.

Discussion

Global resources for paediatric oncology are unequally distributed [35]. While countries like Egypt and South Africa are spearheading bone marrow transplantation and targeted therapies, Burundi and Niger are initiating services and Mauritius has no paediatric oncologists.

Since the launch of the 2018 WHO GICC, Africa has prioritised the principles of the initiative. Morocco, Ghana and Uganda independently supported greater government involvement at all levels of systems development for childhood cancer care: independent paediatric oncology cancer care plans, childhood cancer registries, securing access to chemotherapy supplies and developing surgery and radiotherapy services.

Education programmes were a focus of many free papers' presentations, reflecting the current need in Africa. Inaugural workshops (pharmacy, IPSO, radiotherapy and Young SIOP Africa Education Day) and those addressing priority areas (adapted management guidelines, nursing, paediatric palliative care and nutrition) focused on building capacity [36–38]. Africa has shown its ability to adapt, while innovation is growing.

In line with the six priority cancers of the WHO GICC, many presentations focused on retinoblastoma, HL, ALL and nephroblastoma, with more challenging tumours like rhabdomyosarcoma and neuroblastoma receiving limited exposure. Similarly, bone tumours and rare tumours received little attention, while multidisciplinary management of brain tumours is still in its infancy in some countries.

The GICC should receive greater attention moving forwards in North-South African collaborations [39]. Although the GFAOP and CANCaRe groups presented multinational projects, demonstrating the value and feasibility of collaboration, a large number of abstracts focused on single institution studies. HIC collaborators like WCC have led the way in this regard. Hopefully, this approach will be applied increasingly in Africa with the GICC as guiding principles even independent from direct WHO involvement [40].

Civil society (NGOs, parent groups and commercial groups) in the African context will play a large role in financing, managing and advocacy towards reaching the goals of the GICC in Africa in partnership with governments. Africa faces unique challenges related to political instability, internally displaced persons, refugees and diseases like tuberculosis and HIV that are largely managed by NGOs, which remain an important link between centres of expertise and the community [41, 42].

Conclusion

The 14th SIOP Africa Continental conference delivered in hybrid mode gave an opportunity to reach more people who may not have attended due to concerns about the pandemic. Delegates were enthusiastic about sharing their experiences and innovative approaches in paediatric

oncology after two challenging years of COVID-19. This year's conference featured a record number of pre- and post-conference workshops, reflecting the excitement at being able to participate in person once more. The conference highlighted the need for greater collaborative efforts to consolidate resources for improved childhood cancer outcomes and increased involvement of government to support efforts to achieve the WHO 2030 GICC goals. Whether countries have been officially named as WHO focus countries in the GICC movement or not, the commitment to alignment with these goals was evident in plenary sessions, free papers and discussions. The latest conference of SIOP in Africa rekindled enthusiasm in a depleted but ultimately resilient African paediatric oncology community.

Acknowledgments

The authors would like to acknowledge the significant contributions of the rapporteur team, who are all affiliated with the Uganda Cancer Institute: Jatho Alfred, Beatrice Rukundo, Yiga Ashiraf, Immelda Alikaya, Judith Asasira, Bosco Egesa, Catherine Amuge, Collins Jackson Mpamani, Barbra Kyobula, Annet Nalumansi and Immaculate Mbarusha.

Abbreviations

AMCC	Alliance Mondiale Contre le Cancer
BL	Burkitt lymphoma
CAR	Chimeric antigen receptor
GFAOP	Francophone African Group of Paediatric Oncology
GICC	Global Initiative on Childhood Cancer
GNI	Gross national income
HL	Hodgkin lymphoma
ICPCN	International Children's Palliative Care Network
IIPAN	International Initiative for Paediatrics and Nutrition
IPSO	International Paediatric Surgery Organisation
LMIC	Low- and middle-income countries
POU	Paediatric oncology unit(s)
PROS	Paediatric radiation oncology society
RT	Radiotherapy
SIOP	International Society of Paediatric Oncology
UCI	Uganda Cancer Institute
UNCCP	Uganda National Cancer Control Programme Plan
WCC	World Child Cancer
WHO	World Health Organisation

Conflicts of interest

The authors declare that they have no conflict of interests.

Funding

Funding for the publication of this report was provided by the Paediatric Oncology Department, Antwerp University Hospital, Antwerp, Belgium.

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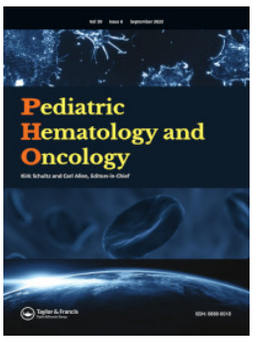

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Pediatric Hematology and Oncology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipho20

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To cite this article: Jaques van Heerden, Irumba Lisa Christine, Julia Downing, Alan Davidson, Laila Hessissen, Judy Schoeman, Elena J Ladas, Hafeez Abdelhafeez, Shauna Georgia Odongo Arao, Atalay Mulu Fentie, Sherif Kamal, Jeannette Parkes, Thurandrie Naiker, Adri Ludick, Joyce Balagadde-Kambugu & Jennifer Geel (2022): Current status of African pediatric oncology education efforts aligned with the Global Initiative for Childhood Cancer, Pediatric Hematology and Oncology, DOI: 10.1080/08880018.2022.2117882

To link to this article: https://doi.org/10.1080/08880018.2022.2117882

Published online: 09 Sep 2022.

PEDIATRIC HEMATOLOGY AND ONCOLOGY
https://doi.org/10.1080/08880018.2022.2117882

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REVIEW

Current status of African pediatric oncology education efforts aligned with the Global Initiative for Childhood Cancer

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ABSTRACT

Education of the pediatric oncology workforce is an important pillar of the World Health Organization CureAll technical package. This is not only limited to healthcare workers, but all stakeholders in the childhood cancer management process. It includes governmental structures, academic institutions, parents and communities. This review evaluated the current educational and advocacy training resources available to the childhood cancer community, the contribution of SIOP Africa in the continental educational needs and evaluated future needs to improve the management of pediatric malignancies in reaching the Global Initiative for Childhood Cancer goals. Childhood cancer, unlike adult cancers, has not been prioritized in African cancer control plans nor the teaching and advocacy surrounding pediatric oncology. The availability of formal training programs for pediatric oncologists, pediatric surgeons and radiotherapy specialists are limited to particular countries. In pharmacy and nutritional services, the exposure to pediatric oncology is limited while training in advocacy doesn't exist. Many nonacademic stakeholders

ARTICLE HISTORY
Received 31 May 2022
Revised 1 August 2022
Accepted 20 August 2022

KEYWORDS
Advocacy; Africa; childhood cancer; education; pediatric oncology; teaching

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are creating the opportunities in Africa to gain experience and train in these various fields, but formal training programs should still be advocated for.

LEARNING POINTS

- The African continent has various resources to increase the capacity of childhood cancer care stakeholders to increase their knowledge.
- African pediatric oncology teams rely on a multitude of international sources for training while developing their own.
- There is a greater need for formal, standardized cancer training especially for pediatric surgeons, radio-oncologists and nurses.
- Greater inclusion of pathologists, pediatric oncology pharmacists and dieticians into multidisciplinary care and childhood cancer training should be facilitated and resourced.
- Successful advocacy programs and tool kits exist in parts of Africa, but the training in advocacy is still underdeveloped.

Abbreviations: AMG: Adapted management guidelines; APFP: African Pediatric Fellowship Program; CPC: Children's palliative care; EAOP: Ecole Africaine d'Oncologie Pédiatrique (African School for Pediatric Oncology); EWS: Early warning signs; GFAOP: Francophone African Group of Pediatric Oncology; GHN: Global Health Network; GICC: Global Initiative on Childhood Cancer; HIC: High income countries; IAEA: International Atomic Energy Agency; ICPCN: International Children's Palliative Care Network; IIPAN: International Initiative for Pediatrics and Nutrition; LMIC: Low- and middle-income country/ies; MDT(C): Multidisciplinary team (multidisciplinary care); PCCP: Pediatric cancer control plans; POU: Pediatric oncology unit(s); PROS: Pediatric radiation oncology society; SIOP: International Society of Pediatric Oncology; SNOSSA: Society of neuro-oncology in Sub-Saharan Africa; SSA: Sub-Saharan Africa; WCC: World Child Cancer; WHA: World Health Assembly; WHO: World Health Organization

Introduction

The technical package of the World Health Organization (WHO) Global Initiative for Childhood Cancer (GICC) consists of seven components (four pillars and three cross-cutting enablers) abbreviated into the acronym: CureAll.[1] The CureAll package encompasses an approach to assess a country or region's current pediatric oncology management capabilities, development of an action plan for the improvement of services, and implementation strategies to monitor the progress.[1] Two of the pillars are "centers of excellence and care networks with enough trained workers to deliver services" and "evaluation and monitoring."[1] Robust information systems and research that ensure effective implementation, quality assurance and constant improvement are of great importance with the cross-cutting enabler of "Advocacy."[1]

Education and training underpin these three components to assess, develop, implement and monitor the systems needed to achieve the GICC goals and ensure sustainable pediatric oncology care in Africa.[2] Partners in the implementation steps span Ministries of Health, administrative and medical staff and civil society.[2] The core projects aim to establish national networks and referral pathways to ensure the accurate

identification of childhood cancers, diagnosis and treatment of patients as well as palliative and supportive care.[2] Therefore, implementation of cancer workforce training and defining of national standards and guidelines for index cancers are essential.[1] The aim of this review is to evaluate the current educational and advocacy systems for pediatric oncology and future needs in Africa in line with the WHO 2030 GICC goal.

Multidisciplinary care (MDC) is crucial to effective childhood cancer management.[3,4] In resource-constrained settings this often requires adaptation of standard international guidelines to administer treatment that is available and deliverable within the confines of limited supportive therapies and higher rates of toxicity.[4] These teams include healthcare medical personnel, administrators, civil society and the government.[3,4] Education of the general public and institutions such as the government is enhanced by advocacy from civil society who may have greater access to communities and their leaders.[1,2]

Methodology

The organizers of the SIOP Africa 2022 conference, including pre- and post-conference workshops (Appendices A and B), reviewed Africa's pediatric oncology educational needs based on activities during workshops, conference presentations and literature reviews.[5] Advocacy programs were included as intrinsic components of comprehensive pediatric oncology care improvement.

Core management of childhood cancers

Pediatric oncologists

Currently there are only six countries (Egypt, Ghana, Morocco, South Africa, Tanzania and Uganda) with formal institutions and/or programs for training pediatric oncologists.[6] Pediatric oncologists from other African countries are trained with the support of the African Pediatric Fellowship Program (APFP), dedicated to building the specialist pediatric workforce in Africa.[7] The APFP facilitates fellowship training for African candidates in accredited centers in African countries, with the intention to return to their countries of origin.[7] The Global HOPE program trains pediatric oncologists and nurses through a combination of local and USA-based modules while the Aslan project supports training in LMICs such as Ethiopia.[8,9] The French African Pediatric Oncology Group (GFAOP) runs the African School of Pediatric Oncology (EAOP) for providers in Francophone Africa.[10] who develops practical clinical applications for local challenges such as deciding when to use palliative or curative protocols[11] and clarifying the definitions of "advanced stage" and "late stage" that are not related to standardized international staging systems.[11] Lusophone African countries (Angola, Cape Verde, Guinea-Bissau, Mozambique, São Tomé and Príncipe and Equatorial Guinea) do not have formal pediatric oncology fellowship programs but are supported by efforts from Brazil. North Africa (Algeria, Egypt, Libiya, Morocco, Sudan and Tunisia) are supported by educational and development efforts of the Pediatric Oncology East and Mediterranean (POEM) Group.[12]

Management of pediatric malignancies in low- and middle-income countries (LMIC) takes place in hospitals which often lack essential diagnostics and MDC.[4] High-income countries (HIC) protocols should be interpreted and adapted for local settings based on available resources[4] but this process is not standardized. Individual countries (South Africa and Egypt) and the GFAOP have national, resource-adapted prospective protocols[13–16] emphasizing the need for more interpretive teaching relevant to local settings parallel to conventional teaching of pediatric oncology principles rather than duplication of protocols unsuitable for African settings.[17]

Pediatric surgery

The global deficit of cancer surgeons has been quantified,[18] but similar figures are not available for pediatric oncology surgeons nor training programs[19–22] nor data describing the number of pediatric oncology surgeons.[19,20] In Africa, the number of general pediatric surgeons ranges from none in Mauritania to approximately two pediatric surgeons per million population in Gabon, with an estimated deficit up to approximately 700 surgeons.[19] This deficit in the surgical workforce and surgical services results in limited access to care and high surgical morbidity and mortality.[21,23,24] Patients with surgically resectable tumors are not offered curative resection in many African countries, therefore, a one day workshop at SIOP Africa 2022 was hosted by the International Society of Pediatric Surgical Oncology (IPSO), addressing GICC index solid tumors, with the intention to host similar events at future SIOP Africa conferences.

In Africa, training programs in pediatric surgery exist in a number of countries such as Ethiopia, Kenya, Malawi, Nigeria, Uganda, Zambia and Zimbabwe. Although during pediatric surgery training trainees are exposed to pediatric cancer cases, the College of Surgeons of East, Central, and Southern Africa and the West African College of Surgeons do not provide formal adult or pediatric cancer surgery training.[20] Egypt and South Africa remain the only countries that provide adult or pediatric cancer surgery training while the College of Surgeons of East, Central and Southern Africa incorporate practical pediatric cancer surgical components during training.[20,25] Super-specialization in pediatric cancer surgery is not feasible or cost effective, but didactic and practical components of pediatric cancer surgery during training is essential to sustain these skills in Africa.

Radiation oncologists with an interest in pediatric care

Access to radiotherapy in Africa is limited, due to a lack of trained radiation oncologists, radiotherapists and equipment.[26] The high rate of late presentation and patients requiring palliative radiotherapy for pain control leads to an increased need for radiotherapy services.

Pediatric radiotherapy is a highly skilled field requiring a broad understanding of pediatric oncology treatment regimens, local resources, late effects, best functional outcomes, and the best probability of local control and cure.[26,27] Although there are at least 11 African institutions training radiation oncologists, in a number of these the education and experience during training fall short of the needs of the pediatric oncology community.[27] Pediatric radiotherapy training remains a small part of radiation

oncology training programs and as a result, radiation oncologists frequently do not feel confident to treat children who require specific expertise and additional time.[26,28]

The International Atomic Energy Agency (IAEA) and the Global Access to Cancer Care Foundation collaborate with governing stakeholders to improve professional skills in radiation therapy and nuclear medicine through training courses, clinical education programs and e-learning platforms.[29] The Pediatric Radiation Oncology Society (PROS), advocates for educational programs with high standards, improved care in LMIC, multi-stakeholder cooperation and innovative pediatric radiation oncology education initiatives.[26] The IAEA's AFRONET provides talks on pediatric radiotherapy, and the IAEA is in process of developing a pediatric radiotherapy guideline with help from PROS LMIC, a SIOP Global Health Network (GHN) working group.

Pediatric radiotherapy training is offered as part of the Access to Care Cape Town project.[30] The society of neuro-oncology in Sub-Saharan Africa (SNOSSA) hosts monthly webinars which include pediatric neuro-radiotherapy.[31] PROS, together with IAEA, hosts an LMIC session at their annual conference and sources funding for travel scholarships allowing pediatric radiation therapy workers of all designations the opportunity to travel and learn. Other education tools include smartphone apps for cancer staging, telemedicine and virtual sessions and development of competency-based educational packages.

Auxiliary management of childhood cancers

Pediatric oncology pharmacy services

Chemotherapy security, safety and prevention of toxicity are important contributors to survival for children with cancer.[32,33] African pharmacists have limited exposure and experience in pediatrics during graduate and postgraduate training. Globally, one pediatric oncology pharmacy society and three pediatric pharmacy societies support pediatric oncology pharmacy, advocating for a structured, objective training program.[34–38] Continental awareness of the pharmacist's vital role in the MDT and further integration into the SIOP Africa community should be increased.[39] The early educational exposure to pediatric oncology pharmacy may potentially motivate pharmacists to further specialize, inhabiting defined roles in the MDT and increasing impact in improving outcomes in childhood cancer care.[39]

The newly formed SIOP Africa pharmacists group will meet virtually, organize workshops to formalize the African pediatric oncology pharmacy agenda and advocate for greater pediatric oncology pharmacy teaching in training programs where a pharmacist is trained in basic pharmacology, followed by pediatric pharmacy and pediatric oncology pharmacy.[40]

Nutritional services

Undernutrition at diagnosis in children with cancer is associated with increased treatment-related morbidity and abandonment of care.[41,42]

International Initiative for Pediatrics and Nutrition (IIPAN) launched a regional initiative in 2016 consisting of (1) mentorship training to doctoral candidates in

nutrition, (2) financial support to dieticians/nutritionists in African POUs, (3) support for ancillary personnel to assist IIPAN dieticians/nutritionists with routine assessments and (4) shadowing opportunities for nutritionists in South Africa. Currently eight African countries are supported with personnel and/or educational initiatives to advance nutritional care for children with cancer.

In 2017 the SIOP GHN nutrition committee surveyed POUs to delineate baseline standards of practice in nutritional care and barriers/facilitators of its delivery.[43] Inadequate staffing numbers, a lack of knowledge and educational opportunities were reported as barriers to care. SIOP GHN launched a collaboration with the IIPAN to increase staffing capacity within African POUs and to establish opportunities for education and advancement of clinical skills.[44]

SIOP GHN and IIPAN support regular workshops at biennial SIOP Africa conferences, monthly educational meetings and standalone educational programs.[43] Most recently, SIOP GHN, IIPAN, and World Child Cancer hosted a one-week intensive training program in Accra, Ghana. This training consisted of theory and clinical practice, followed by a practical exercise at POUs in Accra. Nutritional educational efforts should be included in cancer control plans.[43,44] This goal can only be achieved through advocacy and collaboration to ensure that training opportunities are part of standard training programs and accessible for all clinicians providing nutritional care to children with cancer.

Training nurses in aspects of palliative care

Palliative care, the comprehensive alleviation of all suffering associated with a life-threatening condition, is considered an essential component of Universal Health Coverage[45] and the CureAll technical package.[1] With up to 80% of children with cancer in LMIC presenting with advanced disease[46] making cure more difficult,[1] palliative care provision is essential. Education is a core component of the Public Health strategy for palliative care, the Conceptual Model of Palliative Care Development[46,47] and is recognized by the World Health Assembly (WHA) Resolution on Palliative Care.[48] With many LMIC having little or no children's palliative care provision[49] education and training is essential with most nurses asking for further training in children's palliative care.[50]

The SIOP Africa Nurses network identified childhood palliative care (CPC) for a workshop at SIOP Africa 2022 with the focus on pain assessment and management, management of symptoms other than pain, communication with children, advanced and end-of-life care planning and the role of the nurse in palliative care. Of increasing importance was building resilience amongst nurses working with children with cancer and in particular children's palliative care. These correlate well with the competencies identified, and previous educational needs assessments, along with the WHA resolution[50–53] with a resolution to develop an online CPC program by participants from Botswana, Malawi and Uganda.[54,55]

Additional training programs on CPC include the International Children's Palliative Care Network e-learning courses, the Education in Palliative and End-of-Life Care Africa course, the Diploma and Degree courses at Hospice Africa Uganda/Makerere University, amongst others. Palliative care should be an integral part of cancer care

for children and nurses should possess competencies of children's palliative care in order to address the complex needs of children with cancer.[1]

Advocacy as an education tool

Civil society groups play an important role in educating parents, families, healthcare staff, governmental and non-governmental organizations about issues specific to the childhood cancer experience.[56] The SIOP Africa 2022 Civil Society and Parents Symposium brought together stakeholders involved in psychosocial and supportive care of children with cancer to champion advocacy, awareness raising, psychosocial support and capacity building. The early warning signs (EWS) of childhood cancer to lower the rate of advanced stage at diagnosis and prevention of abandonment of treatment is a starting point at community level.[57,58] For health professionals training enables increased ability to identify cancers early and refer to experts. The Saint SILUAN mnemonic for EWS of childhood cancer was promulgated in 1999 and endorsed by SIOP as part of childhood cancer tools kits.[59] The advocacy increased referrals of children with cancer, but failed to increase referrals at earlier stages.[60] A longer, formal educational period with intermittent refresher courses was identified as a possible method to increase referrals of earlier stages of disease.[61] Targeting community trainers advocate and teach healthcare workers, traditional healers and communities on EWS, correct referral pathways and how to decrease stigma.[60] Although tools kits for advocacy and a number of organizations advocating in communities and to governments, exists in Africa, the training in advocacy, especially in childhood cancer, has not been developed.[62] The training should include understanding how to organize and mobilize constituencies in their regions, training, supporting and networking with other advocates, effective utilization of media and participating in debate, approaching policy makers as well as interpreting and participating in research to translate science into a communication tool for public communication.[63]

Poor treatment outcomes from childhood cancers are partially attributed to treatment abandonment, financial impoverishment, lack of information and knowledge about the condition.[64] In this case, community-based civil society organizations usually combine people from diverse backgrounds to raise awareness by sharing their lived experience.

The education of governmental and commercial entities about public-private partnerships in shaping common strategic directions have improved childhood cancer experiences and outcomes globally.[65,66] World Child Cancer (WCC) demonstrated how focused efforts can be cost-effective whilst improving childhood cancer management in sub-Saharan Africa by creating centers of experience in Ghana.[67] The model developed by the Policy and Economics Research in Childhood Cancer (PERCC) unit showed the cost of treatment per patient compared to daily adjusted life year (DALY) saved and compared this to the gross national income (GNI) per person.[68] The cost per DALY was less than the GNI per capita indicating that the Ghanaian project was cost-effective. The advocacy of the non-governmental organization WCC aided the development of a nursing education program in Ghana ranging from the Foundation Phase to Training the Trainers.[69] The benefit of this public-private partnership resulted in (1) increased numbers of trained medical, nursing and pharmacy specialists, (2)

development of national treatment guidelines and improvements in supportive care, (3) initiatives to decrease abandonment such as the establishment of funded family accommodation near POU.[70] The sustainability of childhood cancer care was ensured by the involvement of the Ghanaian Health Ministry through the National Childhood Cancer Strategy, with the sustainable supply of chemotherapy for four common childhood cancers by the government. The continued training of pediatric oncology nurses will be ensured by the commitment by the Ghana College of Nurses and Midwives (GCNM) to establish an accredited specialist program in pediatric oncology nursing.

Emerging researchers

Over the last decade, SIOP has prioritized Young SIOP to foster new talent, increase capacity, research and scientific skills.[71] There has been minimal engagement by Africans in this movement as African career pathways are often quite different to those in most HIC and the Young SIOP movement may exclude many clinician-researchers who start their research careers later. Few African countries have dedicated clinical research programmes.[6] Clinical research is a critical driver of novel therapies and quality of care to cure childhood cancer. Systematic development, implementation, and evaluation of standardized care practices are essential prerequisites to building a foundation for multi-center clinical research and incorporating these research discoveries into routine care.

The Young SIOP Africa/Emerging Researchers workshop during SIOP Africa 2022 is an example of developing academic and research competencies that should translate evidence-based research into standardized clinical practice.

Conclusion

The MDT ensuring improved outcomes for childhood malignancies reaches beyond the clinical and academic scopes of the POUs. All MDT members should be trained with a pediatric oncology curriculum, as any other specialties. Few formal African pediatric oncology curricula exist, but many non-core curriculum educational opportunities are available and were established out of the great need to cater for pediatric malignancies. Yet, training for especially auxiliary services is still lacking. The MDT structure is an integral part of national strategies such as pediatric cancer control plans (PCCCP). Quality, standardized training of the workforce is a prerequisite for quality childhood cancer care. Multi-stakeholder collaboration is paramount to develop an authentic curriculum addressing identified gaps, deliver outcome-based education, and equip teams with resource-adapted skills. A systematic approach is needed for implementation where teaching, learning, and assessment are planned according to the desired outcome in the local setting. Although there is a need for a larger trained pediatric oncology workforce, current training programs should focus quality while training a greater workforce, rather than increasing the number of countries with training programs.

Taking in consideration the current epidemiology of advanced disease presentation at diagnosis, high rates of abandonment and reasons for patients being lost to follow up, children's palliative care, dietetic services, civil society advocacy and training are

not optional extras, but part of the core management team. Therefore, when PCCP is developed, both Ministries of Health and Education should be engaged so that formal teaching and specialty curriculums are revised for doctors, nurses, pharmacists and dieticians. Practical opportunities to gain knowledge and experience should become a greater priority. Partnerships remain crucial but it is hoped/envisioned that more African training happens by Africans. The GICC has been embraced by most members of the MDT, encouraging progress.

Authors' contributions

All authors conceptualized, drafted and wrote the manuscript. All authors critically reviewed and authorized the final manuscript.

Disclosure statement

The authors declare that they have no conflicts of interest.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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Appendix A: Pre-and post-conference workshops and meetings

Wilms tumor Group and Collaborative African Network for Childhood Cancer Care and Research (CANCaRe Africa)

Chair: Trijn Israels

CANCaRe Africa is an inclusive platform for multi-center clinical research and improvement of care of children with cancer in sub-Saharan Africa. This meeting is a group of clinicians caring for children with cancer in Africa who give priority to interventions and projects with the highest expected impact on survival. The Wilms tumor Project aims for long term, sustainable impact by doing simple things well for children diagnosed with this kidney tumor. The meeting will focus on continuing the work done in this field.

Radiation Oncology Workshop

Chair: Jeannette Parkes

This workshop is supported by the *Pediatric* Radiation Oncology Society (PROS) and looks practically at some of the issues regarding provision of pediatric radiotherapy. The workshop provides practical case-based information on contouring and planning for common pediatric malignancies.

Groupe Franco-Africain d'Oncologie Pédiatrique (GFOAP) meeting

Chair: Laila Hessissen

Founded in 2000 by African and French doctors, the Franco-African Group of Pediatric (GFOAP) Oncology is a medical association that brings together within its network specialists in childhood cancer in 18 countries of the Maghreb and Sub-Saharan Africa. Around a common and innovative vision: "Children with cancer in Africa can and should be treated locally by trained staff."

Alliance Mondiale Contre le Cancer (AMCC) Retinoblastoma Workshop

Theme: Retinoblastoma in sub-Saharan Africa

Chair: Karim Assani

The Retinoblastoma Workshop aims to bring together retinoblastoma multidisciplinary teams of eastern Africa, Ghana and Mozambique. The primary goal is to bring eye cancer specialists from all those countries to discuss retinoblastoma care, challenges and actions that can be taken to improve early diagnosis and reduce mortality in the context of sub-Saharan Africa. AMCC has made a commitment to support retinoblastoma multidisciplinary teams. This effort aims to improve survival rate beyond 70% in 2028 for this most common eye cancer in children.

Young SIOP Africa Educational day

Theme: Standardization of care as a foundation for pediatric cancer cooperative group research in Africa.

Chair: Jennifer Geel

Clinical research is a critical driver of novel therapies and quality of care that results in the cure of childhood cancer. Systematic development, implementation, and evaluation of standardized care practices are an essential prerequisite to building a foundation for multi-center clinical research and incorporating these research discoveries into routine care. The purpose of this session is to explore methods that foster standardization of care that enables the conduct of multicenter pediatric cancer across Africa.

Nurses Children's Palliative Care Workshop

Chair: Julia Downing

This workshop will introduce you to the principles and practice of palliative care and its integration into the management of children with cancer. A range of topics will be discussed including pain assessment and management, communication, managing other symptoms, advanced care planning, end of life care, the nurses role and caring for ourselves. Experienced facilitators from the International Children's Palliative Care Network (ICPCN), the Palliative Care Education and Research Consortium (PcERC) and World Child Cancer (WCC) will lead an interactive day of sessions and provide opportunities for discussion and sharing experiences.

Civil Society and Parents Symposium

Chair: Paul Ebusu

The patients are the primary reason why we are engaged in the discussion of how childhood cancer prevention, care and management, as well as rehabilitation/reintegration of survivors can be improved. This means that there must be nothing for the patients without the patients and their caregivers who are living through the experience. As opposed to adult cancers, childhood cancer care may not succeed without the parents as caregivers, supporting and providing for the children during the process of receiving care. Civil society organizations usually combine people from diverse backgrounds trying to make a contribution across the continuum of childhood cancer care. They are drawn in to address specific gaps as they may find fit and where they respectively believe their skillsets, expertise and more so passion may befit. As such, a number of civil society organizations are formations based on experiences of individuals and groups who have lived through the experiences of childhood cancer itself. It also involves practitioners and professionals who believe they can make a difference in the fight against childhood cancer and support the work of government in one way or another.

With this workshop we aim to bring together these groups involved in the management of children with cancer and discuss initiatives to benefit their experience during treatment.

IPSO Surgical Symposium on pediatric oncology surgery

Chair: Hafeez Abdelhafeez

The Surgery workshop will focus on surgical management of pediatric index solid tumors. Management challenges will be discussed across the three phases: preoperative, operative, and postoperative. The workshop will be a hybrid in person and virtual active discussion with demonstrations.

The ARIA Adapted Management Guidelines workshop

Chair: Jaques van Heerden

The Adapted Treatment Regimens workshop will be an interactive workshop led by African and International experts who have developed resource-based management guidelines and protocols for the African setting. The workshop will focus on a practical approach in initiating the development of treatment approaches for the MDT independent of tumor type or resource setting. The workshop aims to mentor participants in the development process and stimulate problem solving abilities during the development of guidelines or protocols.

Pediatric Oncology Pharmacy Workshop

Chair: Shauna Georgia Odongo Arao

It is with pride that we are conducting the first pediatric oncology pharmacy workshop hosted by SIOP Africa that includes various stakeholders in the management of childhood cancers. The workshop aims for pharmacists to acquaint themselves with the new innovations that contribute to the management in the pediatric oncology pharmacy world. These may assist pharmacists to face the challenges associated with care in the African setting.

World Child Cancer Workshop

Theme: 'Improving Childhood Cancer Management in Sub-Saharan Africa'

Chair: Alan Davidson

This workshop will provide a space to share experiences on improving childhood cancer management and supporting the establishment of a center of excellence for pediatric oncology in Sub-Saharan Africa. During the session we will discuss main challenges, successes, lessons learned and plans for the future. There will be a special focus on the cost effectiveness of human resources interventions. The workshop is aimed at pediatric oncologists, nurses, professors, and anyone that has worked and is interested in the field of pediatric oncology. The session is hosted by World Child Cancer, a leading international children's charity dedicated to improving services for children with cancer since 2007.

Nutrition Workshop

Chairs: Elena J Ladas, Judy Schoeman and Michelle Walters

This workshop will review fundamentals in nutrition assessment and intervention as well as provide instruction on the management of challenging nutrition conditions common in childhood cancer and challenging for their management in LMICs.

Appendix B: Topics from the SIOP Africa 2022 pre- and post-conference workshops

Radiation oncology workshop program

Theme	Presenter
Pediatric radiotherapy: Why is it different to adult radiotherapy?	Thurandrie Naiker (South Africa)
Treating children in LMIC: When to use which technology?	Jeanette Parkes (South Africa)
Radiology: Imaging for pituitary fossa tumors	Tracy Kilborn (South Africa)
Pediatric anesthesia for radiotherapy	Graeme Wilson (South Africa)
What the pediatric oncologist needs from the radio oncologist	Alan Davidson (South Africa)
The role of the radiation therapist in pediatric radiotherapy	Daniella Marziale (South Africa)
Contouring the organs at risk in pediatric radiotherapy	Michelle Kwok-Williams (UK)
Late effects in pediatric radiotherapy	Michelle Kwok-Williams (UK)
Wilms tumor: Fast facts and cases	Jeannette Parkes (South Africa)
Palliative radiotherapy for children: Fast facts and cases	Thurandrie Naiker (South Africa)
Rhabdomyosarcoma: Fast facts and cases	Natia Esiashvili (USA)
Medulloblastoma: Fast facts and cases	Arnold Paulino (USA)

Young SIOP educational day

Theme	Presenter
Hodgkin Lymphoma	Nmazuo Ozuah (Malawi)
Acute lymphoblastic leukemia	Janet Poole (South Africa)
Burkitt Lymphoma	Catherine Patte (France)
Nephroblastoma	Wilms tumor group
Retinoblastoma	Pierre Bey (GFAOP, France
Low grade glioma	Moatasem Elayadi (Egypt)
Approaches and strategies to integrate clinical research into busy clinical workflows	Philipa Musoke (Uganda)
Pathways to research leadership careers to improve patient outcomes in Africa.	Nelson Sewankambo (Uganda)
Writing abstracts for conferences and publications	Jennifer Geel (South Africa)
Translating research evidence into standardized clinical practice	Marilyn Hockenberry (USA)
Standardization of care: clinical protocols	Lisa Bomgaars (USA
Publishing and Peer Review	Carl Allen (USA

Children's palliative care in cancer care workshop

Theme	Presenter
The principles of palliative care and integration into the management of children with cancer	Julia Downing (ICPCN) UK
Pain assessment and management in children with cancer	Liz Nabirye (PcERC) Uganda
Communicating with children in palliative care	Florence Nalutaaya (PcERC) Uganda
Communicating diagnosis and prognosis with children and their parents	Alex Daniels (ICPCN) South Africa
Managing symptoms other than pain	Florence Nalutaaya (PcERC) Uganda
Advanced care planning and end-of-life care	Liz Nabirye (PcERC) Uganda
The nurse's role in children's palliative care as an integral member of the multidisciplinary team	Alex Daniels (ICPCN) South Africa
Caring for ourselves—managing stress and coping strategies	Megan Cruise (WCC) UK

ARIA Adapted Management Guidelines Workshop Program

Theme	Presenter(s)
Pre-workshop educational sessions	
ARIA (Adapted Resource and Implementation Application for Childhood Cancer Guidelines)	Michael Sullivan Australia
Guideline Methods with update on SIOP Africa Guideline	Sheena Mukkada USA
Quality Improvement methods	Paola Friedrich USA
Implementation science	Caitly Dufft USA
Managing symptoms other than pain	Florence Nalutaaya (PcERC) Uganda
Facilitator led discussions	
Facilitator led group discussions on: • Multi-disciplinary team and adapted management guidelines • Local resources • Research and answering questions • Data management • Guideline Development Methods	Joyce Balagadde-Kambugu (Uganda) Alan Davidson (South Africa) Moatasem Elayadi (Egypt) Jennifer Geel (South Africa) Laila Hessissen (Morocco) Marc Hendricks (South Africa) Vivian Paintsil (Uganda) Jaques van Heerden (South Africa/ Belgium) Jeanette Parkes (South Africa)
Panel led discussion	
Developing pediatric services in resource limited setting " Real World Experience" • Pediatric oncology • Pediatric surgery • Pediatric radiotherapy • -Palliative care	Panel consisting of: Alan Davidson Pediatric oncologist: Vivian Paintsil Radio-oncologist: Thuran Naiker Pediatric surgeon: Helen Martelli Palliative care expert: Lyndal Gibbs
Facilitator led group discussions	
The application of evidence-based adapted management guidelines in the six focus childhood cancers: retinoblastoma, Wilms' tumor, acute lymphoblastic leukemia, Hodgkin lymphoma, low grade gliomas and Burkitt lymphoma	Joyce Balagadde-Kambugu (Uganda) Alan Davidson (South Africa) Moatasem Elayadi (Egypt) Jennifer Geel (South Africa) Laila Hessissen (Morocco) Marc Hendricks (South Africa) Vivian Paintsil (Egypt) Jaques van Heerden (South Africa/ Belgium) Jeanette Parkes (South Africa)

IPSO surgical symposium

Theme	Presenter
Pediatric Surgical oncology in practice in Uganda. A journey of 20 years	John Sekabira (Uganda)
Vascular Access and modifications for LMIC	Sharon Cox (South Africa)
Wilms: principles of surgical management	Nasser Kakembo (Uganda)
Wilms: Surgical Challenges—bilateral, IVC extension, massive tumor	Derek Harrison (South Africa)
Hepatoblastoma principles of surgical management and challenges	Hafeez Abdelhafeez (USA)
Germ Cells tumor surgical principles and challenges	Bindi Jayendra Naik-Mathuria (USA)
Sarcoma principles of surgical management and challenges	Hafeez Abdelhafeez (USA)
Neuroblastoma principles of surgical management and challenges	Jed Nuchtern (USA)
Case discussions	
Nephroblastoma	Rovine Naluyimbazi (Uganda)
Neuroblastoma	Kagiso Batka (South Africa)
Pelvic Rhabdomyosarcoma	Stella Nimanya (Uganda)
Germ cell tumor	Amarylis Mapurisa (Malaw
Hepatoblastoma	Cecelia Rengura (Namibia)

Pediatric Oncology Pharmacy workshop

Theme	Presenter
Pediatric Oncology Pharmacy in Africa	Shauna Georgia Odongo Arao (Uganda)
Use of off-label and off-license drugs in the pediatric oncology pharmacy	Deogratius Kyambadde (Uganda)
Safety of Chemotherapy preparation and new innovations	Alfred Komakech (Uganda)
Access to pediatric medicines "Complementary medicine"	Adeka Boniface (Uganda)
Clinical Trials for the pediatric population in Africa	Kyambadde Deo (Uganda)
Nutrition innovations for the pediatric population	Benjamin Mwesige (Uganda)
Pharmaceutical Care after Medical Interventions	Brian Mugerwa (Uganda)
Experience of innovativeness in pediatric oncology from a healthcare professional (pharmacist) who is from a different African country	Atalay Mulu Fentie (Ethiopia)

Nutrition Workshop

Theme	Presenter
Overview of IIPAN activities in Africa	Elena J. Ladas (USA)
SIOP Global health nutrition	Judy Schoeman (South Africa)
Nutritional assessment of children with advanced diseases	Anna Henrh (Tanzania)
Tube feeding in patients with large abdominal masses	Judy Schoeman (South Africa)
Common complications associated with the nutritional management of children with Stage III/IV solid tumors	Minke Huibers (The Netherlands)
The role of appetite stimulants in childhood cancer	Karina Viani (Brazil)
Nutritional complications of cancer patients with liver impairment	Maha Barbar (Jordan)
Nutritional modification with compromised kidney function (virtual)	Michelle Walters (USA)
Nutritional management of children with severe acute malnutrition and newly diagnosed cancer	Elena J. Ladas (USA)
Case presentation: Nutrition support in patients with mucositis and severe acute malnutrition	Diriba Fufa (Ethiopia)
Case presentation: Tube feeding with advanced disease	Primus Ewald (Tanzania)
Case presentation: Total parenteral nutrition	Barbara Muliro (Kenya)
Case presentation: Severe acute malnutrition	Joseph Mary Semujju (Uganda)

Received: 29 September 2019 | Revised: 20 January 2020 | Accepted: 25 January 2020

DOI: 10.1002/pbc.28211

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

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WILEY

SUPPLEMENT ARTICLE

Assessment of nutritional status in children with cancer: A narrative review

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Abstract

A child's appropriate development stems in large part from proper nutrition. Malnutrition is an adverse prognostic factor in children with cancer, and its prevalence is highly variable. Currently, there is no standardized definition and assessment method of nutritional status in pediatric oncology. A complete nutritional assessment includes anthropometry, biochemical, clinical, and dietary assessments. In this article, we explore these methods and suggest practical approaches for pediatric cancer units depending on the levels of care that these can provide. We also advise on the monitoring and follow-up of children with cancer during and after treatment, and discuss potential areas for future research.

KEYWORDS

anthropometry, levels of care, malnutrition, nutritional assessment, pediatric oncology

1 | INTRODUCTION

"If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have the safest way to health" (Hippocrates). The outcome of pediatric cancer is one of the success stories of the last century. However, the excellent outcome is restricted to high-income countries (HICs).[1] A large majority of children with cancer live in low- and middle-income countries (LMICs) and frequently have associated comorbidities, one of them being undernutrition, a modifiable risk factor for the outcome in pediatric malignancies.[2,3] In HICs, overweight and obesity is a public health issue and impacts cancer survival. Thus, it is also a modifiable prognostic factor.[4,5] The "double burden" of malnutrition is an increasing problem in LMICs.[6] In order to address these modifiable nutritional prognostic factors, it becomes necessary to implement longitudinal nutritional assessment in children with cancer, on the basis of which well-informed, appropriate nutritional interventions can be implemented. This article is written in the context of a comprehensive supplement of *PBC* on nutritional perspectives in pediatric oncology.

Nutrition is essential for appropriate growth and development and a critical component in optimization of clinical outcomes. Malnutrition, which includes under and overnutrition, has an adverse effect on health and health-related quality of life.[7] The importance of an optimal nourished state cannot be overemphasized. Undernutrition, which is rampant in LMICs, can increase treatment-related morbidities, mortality, and abandonment of therapy, as well as negatively affect quality of life.[7-10] Overnutrition is also associated with adverse clinical outcomes.[3,11]

Traditionally, nutritional assessment is performed by (i) anthropometric measurements, (ii) biochemistry, (iii) clinical assessment, and (iv) dietary history. Assessment is a dynamic process and is required at diagnosis, during therapy, and survivorship to evaluate the child's

Abbreviations: ALL, acute lymphoblastic leukemia; AMDR, acceptable macronutrient dietary ranges; BIA, bioelectrical impedance analysis; BMI, body mass index; BMI/A, body mass index for age; CRP, serum c-reactive protein; CT, computerized tomography; DXA, dual energy X-ray absorptiometry; EFS, event-free survival; H/A, height-for-age; HC, hip circumference; HICs, high-income countries; HSCT, hematopoietic stem cell transplant; LMICs, low- and middle-income countries; MUAC, mid-upper arm circumference; MUAC/A, mid-upper arm circumference for age; PODC, Pediatric Oncology in Developing Countries; SAM, severe acute malnutrition; SIOP, International Society of Pediatric Oncology; TSFT, triceps skinfold thickness; TSFT/A, triceps skinfold thickness for age; UNICEF, United Nations Children's Fund; W/A, weight for age; W/H, weight for height; W/H, weight for height; WC, waist circumference; WHO, World Health Organization; WHR, waist-to-hip ratio.

TABLE 1 High-risk factors for malnutrition (undernutrition and overnutrition) in children with cancer[12,16,56,62,63]

Diagnosis
Solid tumors in advanced stages (neuroblastoma, Wilms tumor, rhabdomyosarcoma, Ewing sarcoma)
Central nervous system tumors (craniopharyngioma, medulloblastoma, astrocytoma, ependymoma)
High-risk acute lymphoblastic leukemia, lymphoma
Nasopharyngeal carcinoma
Multiple relapsed and high-risk leukemias
Treatment
Irradiation to the gastrointestinal tract
High-dose cranial/craniospinal radiotherapy
Prolonged corticosteroid therapy with large doses
Major abdominal surgery
Undergoing HSCT or presenting graft vs host disease
Symptoms
Nausea, vomiting
Diarrhea
Severe mucositis
Patient demographics
Infancy
Anthropometry
W/H or BMI/A Z-score < −2 or > +2
MUAC < percentile 10 or > percentile 90
Weight loss or poor weight gain during the last few weeks
Dietary intake
Inability to meet energy and protein needs for the last few days

Abbreviations: BMI/A, body mass index for age; MUAC, mid-upper arm circumference; W/H, weight for height.

TABLE 2 Nutritional screening tools for risk assessment of malnutrition in children and adolescents

Screening tool	Information collected to determine the risk of malnutrition
Simple Pediatric Nutritional Risk Score to identify children at risk of malnutrition (PNRS)[54]	Anthropometric data Food intake Gastrointestinal problems (diarrhea and vomiting) Symptoms that may interfere with appetite (pain, dyspnea, depression) Disease classified according to severity
Screening Tool for the Assessment of Malnutrition in Paediatrics (STAMP)[55]	Weight and height Questions regarding food intake and disease risk
Screening Tool for Risk of Nutritional Status and Growth (Strong $_{Kids}$)[56]	Subjective clinical evaluation of undernutrition High risk of undernutrition Food intake Weight loss or other losses (diarrhea, nausea, vomiting)
Pediatric Yorkill Malnutrition Score (PYMS)[64]	Body mass index Recent weight Loss Changes in food intake
Nutrition screening tool for childhood cancer (SCAN)[18]	Type of cancer determines whether or not there is a risk of malnutrition Intensity of treatment (chemotherapy, radiotherapy, HSCT)
*Pediatric oncology-specific instrument	Gastrointestinal complications and symptoms Food intake Weight loss Subjective clinical evaluation of malnutrition

HSCT: hematopoietic stem cell transplant.

nutritional status and the adequacy of intake to allow for appropriate timely intervention.[12] However, to date, there are no standard clinical practice guidelines for the prospective uniform monitoring of the nutritional status in children with cancer.[13-15] In this article, we revise methods for nutritional assessment to determine the nutritional status of children with cancer, which can be adapted to the resources and levels of care of each institution.

2 | NUTRITIONAL ASSESSMENT METHODS

The Nutrition Working Group (NWG) of the International Society of Pediatric Oncology (SIOP), Committee on Pediatric Oncology in Developing Countries (PODC) recommends a standardized method of nutritional assessment of children with cancer.[16] The assessment needs to be simple and cost effective, and done with ease even in resource-limited settings. In most LMICs, the goal is to determine a child's nutritional status with minimal assessments.

The extent of the nutritional assessment is dependent on the infrastructure and personnel of the pediatric cancer unit. The NWG recommends the minimum nutritional assessment to include weight, height, and mid-upper arm circumference (MUAC), plotted on growth charts, calculation of body mass index (BMI), along with a directed clinical examination for signs of inadequate intake and micronutrient deficiencies. As capacity increases, nutritional laboratory tests can be undertaken, as well as an in-depth dietary intake analysis together with advanced body composition studies.[16]

2.1 | Nutrition screening tools

In institutions with limited resources, a screening tool can be used, and patients at higher risk for nutritional depletion can be prioritized. Nutritional screening in pediatrics aims to recognize patients at risk to enable proactive care to those at the highest need of nutrition intervention. In children with cancer, however, most patients present a baseline degree of nutritional risk, depending on the type and stage of the malignancy. For example, patients with advanced disease, receiving intensive therapy and having borderline nutritional status at diagnosis have high nutritional risk, as presented in Table 1.

There are various screening tools in pediatrics to assess a child's nutritional risk; some are depicted in Table 2. There is insufficient

TABLE 3 Anthropometry parameters in order of importance according to the level of care[16,32]

Level of care	Levels 0 and 1 (none and basic)	Level 2 (limited care)	Levels 3 and 4 (optimal and maximal care)
Parameters	Height	Height	Height
	Weight	Weight	Weight
	MUAC	MUAC	MUAC
	H/A	H/A	H/A
	W/A	W/A	W/A
	W/H	W/H	W/H
	MUAC/A	MUAC/A	MUAC/A
		BMI/A	BMI/A
		TSFT	TSFT
		TSFT/A	TSFT/A
		Waist circumference	Waist circumference
			BIA
			DXA
Frequency	None Follow-up at-risk patients if possible, on scheduled visits	Follow-up at-risk patients on scheduled visits	Routine follow-up visits

Abbreviations: BIA, bioelectrical impedance analysis; BMI/A, body mass index for age; DEXA, dual energy X-ray absorptiometry; H/A, height for age; MUAC, mid-upper arm circumference; MUAC/A, mid-upper arm circumference for age; TSFT, triceps skinfold thickness; TSFT/A, triceps skinfold thickness for age; W/A, weight for age; W/H, weight for height.

evidence to choose one over another based on their predictive accuracy; however, it is important to use validated instruments. The subjective global nutritional assessment (SGNA) for children is a validated tool able to predict nutrition-related complications in pediatrics.[17] SCAN is the only nutritional screening tool developed specifically for childhood cancer, identifying patients at risk for nutritional compromise based on a simple scoring system determined by the patients' dietary intake, weight loss, type and stage of disease, treatment, and clinical signs of undernutrition.[18]

2.2 | Anthropometric measures

The World Health Organization (WHO) uses weight, height, and BMI for classifying a patient's nutritional status. These measurements are then plotted on WHO growth charts or data tables according to age and gender to determine the appropriate percentile or Z-score for height for age (H/A), weight for age (W/A), weight for height (W/H), BMI for age (BMI/A), MUAC for age (MUAC/A), and triceps skinfold thickness (TSFT) for age (TSFT/A). The Z-score determines if the child is stunted, underweight, or wasted.[19,20] The parameters used in the different levels of care as described by SIOP PODC are given in Table 3. The classification of nutritional status based on weight and height has drawbacks for children with cancer as measures of weight can be distorted by large tumor masses, hydration status, and organomegaly.[21] MUAC is a cheap, rapid, and easy measurement of a child's nutritional status, and one that is sensitive for measuring musculature, available protein stores, and lean body mass. Arm anthropometry is considered more sensitive in the nutritional assessment of children with cancer as it has the advantage of being independent of abdominal tumor mass, temporary gains in total body water, and ethnicity.[4,8,21-23] SIOP PODC recommends that MUAC be used as an anthropometric measurement in children with malignancies.[4,16]

TABLE 4 SIOP PODC recommendations for nutritional status cutoffs[4,19]

Age group	Acute malnutrition	SAM
6 months to five years	MUAC < 12.5 cm	MUAC < 11.0 cm
> 5 years *without* tumor mass	W/H < −2 Z-score	W/H < −3 Z-score
> 5 years *with* a tumor mass	MUAC < 13.5 cm	MUAC < 11.5 cm

Abbreviations: MUAC, mid-upper arm circumference; W/H, weight for height; SAM, severe acute malnutrition.

It is essential to ensure the correct methods of measurements of all parameters in monitoring nutritional status as described by the United Nations Children's Fund (UNICEF) and WHO.[24] MUAC measurements in children under five years of age can be done with the UNICEF color band as seen in Figure 1,[24] and for older children a nonstretching measuring tape can be used.[4,25] A MUAC less than < 110 mm is indicative of severe acute malnutrition (SAM), whereas for older children, measurements less than the 5th percentile or −2 Z-score for age and sex indicates undernutrition.[4,26] The SIOP PODC recommendations for assessing children with cancer to determine nutritional status by MUAC are given in Table 4 and are feasible for centers levels 0 and 1.[4,16]

As an example, we assess a six-year-old female admitted with a big abdominal mass. On anthropometric evaluation, she weighs 18.5 kg (W/A Z-score −0.60), has a height of 119 cm (H/A Z-score 0.75), and BMI/A Z-score −1.67 (by WHO growth charts). Her MUAC is 105 mm (Z-score < −3). Although the BMI diagnoses a normal child with a risk for undernourishment, MUAC indicates SAM. The evident discrepancy

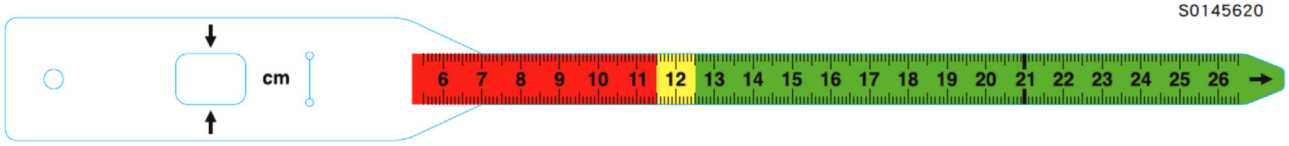

FIGURE 1 UNICEF mid-upper arm circumference (MUAC) color band. Green indicates good nourishment, yellow moderate acute malnutrition, and red indicates severe acute malnutrition (SAM)

TABLE 5 Biochemical parameters to determine nutritional status[22,31]

Level of care	Levels 0 and 1 (none and basic)	Level 2 (limited care)	Levels 3 and 4 (optimal and maximal care)
Parameters protein status	Albumin (half-life 14-21 days)	Albumin (half-life 14-21 days)	Albumin (half-life 14-21 days)
		Transferrin (half-life 8-9 days)	Transferrin (half-life 8-9 days)
			Prealbumin (half-life 2-3 days)
			Retinol binding protein (half-life 12 hours)
Parameters electrolytes	Magnesium	Magnesium	Magnesium
		Calcium	Calcium
			Zinc
			Selenium
Parameters vitamins	Thiamine (vitamin B1)	Thiamine (vitamin B1)	Thiamine (vitamin B1)
		Cobalamin (vitamin B12)	Cobalamin (vitamin B12)
			Riboflavin (vitamin B2)
			Vitamin A
			Vitamin D
			Vitamin E
Frequency	0. None 1. Follow-up at-risk patients if possible, on scheduled visits	Follow-up at-risk patients on scheduled visits	Routine follow-up visits

supports MUAC to be a better indicator of nutritional status in children with cancer at diagnosis, attributed to a falsely elevated weight owing to the abdominal mass.

2.3 | Body composition

Cancer treatment can alter the energy reserves in muscle and fat. An evaluation to identify the type of nutritional impairment, adipose and/or muscle, is required. Fat and fat-free mass can be reflected by MUAC, TSFT, dual energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), and quantitative computerized tomography (CT) scan, among other techniques.[27,28] BMI is unable to distinguish between fat mass and lean mass, rendering it a poor measure for body composition.[27] Body composition can be appraised by sophisticated methods such as total body potassium and air plethysmography, with the current clinical gold standard being DXA.[28] BIA measures total body water, fat mass, and fat-free mass by calculating resistance of the body to a small alternating current. Regression equations used to estimate body composition are based on a specific population and thus are useful for subjects who match the control population in size and shape. The available BIA prediction equations are, however, not suitable for obese children, as hydration of fat-free mass decreases in obesity, leading to underestimation of fat-free mass in these individuals.[29]

DXA has been described as the most commonly used densitometric technique for children throughout the world as it gives accurate measures of whole-body fat mass, lean body mass, and bone mineral content. Its advantages include accuracy and reproducibility; however, it does not discern visceral from subcutaneous fat, which can be done with three-dimensional imaging techniques.[27] DXA scans and CT imaging are recommended for body composition analysis when available.

It is to be noted that body composition can also be easily assessed by simple anthropometric measures. MUAC is a validated measure for assessing fat-free mass and TSFT measures the fat mass.[22] These measures can be done in any setting, obviating the need of expensive equipment. Sophisticated methods of body composition are not easily available in routine clinical practice and are only recommended for centers with compatible capacity.

2.4 | Biochemical evaluation

Biochemical measures can give additional information about a patient's protein status *(serum albumin, pre-albumin, transferrin, and creatinine)*,[22] organ function (serum urea, creatinine, and liver enzymes),[12] bone health (serum calcium, magnesium, and vitamin D), anemia (iron studies and vitamin levels), evidence of inflammation (serum c-reactive protein [CRP]), and nutritional deficiency (specific mineral- and vitamin levels),[30] as depicted in Table 5. Albumin is commonly used as an index of nutritional assessment, with a value of < 32 g/L being taken as low.[8] However, it is affected by hydration status, inflammation, and liver function. A study in 40 children with cancer found hypoalbuminemia to be a poor indicator of undernourished status as it was not associated with weight loss during treatment.[31] However, as reported by Sala et al. in a study of more than 1500 children with cancer at diagnosis in Central America, the addition of low albumin levels to MUAC and TSFT at diagnosis increased the proportion of those who were classified as severely nutritionally depleted from 45% to 59%.[3]

In LMICs, expensive laboratory tests are not routinely available. Depending on the institutional infrastructure, nutritional laboratory tests can be done to screen for endemic and preventable micronutrient

TABLE 6 Clinical signs[32,37]

Parameters clinical status	Presence of muscle wasting
	Loss of subcutaneous fat
	Recent weight change (*loss must not be related to fluid retention or loss of fluid*)
	Presence of edema at ankles, sacrum or face
	Hair changes *hair changes, sparse, depigmentation)*
	Eye changes *(dry conjunctiva, keratomalacia)*
	General signs of vitamin and mineral deficiency
Conditions that may affect the nutritional status	Inability to chew and swallow Loss of appetite Presence of vomiting, diarrhea, constipation, flatulence, belching or indigestion

deficiencies in at-risk patients.[16] Table 5 details the tests that can be done according to different levels of care.[16]

2.5 | Clinical assessment

A child needs to undergo regular clinical assessment for signs of malnutrition and vitamin and/or mineral deficiencies (Table 6). Evaluation of loss of subcutaneous fat, muscle wasting, skin and hair changes, recent change in weight, edema, and evidence of vitamin and mineral deficiencies are vital in children with undernutrition.[25,32-34]

Nutritional status is also often affected by the patient's primary disease, associated comorbidities such as tuberculosis, HIV, and parasitic infections. The treatment of the malignancy per se can compromise the nutritional status by the issues of inability to chew and swallow, the presence of vomiting, loss of appetite, diarrhea, constipation, flatulence, belching or indigestion, mucositis, nausea, dysphagia, taste aversions, and xerostomia.[4,22,32] Furthermore, hospitalization, especially when prolonged, can be very stressful for the children and their families and significantly impact the patient's social life and mental health, resulting in a compromised nutritional status.[35]

2.6 | Dietary intake

Children with cancer require a diet adequate in protein and energy during treatment. A poor oral intake can lead to deterioration of nutritional status affecting immune status and organ dysfunction, thus requiring intervention.[4,32] Therefore, a complete dietary history is required for a nutritional assessment. Baseline evaluation should include dietary history to ascertain the intake of macro- and micronutrients and identify known food aversions, allergies, or intolerances.[12] A retrospective food recall of food and drinks, as well as the quantity the child consumed in the past 24 hours, is a simple and feasible method that allows the assessment of dietary quality and composition. The habitual daily intake of food items consumed during the past week at home can be included, as this is invaluable for determining current eating patterns, family behavior as well as food security at home.[36,37] The recommended macronutrient intake for children can be based upon the acceptable macronutrient dietary ranges (AMDR), which present ranges as a percentage of total calories. For fat, 30% to 40% is recommended between the ages of 1 and 3 years, and 25% to 35% between the ages of 4 and 18 years, with 45% to 65% of energy from carbohydrate, and 10% to 35% from protein.[38]

3 | MONITORING AND FOLLOW-UP

Children with cancer often undergo treatment for prolonged periods of time depending on disease state and response to therapy. Regular nutritional monitoring, during and after treatment, is essential to ensure adequate growth and development, provide appropriate interventions when required, and prevent worsening of a child's nutritional state. The nutritional risk changes with time according to duration and intensity of treatment. The patient's follow-up with a dietitian should conform to the intensity of treatment and consist of a nutritional support strategy adapted to individual nutritional needs, nutritional status, gastrointestinal function, and current or expected side effects of treatment. Patients receiving periods of intensive treatment require follow-up at a maximum interval of 3 weeks. Children on less intensive treatment need to be optimally evaluated three monthly, and six to 12 monthly intervals while on the maintenance phase of treatment. The intensity of treatment can be evaluated according to the intensity of treatment rating scale.[39]

Ideally, we suggest that all patients be provided with routine follow-up assessments as constant nutritional monitoring consults are important opportunities to provide the home caregiver with continuing nutrition education. However, this may not be feasible for many pediatric cancer units, since repeated visits require resources and trained personnel. It is recommended that, depending on institutional nutritional infrastructure, nutritionally at-risk patients should be followed up as a priority, when possible, on a consistent schedule.[16]

4 | NUTRITIONAL ASSESSMENT IN SURVIVORS

The nutritional status is dynamic, and nutritional changes in survivors are often overlooked because of lack of follow-up. Nutritional assessment and guidance should start soon after the oncological diagnosis and extend through survivorship. This aids in preventing or reversing nutritional deficiencies, preserves lean body mass, minimizes nutrition-related side effects, and improves the quality of life of future survivors.[40] Priority must be given to patients who underwent hematopoietic stem cell transplantation or prolonged intensive chemotherapy, especially at a younger age, as they are more prone to nutrition-related late effects of cancer therapy.[41,42] Survivors of childhood cancer have an increased risk of developing metabolic syndrome and reduced bone mass as treatment-related side effects. Bone mass reduction may be exacerbated by vitamin D deficiency during

TABLE 7 Proposed nutritional assessment for childhood cancer survivors

Nutritional risk	Proposal
No nutritional risks	First year: every six months After first year: annually
Presence of nutritional risk (inadequate eating habits, hypertriglyceridemia, high cholesterol levels, etc.), or well-nourished	First year: every three months Second to fifth years: every six months From fifth year onward: annually
Undernourished	Monthly assessment until normal nutrition status
Obese	Every three months

and after completion of therapy.[43-46] Additionally, patients with other nutritional risk factors, such as inadequate eating habits, smoking, sedentary lifestyle, alcoholism, require follow-up. On completion of the treatment for the primary disease, a nutrition follow-up timeline and recommended evaluations should be established. Nutritional education should be part of this follow-up.[47] A suggested plan is outlined in Table 7.

Waist circumference (WC) and hip circumference (HC) are used to determine the waist-to-hip ratio (WHR). The cutoff points for WC, indicating increased visceral fat, classification are 80 cm for women and 94 cm for men.[48] To determine the risk of cardiovascular disease, the cutoff point for WHR is 0.85 for women and 0.90 for men.[48] Furthermore, waist-to-height ratio, a proxy for central (visceral) adipose tissue, has been shown to be better than BMI for obesity classification in childhood cancer survivors.[49] BMI, from 18 years of age, is categorized as underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2), or obese (BMI ≥ 30 kg/m^2).[50] To assess the dietary intake of survivors, we suggest habitual daily intake or 24-hour recalls to be utilized. Some laboratory tests (lipids, cholesterol, creatinine, fasting blood sugar, calcium, and vitamin D) may improve the detection of nutritional abnormalities. TSFT, biceps, subscapular, and suprailiac skinfolds can be used to estimate body fat percentage.[51] However, for centers with limited resources, we suggest BMI along with WC and MUAC, an evaluation of diet quality and nutritional clinical examination are sufficient for the assessment of survivors. In resource-rich centers, whole body composition, best analyzed using DXA, is recommended to evaluate sarcopenic obesity, which cannot be assessed by BMI.

5 | NUTRITIONAL ASSESSMENT AS A RESEARCH TOOL

No "gold standard" for nutritional assessment in children with cancer has achieved consensus opinion in studies of nutrition and outcome. Complete accurate and continuous nutritional assessment is required to enable research with regard to nutrition and its complex relationship with the response to therapy, prognosis, and survival. This will also help establish research priorities and clinical interventions, adapted to different levels of care.

Areas for research include (i) extremes of weight alter the outcome in pediatric cancers. Undernutrition at diagnosis is a significant poor prognostic factor in children, demonstrating a lower event-free survival (EFS) and greater treatment-related mortality.[3,8,13] The pathophysiology is considered to be linked to poor tolerance to chemotherapy, increase in risk of infections, and a poor bone marrow reserve.[3] In recent years, obesity and overweight have been observed to have an undesirable impact on EFS. These adverse effects are considered to be related to adipocytes, decreasing the efficacy of chemotherapy and pharmacodynamic changes related to obesity.[11,13,52] (ii) Nutritional status is dynamic; it changes while a patient with a malignancy is on therapy and is infrequently included as one of the variables for clinical outcomes in clinical trials.[14,15] Body composition changes during and after therapy.[27] The relationship of the nutritional status before, during, and after treatment on survival is required for the advancement of nutritional science. Childhood cancer survivors are known to have a predisposition toward obesity and the metabolic syndrome. Sarcopenic obesity has been identified in approximately 40% of survivors of acute lymphoblastic leukemia.[53] Longitudinal multicentric studies that include body composition are desirable to identify the cause and effect and allow for early intervention. (iii) Research has focused more on outcomes in hematological malignancies and their relationship to the nutritional status. Literature on the impact of nutritional status on the outcome in solid tumors is limited. The pathophysiology and interplay of mechanisms of the cause and effect of the tumor with the status of nourishment needs elucidation.[8,21,50,54] (iv) Interventional studies involving dietary modifications are faced with methodological challenges as these studies require to be randomized and double blinded for an accurate assessment.[55] Food is complex and diverse with dietary behaviors differing from person to person. Measures to evaluate compliance and adherence are lacking. In addition, the type of cancer and type of treatment further confound an interventional study. Phase III clinical trials of focused nutritional interventions, with nutritional supplements (proteins/energy rich products), in the setting of pediatric cancers are required to analyze the efficacy of the intervention during and after completion of therapy. (v) Pharmacokinetics and pharmacodynamics of drugs are known to alter with a change in the nutritional status. The dosing required in severely undernourished and obese patients is not clear. Studies have been performed in animal models with minimal research in humans. Increased bone marrow toxicity and prolongation of the half-life of drugs with greater undesirable effects have been observed with extremes of body weight. A better understanding of pharmacokinetic variance depending on the body composition is required to facilitate appropriate therapeutic dosing.[56] (vi) Trace elements and vitamins may have an impact on the outcome of a malignancy. Micronutrient deficiencies are rampant, especially in LMICs. Vitamin deficiencies can damage DNA, which may be a factor in the causation of malignancies. Considerable metabolic damage can occur when there is a suboptimal intake of vitamins and minerals. Deficiency of folate has been implicated in treatment-related mortality in studies from India. Selenium, a trace element, has been seen to

affect outcomes in hematological and solid malignancies. The cause and effect of these deficiencies are an area needing research.[52,53] (vii) Nutrition and genetics (nutrigenomics and proteomics). Nutrients can regulate transcription factors and modify gene expression. The interplay between diet and the genome can determine an individual's health and susceptibility to disease with cancer and cardiovascular disease being the foremost diseases being linked to genomics.[57,58] In addition, nutrients can alter and modify the epigenome. Epigenetically active nutrients can damage DNA, which may be a factor for the causation of malignancies. Certain nutrients (e.g., amino acids, B complex group of vitamins) have a profound effect on the metabolic pathway with resultant defects and diseases. "Nutritional epigenetics" could be the future for personalized medicine and targeted interventions.[59,60] (viii) The gut microbiome plays a role in the development of the body's immune system, and an altered microbiome can change the inflammatory response, result in DNA damage and bacterial metabolites, which can be carcinogenic or tumor suppressor in nature. Dysbiosis of the gut microbiome has been observed at diagnosis of a malignancy and following chemotherapy. This change of the microbiome is considered to play a role in decreasing the outcome of cancer by influencing treatment. The role of microbiota in the cause and effect and the therapeutics of childhood malignancies is a less explored area for future research.[61]

6 | CONCLUSIONS

Nutritional assessment is easy, can be tailored to the institution's available resources, and is critical to allow for appropriate and timely nutritional intervention in children with malignancies. Both under- and over-nutrition have adverse consequences in the outcome of childhood cancers; thus, longitudinal nutritional assessment is important as childhood cancer survivors have been seen to have major issues related to nutrition. The role of nutritional status in pediatric cancer is a potential area for future research. This article is written to educate and advise on the nutritional assessment of children with cancer and is complementary to the other articles in this *PBC* supplement.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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How to cite this article: Viani K, Trehan A, Manzoli B, Schoeman J. Assessment of nutritional status in children with cancer: A narrative review. *Pediatr Blood Cancer*. 2020;67:(Suppl. 3):e28211. https://doi.org/10.1002/pbc.28211

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Highlights from the 13th African Continental Meeting of the International Society of Paediatric Oncology (SIOP), 6–9 March 2019, Cairo, Egypt

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Conference Report

Abstract

The 13th African continental meeting of the international society of paediatric oncology, held on 6–9 March 2019 in Cairo, was organised in collaboration with the Children Cancer Hospital (57357) in Egypt and the global parents' organisation (Childhood Cancer International) and supported by a large international faculty. With 629 delegates from 37 countries (24 African), this was the largest forum of healthcare professionals focused on children and young people with cancer in Africa to showcase advances and discuss further improvements. Three targeted workshops, on nursing care, pharmacy and nutrition, attracted large numbers and catalysed new collaborative initiatives in supportive care studies, extended roles for pharmacists in quality control and care delivery and addressed malnutrition concurrently with cancer treatment. The Collaborative Wilms Tumour Africa Project, open in seven sub-Saharan countries, and the trials in Burkitt's lymphoma reported encouraging outcomes with further initiatives in supportive care (the supportive care for children with cancer in Africa project). While acknowledging deficits in radiotherapy provision, available in only 23 of 52 African countries, centres with facilities reported their technical advances that benefit patients. Of great importance for children with brain tumours, who are underdiagnosed in Africa, was the first announcement

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ecancer 2019, **13**:932
https://doi.org/10.3332/ecancer.2019.932

Published: 28/05/2019
Received: 10/04/2019

Publication costs for this article were supported by the *e*cancer Global Foundation.

of African paediatric neuro-oncology society, whose 63 current members aim to tackle the shortage of neurosurgeons through training fellowships, workshops and a dedicated conference. The congress provided the opportunity to discuss how African countries will work with the WHO global initiative aiming to improve childhood cancer survival to 60% in all countries by 2030. This conference report is dedicated to the three Kenyan delegates who died tragically on the Ethiopian Airlines flight ET302 on their way home, full of new ideas and pride in what they had achieved so far. All those who heard their presentations are determined to continue their excellent work to improve cancer care for children in Africa.

Keywords: *childhood cancer, clinical pharmacy, nutritional assessment, paediatric cancer nursing, paediatric neurosurgery*

Introduction

Successful treatment of childhood cancers in Africa is of increasing importance due to the high proportion of children and adolescents in the African population and the continuous decrease in death rates from other causes [1]. This 13th biannual continental meeting of the international society of paediatric oncology (SIOP), in conjunction with African representatives from parents' organisations [Childhood Cancer International (CCI)] and the Children's Cancer Hospital (57357) in Egypt (CCHE), Cairo, aimed to showcase progress in this field across multiple disciplines and received 340 abstracts from more than 33 countries, many describing very positive progress through collaborative prospective clinical research [2].

Delegates were welcomed to the congress by Prof Elhamy Rifky A.Khalek (President of the Conference and the host of the event), Prof Laila Hesssissen, President of SIOP Africa and the members of the Local Organising Committee. Prof Rifky welcomed the participants and gave a brief summary of the congress and the schedule. The congress was attended by a total of 629 delegates from 37 countries (24 African), including 156 paediatric oncologists, 53 paediatricians, 32 radiotherapists, 27 surgeons, 92 nurses, 59 pharmacists, 14 diagnostic services (including nine pathologists), 102 nutritionists and 38 parents. Scholarships were available for 156 medical and nursing delegates, for which support from Sanofi Espoir Foundation, CCI, CCHE (57357), Egyptian National Cancer Institute, Ministry of Public Health, Pfizer Pharmaceuticals, New Bridge and Abbott Nutrition is acknowledged.

Professor Sherif Aboul Naga (CCHE, Cairo, Egypt) described in the opening ceremony how the CCHE 57357 (CCHE, widely known as Hospital 57357) was created, inspired by the model of the St. Jude Research Hospital in Memphis. The people of Egypt and friends from all over the world and most particularly in the Arab World generously contributed, and it was built completely by donations. The hospital's mission is to provide the best comprehensive family-centred quality care and a chance for cure to all children with cancer seeking its services, free of charge and without discrimination. It opened in 2007 with 179 beds and, by 2018, had grown to 320 beds and has over 15,000 patients under active treatment. It has all the 'state-of-the art' clinical facilities (including two linear accelerators with plans for proton beam therapy) and comprehensive support services, in-house schooling and child life and play. Since its inception, the CCHE leadership realised that carrying out research in medical and non-medical areas was a prerequisite to progress in achieving cures and a better future for children with cancer. Hence, the adoption of an advanced health informatics system, which enabled it to be a paperless hospital, with the complete digitalisation of operational aspects and acquisition of a strong database. They made a significant and transformational investment in clinical pharmacy staff and processes. He emphasised the importance of investing in people, with all staff given time for and expected to contribute to research and education. Leadership training and embedding key performance indicators at all levels, with regular targeted feedback to departments and teams, have enabled the organisation to make remarkable progress in improving survival rates to an estimated 73% average overall survival rate for those treated today.

One of the biggest barriers for delegates who wished to attend was obtaining a visa in a timely fashion. Of the 33 participants affected, some of whose work had been selected for prize consideration, only 22 were able to obtain a visa on time to attend. Visas were only issued after personal interventions by the local organising committee, adding considerably to the administrative burden of organising a clinical conference in Africa. This issue needs to be considered by both future delegates and conference organisers, to ensure timely sharing of learning to benefit children with cancer and the healthcare professionals who care for them.

The programme covered almost all aspects of childhood cancer care, from improving diagnosis to delivering successful treatment adapted to the available resources. The importance of working collaboratively and involving parents to define needs was emphasised to demonstrate that, even in the most resource-challenged settings, progress in survival rates and quality of care can be achieved through targeted interventions (Figure 1). Three dedicated workshops in the key areas of nursing, pharmacy and nutrition, described in detail in the following section, were very well attended and focused on the specific challenges faced by African children with cancer and the paediatric services who care for them. The congress highlighted the impressive progress made through prospective clinical trials and studies and how this research effort has reaped wider benefits for paediatric care and built durable collaborative research networks. Further information is available from [2, 3].

Nursing workshop

The nursing programme at SIOP Africa Cairo 2019 comprised two full days of workshop, keynote lectures, free-paper sessions and discussions of collaboration, attended by nurses from seven countries. A workshop on nursing research was delivered by Dr Faith Gibson, laureate of the SIOP Nurse lifetime achievement award 2018. Dr Gibson taught the nursing group how to identify useful research topics, various types of quantitative and qualitative research methodologies suitable for answering multiple research questions and research steps from planning to the dissemination of findings. Nurses expressed several areas of research priorities, a list of which was collated for further exploration within the group.

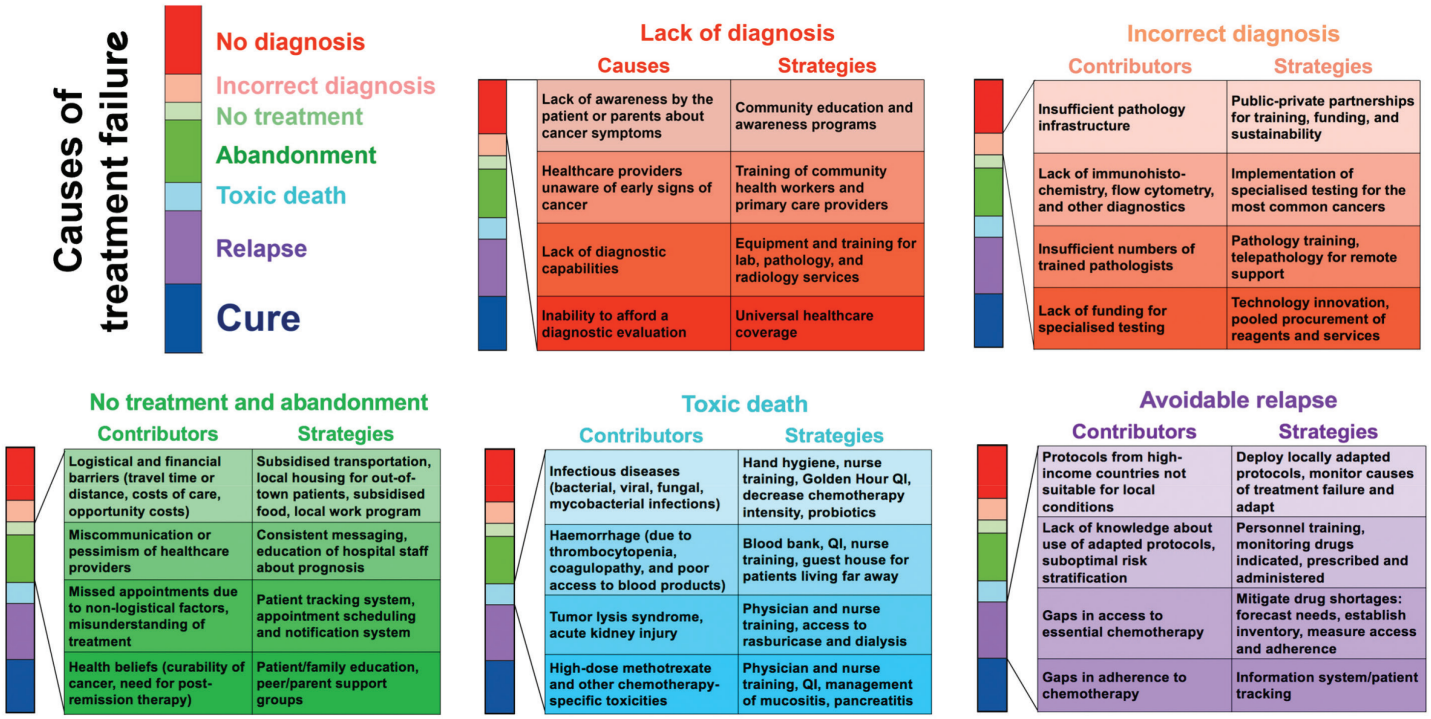

Figure 1. Cause-specific interventions to reduce treatment failure for children with cancer in low- and middle-income countries. (Used with the permission of Scott C Howard, MD, MSc.)

Three keynote lectures were delivered. Prof Nagwa Elkhateb from Egypt emphasised the importance of pain assessment using culturally and age-appropriate tools, followed by the meticulous pharmacological or non-pharmacological intervention. Sr Rachel Hollis (Leeds Hospitals NHS Trust, UK) gave a keynote lecture on the SIOP Paediatric Oncology in Developing Countries (PODC) nursing baseline standards for low- and middle-income countries (LMICs) and advocacy. These six standards for quality nursing care include staffing based on patient acuity; formal orientation programmes; continuous education; recognition of nurses as integral members of the multidisciplinary teams; resources for safe care; and research for evidence-based nursing practise [4]. A recent survey showed that the disparities in the attainment of the baseline standards with LMICs were largely disadvantaged [5]. An advocacy toolkit for these standards is available on the SIOP website [6]. Prof Zeinab Lotfy (Modern University for Technology and Information, Cairo, Egypt) of Egypt talked about the essence of communication skills in nursing education, highlighting the need for the consideration of local cultural realities in important aspects of nursing care such as breaking bad news and educating children and families on their treatment.

There were 11 free papers, three of which were recognised for their quality and relevance. Joan Nakabiri (Uganda Cancer Institute, Kampala, Uganda) from Uganda presented on how a continuous nurse's education programme has increased the knowledge and confidence of paediatric oncology nurses at the Uganda Cancer Institute. Hany Eskander from CCHE was recognised for an assessment of intensive care nurses' knowledge and practises regarding utilisation of infection control standards which showed a positive correlation between knowledge and practise of infection control [7]. He recommended continuous education on the latest evidence-based infection control practises. Finally, Vera Njamnshi (Cameroon Baptist Convention Health Services, Cameroon) from Cameroon was recognised for presenting on the contribution of the nurses' role in planning, patient follow-up, informed consent and data collection for assessing the fertility of long-term female Burkitt lymphoma survivors.

Collaboration was one of the central themes of the nursing programme. In order to facilitate communication and sharing of knowledge and initiative in-between conferences, the nurses decided to create SIOP Africa nursing WhatsApp and Facebook groups. An evaluation form completed by most participants showed that they were satisfied with its various components. A few suggestions for future meetings were: to include more content related to palliative care and psychosocial support, to arrange sitting in a U-shape for better interaction and to allocate more time for group work.

Clinical pharmacy workshop

For the first time in Africa, a one-day workshop was held to bring together all those working in clinical pharmacy services and those prescribing chemotherapy for children with cancer. Sessions were interactive with networking resulting in several future cooperative projects—in particular, those that empowered pharmacists in Africa to enhance their role to improve safety and efficacy of treatment for children with cancer and to use resources more efficiently. Dr SA Naga, the founder of clinical pharmacy in Egypt, opened with the history of the clinical pharmacy concept, the recognition of its value and examples of practical implementation in Egypt. Klaus Meier (HKK (Heidekreis-Klinikum GmbH Krankenhaus), Soltau, Germany), current President of the European Society of Oncology Pharmacy (ESOP), presented the ESOP's plan to develop oncology pharmacy practise over a period towards 2025, including the launch of a certification programme for Oncology Pharmacists comprising 100 hours of training including webinars and face-to-face international and national educational activities. He discussed how the current ESOP programme includes oral chemotherapy, QUAPOS (oncology pharmacy practise standards), the contamination project, safe handling and clean working, the essential requirement for oncology practise, the EUSOP certification programme and, finally, the ECOP conference in Malta. Both speakers urged oncology pharmacists in Africa to unite and work together to implement the best evidence-based pharmacy practise.

The surgical session was well attended by different generations of different sub-specialties including paediatric surgeons, paediatric oncologists and paediatric radiotherapists from different institutes from all over Egypt as well as different African countries. The session was also enriched by fruitful discussions following each presentation. One of the main recommendations during these discussions was to encourage multicentric studies and surveys suggested by physicians and researchers interested in cancer children with all of its different specialties in Egypt. It was proposed that a future conference should ensure greater attendance by international paediatric oncology surgical faculty from the International Society of Paediatric Surgical Oncology (IPSO).

Nutrition workshop

Malnutrition is widespread among children living in Africa with approximately 46% of children diagnosed with cancer also being diagnosed with malnutrition [8]. Managing malnutrition can be challenging for paediatric cancer units (PCUs) with limited resources [9]; however, the clinical implications of not remediating malnutrition leads to reduced survival and increased treatment-related toxicities [10]. On the final day of the conference, a nutrition workshop was convened, which included dieticians, nurses, physicians, parent groups and nongovernmental organisations (NGOs). Dr Elena Ladas (Columbia University, USA) and Dr Ronald Barr (McMaster University, Canada) opened the workshop with presentations on the impact of nutritional status on survival and outcome and the importance of performing sequential nutritional assessments throughout treatment. An important highlight was the ease and use of mid-upper circumference (MUAC) to determine nutritional status. Regional data on nutritional status, and barriers to care, were provided by clinicians in Ethiopia (Dr Daniel Hailu), South Africa (Judy Schoeman), Malawi (Dr Trijn Israels) and Egypt (Dr Sahar Khairy). Striking figures on the rates of malnutrition among children with cancer were presented; for example, in Malawi, incidence reaches 95% when MUAC or triceps skinfold thickness is utilised for nutritional assessment.

Limited access to nutritional products has been reported among PCU in Africa [9]. Ms Bella Beryl Jamona (Hope for Cancer Kids, Kenya) discussed the challenges clinicians face in providing optimal care to Kenyan children. Prof Mariana Kruger (Tyerberg Children's Hospital, Stellenbosch, South Africa) (South Africa) and Dr Lillian Gesami-Steytler (Windhoek, Namibia) presented on limited access to enteral products and challenges faced when implementing ready-to-use therapeutic formulas. A persistent barrier was the poor availability of these products in PCUs and the lack of trained personnel able to manage children with cancer when they also have severe acute malnutrition. Several case studies illustrated varied approaches to the delivery of nutritional care in a limited resource setting by Dr Samer Mohamed (CCHE, Egypt), Dr Jane Kaijage (Tumaini la Maisha, Tanzania) and Dr George (College of Medicine, Blantyre, Malawi). For example, clinicians in Tanzania use home-made smoothies as supplements during cancer care, whereas Malawi relied upon supplements provided by the acute malnourished ward. Education of staff has been reported as a barrier to nutritional intervention [9]. The International Initiative for Paediatrics and Nutrition (IIPAN) has established an intensive programme in Africa to begin to close this gap in clinical care. Happiness Ndifon, a nutritionist from Cameroon Baptist Convention Health Services, Cameroon, presented how she had implemented a nutrition programme in Cameroon after attending a 2-week intensive training course at an IIPAN training site (South Africa).

Finally, the oncology team from 57357 Children's Hospital in Egypt presented on the centre's research. Topics included the role of nutritional therapy and sensitisation to radiotherapy (Dr Ahmed El-Saka), high aflatoxins in Egyptian food (Dr Afaf Amin) and the important role of breastfeeding as part of immunomodulatory therapy (Gihan Fouad).

In conclusion, the workshop established that there is a need for collaborative, prospective studies on nutritional status in PCU in Africa and, by including MUAC, standardised assessment can be achieved. Education of staff members and synergy among nutritional groups within hospitals, particularly with existing malnutrition clinics, is a pressing need for PCU in Africa. Moreover, PCU need financial and product support to be able to increase nutritional interventions. The request for similar workshops to improve nutritional care in their PCU in future years was received, with the first workshop planned in Kenya and subsequent plans for the next SIOP Africa congress to be held in Kampala, Uganda, in 2021.

Progress in optimising management of the most curable childhood solid tumours

Burkitt's lymphoma

Catherine Patte (Institut Gustav Roussy, France) reported the latest results of the international intergroup randomised trial, the 'Inter-B-NHL Ritux 2010 trial,' run in eight European countries, Australia, Canada, Hong Kong and the USA. This showed that the addition of rituximab to a standard backbone of intensive chemotherapy (the Lymphomes Malins B (LMB) regimen) improved event-free survival (EFS) from 84% to 92% for advanced stage B-cell lymphoma and B-cell acute leukaemia, and it is now used as a standard in high-income countries (HICs) [11]. Although the longer term immune status of these patients is still under evaluation, a few long-lasting profound B

immunodeficiencies have been observed. Hence, rituximab is not currently recommended in addition to chemotherapy in patients with low (stages I and II) or intermediate (stage III with low lactate dehydrogenase level) stages who have an EFS > 97% with no expected late sequelae related to chemotherapy. In particular, the benefit of rituximab in sub-Saharan countries, where most children are malnourished and more susceptible to infections, must be evaluated before recommending its use. C Patte also reported results of GFAOP studies showing that LMB-based chemotherapy is feasible in sub-Saharan countries and that initial dose intensity is crucial. H Abdel Rahman (National Cancer Institute, Cairo University and CCHE, Egypt) showed in a prospective study of fluorodeoxyglucose positron emission tomography (FDG-PET) for assessment of residual masses in mature B cell non-Hodgkin lymphoma that it is not specific enough and recommends the continued need for histological confirmation to avoid unnecessary treatment escalation. Dr Jenny Geel (University of Witswatersrand, Johannesburg) described efforts to improve overall survival for childhood cancer in South Africa, a country with 16.5 million children aged <15 years. They are taking a disease-by-disease approach to implement a unified national diagnostic and treatment protocol, aiming to improve survival rates, decrease toxicity, and understand and control the costs. The first tumour chosen is Hodgkin's lymphoma. E Moussa (National Cancer Institute, Cairo University and CCHE, Egypt) developed the controversies in the treatment of Hodgkin Lymphoma. Posters reported on North African single centre result in NHL and high-dose (HD), focussing on unusual sites and causes of treatment failures (toxic deaths and malnutrition). One poster on Burkitt highlighted the benefit of a second pre-phase before starting the induction chemotherapy. Another one confirmed the value of PET after two courses of chemotherapy as a predictor of outcome in HD. Prof Peter Hesseling (Stellenbosch University, South Africa) presented results indicating a risk of decreased fertility in girls receiving important doses of cyclophosphamide for the treatment of Burkitt lymphoma.

Wilms tumour

In the session on renal tumours, Prof Kathy Pritchard-Jones (University College London, UK) gave an update on optimisation of clinical risk stratification for the treatment of Wilms tumour (WT) in the SIOP Renal Tumours Study Group new 'UMBRELLA' protocol following further analyses of the previous randomised trial that had recommended omission of doxorubicin from postoperative chemotherapy for all stage II/III intermediate-risk histology WTs [12]. Pending the outcome of ongoing molecular biomarker research, focused on the somatic gain of chromosome 1q, she showed evidence for excess relapse in tumours with volume greater than 500 mL after pre-operative chemotherapy, when the histological subtype was mixed or regressive subtype. It is now recommended that these tumours continue to be treated with doxorubicin included in postoperative chemotherapy [13]. Modest doses of doxorubicin are also now recommended for children with micrometastases visible only on computed tomography (CT). However, it is still acceptable to do staging using a chest X-ray, which is widely available in LMICs.

The collaborative WT Africa Project, presented by Dr Francine Kouya (Cameroon Baptist Convention Health Services, Cameroon) has implemented an adapted WT treatment guideline in sub-Saharan Africa, based on SIOP Renal Tumours Study Group (RTSG) protocols, as a multicentre prospective clinical trial. Seven centres in Malawi, Cameroon, Ghana and Zimbabwe are participating (Figure 2). The collaborative project's primary aims are to improve survival to more than 50% by reducing abandonment of treatment and death during treatment to below 10%. A retrospective, baseline evaluation of end of treatment outcome was done for a 2-year period prior to the introduction of the guideline. Compared to the baseline evaluation, abandonment of treatment decreased from 23% to 13% (p = 0.03) and death during treatment decreased from 21% to 13% (N.S.). End-of-treatment survival without evidence of the disease increased in the first 2 years of the project from 52% to 68% (p = 0.01) [14].

This collaboration, using relatively simple and low-cost interventions has strengthened the local healthcare teams' knowledge and use of sustainable tools to decrease abandonment of treatment and reduce toxic deaths. The increase in survival without evidence of disease at the end of treatment is expected to translate into improved long-term survival. The group is currently analysing the data of the first 4 years of the project and preparing to start phase II of the project in January 2020. This is expected to include some modifications to postoperative chemotherapy and a uniform relapse strategy. The group is also developing supportive care for children with cancer in Africa (SUCCOUR), a project to improve supportive care for children in sub-Saharan Africa. Centres in Africa wishing to join these projects are most welcome.

Figure 2. The Collaborative Wilms Tumour Africa Project brings together healthcare providers, hospitals, academic institutions, professional societies, and non-governmental organisations to improve cancer care and outcomes in several countries of Africa.

Supportive care for children with cancer in Africa

Improved supportive care has the potential to benefit children with all types of cancer and those in general paediatric care. SUCCOUR is a comprehensive, inclusive project led by doctors and nurses to promote improvements in supportive care. It builds on the lessons learnt from the Collaborative WT Africa Network with step-by-step development and implementation of simple, effective and cost-effective supportive care interventions, giving priority to those with the highest expected impact on child survival [15, 16] (Figure 1). Each site first conducts a baseline evaluation of current practises and outcomes in several areas of supportive care such as febrile neutropenia, nutrition, abandonment and the use of traditional medicine. Gaps in care and best practises will be identified and addressed through educational workshops, advocacy, developing local appropriate supportive care guidelines, rigorous outcome evaluation and development of specific interventions based on the collected local evidence. It will reference the well-developed framework for cause-specific interventions to reduce treatment failure for children with cancer in LMICs (Figure 1).

Prevention and management of toxicity associated with high-dose methotrexate

High-dose methotrexate (HDMTX), defined as a dose higher than 500 mg/m^2, is used to treat a range of adult and childhood cancers. Although HDMTX is safely administered to most patients, it can cause significant toxicity, including acute kidney injury (AKI). AKI constitutes an oncologic emergency in patients receiving HDMTX but can be successfully prevented and managed even in LMICs. Monitoring of serum creatinine, urine output and serum methotrexate concentration is used to assess renal clearance, with concurrent hydration, urinary alkalinisation and leucovorin rescue, to prevent and mitigate toxicity. Maintenance of alkaline urine pH is especially important because it prevents methotrexate crystallisation in the urine and greatly reduces the rate of methotrexate entry into urothelial cells, thus protecting the kidney by two distinct mechanisms. Where measurement of methotrexate levels is not available or not available within a clinically useful timeframe, successful

management of patients requiring HDMTX therapy depends on using somewhat lower doses (2–3 g/m^2 instead of 5–8 g/m^2), meticulous measurement of urine output and mucosal erythema, prevention of vomiting, assuring no loss of IV access during the infusion and frequent measurement of creatinine to allow rapid response to any increase. A recent study from Chandigarh, India, used methotrexate 5 g/m^2 for children with acute lymphoblastic leukaemia (ALL) in a setting where they could not measure methotrexate levels. Using extra hydration, close monitoring and frequent checks of urine pH and creatinine, they delivered 100 courses of HDMTX without worrisome toxicities [16, 17].

Importance of asparaginase in treating acute lymphoblastic leukaemia

ALL affects 120,000 people each year worldwide, including children and adults. It can be permanently cured more than 80% of the time with treatment regimens that combine glucocorticoids, anthracyclines, vincristine, mercaptopurine and asparaginase [18]. Scott Howard (University of Tennessee, Memphis, USA) discussed approaches to the most effective use of asparaginase, which rely on minimising the likelihood of initial allergic reactions and having access to at least a second formulation of the drug for those who do react. Native *Escherichia coli* asparaginase (Elspar, Leunase, Kidrolase and others) is on the WHO list of essential medications, while other formulations, currently PEGylated-*E. coli* asparaginase (Oncaspar), and Erwinia asparaginase (Erwinaze), as second-line asparaginase for patients who develop hypersensitivity to *E. coli* asparaginases, are not.

In recent times, there have been problems felt around the world regarding the availability and affordability of asparaginase and question marks have been raised about the quality of some suppliers [1]. In HICs, PEG-*E. coli* asparaginase is used as frontline therapy because it is long-acting and has low rates of hypersensitivity (10%–15%) and silent neutralising antibody formation (1%) than native *E. coli* asparaginase. Most LMICs use the much cheaper native *E. coli* asparaginase, to which allergic reactions (20%–42% of patients with ALL) and neutralising antibody formation (in another 30%–40%) are much common. This means that two-thirds of patients do not attain the required asparaginase depletion unless they have access to a second asparaginase product, usually Erwinia asparaginase. Unfortunately, the supply of Erwinia asparaginase has been limited to HIC, and recent shortages have affected patients even in HIC. When no second product is available, the inability to complete asparaginase treatment increases the risk of relapse. Therefore, minimisation of allergic reactions to the initial form of asparaginase improves outcomes and reduces costs.

The recently published UKALL 2003 trial used PEG-*E. coli* asparaginase in a schedule that included several days of glucocorticoids prior to each dose of PEG-*E. coli* asparaginase in the low-risk and intermediate-risk patients, who had a 1% rate of allergic reaction and excellent event-free survival [19]. Patients on the high-risk arm received several doses of PEG-*E. coli* asparaginase without preceding glucocorticoids and had a reaction rate of 6%, such that, in the whole study, the reaction rate was 2% [19]. This has led to an immediate change in practise, and modification of existing protocols to include glucocorticoids a couple of days before each PEG-*E. coli* asparaginase dose, in the hope of reducing allergic reactions to 1%, thus allowing patients to complete all asparaginase and reducing the need for second-line asparaginase (e.g. Erwinia). Prof Howard discussed five strategies to the choice of first-, second- and third-line asparaginase, and concluded that the most clinically effective and cost-effective strategy is upfront use of PEG-*E. coli* asparaginase with second-line *Erwinia* asparaginase, when available, in the 10%–15% of patients who develop hypersensitivity. The average patient who receives PEG-asparaginase 1000–2500 U/m^2 has adequate asparaginase activity for 14–24 days, a duration that would require repeated dosing of native *E. coli* asparaginase 2–3 times per week during this interval, or a total of 6–9 doses, to achieve comparable asparaginase activity [20].

Information systems

All strategies to reduce treatment failure for children with cancer depend on a robust information system to facilitate continuous, relentless quality improvement. The advanced health informatics system of CCHE, hospital 57357, is not affordable in most African settings. Alternative systems adapted to the practical challenges faced in Africa were presented. Prof Scott Howard described Resonance Oncology (www.ResonanceOncology.org), an academically led, cloud-based, cancer information system, available at no cost to centres in LMICs. Baseline risk assessment for abandonment can be stored in the oncology adapted resonance patient centre (RPC) abandonment module and the risk score calculated there. RPC can also contain all the patient's clinical information, chemotherapy roadmap and appointments, and serves as a unified source of information about the patient's care and outcomes. The system supports multiple languages, and the abil-

ity to produce analytics and visualisations in real time allows sites to quickly and frequently assess the causes of treatment failure by region, country, cancer centre, year of diagnosis or cancer type [21]. When cancer registry data, abandonment risk factors, treatment appointment adherence and outcomes (causes of treatment failure) are collected in real time for all patients, deployment of interventions can be based on local needs and priorities (Figure 1). A prize-winning oral presentation by Jeremie Hassan (Tumaini la Maisha, Tanzania) 'Increasing Safety and Consistency of Chemotherapy Treatment in Resource-Limited Countries via Excel-Based Prescription Automation' described the work in Microsoft Excel to create printable chemotherapy prescription smart sheets for common childhood cancer. Eight protocols have been fully automated until now. There were highly interactive discussions with the audience who found it as a very good method to reduce treatment errors that could lead to a greatly improved treatment safely and efficiency.

The surgical session was well attended by different generations of paediatric surgeons and other medical specialities and emphasised the importance of formal multidisciplinary discussion with oncologists and radiotherapists to optimise individual patient care. A major recommendation was to promote the importance of involvement in multicentric studies and surveys. It was proposed that a future conference should be organised with a larger faculty from IPSO, the SIOP surgeons.

Treatment of brain tumours in childhood

The neuro-oncology session provided the opportunity to address the challenges associated with the development of paediatric neuro-oncology programmes in countries with limited resources. A number of factors affect these efforts, such as lack of awareness of paediatric brain tumours, late diagnoses, limited imaging facilities, absence of paediatric neurosurgical training, lack of expertise in neuropathology, difficulties to access radiation services and absence of multidisciplinary approach. Several solutions have been investigated, and, so far, the most successful experiences are with the development of twinning programmes between institutions in high-income and low-income countries. The use of teleconferences allows face-to-face interactions, and regular reviews and discussions of challenging cases have a major impact on clinical practise.

In this context, Dr Giorgio Perilongo (University of Padova, Italy) discussed the management of paediatric low-grade gliomas, reminding the audience that this condition has been listed in the six diseases targeted by the WHO Global Initiative for Childhood Cancer. Major advances in the understanding of the molecular biology of this condition have happened during the last decade, leading to the development of new strategies targeting the RAS/MAP-Kinase pathway. However, these progresses are unlikely to benefit African patients in the near future, and the management of African patients should take into account a number of factors, including distance from the hospital, side effects of chemotherapy and risk of abandonment. In this context, radiation may have still an important role, in particular, when conformal radiation is available. The management of medulloblastoma is far more complex, as it requires a timely and multidisciplinary approach. Dr Kieran (Boston Children's Hospital, USA) reviewed the recent progress in the management of this condition and addressed the main factors of success which include access to a paediatric neurosurgery facility, timely referral to the radiation oncology unit, and adjuvant chemotherapy and follow-up provided by an experienced neuro-oncology team. Dr Bouffet provided an overview of paediatric cancers associated with mismatch repair deficiency (MMRD), an often under-recognised condition closely associated with parental consanguinity. MMRD is not exceptional in Africa where consanguinity is common. Children with MMRD develop malignant brain tumours, lymphoma and colon cancers. There is emerging evidence that some MMRD-related solid tumours can be successfully treated with immune checkpoint inhibitors, and the management of cancers associated with this condition may require a specific approach. Dr Zaghloul reported on the ongoing trial of radiotherapy for patients with diffuse intrinsic pontine glioma (DIPG), which suggests that hypofractionated radiation is given over 13 or 15 sessions at a dose of 3 Gy per session (39 or 45 Gy). Both are equivalent (non-inferior) to standard fractionation (54 Gy in 30 fractions). This experience has certainly important implications, in particular, when access to radiation facilities is limited.

Radiotherapy

In the Radiation Oncology session chaired by Jeannette Parkes (University of Cape Town, South Africa) and Mohamed Zaghloul (National Cancer Institute, Cairo University and CCHE, Egypt) eight important topics were discussed exploring the problems, limitation and future

of radiation oncology in Africa. Parkes (South Africa) presented the important issue of the interdependence of radiotherapy and neuroimaging, with the need for services to keep abreast of advances in imaging to improve the quality and accuracy of radiotherapy. Zaghloul (Egypt) presented the situation of radiation oncology in Egypt and on the continent of Africa. The causes of the deficiencies in radiotherapy service availability were widely discussed together with the suggested ideas to improve its level [22]. Egypt, as an example, could showcase the importance of collaboration between governmental institutions, universities, NGOs, international bodies and societies like IAEA, ASTRO, ASCO, ESTRO, PROS (Paediatric Radiation Oncology Society) to improve both the quantity and quantity of radiotherapy to serve African patients [23]. Dorra Aissoui (Habib Bourguiba University Hospital, Tunisia) presented a profile of the positive changes for paediatric radiation oncology that had occurred in her centre during 2010–16. The improvements achieved are expected to reflect upon survival and quality of life for the children treated.

Several presenters from Egypt described clinical and technical advances in treating patients at their centres. Soha Ahmed (Aswan University and CCHE, Egypt) presented the experience at CCHE to salvage children with recurrent ependymoma after re-excision of the recurrence (or without surgery) through reirradiation. She summarised the international as well as CCHE experience and concluded that it is not only feasible but also beneficial in terms of overall survival and progression-free survival. Engy Salah (CCHE) presented the experience of re-irradiation in DIPG patients in their first progression. Comparison of 27 re-irradiated patients with a retrospective matched cohort of 27 patients receiving best supportive care demonstrated safety and suggested efficacy. Further presentations described a new technique, deep inspiratory breath hold (DIBH) in mediastinal Hodgkin's Lymphoma in adolescents. Haytham Shaheen (CCHE) presented a full description of the technique, its scientific background and advantage using the novel surface scan (Catalyst) together with cone beam CT. Shaheen convinced the audience of the simplicity, accuracy and efficiency of the system. Hany Ammar (CCHE) compared the different radiotherapy techniques during treatment with DIBH. The DIBH offer much superior dosimetric distribution than free breathing.

Volumetric modulated arc therapy was shown to be more accurate and to provide improved tumour coverage with reduced dose to surrounding normal structures, while requiring reasonable monitor units and time on the machine compared to intensity-modulated radiotherapy and conformal radiotherapy. Finally, Caroline Elmaraghy (CCHE, Egypt) presented the CCHE experience in treating focal brainstem glioma. In a retrospective study, 72 patients were treated either by careful watching, chemotherapy or radiotherapy according to certain criteria depending on symptoms, site, size and progression of the tumour. Although those who received radiotherapy had slightly better overall survival and progression-free survival, the differences were not statistically significant. The interaction between the audience and the speakers were high with exchanging ideas and experiences.

Professor El Beltagy, professor of neurosurgery, Cairo University and Head of Neurosurgery, CCHE, Egypt presented the rationale for and the official launch of the African paediatric neuro-oncology society (APNOS). Many problems are encountered in the diagnosis and treatment of childhood brain tumours in Africa due to lack of resources and scarcity of appropriately trained neurosurgeons and other physicians. There is a deficiency in paediatric neurosurgeons in Africa with a median number of neurosurgeons per 100,000 population of 0.01. Not only is there a severe shortage of trained neurosurgeons, but also equipment, funding and teaching programmes. These signify poorly developed health systems and uneven distribution of neurosurgical and radiotherapy facilities in many countries and across the continent. The consequences are the high mortality and morbidity rates seen today from conditions requiring neurosurgical interventions, with a delay in diagnosis and complicated clinical presentations.

After successful activities over the past 3 years, including workshops for neurosurgery and training programmes for African doctors, the decision was taken to initiate the APNOS and announce its creation during the SIOP Africa 2019 conference. APNOS is an initiative to strengthen collaboration between African countries to improve diagnosis and management of paediatric brain tumours between experts in neuro-oncology and neurosurgeons from many African countries. APNOS has 63 members and board members from different African countries (Egypt, Morocco, Algeria, Tunisia, Libya, Sudan, Nigeria, Zimbabwe and Kenya). APNOS aims to be a leading model of collaboration towards a childhood brain cancer-free Africa, through establishing, facilitating and supporting the paediatric neuro-oncology services across Africa through continuous training, education and capacity building to help alleviate the suffering of African children with brain tumours. The first APNOS congress is planned for the first half of 2020, to be held in Cairo, Egypt, as the first of a series of planned semi-annual neurosurgery workshops in Egypt, Morocco and Sudan, covering different topics including hydrocephalus, endoscopic surgery and tumour surgeries. APNOS is also supervising the neurosurgical fellowship programme (CCHE-57357; starting 2019). In the field of radiation oncology, APNOS collaborated with the Paediatric Radiation Oncology Society (PROS) to help the implementation of the first practical radiotherapy course in

2016 (CCHE-57357), and continues to collaborate on the medical biophysics training programme and preparation for the paediatric medical biophysics 57357 fellowship together with the radiation oncology fellowship programme (CCHE-57357; starting 2019). There is also an ongoing Paediatric Oncology fellowship programme for neuro-oncology training (currently ongoing at CCHE-57357). It is a 30-month fellowship programme in collaboration with the Dana Farber Cancer Institute, including a 6-month paediatric neuro-oncology subspecialty training. Through this programme, there are two African graduates so far from Ethiopia and Kenya.

Report of the joint session with parents

CCI Africa was established a year ago in Johannesburg, under the supervision of Ruth Hoffman, the CCI global president. The SIOP Africa congress was the first meeting held in partnership with CCI Africa, with an integrated 'parent track.' The programme was led by Ruth Hoffman and the board of CCI Africa, which has seven members from South Africa, Zimbabwe, Uganda, Kenya, Nigeria, Ghana and Egypt, with Carl Queiros as elected President of the CCI African Regional Committee. There were presentations from representatives of parent groups from South Africa, Zimbabwe, Nigeria, Kenya and the Alexandria group of childhood cancer care (AGCCC) in Egypt. Three members of AGCCC presented on the Egyptian experience of founding the first support group for children with cancer and their families in Alexandria city, describing how they mobilised all the potential powers of the community as well as NGOs to establish the Hospitality House Caring for Cancer Children. There was a very fruitful discussion and dialogue between two survivors: one from Kenya (Mr Sydney) and one from Cairo, Egypt (Mr Mahmoud). Overall, this first joint session between CCI Africa and healthcare professionals involved in SIOP Africa was very fruitful and pointed the way for other regions to achieve better care and support for cancer children and their families in the African setting.

Conclusion

This SIOP Africa congress highlighted many positive actions in improving care and survival rates for children with cancer in Africa. It provided an important forum for policy discussions with WHO in relation to their global mapping initiative of childhood cancer services, that commenced with African countries. All but six African countries responded, but some stated they have no specific services for cancer in children and young people. WHO's 2015 ambition was to reduce deaths from four non-communicable diseases by 25%. Cancer was not mentioned specifically, although it was included in the overall target. Now the WHO 2018 Global Initiative for Childhood Cancer has a specific target to improve childhood cancer survival rates in all countries to at least 60% by 2030. This target is tractable by the knowledge we have now.

The conference showcased many twinning initiatives that will contribute to sustainable improvements, such as the Francophone GFAOP that has helped to establish 20 childhood cancer units in 16 countries, offers a 1-year diploma course from the University of Paris Sud and has trained 240 doctors and nurses who have treated >8,000 children. The business meeting of SIOP Africa highlighted that governments need to listen to the issues and the potential solutions provided—only 18 African countries have cancer plans identified through the survey and only six mentioned the specific needs of children with cancer. Furthermore, the importance of partnership working with parents' organisations cannot be ignored—while CCI Africa is now a visible improvement partner, there are large parts of Africa without parents' organisation registered with CCI. The SIOP Africa 2019 conference has provided model solutions that now need to be adopted at scale. We hope that our governments are listening!

As our closing remarks, we would like to dedicate this conference report to three wonderful healthcare professionals and human beings, who lost their lives on their way home from the conference, full of new ideas and pride in what they had achieved so far. We hope that all those who read this report will be inspired by their work and will continue their excellent work to improve cancer care for children in Africa. https://siop-online.org/a-tribute-to-jayne-bella-grace/

Acknowledgments

The authors would like to thank Ms Esraa El Hussieny for valuable administrative assistance. The authors thank all delegates for their participation and enthusiasm to build on the work discussed during the conference and described in this report.

Conflicts of interest

All authors declare that there are no conflicts of interest in relation to this article.

Funding

This article received no specific funding.

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ISSN 0019-509X

PubMed Indexed

Indian Journal of CANCER

Volume 52 | Issue 2 | April - June 2015

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Official Publication of
The Indian Cancer Society,
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Indian Co-operative Oncology Network

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Review Article

Nutritional assessment and intervention in a pediatric oncology unit

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Abstract

Nutritional status in children with cancer is an important prognostic factor. Assessment consisting of anthropometry, biochemistry, clinical, and diet that needs to be done on diagnosis and regularly to ensure that patient's nutritional status does not deteriorate. In developing countries, assessment will depend on the availability of all resources, but monitoring is essential. The development of malnutrition during treatment is possible and the reasons are multifactorial. Nutrition plays a deciding role and a key factor in children with cancer and can influence their outcome.

Key Words: Nutritional assessment, nutritional intervention, pediatric oncology

Introduction

Adequate nutrition in childhood is important to ensure proper neurodevelopment, a functional immune system, quality of life and in case of illness, response to the treatment given. In children with cancer, their nutritional status on diagnosis is very important because it has an impact on their outcome.[1]

Children treated in a pediatric oncology unit's nutritional status need to be assessed on a regular basis to ensure adequate growth, maintenance of nutritional status, and tolerance to treatment. Nutritional assessment involves anthropometry, biochemistry, clinical, and diet history and the following are recommended.

Nutritional Assessment

Anthropometry consists of length/height and weight to determine the height for age, weight for age, weight for height (W/H), or body mass index for age (BMI/A). The values are then compared with the age- and gender-applicable WHO tables to determine if a patient is stunted, underweight, and/or wasted as seen in Table 1.[1,2]

In children with cancer, weight can be misleading due to excessive weight gain in leukemia/non-Hodgkins lymphoma patients, consequences of their similar treatment,[3] and the tumor mass or ascites in patients with solid tumors.[4] Arm anthropometry is recommended to prevent deterioration in patients' nutritional status that can be masked by edema and/or the fact that no weight loss occurred.[4,5]

Mid-upper arm circumference (MUAC) and triceps skinfold thickness (TSF) are needed to determine patient's fat and muscle stores according to age- and gender-specific reference tables.[6] MUAC can be used as a single marker for nutritional status or in combination with W/H as seen in Table 2,[7] to determine severe acute malnutrition or acute malnutrition and can be useful in a unit with lack of personnel or nutritional resources, where a single measurement can identify the patients at nutritional risk.[1,7]

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Quick Response Code:

Website: www.indianjcancer.com

DOI: 10.4103/0019-509X.175832

Biochemistry values can be used to determine a patient's nutritional status but vary at every institution, due to availability of tests and cost involved. Expensive tests are not always possible, therefore the dietician needs to make use of values available to evaluate and monitor his/her patients "nutritional status," for example, protein stores, kidney function, and liver enzymes as seen in Table 3.[8-11]

Clinical assessment is an important tool that indicates signs known to malnutrition/nutrition deficiencies in patients as well as physical signs that might influence dietary intake.[1,9] It also includes patient's history, social-economic, cultural and environmental status of the patient.[12] The side effects of the treatment are part of the clinical assessment and it needs to be done daily while patient on treatment in hospital or seen at the clinic.

Diet history includes surveys of the quantity and frequency of food consumed during the past week at home and/or other hospital.[6] It is also important to help determine the food security at home and the availability of variety of food items. This is one of the challenges experienced in an oncology unit because parents are faced with a diagnosis of cancer and cannot recall what and how much their children ate before admission.[13] One recommendation is to ask a summary what the child ate the past 2 days and then do full assessment a week or two later when parents are more settled in the unit.

Nutritional Intervention

Nutritional intervention is the nutritional care plan that consists of the patients' requirements, challenges, possible problems, oral hospital diet and/or enteral feeds, and/or parenteral nutrition patient will receive, as well as homecare.[1] Each child with cancer needs their own nutritional care plan because a patients' diagnosis, treatment modality, and demographics have shown an influence on a patient's risk for malnutrition and adiposity as seen in Table 4[14] and therefore depends on their:[18]

How to cite this article: Schoeman J. Nutritional assessment and intervention in a pediatric oncology unit. Indian J Cancer 2015;52:186-90.

Table 1: Determine nutritional status according to *Z*-scores

Z-score	H/A	W/A	W/H and BMI/A
>+3 SD	Above normal	Possible growth problem	Obese
>+2–+3	Normal height	Possible growth problem	Overweight
−1–≤+2	Normal height	Possible growth problem	Possible risk of overweight
<−1–≥−2	Normal height	Normal weight	Normal weight
<−2–≥−3	Stunted	Underweight	Wasted
<−3 SD	Severely Stunted	Severely Underweight	Severely Wasted

H/A=Height for age; W/A=Weight for age; BMI/A=Body mass index for age; SD=Standard deviation; W/H=Weight for height

Table 2: Measurements to determine malnutrition according to mid-upper arm circumference and weight for height

Age group	AM	SAM
6 months to 5 years (cm)	MUAC <12.5	MUAC <11.0
>5 years without tumor mass (*Z*-score)	W/H <−2	W/H <−3
>5 years with a tumor mass (cm)	MUAC <13.5	MUAC <11.5

MUAC=Mid upper arm circumference; W/H=Weight for height; SAM=Severe acute malnutrition; AM=Acute malnutrition

Table 3: Factors that can indicate nutritional status

Laboratory tests	Function
Potassium	Role: Muscle contraction, glycolysis, glycogen formation, protein synthesis and utilization, cellular enzyme functioning, and water balance
CO_2 ↓	Vomiting, intestinal obstruction, starvation
Urea ↓	Negative N_2-balance; ↓protein ↑CHO diet
Creatinine ↓	Low muscle protein stores
Magnesium	Helps maintain normal energy metabolism and protein synthesis, enzyme activation, glucose utilization
PO_4	10% bound to protein. Role in: Energy metabolism, fat, amino acid and CHO metabolism, calcium regulation, vitamin utilization
ALT and AST	Useful to monitor liver function while patient on PN

ALT=Alanine transaminase; AST=Aspartate transaminase; PN=Parenteral nutrition; CHO=Carbohydrate

- Nutritional status at diagnosis
- Diagnosis that determine the risk for malnutrition
- Age of child
- Oncology treatment plan
- Activity level of child
- Chronic medicine patient receive
- Social-economic status at home.[15]

Nutritional Requirements

Over the years, different studies indicated that only children with solid tumors have increased resting energy expenditure (REE) at diagnosis, that normalize after treatment started. Children with leukemia had normal REE.[16-18] It has been well documented that cancer changes the metabolism of patients and they have a risk to become malnourished,[4,19] and this led to different opinions about requirements for children with cancer. Suggestions were proposed that patient's nutritional status at diagnosis is used as a guideline to determine which requirements to use. It must also be remembered that if a patient is malnourished, for an increase of 10 g/day in weight patients need 126 kcal/kg and 2.82 g/kg/day protein.[20] At this stage, there is no dedicated formula to determine a patient's nutritional requirements, so different formulas are used such as the American Society of Parenteral and Enteral Nutrition (ASPEN), daily recommended intake, WHO, recommended daily allowance (RDA) with an activity factor and protein-energy malnutrition (PEM). An example of the different formulas available are shown in Table 5.[1,20-23]

Mr. SM is a 14-year-old boy with weight 22 kg and height 130 cm; he is severely stunted and wasted. The formulas were used to determine the difference in his nutritional requirements according to each. If taking into account this patient needs to increase his weight, the best option, in this case will properly be ASPEN heavy activity, RDA+ activity factor, or WHO for PEM.[1,20-23]

Possible problems and challenges

About 46% of children diagnosed with cancer are malnourished[4,16] and this leads to a change in their body composition[16] that can influence drug metabolism and increase their risk for infections.[1]

Patients that receive corticosteroids as part of their treatment experience an increase in appetite, especially cravings for fatty food high in sodium that leads to an increase in adipose tissue, but decrease in lean body mass.[3,24,25] Patients are also scared of vomiting, learn food aversions and therefore their oral intake can decrease, leading to nutritional status that deteriorates. It is also known that parents and/or patients do not always follow nutritional advice given to them by dieticians, doctors, or nursing personnel.

Children get caught up in this situation of going to hospital and receiving treatment and so lose total control of their lives.[26] Often, the only thing they can control is the types of foods they are willing to consume. This may lead them to manipulate their caregivers to give them whatever they want to eat, what is most of the time not healthy food.[27]

Monitoring

Monitoring patient's nutritional status is the most important role of a dietician in a unit because if a patient's nutritional status deteriorates, it can influence the outcome. Anthropometry needs to be repeated at least once in 2 weeks while on treatment, either in- or out-patients. Biochemistry needs to be evaluated when repeated for medical purposes and to request that special tests be done if necessary. Clinical assessment is done on a daily basis to assess if patients are vomiting, have diarrhea, are constipated, or have edema. Diet intake should be monitored daily and if a patient is eating <70% of their nutritional requirements, a nasogastric (NG) tube should be inserted for enteral feeds to maintain or improve a patient's nutritional status. A patient on NG-feeds should be monitored daily.[1]

Table 4: Pediatric patients risk for malnutrition according to disease, treatment and demographics

	High risk of malnutrition	High risk of adiposity
Tumor type	Presentation with and/or undergoing treatment for Solid tumor in advance stages Neuroblastoma Wilms tumor Rhabdomyosarcoma Undergoing treatment for Advanced stage Ewing sarcoma Multiple relapsed and some high-risk leukemia Head and neck tumors Diencephalic tumors Poststem cell transplantation (graft vs. host disease)	Presentation with and/or undergoing treatment for Central nervous system tumors Craniopharyngioma Medulloblastoma Astrocytoma Undergoing treatment for ALL Ependymoma Nasopharynx carcinoma Sarcoma Lymphoma Disseminated testicular cancer
Treatment modality	Irradiation to the GIT Major abdominal surgery Bone marrow transplant Intense frequent intervals of chemotherapy (<3 weeks) in the absence of corticosteroids	Extensive brain surgery High dose cranial/cranial spinal radiotherapy Total body or abdominal radiotherapy Prolonged corticosteroid therapy with large doses or other drugs that can increase body fat stores
Patient demographics	Infancy Low social-economic status Lack of family or health supports system	Brain tumors Female Greater than %BMI at diagnosis ALL <10 years at diagnosis Hispanic Male

GIT=Gastrointestinal tumor; ALL=Acute lymphoblastic leukemia; BMI=Body mass index

Table 5: The different formulas available to determine patient's nutritional requirements

	ASPEN			DRI	WHO	RDA + activity factor	WHO for PEM
	Light activity	Moderate activity	Heavy activity				
Energy (kcal/kg/day)	48	56	65	88.5 − (61.9 × age) + Ac ([26.7 × kg] + [903 × m]) + 25	17.5 × weight + 651	45×1.5	60
kcal	1056	1232	1430	1237	1036	1485	1320
kJ	4435.2	5174.4	6006.0	5195.4	4351.2	6237.0	5544.0
kcal/kg	48	56	65	56.2	47.1	67.5	60
Protein (g/kg/day)	0.85	0.85	0.85	0.85	0.90 for 11-14 years	1×1.2	1.5-2
g/day	18.7	18.7	18.7	18.7	19.8	26.4	33-44
	DRI for 14-18 years						

ASPEN=American Society of Parenteral and Enteral Nutrition; DRI=Daily recommended intake; PEM=Protein energy malnutrition; RDA=Recommended daily allowance

Homecare

Patients that are well enough can go home between treatments, for a weekend or sometimes a week. On discharge, the patients' nutritional status will be determined and decided if nutritional supplements can be given home or not. Due to budget constraints, not all patients can receive supplements.

There are still a significant number of people suffering from hunger and malnutrition in poor-and middle-income countries; in fact, between 2000 and 2005, the number of undernourished and underweight children in Africa and Asia increased.[28] The possibility of patients coming from very poor social-economic background and food insecurity is therefore high; the Ideal would be to give food parcels home to those patients.

Support groups such as nonprofit companies can play a role here by collecting food parcels for homecare, but there is always the problem that we do not know how food is divided in a family. In HIV patients, food parcels with nutritional supplements were sent home, and the conclusion was that the family benefitted from the food parcels, and the supplements were used for the individual patient.[29] Advice on how to enrich food items with protein and energy must be given as well to ensure adequate nutrient intake at home.[1]

Malnutrition

The reason children with cancer become malnourished during treatment is multifactorial.[1] The altered metabolism is due to the oxidation of energy substrates that leads to loss in body protein and nutrient losses that cause gastrointestinal tumor problems. Pain or stress, hormonal and inflammatory components,[4] psychological problems, low physical activity, taste aversions, and chronic medications are all reasons for decreased oral intake and can contribute to the development of malnutrition.[1,4,16,30] In Table 6, the factors contributing to cancer cachexia are explained in detail.[14]

Conclusion

The nutritional status of pediatric oncology patients at diagnosis can have an effect on outcome, therefore it

Table 6: Factors contributing of cancer cachexia in pediatric oncology patients

Sources of energy imbalance	Potential mechanism
Inflammation causing low energy intake and/or anorexia	Cytokines released by tumor, immune and stromal cells alter central nervous system transmitters and affect appetite TNF-α and IL-1 may increase levels of corticotrophin-releasing peptide, a neurotransmitter that suppresses food intake
	Modulation of gastric motility and emptying Direct effect on GIT system Alteration of efferent signals regulating satiety; IL-a blocks feeding stimulated by neuropeptide Y
Metabolic and endocrine alterations leading to increased catabolic drive	CHO metabolism Increased fasting insulin levels Increased glucose demand
	Protein metabolism Loss of normal compensatory protein conservation mechanisms seen in starvation Increased whole-protein catabolism Increased protein catabolism in muscle cells Decreased regulators of muscle protein synthesis
	Fat metabolism Accelerated lipolysis driven by inflammatory cytokine inhibition of lipoprotein lipase, TNF-α and IL-6 implicated Increased rate of fat oxidation and clearance Decreased lipoprotein lipase may shift energy burden to lean body mass
	Disease burden Metabolic demands of tumor in progressive disease

TNF-α=Tumor necrosis factor alpha; IL-1=Inerleukin-1; GIT=Gastrointestinal tumor; CHO=Carbohydrate

is extremely important that their nutritional status be maintained or improved during treatment. Assessment needs to be done regularly to determine if there were any deterioration in their nutritional status since last assessed and then the proper nutritional intervention is needed. In units with lack of resources, the patients at high risk for malnutrition should be prioritized and assessed at diagnosis and follow-up throughout treatment to ensure well-being of these patients.[1] It is clear that nutritional support should be a major part of supportive care to prevent or reverse malnutrition and increase well-being of children with cancer.[26]

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Appendix E: Paediatric oncology related journal articles as co-author (2018-2023)

Travel burden and clinical presentation of retinoblastoma: analysis of 1024 patients from 43 African countries and 518 patients from 40 European countries

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► Supplemental material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bjophthalmol-2020-316613).

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Received 29 April 2020
Revised 28 July 2020
Accepted 17 August 2020

To cite: Fabian ID, Stacey AW, Foster A, *et al. Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjophthalmol-2020-316613

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ABSTRACT

Background The travel distance from home to a treatment centre, which may impact the stage at diagnosis, has not been investigated for retinoblastoma, the most common childhood eye cancer. We aimed to investigate the travel burden and its impact on clinical presentation in a large sample of patients with retinoblastoma from Africa and Europe.

Methods A cross-sectional analysis including 518 treatment-naïve patients with retinoblastoma residing in 40 European countries and 1024 treatment-naïve patients with retinoblastoma residing in 43 African countries.

Results Capture rate was 42.2% of expected patients from Africa and 108.8% from Europe. African patients were older (95% CI −12.4 to −5.4, p<0.001), had fewer cases of familial retinoblastoma (95% CI 2.0 to 5.3, p<0.001) and presented with more advanced disease (95% CI 6.0 to 9.8, p<0.001); 43.4% and 15.4% of Africans had extraocular retinoblastoma and distant metastasis at the time of diagnosis, respectively, compared to 2.9% and 1.0% of the Europeans. To reach a retinoblastoma centre, European patients travelled 421.8 km compared to Africans who travelled 185.7 km (p<0.001). On regression analysis, lower-national income level, African residence and older age (p<0.001), but not travel distance (p=0.19), were risk factors for advanced disease.

Conclusions Fewer than half the expected number of patients with retinoblastoma presented to African referral centres in 2017, suggesting poor awareness or other barriers to access. Despite the relatively shorter distance travelled by African patients, they presented with later-stage disease. Health education about retinoblastoma is needed for carers and health workers in Africa in order to increase capture rate and promote early referral.

INTRODUCTION

Rare cancers, defined as having an incidence of less than six cases per 100 000 population per year,[1] pose a particular burden on patients and professionals alike because of the need for specialist care, frequent lack of standardised treatments and lack of funding for research.[2 3] It is not uncommon to have only one or two specialised referral centres in a country for a given type of rare cancer, to which most cases are referred. Such a policy of centralised tertiary centres may result in reduced access and a high travel burden on patients, which can lead to poorer quality of life, advanced disease at diagnosis, late treatment and worse prognosis.[4 5]

Retinoblastoma is a rare, potentially deadly, childhood cancer. Its incidence is believed to be constant across populations, ranging from 1:16 000 to 18 000 live births.[6] In most countries, only few specialised retinoblastoma centres exist. In Europe, for example, there is a single centre in France, two in the UK and three in Russia, all in Moscow. Travel burden associated with retinoblastoma, to the best of our knowledge, has not been explored. This information, which also reflects on the accessibility to tertiary centres and their catchment area, is important for healthcare planning.

Prognosis of patients with retinoblastoma has improved significantly over the past 50 years to reach over 90% 5-year survival in Europe.[7–9] These improvements are attributed to several factors, including the implementation of national strategies associated with retinoblastoma referral pathways, and the introduction of novel and improved treatment modalities, several of which were developed in European specialised referral centres.[10–13] Indeed, in the field of retinoblastoma, Europe serves as a potential model for under-resourced regions of the world. In Africa, where birth rate is higher, resulting in higher retinoblastoma prevalence, these improvements in survival have not been observed. Reports on retinoblastoma from Africa are scarce, and anecdotal evidence suggests that survival rates are as low as 50%,[14 15] and in some regions of sub-Saharan Africa are even less than 30%.[16]

We have recently reported the stage at presentation of more than 4000 newly diagnosed patients with retinoblastoma from over 150 countries analysed by national-income level.[17] The aim of the present study is to use the data from all countries in Africa and Europe to (1) investigate and compare the travel burden experienced by patients, (2) compare the stage at the time of diagnosis and (3) investigate risk factors for advanced disease at the time of diagnosis. Such information is important to better understand the current gaps in retinoblastoma service provision and to inform policymakers at national and international levels.

METHODS

The study methodology, data collection and quality assurance process have been described in detail previously.[17] Briefly, the data were collected through a 1-year cross-sectional analysis of treatment-naïve patients with retinoblastoma who presented to retinoblastoma referral centres across the world from 1 January 2017 to 31 December 2017. Data on country of residence, sex and laterality of retinoblastoma were considered essential minimum criteria for inclusion. In the present analysis, patients that resided in African and European countries were included. The study was approved by the Institutional Review

Board of the London School of Hygiene & Tropical Medicine (reference number 14574) in accordance with the tenets of the Declaration of Helsinki. Participating centres, according to local institutional and national guidelines, applied to and received ethics clearance in their countries.

Data collected from medical charts included patient country of residence, initial clinical sign leading to referral, distance travelled from home to retinoblastoma centre, sex, family history of retinoblastoma, age at the time of diagnosis at retinoblastoma centre, tumour laterality, and stage according to the eighth edition of the American Joint Committee on Cancer (AJCC) clinical Tumor, Node, Metastasis, Hereditary (cTNMH) scheme[18] and the International Retinoblastoma Staging System.[19] For travel distance calculation, a Google-based map was used and the orthodromic distance (ie, 'as the crow flies') between home and the retinoblastoma centre was measured. In case both were in the same city or site, the distance was considered to be zero, unless mentioned otherwise by the retinoblastoma centre that submitted the data. Data on national-income level, crude birth rate, country surface area and population size were retrieved from the United Nations World Population Prospects.[20]

Statistical analysis

Analyses were performed using R software[21] and IBM SPSS statistics v25.0 (IBM Corp, Chicago, IL, USA). The predicted number of new patients with retinoblastoma per country was calculated as follows: country population×crude birth rate/1000/17 000.[22] The predicted number does not take into account deviations from the average percentage with familial retinoblastoma, in which the risk of the offspring is ~1/2 rather than 1/17 000. The predicted number per continent was the sum for all countries in that continent. Fisher's exact test and Student's t-test was used to compare categorical and continuous variables between groups. A one-way analysis of variance was used to test differences in the age at the time of diagnosis between the continents and the Kruskal-Wallis test to test for differences in travel distance between the continents. Binomial logistic regression was used to model the effect of income level, continent, travel distance from home to retinoblastoma centre, age at diagnosis, family history of retinoblastoma and tumour laterality on the likelihood of children having advanced disease at presentation (cT4). A value of $p<0.05$ was considered significant, and data throughout the manuscript are presented as mean (SD) with 95% CI.

RESULTS

The analytic sample included 1542 newly diagnosed patients with retinoblastoma. Of these, 518 (33.6%) resided in 40 European countries and 1024 (66.4%) in 43 African countries. Using an average incidence figure of 1/17 000 live births,[6] the observed capture rates were 42.2% and 108.8% of expected patients from Africa and Europe, respectively.

Clinical data were available for both the African and European subcohorts for over 90% of the patients, with the exception of travel distance, which was available for 81.5% and 84.6% of the patients, respectively. Table 1 shows the clinical data of the study patients by continent.

Travel burden and retinoblastoma centre catchment area

Overall, the mean travel distance from home to a retinoblastoma centre was 233.3 km (SD 468.78, 95% CI 207.0 to 259.0). To reach a retinoblastoma centre within the country of residence, patients from European countries travelled on average more than twice the distance compared to patients from African countries: 421.8 km (SD 814.6, 95% CI 328.6 to 537.5) and 185.7 km (SD 201.0, 95% CI 168.0 to 205.2), respectively ($p<0.001$, online supplemental table 1 in the appendix). Figure 1 shows the number of retinoblastoma centres by country and continent (see online supplemental figure 1 in the appendix for geographical location of the centres). No significant differences were found in the mean number of retinoblastoma centres per country in Africa and Europe: 1.8 (SD 1.8, 95% CI 1.2 to 2.4) and 1.4 (SD 0.9, 95% CI 1.1 to 1.7), respectively ($p=0.22$). Similarly, on analysis of the mean country population size and country surface area, differences between African and European countries were non-significant ($p=0.32$ and $p=0.89$, respectively). The catchment area of each retinoblastoma centre in Africa and Europe is represented in figure 2 by the mean travel distance ±SD. While the distribution of retinoblastoma centres in Europe covers the entire continent, in many African countries, large parts remain underserviced.

Presentation to retinoblastoma centre

Age at the time of diagnosis

For the entire sample, the mean age at the time of diagnosis at a retinoblastoma centre was 27.9 months (95% CI 26.7 to 29.0): 22.0 months (SD 27.6; 95% CI 19.7 to 24.4) for European patients compared to 30.9 months (SD 21.0; 28.7 to 32.8) for those from Africa (diff = (−8.9), 95% CI −12.4 to −5.4, $p<0.001$).

Bilateral and familial retinoblastoma

Overall, 28.1% of the patients presented with bilateral disease, and 4.5% had a family history of retinoblastoma. Of the African patients, 26.7% had bilateral disease at the time of diagnosis compared to 31.1% of the European patients (OR 0.8, 95% CI 0.6 to 1.0, $p=0.07$). A positive family history was reported for 2.8% vs 8.4% of the African and European patients, respectively (OR 3.2, 95% CI 2.0 to 5.3, $p<0.001$).

Referral to a retinoblastoma centre for screening in case of positive family history of retinoblastoma was uncommon in Africa as compared to Europe: 3/26 (11.5%) of the familial cases in Africa vs 31/42 (73.8%) in Europe (OR 20, 95% CI 5.3 to 100.0, $p<0.001$). All three screened African patients were staged cT1 at the time of diagnosis. Of the African familial cases, 57.7% had advanced intraocular (cT3) or extraocular retinoblastoma (cT4) at the time of diagnosis. In comparison, of the European familial cases, 64.3%, 31.0% and 4.8% were staged cT1, cT2 and cT3, respectively.

Tumour staging

Overall, the most common cTNM stages were cT3 (44.7%), N0 (74.3%) and M0 (89.6%). Significantly more patients from African countries as compared to European countries had at the time of diagnosis advanced retinoblastoma (ie, >cT2; OR 7.7, 95% CI 6.0 to 9.8, $p<0.001$), extraocular retinoblastoma (OR 25.7, 95% CI 15.1 to 43.6, $p<0.001$), lymph node involvement (OR 65.2, 95% CI 9.0 to 469.7, $p<0.001$) and metastasis (OR 18.7, 95% CI 7.6 to 45.8, $p<0.001$). Overall, 43.4% and 15.4% of the African patients had at the time of diagnosis extraocular retinoblastoma and distant metastasis, respectively, compared to 2.9% and 1.0% of the European patients, respectively.

Table 1 Clinical data of 518 European and 1024 African patients with retinoblastoma

Parameter	European sample, n (%)	African sample, n (%)	Significance
Travel distance from home to retinoblastoma centre*			p<0.001
Mean distance in km (SD, 95% CI)	421.8 (814.6, 328.6 to 537.5)	185.7 (201.0, 168.0 to 205.2)	
Reported cases	396/468 (84.6)	736/903 (81.5)	
Age at diagnosis			p<0.001
Mean age in months (SD, 95% CI)	22.0 (27.6, 19.7 to 24.4)	30.9 (21.0, 28.7 to 32.8)	
Reported cases	514/518 (99.2)	1015 (99.1)	
Sex			p=0.75
Male	280 (54.0)	544 (53.1)	
Female	238 (46.0)	480 (46.9)	
Reported cases	518/518 (100)	1024/1024 (100)	
Laterality			p=0.07
Unilateral	357 (68.9)	751 (73.3)	
Bilateral	161 (31.1)	273 (26.7)	
Reported cases	518/518 (100)	1024/1024 (100)	
Familial retinoblastoma			p<0.001
No	468 (91.6)	910 (97.2)	
Yes	43 (8.4)	26 (2.8)	
Reported cases	511/518 (98.6)	936/1024 (91.4)	
Primary tumor (T)			p<0.001
cT1	76 (14.9)	32 (3.3)	≤cT2 versus >cT2
cT2	237 (46.6)	134 (13.9)	
cT3	192 (37.7)	465 (48.3)	
cT4	4 (0.8)	331 (34.4)	
Reported cases	509/518 (98.3)	962/1024 (93.9)	
Regional lymph node (N)			p<0.001
NX	34 (6.6)	265 (26.8)	N0 versus N1
N0	482 (93.2)	636 (64.4)	
N1	1 (0.2)	86 (8.7)	
Reported cases	517/518 (99.8)	987/1024 (96.4)	
Distant metastasis (M)			p<0.001
M0	513 (99.0)	830 (84.6)	M0 versus M1†
cM1	1 (0.2)	110 (11.2)	
pM1	4 (0.8)	41 (4.2)	
Reported cases	518/518 (100)	981/1024 (95.8)	
Extraocular retinoblastoma			p<0.001
No	503 (97.1)	561 (56.6)	
Yes‡	15 (2.9)	430 (43.4)	
Reported cases	518/518 (100)	991/1024 (96.8)	

*50/518 (9.7%) European and 121/1024 (11.8%) African patients with retinoblastoma travelled across borders for diagnosis and primary treatment (not included in the analysis).
†M1=cM1+pM1.
‡Based on the International Retinoblastoma Staging System.[19]

Risk factors for advanced disease at the time of diagnosis

Lower-national-income level, African continent, older age at presentation, familial retinoblastoma and bilateral retinoblastoma (p≤0.010), but not distance from home to retinoblastoma centre (p=0.19), were found to be significant factors for the prediction of cT4 category (ie, extraocular disease). On logistic regression, national-income level, continent and age at presentation were found to be independent, significant predictors for cT4 category (table 2). On further analysis by continent, no predictors were found for the European subgroup, whereas for the African subgroup, older age and lower-income level (p<0.001) were found to be significant predictors of cT4 category (online supplemental table 2 in the appendix).

DISCUSSION

Our findings confirm a large disparity in the presentation patterns of retinoblastoma between patients from African and European countries. Patients from Africa were significantly older, nearly half of them had extraocular spread at the time of diagnosis, and nearly one-fifth had distant metastasis. Of the European patients, less than 3% had extraocular tumour spread and only 1% had metastatic spread at the time of diagnosis. Patients from lower-income level countries, those from the African continent and older patients at the time of diagnosis were at increased risk to have advanced retinoblastoma. Interestingly, distance patients travelled in order to reach a retinoblastoma referral centre did not play a role in this risk. These results are in contrast to previous analyses of other

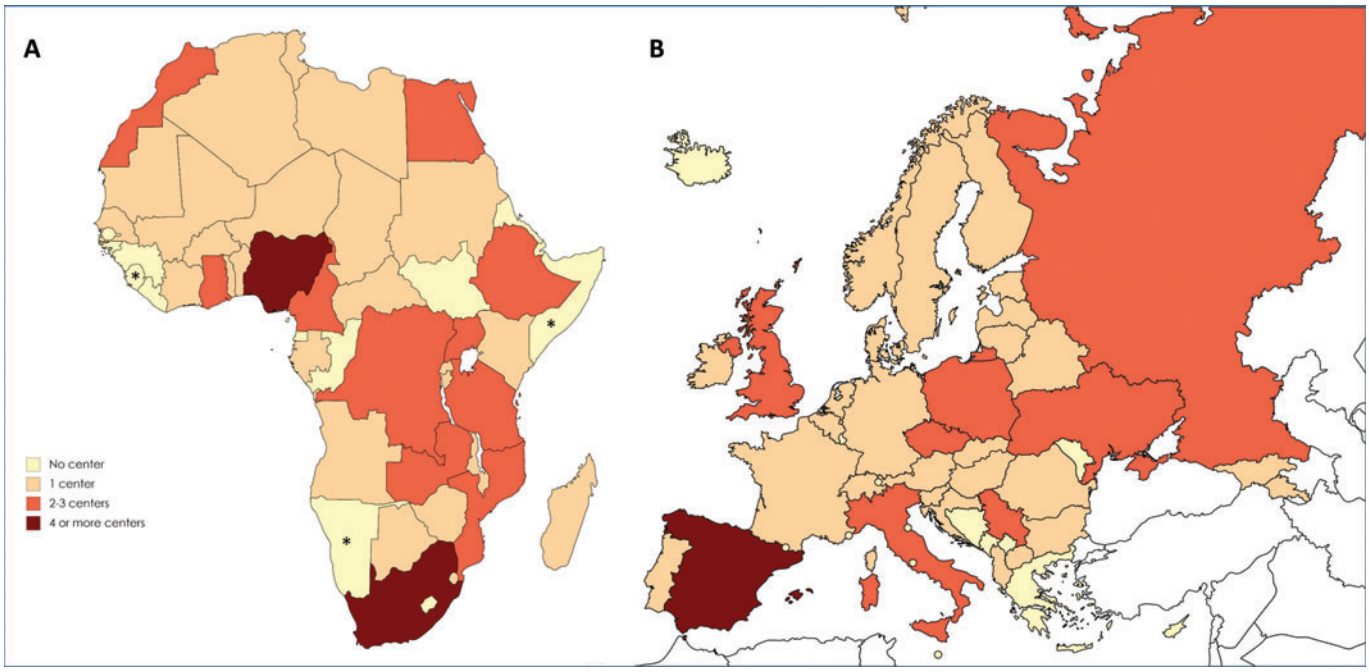

Figure 1 Number of retinoblastoma centres in (A) Africa and (B) Europe. *Centers in Namibia (n=1), Sierra Leone (n=1) and Somalia (n=1) that were contacted did not join the study; hence, no information was available from these centres. Of the two known Kenyan centres and two known Algerian centres that were contacted, only one from each country has joined in the study.

forms of cancer, including breast, colon, lung and skin melanoma,[23–26] as well as rare cancers such as Merkel cell carcinoma,[27] in which high travel burden correlated with advanced-disease stage. Noteworthy, all of the above-referenced studies were single-centre rather than multicentre multinational studies, as the present one.

Analysis of the travel burden, however, in conjunction with data on the number of retinoblastoma centres in African and European countries, and demographic data, including country population and surface area, suggests a more complex picture. Patients from African countries travelled less than half the distance compared to European patients in order to reach a specialised retinoblastoma treatment centre. Assuming that nearly all retinoblastoma centres in the participating African countries were contacted and recruited, our findings suggest that these centres serve mainly patients that reside in close vicinity.

Taking into account the low capture rate in Africa, underlying causes for the findings of this study are multifactorial; they include poor awareness by carers and health workers, lack of knowledge about clinical presentation by health workers, travel distance and cost to reach a specialised retinoblastoma treatment centre, and probably the absence of specialised retinoblastoma treatment centres in some parts of Africa.

It is well documented that poor awareness of retinoblastoma both by the public and health workers can lead to delays in diagnosis.[28–31] Delayed retinoblastoma diagnosis, in turn, leads to poor outcome.[32–34] Poor awareness and health education is likely to be the main factor for those cases that reside in proximity to a treatment centre, yet presented late. Initiatives are addressing this need by creating twinning programmes that link centres from higher- and lower-resource countries, as well as interventions such as public awareness campaigns, and health worker education.[29 31 35–39] There is a pressing need, to promote this action at national and global level. In a rare curable cancer such as retinoblastoma, with a finite number of patients worldwide, such action is feasible.

Barriers to healthcare in Africa have been reported in relation to several medical fields, including oncology,[40 41] ophthalmology[42–46] and paediatrics.[42 44 47] Most barriers, whether financial, structural (ie, accessibility), lack of transport, poor roads, were also found relevant in the context of retinoblastoma in Africa.[33 48 49] Possible solutions should be inclusive and account for all factors; most are not in the scope of the present study. Number and distribution, however, of retinoblastoma centres in a country is a matter that warrants further discussion. The need for and number of retinoblastoma centres derive first and foremost from the number of new retinoblastoma cases in a country. There should be enough centres with an appropriate distribution to serve all patients within a country. On the other hand, there should not be too many, as expert centres need to remain 'vivid', an ability that relates directly to the number of cases managed, as was shown in other rare malignancies.[50] In this sense, European and African countries face different challenges. In Europe, with a low birth rate and therefore low prevalence of retinoblastoma, the need for a treatment centre in countries with 1–2 new cases per year is questionable. In Africa, with a high birth rate and increasing population, the situation is more complex. New retinoblastoma centres will be needed where there is a large population (10 million population and 20–30 new retinoblastoma cases/year) with no available centre. The number and distribution of retinoblastoma treatment centres need to be tailored to the country's requirements.

Familial retinoblastoma was significantly more common in European than in African countries. A possible explanation is the high survival rate of hereditary cases in Europe due to early diagnosis and efficient treatments. This possibly could

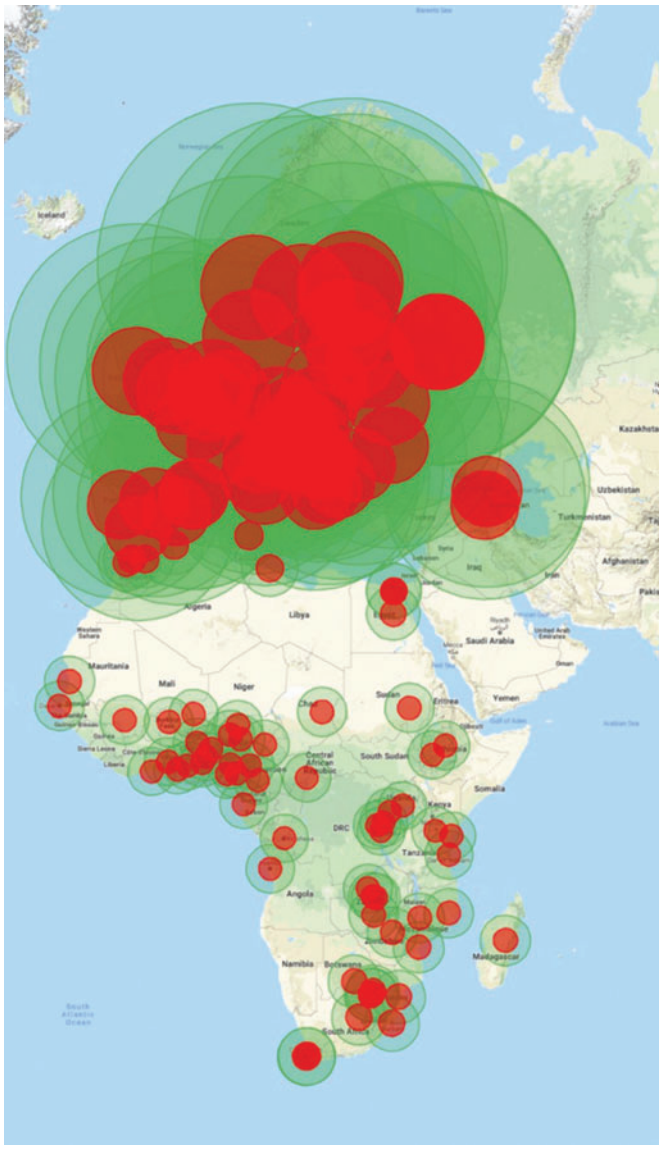

Figure 2 Retinoblastoma centre catchment area in Africa and Europe. The red circles represent the mean patient travel distance and green circles, the travel distance SD. Patients in European countries travelled in average significantly longer distances (421.8 km±814.6) compared to patients from African countries (185.7 km±201.0) in order to reach a retinoblastoma centre (p<0.001). Superimposing the red and green circles on the map, retinoblastoma centres in European countries cover the whole continent, whereas in Africa, large parts in many African countries remain uncovered.

explain the high capture rate of retinoblastoma in Europe too, higher than the predicted annual number. Further studies are warranted to better understand the trends in retinoblastoma incidence in Europe. Three-quarters of the European familial cases were screened for retinoblastoma (ie, examined before clinical signs were evident) and most were diagnosed with early disease stage. In Africa, screening rate was as low as 11.5% of the familial cases, lower than previously reported in 'developing countries' outside Africa.[51] Screening may result in less invasive treatments being needed, resulting in higher chances for eye salvage and better vision.[52 53] Patients with retinoblastoma from both continents should receive future counselling regarding the need for screening of their offspring, especially the ~30% that presented with bilateral disease whose children have a nearly 50% chance of developing retinoblastoma. Interestingly, the rates of bilateral cases were similar between Africa and Europe. Most of them are known to result from sporadic germline mutations. The proportion of cases with familial retinoblastoma who presented with bilateral disease was also similar. Given the risk factor analysis, which showed that lower-income level and African continent were independently associated with advanced disease, it is possible that other, unrecorded variables are responsible for disease progression before diagnosis is made in Africa, as well as for tendency to present with bilateral retinoblastoma. Further studies should explore these possibilities.

Our study has limitations. First, the orthodromic distance was used as a surrogate for the travel burden, whereas other related factors that may play a role were not taken into account, especially travel costs, time costs, loss of parental income, availability and mode of transportation, road conditions, availability of transport and the actual distance travelled from home to a specialised referral retinoblastoma centre. Second, our study was cross-sectional by design and some of the data were collected in a retrospective manner (centres that were recruited after January 2017), with the inherent limitations of such a design. Nevertheless, we were able to collect data from an unprecedented number of retinoblastoma centres and countries, and to perform a quality and assurance process to make sure that the data are accurate. Third, our sample was a convenience sample, and although repeated attempts were made to reach every retinoblastoma treatment centre in Africa and Europe, it is possible that some were missed. Notably, centres in Namibia (n=1), Sierra Leone (n=1) and Somalia (n=1) that were contacted did not join in the study; hence, no information on these centres was available. In addition, only 1 out of 2 centres in Kenya, and 1 out of 2 in Algeria, joined in the study, and similarly, no information was available on those centres that did not join in.

In summary, our findings show that in European countries, travel distance from home to retinoblastoma centre is not a barrier to early disease diagnosis. European patients travel on average more than 400 km and >60% present at stage cT2 or earlier. In Africa, the picture is more complex —patients travel on average less than 200 km, yet >80% present at stage cT3 or worse, suggesting that factors other than geographic distance to retinoblastoma centre play a role in late disease diagnosis. Poor awareness and education by both caregivers and health workers, other barriers to access, and possibly, number and distribution of specialist retinoblastoma treatment centres in those African countries in which the population is underserved, are key factors that warrant intervention on national and international levels. Familial retinoblastoma is more common in Europe than in Africa, most probably due to death related to late disease presentation, and screening of patients at risk of developing retinoblastoma is more common in Europe. Comprehensive counselling of families and patients with germline disease (ie, bilateral retinoblastoma and/or positive family history) may be found useful in order to detect the disease at early stage to increase survival rates in this highly curable malignancy.

Table 2 Predictors of advanced retinoblastoma disease at presentation (cT4): univariate and multivariate analyses

Variable	Category	B	SE	Corrected pvalue	OR	95% CI for OR Lower	95% CI for OR Upper
Univariate analysis							
Income level	Low versus lower-middle	1.04	0.14	<0.001	2.82	2.13	3.74
	Low versus upper-middle	1.25	0.15	<0.001	3.50	2.60	4.70
	Low versus high	1.89	0.34	<0.001	6.64	3.44	12.82
	Lower-middle versus upper-middle	1.47	0.31	<0.001	4.33	2.38	7.90
	Lower-middle versus high	2.32	0.50	<0.001	10.19	3.80	27.35
	Upper-middle versus high	3.18	1.04	<0.001	23.96	3.11	184.62
Continent	Africa versus Europe	0.84	0.10	<0.001	2.32	1.90	2.82
Familial retinoblastoma	Yes versus no	1.51	0.52	0.001	4.54	1.64	12.57
Bilaterality	Yes versus no	0.38	0.15	0.010	1.46	1.10	1.94
Distance from home to Rb centre*				0.19			
Age at diagnosis*				<0.001			
Multivariate analysis (binomial logistic regression)							
Income level	Lower-middle	0.90	0.15	<0.001	2.45	1.83	3.30
	Upper-middle	1.48	0.34	<0.001	4.38	2.26	8.47
	High	3.08	1.18	0.001	21.74	2.14	220.82
Continent	Europe	2.34	0.62	<0.001	10.37	3.07	35.01
Age at diagnosis†	≥24 months	–1.33	0.16	<0.001	0.27	0.19	0.37
Constant		1.07	0.16	<0.001	0.34		

*t-Test for numerical variables.
†Median age=24.2 months (categorical variable).

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Ethics approval The study was approved by the Institutional Review Board of the London School of Hygiene & Tropical Medicine (reference number 14574).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open-access repository.

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PEDIATRIC ONCOLOGY

original reports abstract

Reporting Incidences of Neuroblastoma in Various Resource Settings

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PURPOSE The incidences of neuroblastoma (NB) differ significantly between various resource settings because of varying quality of cancer registries and underdiagnoses. This study aimed to evaluate current regional variations as reported by international cancer registries and the theoretical and reported differences in international NB incidences and to evaluate South Africa (SA) as a case for variable reporting.

METHODS A comprehensive literature review on registries reporting on NB was performed to construct incidence tables. The SEER Program incidence of 10.5/million children was used to calculate the expected number of NB cases for each country. Registry data of NB cases between 2000 and 2016 were requested from The South African National Cancer registry (SA-NCR) and the South African Children's Tumour Registry (SACTR) for comparison and to perform a probabilistic linkage study.

RESULTS Internationally, incidences varied between –97.1% and +80% compared with the SEER program. SA under-reported NB cases by an estimated 74.2%. Between 2000 and 2016, the SA-NCR reported between 23 and 51 cases/year, whereas the SACTR reported between 18 and 57 cases/year for the same period. The incidence reported by the SA-NCR varied between 1.5 and 2.8/million children under 15-year per year, whereas the SACTR reported 1.74-2.6 cases/million children. Both registries reported incidences less than high-income country. A probabilistic record linkage of the two registries resulted in a combined incidence of 2.9 cases/million children.

CONCLUSION As with most low- and middle-income countries, SA has either a lower incidence or underdiagnoses of NB cases. The reasons for under-reporting are not clear, but can be due to undiagnosed NB cases with spontaneous regression, missed possible cases because of lack of autopsies, and diagnosed cases not recorded in registries.

JCO Global Oncol 7:947-964. © 2021 by American Society of Clinical Oncology

INTRODUCTION

According to the American SEER program, the incidence of childhood malignancies between 2011 and 2015 for US children under 15-year was 16/100,000 children compared with 953 malignancies per 100,000 adults.[1] Although childhood cancers are rare, compared with adults, the childhood and adolescent incidence of malignancies will increase with growing populations.[2] Combating the increase of childhood malignancies with preventative measures is limited as there are few modifiable risk factors contributing to the etiology.[2] Concerted standardized protocol–based therapy and supportive care for children with cancer have resulted in improved survival outcomes. Yet in many countries, funding for childhood cancers constitutes a small percentage of adult cancer budgets. The planning for these health expenditures is dependent on accurate registration of disease incidences.[2] Therefore, to adequately budget for disease interventions, data to support health planning are important. Although neuroblastoma (NB) is the most common extracranial solid tumor of childhood, it only contributes to 7% of childhood malignancies.[3] It has a very heterogeneous pathophysiologic course that varies from undetected spontaneous regression to advanced metastatic disease with a high mortality, making surveillance in variable resourced settings challenging.[3]

South Africa (SA) is a provincial-based republic with a population of 58.8 million and a male:female ratio of 1.0:1.04. The country has a youthful age structure of the population with 29.2% of the population under the age of 15 years.[4] Since 2011, the Department of Health has made the registration of all malignancies compulsory. Health campaigns promoting early warning signs of childhood illness were initiated by the Department of Health and Childhood Cancer

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on May 19, 2021 and published at ascopubs.org/journal/go on June 17, 2021: DOI https://doi.org/10.1200/GO.21.00054

CONTEXT

Key Objective

Why is the incidence of neuroblastoma (NB) in South Africa lower than that described in the literature and how does it compare with all the countries of the world? This study highlights the variations in reporting of NB in the world and uses South Africa as a case study to indicate possible resources to establish a true incidence of NB in a country.

Knowledge Generated

This study identifies which countries are under-reporting incidences of NB. Variations in the reported incidences are independent of resources in each country. The incidences of NB are not only dependent on tumor registries but also influenced by available clinical services, population distribution, and management systems.

Relevance

By understanding the true incidence of NB in various countries, awareness regarding rare tumors can be increased, which can be diagnosed more rapidly, and adequate resources can be allocated for treatment by policy makers.

Foundation of South Africa in 2016. The reported incidence of 45.2 per million childhood cancer cases in SA and the documented survival rates of approximately 50% are significantly lower than those in high-income countries (HICs). Although the incidence of NB is well-described in HICs, very little is known about the epidemiology of the disease in sub-Saharan Africa. In a region where communicable diseases, neonatal deaths, malnutrition, and the HIV-epidemic contribute the greatest burden to health care systems, the incidences of rare diseases, such as NB, even in the presence of disease-specific registers, are inaccurately recorded. The SEER program reported an incidence of 10.5 cases/million for NB for the United States, but a lower incidence has been recorded in low- and middle-income country (LMIC). The combination of lower reported incidences of most childhood cancers, not just NB, in LMICs and the inaccuracies of cancer registers in these regions limits the distinction between true incidences and false low values. The South African Children's Cancer Study Group (SACCSG) reported a cancer incidence of 2.7/million children younger than 15 years on the basis of data from 1987 to 2007.[5]

Two registries record cases of pediatric malignancies in SA: The South African Children's Tumour Registry (SACTR) established in 1987 by the SACCSG is a clinical-based registry compiled by data submitted by physicians treating children with childhood malignancies.[5] The registry complies with international quality standards for cancer registries. Relapses are linked with diagnostic registration and noted for future use. Cases with incomplete data are not included in reported data. The South African National Cancer Registry (SA-NCR) is the main cancer surveillance system in SA. Although it was established in 1986 as a voluntary, pathology-based cancer reporting system, the register was mandated through legislation in 2011 to monitor and report the national cancer burden.[6]

The aim of this study was (1) to evaluate the theoretical and reported differences in incidences globally and (2) to determine the incidence of NB in SA children under the age of 15 years on the basis of clinical records from pediatric oncology units (POUs) in SA and the two local South African registries.

METHODS

African Index Medicus, ScieLo, PubMed, Global Health, Embase, and Google Scholar were searched to perform a comprehensive literature review of publications with medical subject headings in line with registries reporting on NB such as registries, neuroblastoma, children, and country or territory-specific names. The search was conducted from April 2019 to January 2020. No limitations were set on the date or language, provided that English summaries or abstracts were included. Reports of tumor registries were used to construct incidence tables. If no reports were found, data were requested electronically from relevant cancer registries of each country. The percentage of children under 15 years old per population and the population under 15 years old in each country were sourced or calculated from data from the World Bank[7] and the World Factbook website.[8] The NB incidence of 10.5 cases/million children reported by the SEER Program was used to calculate the expected number of cases for each country. The analysis of international registries reporting incidence of NB was performed for comparative purposes between regions and World Bank country income classifications. Analysis of the regions without reported data was performed to determine possible common factors for the lack of reported data.

Registry data were requested from the SA-NCR and the SACTR for registered NB cases between 2000 and 2016. Cases from the two data were compared across the two data sets. As there are no common unique identifiers in both sets, record linkage was performed using probabilistic record linkage techniques with variables such as name(s), surname, date of birth, sex, and date of diagnosis to link the patients between the two sets. The probabilistic record linkage was performed using statistical software STATA 16

TABLE 1. Reported Incidences of Neuroblastoma Per Country According to World Bank Country Income Classification

Country	AIR/ASR/CIR (percentage of incidence difference from 10.5 cases/million children)	Source
LIC		
Democratic People's Republic of Korea	11.3 (+6.7)	B
Ethiopia	3.1 (–70.4)	A and B
The Gambia	0.4 (–96.2)	A and B
Guinea	0	C
Malawi	2.8 (–73.3)	A and B
Mali	2.2 (–79.0)	A and B
Niger	0.3 (–97.1)	A and B
Uganda	1.0 (–90.5)	A and B
Republic of Yemen	1.9 (–81.9)	B
Range	0-11.3 (0 to +6.7)	
Median	1.9 (–81.9)	
LMIC		
Algeria	7.2 (–31.4)	A and B
Cameroon	0.4 (–96.1)	A and B
Arab Republic of Egypt	10.1 (–3.8)	A and B
Honduras	1.6 (–84.8)	B
India	3.6 (+65.7)	B
Kenya	1.7-2.8 (–73.3 to –83.8)	A and B
Morocco	9.1-9.6 (–8.6% to –13.3)	A and B
Nigeria	1.9 (–81.9)	A and B
Pakistan	1.7 (–83.8)	B
Philippines	2.8 (–73.3)	B
Tunisia	7.7 (–26.7)	B
Vietnam	7.7 (–26.7)	B
Zimbabwe	1.4 (–86.7)	A and B
Range	0.4-10.1 (–96.1 to –3.8)	
Median	1.9 (–81.9)	
UMIC		
Argentina	8.6 (–18.0)	B
Belarus	9.3 (–11.4)	B
Botswana	2.7 (–74.3)	A
Brazil	8.4 (–20)	B
Bulgaria	7.1 (–32.3)	B
China	8.6 (–18.1)	B
Colombia	4.0 (–61.9)	B
Costa Rica	4.0 (–61.9)	B
Cuba	8.5 (–19.4)	B
Ecuador	1.9 (–81.9)	B
Islamic Republic of Iran	2.6 (–75.2)	B
Jamaica	6.8 (–35.2)	C
Jordan	9.0 (–14.2)	B
Lebanon	10.6 (+0.01)	B

(Continued on following page)

TABLE 1. Reported Incidences of Neuroblastoma Per Country According to World Bank Country Income Classification (Continued)

Country	AIR/ASR/CIR (percentage of incidence difference from 10.5 cases/million children)	Source
Libya	8.1 (–22.6)	A and B
Malaysia	6.1 (–41.9)	A and B
Mexico	3.5 (–66.7)	B
Namibia	1.2 (–88.6)	A and B
Romania	9.0 (–14.3)	B
Russian Federation	9.3-9.8 (–6.6 to 11.4)	B
South Africa	2.7 (–74.2)	A
Suriname	0.2 (–98.1)	B
Thailand	4.6 (–52.1)	B
Turkey	10.6 (+0.01)	B
Ukraine	8.2 (–21.9)	B
Range	0.2-10.6 (–98.1 to +0.01)	
Median	7.1 (–32.3)	
HIC		
Australia	11.6 (+10.5)	B
Austria	13.3 (+26.6)	B
Bahrain	9.6 (–8.5)	B
Belgium	13.4 (+27.6)	A
Bermuda	0	C
Canada	13.8 (+31.4)	A
Chile	4.2 (–60.0)	B
Croatia	13.2 (+25.7)	B
Cyprus	13.9 (+32.3)	B
Czech Republic	14.1 (+34.2)	A and C
Denmark	9.6 (–8.6)	B
Estonia	10.0 (–4.7)	B
Finland	2.9 (–72.3)	B
France	14.2 (+35.2)	B
Germany	13.7 (+30.5)	B
Greece	14.4 (+37.1)	B
Hungary	17.0 (+61.9)	B
Iceland	6.2 (–40.9)	B
Ireland	10.9 (+3.8)	B
Israel	14.6 (+39)	B
Italy	18.9 (+80)	B
Japan	15.7 (+49.5)	B
Kuwait	9.8 (–6.7)	B
Lithuania	9.8 (–6.7)	B
Malta	14.2 (+35.2)	B
Mauritius	4.1 (–60.9)	B
Netherlands	8.1 (–22.9)	B
New Caledonia	12.9 (+22.9)	B
New Zealand	11.3 (+7.6%)	B

(Continued on following page)

TABLE 1. Reported Incidences of Neuroblastoma Per Country According to World Bank Country Income Classification (Continued)

Country	AIR/ASR/CIR (percentage of incidence difference from 10.5 cases/million children)	Source
Norway	9.2 (–12.4)	B
Poland	13.9 (+32.4)	B
Portugal	10.9-16.5 (+3.8 to 57.1)	B
Qatar	6.6 (–37.1)	B
Reunion	11.1 (+5.7)	A and C
Saudi Arabia	6.3 (–40)	B
Singapore	5.9 (–43.8)	A and B
Slovak Republic	12.8 (+21.9)	B
Slovenia	9.0 (–14.2)	B
Spain	13.8-14.6 (+31.4 to 39)	B
Sweden	9.4 (–10.4)	B
Switzerland	11.7 (+11.4)	B
Taiwan	1.3 (–87.6)	B
Trinidad and Tobago	0.6 (–94.2)	B
United Kingdom	9.6 (–8.6)	B
United States	12.4 (+18.1)	A
Uruguay	11.2 (+6.7)	B
Range	0-18.9 (0 to +80)	
Median	14.1 (+34.2)	

NOTE. Data adapted.[10-23] Abbreviations: AIR, age-adjusted cancer incidence rate; ASR, age-standardized incidence rate; CIR, crude incidence rate; HIC, high-income country; LIC, low-income country; LMIC, lower-middle–income country; UMIC, upper-middle–income country. A—cancer registry B—publication C—personal communication

(StataCorp. 2017. Stata Statistical Software: StataCorp LP, College Station, TX), and the linked data set was then deidentified data. These deidentified data were further used for analysis and reporting. Incidences were calculated with data sourced from Statistics South Africa.[9] Thereafter, comparisons were made between the international incidences, previously reported SA data, SACTR, SA-NCR, and data from POUs.

RESULTS

International Registries

The systemic literature search retrieved 127 articles, abstracts, and documents on NB, which included 13 cancer registry–based reports. These included registry-based incidences from 85 countries and territories. Data requests were sent to 95 of 127 (74.8%) countries or territories without reported data, where contact details could be sourced. Excluding SA, the focus of the linking study, no electronic data were obtained.

The national incidence of NB varied between 0.2 and 18.9/million children under 15 years/year (average 7.9/million), which varied between –97.1% and 80.0% according to the 10.5/million reported by SEER data (Appendix Table A1).

The low-income countries (LICs) had a median incidence of 1.9/million children per year and a range between 0 and 11.3/million children per year. The median and range incidences for lower-middle -income countries (LMICs) were 1.9/million children per year and 0.4-10.1/million children per year, respectively. The median and range incidences for upper-middle–income countries (UMICs) were 7.1/million children per year and 0.2-10.6/million children per year, respectively. The median and range incidences for HICs were 14.1/million children per year and 0-18.9/million children per year, respectively (Table 1).

The highest percentage of countries that did not have incidences reported were from LICs (68.9%), followed by LMICs (68%), UMICs (62.5%), and HICs (42.1%; Table 2).

The South African Case Study and South African Cancer Registries

According to our hypothetical calculations on the basis of an incidence of 10.5/million children, SA should be reporting 153 new NB cases per year (Appendix Table A1) compared with the 49.25 (range 18-57) cases that have been registered in the SACTR (Fig 1). This correlates with an incidence of 2.4/million children under 15 years, which is 74.2% less than the 10.5/million that are expected. The SA-NCR reported between 23 and 51 cases/year between 2000 and 2016, whereas the SACTR reported between 18 and 57 cases/year between 2000 and 2016 (Fig 1). The variation between the two registries was between 0.3 and 0.92 cases/million (Table 3).

TABLE 2. Countries According to World Bank Income Classification Without Neuroblastoma Data

LIC ($1,035 or less/capita/year)	LMIC ($1,036-$4,045/capita/year)	UMIC ($4,046-$12,535/capita/year)	HIC ($12,536 or more)
Afghanistan	Angola	Albania	Andorra
Burkina Faso	Bangladesh	American Samoa	Antigua and Barbuda
Burundi	Benin	Armenia	Aruba
Central African Republic	Bhutan	Azerbaijan	The Bahamas
Chad	Bolivia	Belize	Barbados
Democratic Republic of the Congo	Cambodia	Bosnia and Herzegovina	British Virgin Islands
Eritrea	Cape Verde	Curacao	Brunei Darussalam
Guinea-Bissau	Comoros	Dominica	Cayman Islands
Haiti	Republic of the Congo	Dominican Republic	Channel Islands
Liberia	Cote d'Ivoire	Equatorial Guinea	Faroe Islands
Madagascar	Djibouti	Fiji	French Polynesia
Mozambique	El Salvador	Gabon	Gibraltar
Rwanda	Eswatini (Swaziland)	Georgia	Greenland
Sierra Leone	Ghana	Grenada	Guam
Somalia	Kiribati	Guatemala	Hong Kong
South Sudan	Kyrgyz Republic	Guyana	Isle of Man
Sudan	Laos	Indonesia	Latvia
Syrian Arab Republic	Lesotho	Iraq	Liechtenstein
Tajikistan	Mauritania	Kazakhstan	Luxembourg
Togo	Federated States of Micronesia	Kosovo	Monaco
	Mongolia	Maldives	Nauru
	Myanmar (Burma)	Marshall Islands	Northern Mariana Islands
	Nepal	Moldova	Oman
	Papua New Guinea	Montenegro	Palau
	Sao Tome and Principe	Nicaragua	Panama
	Senegal	North Macedonia	Puerto Rico
	Solomon Islands	Paraguay	Republic of Korea
	Sri Lanka	Peru	San Marino
	Tanzania	Samoa	Seychelles
	Timor-Leste	Serbia	St Kitts and Nevis
	Uzbekistan	St Vincent and the Grenadines	St Lucia
	Vanuatu	Tonga	St Martin
	West Bank and Gaza	Turkmenistan	Turks and Caicos Islands
	Zambia	Tuvalu	United Arab Emirates
		Venezuela, RB	US Virgin Islands
20 of 29 LIC (68.9%)	34 of 50 LMIC (68%)	35 of 56 UMIC (62.5%)	35 of 83 HIC (42.1%)

Abbreviations: HIC, high-income country; LIC, low-income country; LMIC, lower-middle–income country; UMIC, upper-middle–income country.

The Probabilistic Record Linkage Results

From the SACTR (clinical-based registry) and SA-NCR (pathology-based registry), there were 312 and 603 new cases of NB identified, respectively (Fig 2). Furthermore, 463 cases were identified from hospital-based records in POUs. From the 775 cases diagnosed in clinical services, 148 double registered cases were excluded and a further 14 cases were excluded because of insufficient data for linking purposes. Forty-seven cases were excluded from the SA-NCR who did not meet the inclusion criteria (age > 15 years). After manual revision of the probabilistic results, a further 35 duplicate cases were excluded. Of the 824 cases, 329 (39.9%) cases matched and 268 (32.5%) and 227 (27.5%) cases were exclusively identified from the SACTR and SA-NCR, respectively. The combined crude incidence for the SACTR and SA-NCR was calculated at 2.9 cases/million children under 15 years (Table 4).

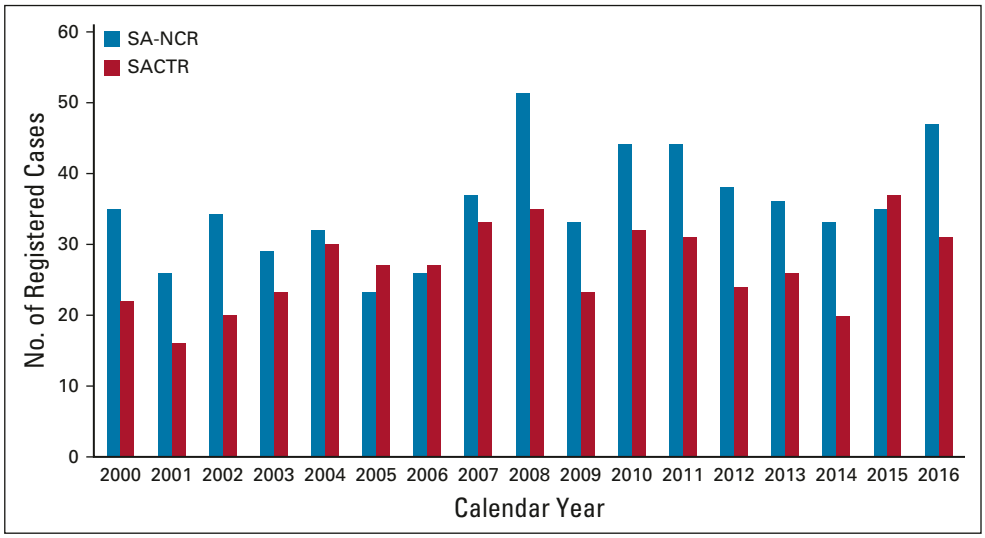

FIG 1. The discordant number of registered neuroblastoma cases in the SA-NCR and SACTR. SACTR, South African Children's Tumour Registry; SA-NCR, South African National Cancer Registry.

DISCUSSION

There is a demonstrable difference in the theoretical expected incidences and the reported incidences of NB in children under the age of 15 years. Although a higher NB incidence for children under 15 years was calculated for SA by combining several sources for reporting NB, the incidence remains far lower than that reported in HICs. The lower reported incidences of NB or absence of reported data is not only highest in LICs and LMICs but also present in UMICs and HICs.

TABLE 3. South African NB Crude Incidence Rates for Children Under the Age of 15 Years

Year	Indicator	SACTR	SA-NCR	Difference
2000	NB (No.)	39	35	0.3
	SA u15	15,084,120		
	Incidence/million children u15	2.6	2.3	
2001	NB (No.)	25	26	0.76
	SA u15	14,365,288		
	Incidence/million children u15	1.74	2.5	
2005	NB (No.)	36	23	0.9
	SA u15	15,150,381		
	Incidence/million children u15	2.4	1.5	
2010	NB (No.)	30	44	0.92
	SA u15	15,100,089		
	Incidence/million children u15	1.98	2.9	
2011	NB (No.)	34	44	0.6
	SA u15	15,812,268		
	Incidence/million children u15	2.2	2.8	
2013	NB (No.)	27	36	0.56
	SA u15	15,454,742		
	Incidence/million children u15	1.74	2.3	
2014	NB (No.)	39	33	0.4
	SA u15	15,812,268		
	Incidence/million children u15	2.4	2.0	
2016	NB (No.)	47	31	0.9
	SA u15	16,852,358		
	Incidence/million children u15	2.7	1.8	

Abbreviations: NB, neuroblastoma; SACTR, South African Children's Tumour Registry; SA-NCR, South African National Cancer Registry; SA u15, South African population under the age of 15 years.

NB is a significant cause of childhood cancer deaths and a burden on resources regardless of the country of diagnosis. When using mortality estimates to calculate disability-adjusted life years, the burden disproportionately affects populations in resource-limited settings.[24] Yet since these calculations are in part based on clinical-based, pathology-based, or population-based cancer registries, the burden might be under-represented.[24] With the heterogeneous presentation of NB, the socioeconomic impact on health services cannot be reliably determined as the national incidences are not accurately recorded.

In LMICs, reliable pediatric cancer registries are variable or are limited to single institutions.[25] This undermines the optimal interpretation of data to reflect the true burden of NB.[10,26,27] According to world-age standardized rates (WSRs), the incidence of NB should be 12% but is $< 10\%$ in Africa.[26] The WSR of 10.5 per million person-years in children in the United States is in contrast to the WSR of 2.7 per million person-years in sub-Saharan Africa.[28] In Figure 3, the current reported number of cases is reflected. The figures show a predominance of NB in westernized countries. Yet, in Figure 4, the expected number of NB cases for each country is reflected on the basis of the incidence of a WSR of 10.5 per million reported by SEER (Appendix Table A1) on the basis of the 0-year to 15-year population figures sourced from the World Bank.[7]

It is generally stated that the incidence of NB is lower in resource-limited settings.[24,25] Yet HICs, Singapore and Qatar, have incidences of 5.9 and 6.6, respectively, whereas Reunion, a French territory in sub-Saharan Africa,

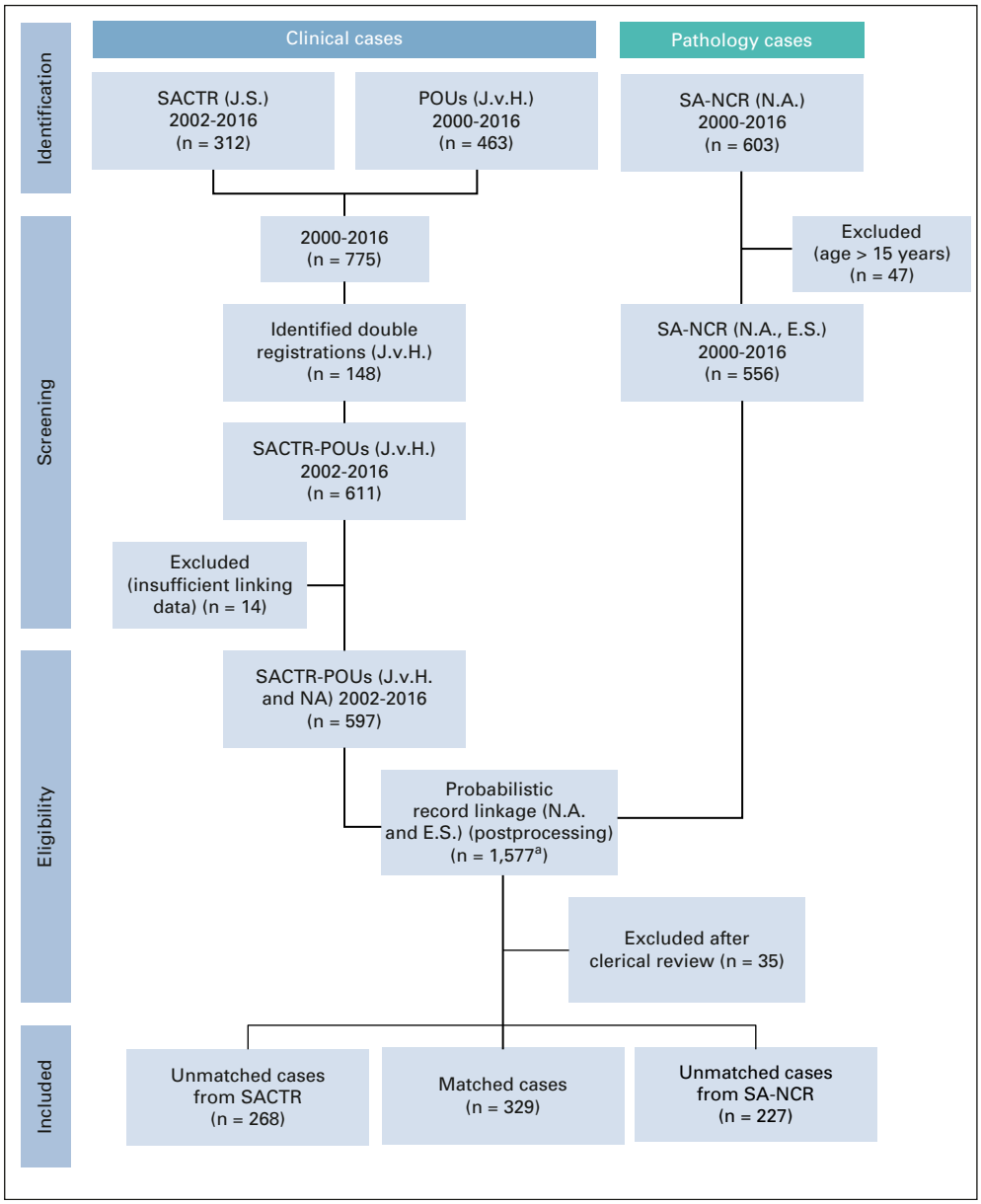

FIG 2. Methodology of the probabilistic linking study between South African pediatric oncology units, the SACTR, and the SA-NCR. POU, pediatric oncology unit; SACTR, South African Children's Tumour Registry; SA-NCR, South African National Cancer Registry. [a]Compounded number of patients including variations in spelling of names and data computations.

has an ASR incidence of 11.1/million children. This is higher than the 10.5/million children reported for the United States.[29] We postulate that Reunion, a French territory part of Africa, has the systems in place similar to France to diagnose and record cases more accurately than the rest of the African continent. The countries without reported data (Table 2) are countries where there are no pediatric oncology services and no cancer registries or no reported data could be sourced.[30] The HICs without data are predominantly islands that might not have the diagnostic services or refer pediatric oncology cases to other countries before they are diagnosed. This is also true for the South Pacific island where children are referred to Australia and New Zealand for care.[31] A landlocked country like Lichtenstein refers their pediatric oncology patients to neighboring countries. Yet this is true for Chad, a resource-limited setting, that is, a large country without services.[32] Therefore, it cannot be stated that there is a true difference in incidence between the same income-classified countries, because of a limited insight where patients are diagnosed and treated.

SA has been reporting NB incidences far lower than expected for the population size.[5] The medical system in SA is a dual public and private medical system that serves 85% and 15% of the population, respectively.[33] To evaluate the incidence of NB in the country, both the public and private medical systems should be surveilled. Innately, these two systems differ in resources, views on research, and the academic contributions to data and both clinical-based and pathology-based registries. The limitation of the SA-NCR pathology-based register system is that NB can be diagnosed on clinical signs in conjunction with radiologic

TABLE 4. Probabilistic Record Linkage Incidences: Previously Reported National and International Indices

Previously reported incidences	
International incidence (SEER data)	10.5 cases/1,000,000
National SA incidence, SACCSG (1985-2007)	2.7 cases/1,000,000
SACTR prelinkage study (2014)	2.4 cases/1,000,000
SA-NCR prelinkage study (2014)	2.0 cases/1,000,000
Probabilistic record linkage results	
SACTR, No. (%)	268 (30.7)
SA-NCR, No. (%)	277 (31.7)
Matched cases, No. (%)	329 (37.6)
Total (2014), No.	874
Population-based incidence (2014)	2.9 cases/1,000,000

Abbreviations: SA, South Africa; SACCSG, South African Children's Cancer Study Group; SACTR, The South African Children's Tumour Registry; SA-NCR, South African National cancer registry.

images and confirmed with urine catecholamine levels. Thereby, no confirmatory biopsy for evaluation in a pathology laboratory is performed. The SACTR is a clinical registry compiled by mainly pediatric oncologists in both the public and private sector. The limitation of this registry is that it excludes patients treated outside pediatric oncology units and patients who died or went undiagnosed before referral for treatment or who were misdiagnosed. Together, the two registries should account for nearly all patients who were biopsied and started with treatment in a health care facility. The incidence should reflect all diagnosed patients while minimizing patients who were not reported. Unreported cases can theoretically be sought by neonatal screening for NB and screening autopsy reports. In SA, nondiagnosis of childhood malignancies has been estimated at about 50%.[34] The undiagnosed NB cases could partly be explained by tumors that underwent maturation and remained undetected. NB screening by urine vanillylmandelic acid and homovanillic acid in infants has identified cases that would have undergone spontaneous regression.[35,36] Screening studies only proved to identify more tumors with favorable histology, but not advanced disease, nor did it improve overall survival outcomes.[35,36] By adopting a wait and see management strategy, tumor regression in untreated patients has been seen in up to 47% of patients with localized stage 1 and 2 NB.[35,36] This represents 0.7 cases/million infants screened.[37] Neonatal screening for NB has never been a policy in SA and would be too costly for a middle-income country. Sudden unexpected death because of neoplastic disease in infancy and childhood is rare.[38,39] Autopsy case series have demonstrated that a variety of neoplasms including cardiac neoplasms and CNS tumors account for the largest number of cases.[38,39] There are limited published pediatric autopsy registers available in SA to determine undiagnosed NB deaths, yet international reports concluded that NB contributed $<$ 8% of autopsy cases.[40] Therefore, these two potential sources of NB cases alone could not explain the low incidence rate in the South African population. By performing a probabilistic record linkage study on the clinical and pathologic registries, the crude incidence only increased marginally to 2.9/million children under age 15

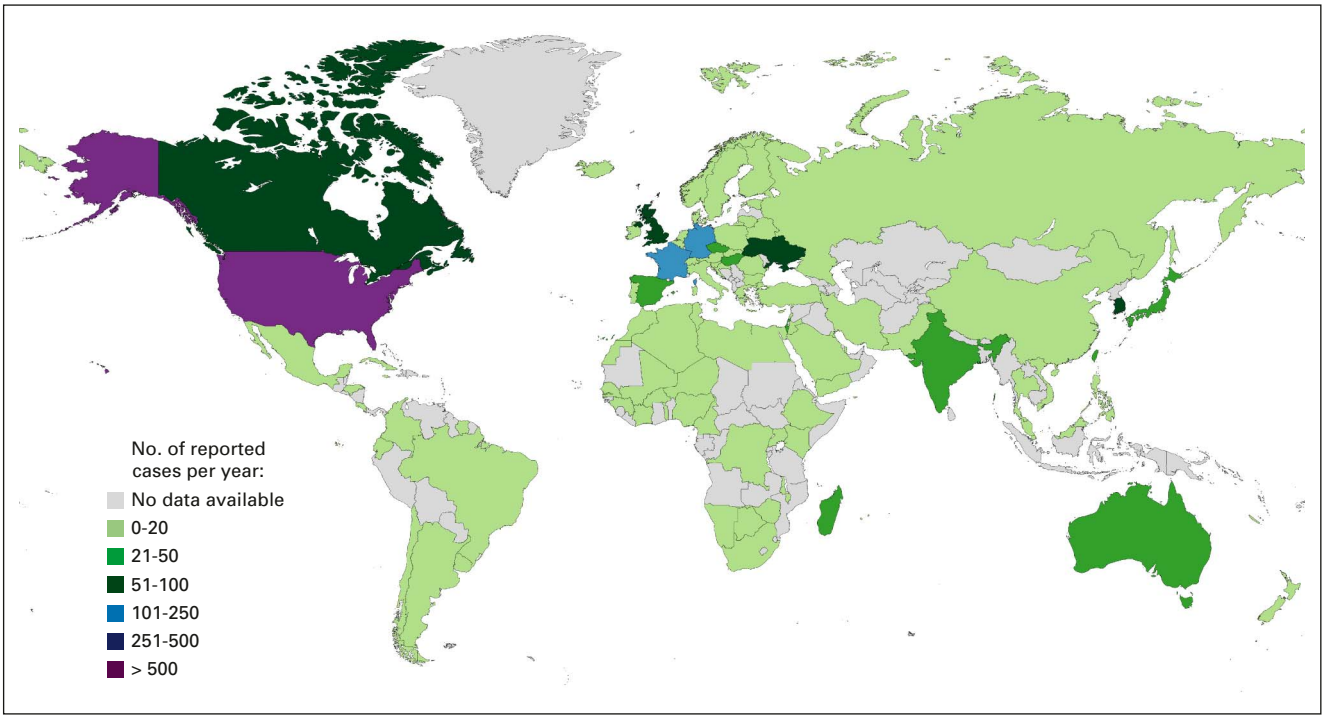

FIG 3. The number of reported cases of neuroblastoma per year in children under age 15 years.

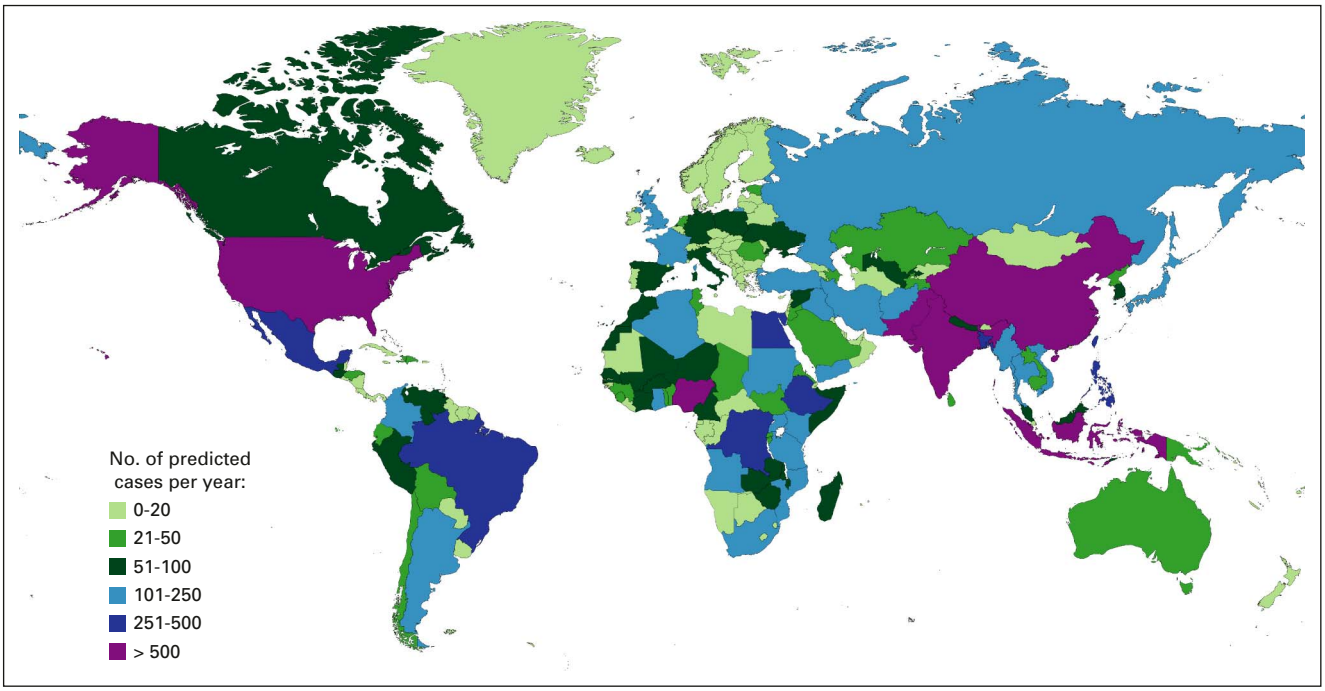

FIG 4. The number of expected cases of neuroblastoma for each country on the basis of an incidence of 10.5/million children/year.

years. This still falls short of incidences reported in higher-resource countries.

Reporting of cancers to the SA-NCR was only legally mandated in 2011. This limits the accuracy of the reports from the private health care sector. Although we expect the numbers of missed cases to be small, the recorded number may be lower. Despite the strengths of using probabilistic record linkage, there is still a possibility for false linkages or missed matches. There was no unique identifier such as national identifying number available, which is considered the gold standard for record linkage.

In conclusion, even with meticulous registration of pathologic and clinical cases of NB, undiagnosed and misdiagnosed cases will lead to under-reporting of cases in many countries. Yet SA either does under-report cases or does have a lower incidence of NB. If indeed the lower incidence is related to population characteristics, the paucity of genetic information regarding NB in LMIC may be a factor to understanding the difference in incidences. In the most likely scenario of under-reporting, increased awareness and diagnosis of childhood malignancies in SA should receive greater emphasis.

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DATA SHARING STATEMENT

Data available on request from the authors.

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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by the authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate

Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.
Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Jaques van Heerden
Research Funding: Bristol Myers Squibb

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors acknowledge the South African Children's Tumour Registry for providing statistical data from clinical pediatric oncology units and Dr Elvira Singh and the National Cancer Registry, National Health Laboratory Service, Johannesburg, South Africa, for providing national statistics on neuroblastoma.
The SACCSG Neuroblastoma Workgroup: Dr Jaques van Heerden, Prof Mariana Kruger, Dr Marc Hendricks, Dr Ronelle Uys, Dr Jan du Plessis, Dr Ané Büchner, Prof Janet Poole, Dr Ele Madzhia, Prof Gita Naidu, Dr Barry van Emmenes, Dr Johani Vermeulen, and Dr Liezl du Plessis.
Dr van Heerden acknowledges the Department of Pediatric Hematology and Oncology, Antwerp University Hospital, University of Antwerp for research support.

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APPENDIX

TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country

Sub-Saharan Africa						
Country	**Percent of Children 0-14 Years Per Population (2017)[1,2]**	**Population < 0-14 Years[1,2]**	**Expected No. of Cases (10.5 per million children per year)**	**Reported No.**	**Reported No. of Cases Per Year**	**AIR/ASR/CIR (percent of incidence difference)**
Angola	47	13.99 million	130	—	—	ND
Benin	43	4.8 million	44	—	—	ND
Botswana	31	710,520	7	9 (2008-2012)	2.25	2.7 (–74.3)
Burkina Faso	45	8.635 million	81	—	—	ND
Burundi	45	4.88 million	45	—	—	ND
Cape Verde	30	163,916	1	—	—	ND
Cameroon	43	10.34 million	96	1 (2004-2006)	< 1	0.4 (–96.1)
Central African Republic	43	2.0 million	19	—	—	ND
Chad	47	5.4 million	50	—	—	ND
Comoros	40	325,564	3	—	—	ND
Democratic Republic of the Congo	46	37.41 million	350	—	—	ND
Republic of the Congo	42	2.2 million	20	—	—	ND
Cote d'Ivoire	42	10.2 million	95	—	—	ND
Djibouti	31	296,665	3	—	—	ND
Equatorial Guinea	37	469,160	4	—	—	ND
Eritrea	49	2.45 million	23	—	—	ND
Eswatini (Swaziland)	37	505,790	5	—	—	ND
Ethiopia	41	43.05 million	402	5 (2011-2013)	1.6	3.1 (–70.4)
Gabon	36	729,000	7	—	—	ND
The Gambia	45	945,450	9	3 (2002-2011)	0.33	0.4 (–96.2)
Ghana	39	11.24 million	105	—	—	ND
Guinea	42	5.3 million	50	0 (2011-2010)	0	0
Guinea-Bissau	41	763,010	7	—	—	ND
Kenya	40	19.88 million	186	19 (2007-2012)	3.8	1.7-2.8 (–73.3 to –83.8)
Lesotho	35	781,550	7	—	—	ND
Liberia	42	1.99 million	19	—	—	ND
Madagascar	41	10.48 million	98	—	—	ND
Malawi	44	5.58 million	52	9 (2003-2010)	1.125	2.8 (–73.3)
Mali	48	6.12 million	57	15 (2006-2014)	1.875	2.2 (–79.0)
Mauritius	18	227,700	2	10 (2003-2012)	1.11	4.1 (–60.9)
Mozambique	45	13.35 million	124	—	—	ND
Namibia	37	937,580	9	12 (2003-2011)	1.3	1.2 (–88.6)
Niger	50	10.74 million	100	1 (2001-2009)	0.125	0.3 (–97.1)
Nigeria	44	83.99 million	785	9 (2003-2012)	1	1.9 (–81.9)
Reunion	26	227,906	2	16 (2002-2008 and 2012)	2.28	11.1 (+5.7)
Rwanda	40	4.8 million	45	—	—	ND

(Continued on following page)

TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

Country	Percent of Children 0-14 Years Per Population (2017)[1,2]	Population < 0-14 Years[1,2]	Expected No. of Cases (10.5 per million children per year)	Reported No.	Reported No. of Cases Per Year	AIR/ASR/CIR (percent of incidence difference)
Sub-Saharan Africa						
Sao Tome and Principe	43	87,860	< 1	—	—	ND
Senegal	43	6.81 million	63	—	—	ND
Seychelles	22	21,085	< 1	—	—	ND
Sierra Leone	42	3.17 million	29	—	—	ND
Somalia	46	6.78 million	63	—	—	ND
South Africa	29	16.4 million	153	197 (2008-2012)	49.25	2.7 (–74.2)
South Sudan	42	5.28 million	49	—	—	ND
Tanzania	45	25.8 million	241	—	—	ND
Sudan	41	16.6 million	155	—	—	ND
Togo	42	3.27 million	31	—	—	ND
Uganda	48	20.86 million	192	8 (2003-2012)	1	1.0 (–90.5)
Zambia	45	7.69 million	71	—	—	ND
Zimbabwe	41	6.77 million	63	7 (2003-2012)	0.78	1.4 (–86.7)
North Africa and the Middle East						
Algeria	29	11.98 million	111	112 (1996-2014)	6.2	7.2 (–31.4)
Bahrain	20	298,600	3	28 (1998-2012)	2	9.6 (–8.5)
Arab Republic of Egypt	33	32.19 million	300	133 (1999-2010)	12	10.1 (–3.8)
Islamic Republic of Iran	24	16.9 million	157	8 (2004-2011)	1	2.6 (–75.2)
Iraq	40	11.04 million	103	—	—	ND
Israel	28	1.94 million	18	568 (1990-2012)	25.8	14.6 (+39)
Jordan	36	3.49 million	33	222 (2000-2012)	18.5	9.0 (–14.2)
Libya	28	1.78 million	17	22 (2003-2008)	3.7	8.1 (–22.6)
Kuwait	21	868,770	8	61 (1994-2012)	3.4	9.8 (–6.7)
Lebanon	23	1.4 million	13	33 (2008-2010)	11	10.6 (+0.01)
Mauritania	40	1.77 million	17	—	—	ND
Morocco	27	9.64 million	90	146 (2005-2012)	20.8	9.1-9.6 (–8.6 to –13.3)
Oman	22	1.01 million	10	—	—	ND
Qatar	14	369,460	3	19 (2002-2014)	1.6	6.6 (–37.1)
Saudi Arabia	25	4.78 million	44	198 (1994-2012)	11	6.3 (–40)
Syrian Arab Republic	37	6.76 million	63	—	—	ND
Tunisia	24	2.76 million	25	121 (1993-2007)	8.6	7.7 (–26.7)
United Arab Emirates	14	1.316 million	12	—	—	ND
West Bank and Gaza	40	1.86 million	17	—	—	ND
Republic of Yemen	40	11.3 million	105	9 (1997-2006)	0.9	1.9 (–81.9)
Asia						
Afghanistan	43	15.27 million	143	—	—	ND

(Continued on following page)

TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

Asia						
Armenia	20	586,000	5	—	—	ND
Azerbaijan	23	2.27 million	21	—	—	ND
Bangladesh	28	46.1 million	430	—	—	ND
Bhutan	27	218,054	< 1	—	—	ND
Brunei Darussalam	23	98,600	< 1	—	—	ND
Cambodia	31	4.96 million	46	—	—	ND
China	18	249.48 million	2,331	389 (1990-2013)	16.9	8.6 (–18.1)
Georgia	19	706,230	7	—	—	ND
Hong Kong	11	813,120	7	—	—	ND
India	28	374.9 million	3,503	526 (1990-2013)	22.9	3.6 (+65.7)
Indonesia	27	71.28 million	666	—	—	ND
Japan	13	16.5 million	154	795 (1990-2013)	34.6	15.7 (+49.5)
Kazakhstan	28	5.05 million	47	—	—	ND
Democratic People's Republic of Korea	21	5.35 million	50	1,130 (1999-2012)	86.9	11.3 (+6.7)
Republic of Korea	13	6.69 million	62	—	—	ND
Kyrgyz Republic	32	1.98 million	19	—	—	ND
Laos	33	2.26 million	21	—	—	ND
Malaysia	24	7.59 million	70	47 (2007-2011)	9.4	6.1 (–41.9)
Maldives	23	100,355	1	—	—	ND
Mongolia	30	922,800	9	—	—	ND
Myanmar (Burma)	27	14.4 million	134	—	—	ND
Nepal	31	9.08 million	84	—	—	ND
Pakistan	35	68.95 million	644	38 (1995-2012)	2.2	1.7 (–83.8)
Philippines	32	33.57 million	313	205 (1993-2012)	10.7	2.8 (–73.3)
Russian Federation	18	26.01 million	243	163 (1998-2015)	9.5	9.3-9.8 (–6.6 to 11.4)
Singapore	15	841,800	8	22 (2003-2007)	4.4	5.9 (–43.8)
Sri Lanka	24	5.15 million	48	—	—	ND
Taiwan	13	3.0 million	286	463 (1996-2010)	30.8	1.3 (–87.6)
Tajikistan	35	3.12 million	29	—	—	ND
Thailand	17	11.73 million	109	156 (1993-2013)	7.8	4.6 (–52.1)
Timor-Leste	44	570,240	53	—	—	ND
Turkey	25	19.9 million	186	134 (1993-2013)	6.7	10.6 (+0.01)
Turkmenistan	31	1.78 million	17	—	—	ND
Uzbekistan	28	9.06 million	85	—	—	ND
Vietnam	23	21.97 million	205	170 (1995-2013)	9.4	7.7 (–26.7)
Europe						
Albania	17	0.49 million	4	—	—	ND
Andorra	14	76,965	< 1	—	—	ND
Austria	14	1.22 million	11	345 (1990-2012)	15.6	13.3 (+26.6)
Belarus	17	1.61 million	15	355 (1990-2015)	14.2	9.3 (–11.4)

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TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

			Europe			
Belgium	17	1.92 million	18	216 (2004-2013)	11.3	13.4 (+27.6)
Bosnia and Herzegovina	14	490,980	4	—	—	ND
Bulgaria	14	994,280	9	178 (1990-2013)	7.7	7.1 (–32.3)
Channel Islands	15	24,681	< 1	—	—	ND
Croatia	15	623,100	6	113 (2000-2014)	8	13.2 (+25.7)
Cyprus	17	145,316	1	27 (1998-2013)	1.8	13.9 (+32.3)
Czech Republic	15	1.58 million	15	467 (1990-2012)	21.2	14.1 (+34.2)
Denmark	16	919,840	9	160 (1981-2000)	8	9.6 (–8.6)
Estonia	16	1.32 million	21	50 (1990-2012)	2.27	10.0 (–4.7)
Faroe Islands	20	51,095	< 1	—	—	ND
Finland	16	880,480	8	26 (1987-2003)	1.6	2.9 (—72.3)
France	18	12.09 million	113	1847 (2000-2012)	142	14.2 (+35.2)
Germany	13	10.76 million	100	2,314 (1996-2012)	136.1	13.7 (+30.5)
Gibraltar	20	34,571	< 1	—	—	ND
Greece	14	1.5 million	14	160 (2009-2016)	9.4	14.4 (+37.1)
Greenland	21	56,171	< 1	—	—	ND
Hungary	14	1.37 million	13	563 (1991-2014)	24.4	17.0 (+61.9)
Iceland	20	67,669	< 1	9 (1990-2014)	0.38	6.2 (–40.9)
Ireland	22	1.05 million	10	159 (1994-2012)	9.3	10.9 (+3.8)
Isle of Man	16	84,287	< 1	—	—	ND
Italy	14	8.48 million	79	142 (1998-2011)	10.9	18.9 (+80)
Kosovo	25	1.831	< 1	—	—	ND
Latvia	15	292,500	3	—	—	ND
Liechtenstein	15	37,810	< 1	—	—	ND
Lithuania	15	427,200	4	55 (2000-2012)	4.2	9.8 (–6.7)
Luxembourg	16	94,506	< 1	—	—	ND
Malta	14	64,441	< 1	17 (1995-2015)	0.85	14.2 (+35.2)
Moldova	16	568,000	5	—	—	ND
Monaco	10	38,695	< 1	—	—	ND
Montenegro	18	112,044	1	—	—	ND
Netherlands	16	2.73 million	26	435 (1993-2013)	20.7	8.1 (–22.9)
North Macedonia	17	350,000	3	—	—	ND
Norway	18	945,000	9	173 (1990-2013)	7.5	9.2 (–12.4)
Poland	15	5.76 million	53	111 (1999-2014)	7.4	13.9 (+32.4)
Portugal	14	1.44 million	13	227 (1990-2010)	11.35	10.9-16.5 (+3.8 to 57.1)
Romania	15	2.95 million	27	25 (2008-2012)	6.25	9.0 (–14.3)
San Marino	15	33,400	< 1	—	—	ND
Serbia	16	1.12 million	10.5	—	—	ND
Slovak Republic	15	815,250	7	122 (2000-2012)	9.3	12.8 (+21.9)
Slovenia	15	309,900	3	57 (1990-2013)	2.1	9.0 (–14.2)
Spain	15	6.98 million	65	1,011 (1990-2013)	42.1	13.8-14.6 (+31.4 to 39)
Sweden	18	1.8 million	16	291 (1990-2011)	13.2	9.4 (–10.4)

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TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

Europe						
Switzerland	15	1.26 million	12	292 (1990-2013)	12.1	11.7 (+11.4)
Ukraine	15	6.724 million	62	633 (2000-2012)	52.7	8.2 (–21.9)
United Kingdom	18	11.89 million	111	1,099 (2000-2011)	91.9	9.6 (–8.6)
North America						
Antigua and Barbuda	24	24,483	< 1	—	—	ND
Aruba	18	18,947	< 1	—	—	ND
The Bahamas	20	79,072	< 1	—	—	ND
Barbados	19	54,286	< 1	—	—	ND
Bermuda	17	65,441	< 1	0 (2013-2018)	0	0
British Virgin Islands	16	31,196	< 1	—	—	ND
Canada	16	5.85 million	55	1,359 (1992-2013)	61.7	13.8 (+31.4)
Cayman Islands	18	61,559	< 1	—	—	ND
Cuba	16	1.84 million	17	193 (2000-2012)	16	8.5 (–19.4)
Curacao	19	30,593	< 1	—	—	ND
Dominica	22	73,925	< 1	—	—	ND
Dominican Republic	29	3.12 million	29	—	—	ND
Grenada	26	28,034	< 1	—	—	ND
Haiti	33	3.62 million	34	—	—	ND
Puerto Rico	18	598,500	6	—	—	ND
Jamaica	23	664,700	6	36 (1982-2012)	1.8	6.8 (–35.2)
St Kitts and Nevis	20	55,345	< 1	—	—	ND
St Lucia	19	33,980	< 1	—	—	ND
St Martin	26	32,125	< 1	—	—	ND
St Vincent and the Grenadines	24	26,375	< 1	—	—	ND
Trinidad and Tobago	21	287,490	2	11 (2001-2006)	1.8	0.6 (–94.2)
Turks and Caicos Islands	22	35,446	< 1	—	—	ND
United States	19	61.88 million	578	9,709 (1993-2012)	511	12.4 (+18.1)
US Virgin Islands	20	21,453	< 1	—	—	ND
Central America						
Belize	31	116,151	< 1	—	—	ND
Costa Rica	22	1.079 million	10	82 (1993-2012)	4	4.0 (–61.9)
El Salvador	27	1.722 million	16	—	—	ND
Guatemala	35	5.9 million	55	—	—	ND
Honduras	32	2.96 million	28	12 (2002-2012)	1.1	1.6 (–84.8)
Mexico	27	34.88 million	326	36 (1997-2013)	2.25	3.5 (–66.7)
Nicaragua	29	1.8 million	17	—	—	ND
Panama	27	1.106 million	10	—	—	ND
Oceania						
American Samoa	30	55,641	< 1	—	—	ND
Australia	19	4.67 million	44	895 (1992-2014)	38.9	11.6 (+10.5)

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TABLE A1. Epidemiologic Characteristics of Neuroblastoma Per Country (Continued)

Oceania						
Fiji	28	253,540	2	—	—	ND
French Polynesia	23	65,091	< 1	—	—	ND
Guam	25	41,057	< 1	—	—	ND
Kiribati	35	40,739	< 1	—	—	ND
Marshall Islands	34	53,127	< 1	—	—	ND
Federated States of Micronesia	33	34,829	< 1	—	—	ND
Nauru	31	13,649	< 1	—	—	ND
New Caledonia	23	64,505	< 1	16 (1990-2013)	0.6	12.9 (+22.9)
New Zealand	20	958,800	9	178 (1993-2012)	9.3	11.3 (+7.6)
Northern Mariana Islands	26	55,144	< 1	—	—	ND
Palau	19	21,729	< 1	—	—	ND
Papua New Guinea	36	2.97 million	28	—	—	ND
Samoa	37	72,682	< 1	—	—	ND
Solomon Islands	39	238,423	2	—	—	ND
Tonga	36	38,887	< 1	—	—	ND
Tuvalu	29	11,192	< 1	—	—	ND
Vanuatu	36	99,447	1	—	—	ND
South America						
Argentina	25	11.06 million	103	164 (1991-2013)	7.5	8.6 (–18.0)
Bolivia	32	3.53 million	33	—	—	ND
Brazil	22	46.04 million	430	134 (1995-2012)	7.9	8.4 (–20)
Chile	20	3.61 million	34	59 (1993-2013)	2.9	4.2 (–60.0)
Colombia	3	11.29 million	105	59 (1992-2003)	5.3	4.0 (–61.9)
Ecuador	28	4.65 million	43	39 (1993-2013)	1.9	1.9 (–81.9)
Guyana	29	225,579	2	—	—	ND
Paraguay	29	1.98 million	18	—	—	ND
Peru	27	8.69 million	81	—	—	ND
Suriname	26	146,484	1	2 (1980-2008)	0.1	0.2 (–98.1)
Uruguay	21	725,970	7	148 (1993-2012)	7.4	11.2 (+6.7)
Venezuela, RB	28	8.95 million	83	—	—	ND

Data adapted.[7,8,10-23]

Abbreviation: ND, no data.

Neuroblastoma: Can lessons from the past help to improve the future?

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Background. The outcome of patients with neuroblastoma in South Africa has always been very poor. We conducted a retrospective study in one state-funded paediatric oncology unit (POU), to describe the clinical course, evaluate prognostic factors and report outcomes of patients with neuroblastoma.
Methods. We analysed routine data from one POU, gathered between 1993 and 2018. Kaplan-Meier curves were used to illustrate 2-year survival rates and to evaluate possible prognostic factors.
Results. Data from 87 patients were included and analysed. The median age was 41 months. The majority of the patients presented with stage 4 disease (77%). The most common presenting symptoms were bone pain, loss of weight, and abdominal distention. Chemotherapy was administered to 74 patients, and only 5 patients (6%) received palliative chemotherapy as first-line treatment. Only 18 of the 87 patients had surgery (21%) and 13 of 87 had radiation (15%), while 10 patients received palliative radioactive iodine (^{131}I-miBG) therapy. Patients with ferritin levels >120 ng/dL did not have a poorer outcome, and those with a raised lactate dehydrogenase (LDH) level displayed a shorter survival time but it was not statistically significant. The 2-year overall survival was 24% for the whole cohort and 16% for the stage 4 patients at diagnosis.
Conclusion. Neuroblastoma is a disease with a dismal outcome in our POU, mostly as a result of late presentation. To improve prognosis the focus should be on recognising danger signs to ensure early diagnosis and referral. We recommend adding danger signs for childhood cancer to the Integrated Management of Childhood Illness (IMCI) strategy in an attempt to improve early recognition and diagnosis of childhood cancer.

S Afr J Child Health 2023;17(1):e1898. https://doi.org/10.7196/SAJCH.2023.v17i1.1898

Cancer can be defined as an abnormal growth of cells, which tend to proliferate in an uncontrolled way, and in some cases metastasise and spread.[1] More people die from cancer every year than from AIDS, tuberculosis and malaria combined.[2] According to GLOBOCAN 2018, the estimated number of new cases of cancer worldwide in 2018 was 18.1 million, with 9.6 million cancer-related deaths.[3] Cancer is the second leading cause of death in children, and it was estimated that 1 190 children would have died from cancer in 2021.[4]

Neuroblastoma (NB) is an embryonal neoplasm arising from the sympathetic nervous system and patients can present with many different and nonspecific signs and symptoms.[5,6] NB generally occurs in children <5 years of age, with the median age at diagnosis being 17 months. It is the most common solid tumour diagnosed in children in the first year of life.[6] The incidence of NB in South Africa (SA) has not reflected the same pattern described in high-income countries.[7-9] Patients with NB in SA usually present late with metastatic disease, implying a poor prognosis and outcome.[10] It is clear that the focus in SA should be on early diagnosis, with the aim of preventing progression to metastatic stage 4 disease.

The role of different biochemical and other prognostic factors in NB has been extensively studied. In 1987 Evans *et al.*[11] published an analysis of prognostic factors in a group of 124 children from the USA. This group included mostly Caucasian children (88%) under the age of 2 years and 41% had stage 4 disease. Their most important finding was that raised serum ferritin was associated with poorer 2-year overall survival (OS). More recently, studies from India[12] and Italy[13] described the use of different biochemical markers in predicting NB outcome. In both these studies raised serum lactate dehydrogenase (LDH) levels were independently associated with worse prognosis. Neuron-specific enolase (NSE) was only significant as a good prognostic factor in stage 4 patients if the levels were <200 ng/mL. The group from Italy also made the valid comment that LDH and catecholamines are routinely tested in most patients worldwide at diagnosis of NB, and that it is an easy, cost-effective way of stratifying patients.[13]

A study by Hesseling *et al.*[7] published in 1999 included all children from the Western Cape Province of SA diagnosed with NB between 1983 and 1997. The findings in this small southern African cohort (n=48) demonstrated that serum LDH has a good prognostic value, with a raised LDH associated with a worse prognosis. This cohort was too small to conclusively prove that a raised ferritin level is also a poor prognostic factor. In the latest large SA study, ferritin >120 ng/dL was significant for poor prognosis and can be used as a threshold value in the SA setting.[14]

Improving early diagnosis for children with cancer in SA is not a novel idea. For the past 20 years, various local and international publications have emphasised the importance of early diagnosis with the aim of improving overall outcomes of childhood cancer in SA.[8,9,14-16] The South African Children's Cancer Study Group (SACCSG) published a document with their priorities in 2007, and achieving early diagnosis was the first priority.[16] The SACCSG adopted the St Siluan warning signs of childhood cancer; their

warning signs were presented in Amsterdam in 2000.[18] In 2001, Poyiadjis *et al.*[18] embarked on a campaign to educate the public and primary healthcare workers on the St Siluan warning signs. This campaign was followed by assessment of the efficacy of these warning signs in promoting awareness of cancer. The study concluded that awareness and referral numbers improved, but unfortunately there was no improvement in earlier diagnoses and identifying localised disease.[15]

NB is a heterogenous disease and treatment strategies have evolved through the years according to the different biological features of these tumours.[6] As in all childhood malignancies, the greatest challenge is to use the treatment strategy with the best outcome and the lowest possible intensity, in order to limit side-effects and complications that could occur with treatment, especially treatment of higher intensity.[6]

The aim of this study was to describe the clinical course of NB in patients treated at the paediatric oncology unit (POU) of Kalafong Provincial Tertiary Hospital and Steve Biko Academic Hospital in Pretoria, with the main objective being to describe the value of possible prognostic factors in this group of patients.

Methods

A retrospective descriptive file review was conducted at a single POU originally situated at Kalafong Provincial Tertiary Hospital (1993 - 2009), and now at Steve Biko Academic Hospital (2010 - 2018) in Pretoria, Gauteng. The POU offers treatment to all patients from northern Gauteng and Mpumalanga provinces, as well as some patients from Limpopo Province and the neighbouring countries Zimbabwe and Mozambique.

All newly diagnosed patients with NB aged <18 years were considered for inclusion. A total of 100 patient files were reviewed; 13 files were excluded because of incomplete data, leaving 87 included in the study. The research protocol was approved by the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (ref. no. 493/2016) as well as the Faculty of Health Sciences MMed Committee of the University of Pretoria. Consent was obtained from the chief executive officer of Steve Biko Academic Hospital to access patient files and information. Data were anonymised using a unique study number to ensure confidentiality. There was minimal risk to patients because this was a retrospective audit of files with no direct involvement of patients.

The data were analysed in a quantitative manner and captured in an Excel datasheet (Microsoft, USA) and transferred into Stata and SPSS version 20 (IBM, USA). Descriptive statistical analysis was done on all the data, using Stata 13 (StataCorp, USA). Owing to the overwhelming number of patients that died, statistically significant analyses could not be performed in order to assess the significance of prognostic factors using *p*-values. However, Kaplan Meier curves were created to illustrate 2-year OS curves for the various possible prognostic factors.

Results

This study was carried out at a single POU. Table 1 illustrates the demographics of the patients included in the study. There were 15 (17%) children under the age of 1 year, with 78% diagnosed before the age of 5 years. The mean age at diagnosis for all 87 patients was 41 months. Only 2% of patients presented with localised stage 1 disease, 77% with stage 4 disease and 3% with stage 4S disease (Table 1).

Children presented with a large number of nonspecific symptoms; however, the diagnosis was made easier by patients presenting with a cluster of symptoms suggestive of NB. The cluster of symptoms usually comprised bone pain, loss of weight, abdominal distention and abdominal mass.

Table 1. Sociodemographic and clinical characteristics of patients at diagnosis

	n (%)
Gender	
Male	46 (53)
Female	41 (47)
HIV status	
Negative	64 (74)
Positive	4 (5)
Unknown	19 (22)
TB	
Negative	20 (23)
Positive	4 (5)
Unknown	63 (72)
Age groups, months	
0 - 12	15 (17)
12 - 60	53 (61)
60 - 120	14 (16)
>120	5 (6)
International Neuroblastoma Staging System	
1	2 (2)
2	3 (4)
3	12 (14)
4	67 (77)
4S	3 (3)

Of the 87 patients included, 85% (*n*=74) received chemotherapy and the remaining 15% (*n*=13) did not receive any chemotherapy. The reason for not treating with chemotherapy was end-stage disease, where patients died before treatment could be started or were sent home for palliative care. Two patients absconded before any treatment could be given. Options for palliative treatment in advanced or relapsed disease in this setting include oral metronomic chemotherapy (cyclophosphamide), radioactive iodine (^{131}I-miBG therapy), and external beam radiotherapy for pain in symptomatic sites of disease recurrence. Fig. 1 outlines the different chemotherapy regimens used in this group of patients. A second regimen was used as extended induction in a few cases but mostly as palliative chemotherapy in relapsed patients. All patients who received a second or third regimen died.

Of the 87 patients enrolled in the study, 83% died and 13% are still alive (absconded patients not included). The main reason why this disease entity resulted in such a high mortality rate is that most patients presented with advanced stage 4 disease. The 2-year OS for the whole cohort was 24% (Fig. 2).

Age at diagnosis was not a significant prognostic factor (p=0.320). Children living with HIV had a worse outcome than HIV-negative children. Despite the small numbers this difference in 2-year OS was statistically significant with a *p*-value of 0.03 (Supplementary Gig. 1; https://www.samedical.org/file/2011). An elevated serum LDH was present in 65% (*n*=44) of the 68 patients whose LDH levels were tested at diagnosis. The patients with high LDL levels at diagnosis (classified as >750 U/L) had a shorter survival time compared with the patients with LDH <750 U/L (p=0.06) (Supplementary Fig. 2; https://www.samedical.org/file/2012). With regard to serum ferritin levels at diagnosis, the value of 120 ng/dL was used as the deciding

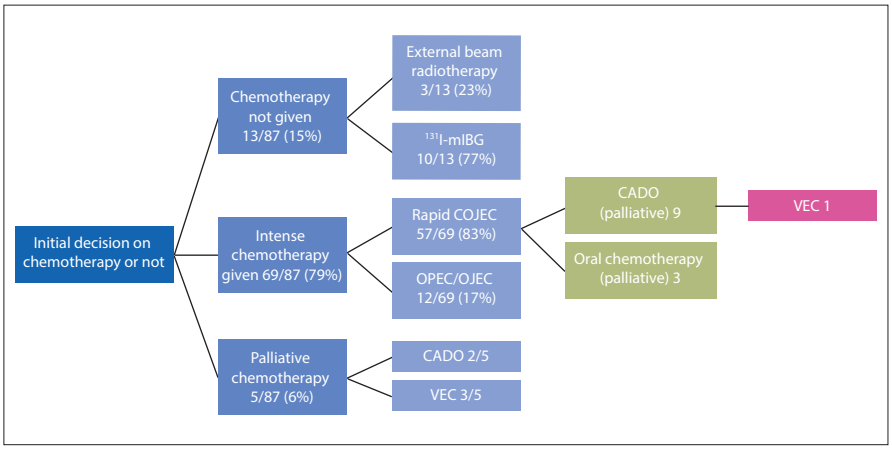

Fig. 1. Chemotherapy regimens used. (^{131}I-miBG = radioactive iodine; COJEC = cisplatin, vincristine (O), carboplatin(J), etoposide, cyclophosphamide; OPEC/OJEC = etoposide, vincristine and cyclophosphamide with alternating cisplatin (OPEC) or carboplatin (OJEC); CADO = cyclophosphamide, doxorubicin, and vincristine with continuous infusion cisplatin and etoposide; VEC = vincristine, etoposide, carboplatin.)

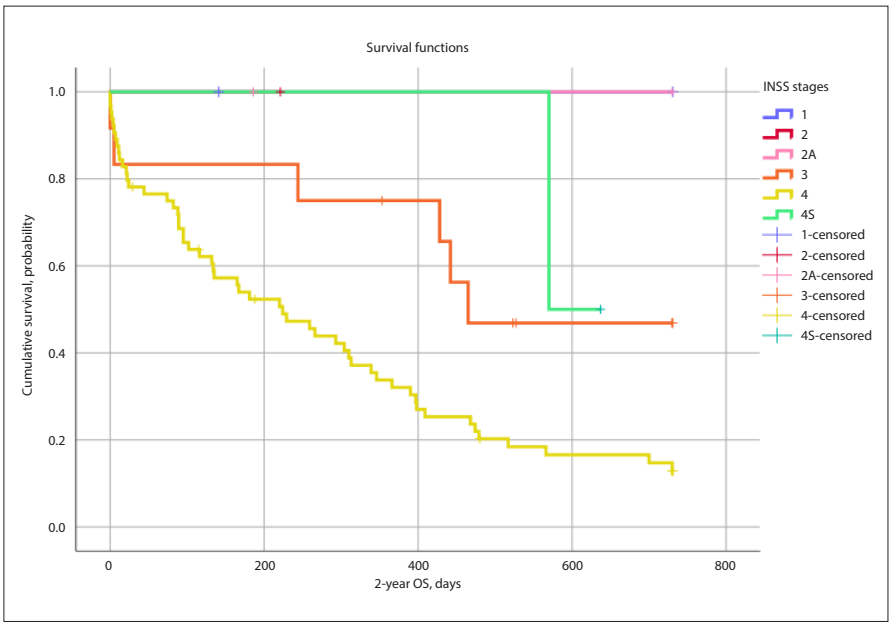

Fig. 2. Survival curve according to International Neuroblastoma Staging System (INSS). (OS = overall survival.)

value (as discussed above); an elevated serum ferritin was present in 77% (n=39) of the 51 patients whose ferritin levels were tested at diagnosis (Supplementary Fig. 3; https://www.samedical.org/file/2013). Just as with LDH levels, the group of patients with elevated serum ferritin at diagnosis did not survive as long as the group with serum ferritin levels <120 ng/dL, but the difference was not statistically significant (p=0.079). *N-myc* testing, despite its historical importance in the staging of NB, was performed infrequently – only 10 patients had their histology sent for testing, of which 5 (50%) were positive. The patients with positive *N-myc* had a median survival of 17 months from diagnosis (range 6 - 18 months).

Discussion

This descriptive study of a cohort of patients with NB treated at the POU in Pretoria, SA, during the period 1993 to 2018 had the specific aim of describing possible poor prognostic factors associated with NB.

The male:female ratio of 1.12:1 in our study is similar to slight male predominance seen in most international and national groups.[18,19] Our small group of patients were significantly older at diagnosis, which is very similar to what was described in the larger SA study by Van Heerden *et al.*,[14] where the mean age was 39.9 months. International data from high-income countries describe a median age of 27 months at presentation,[20] compared with a mean age of 41 months in our group. In our study, 77% of patients presented with stage 4 disease, a much higher incidence than the 41.9% reported from the European studies [19] and the 51.4% from Turkey.[21] Our incidence of stage 4 disease was more comparable with what has been reported from Kenya[22] (92%) and SA's larger cohort (70%).[18]

The most common presenting symptoms in our group were bone pain, loss of weight and abdominal distention, followed by abdominal mass, fever, lower limb weakness and night sweats. These are general nonspecific symptoms that may be present as part of a number of disease entities besides NB. The combination of multiple symptoms in one patient should alert the attending physician to the possibility of NB. The St Siluan warning signs for childhood cancer include most of the common presenting symptoms found in our study group, except for abdominal distention and abdominal mass.[14] These warning signs are shown in Fig. 3, and should be used as a general guideline for patients and family members in rural SA to indicate that they need to seek medical attention immediately.

The values for serum ferritin and LDH described by the International Society of Pediatric Oncology-Pediatric Oncology in Developing Countries (SIOP-PODC) group to be predictive of outcome in NB are 120 ng/dL and 750 U/L, respectively.[23] Despite the small number of patients in this study, when the 2-year OS curves are examined, the trend agrees with what has been described by the PODC. Patients who had a high serum LDH, who formed the majority of patients in our study, had a shorter survival time than those with lower serum LDH. Ferritin values were increased in 76% of patients and those patients with values >120 ng/dL had shorter survival times. If patients present with symptoms suspicious of NB, serum LDH and ferritin levels should help facilitate earlier referral in patients where these values are markedly raised.

One of the limitations of this study was that the study population was relatively small. A larger sample size would perhaps represent the data more accurately. This was a single POU study carried out in two different settings. The relocation of the unit itself could have resulted in data being lost from files. The documentation of patients' information, tests performed, investigations carried out, treatment implemented, and other data were not standardised. This may lead to data not being accurately compared. During this study period access to genetic tests such as *N-myc* amplification and nuclear medicine procedures were limited, and this could possibly have impacted

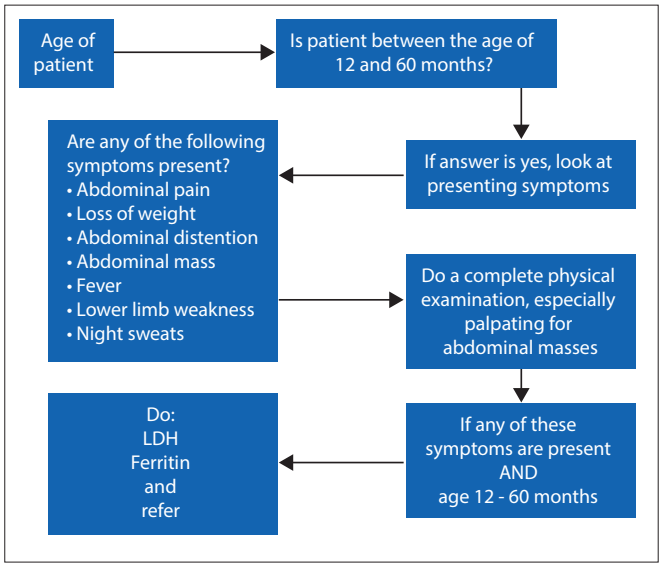

Fig. 3. Algorithm that could be included in the Integrated Management of Childhood Illness (IMCI) manual. (LDH = lactate dehydrogenase.)

negatively on risk stratification determination, as well as staging of disease and overall outcome.

As was shown in the assessment of using the St Siluan warning signs in SA previously, a single campaign to optimise early diagnosis of cancers such as NB is not a long-term solution.[15] Owing to the fast turnover of healthcare providers in the country, these warning signs need to be continually taught as part of medical and nursing curricula. They should also be part of all information sessions held in primary care clinics, and primary care screening using systems such as the Integrated Management of Childhood Illness (IMCI) strategy.

Conclusion

NB is a disease with a dismal outcome in Pretoria, mostly as a result of patients presenting with stage 4 disease. Despite the initial good response of most patients (including those with advanced disease) to intensive chemotherapy and surgery, more than 50% of patients with high-risk NB can be expected to relapse and die. To improve prognosis the focus should be on recognising danger signs and referral for early diagnosis. Including danger signs of childhood cancer in the IMCI documents and guidelines should improve recognition and diagnosis at primary healthcare levels. Additionally, multicentre pooling of data should be conducted to develop and test an early diagnosis algorithm. Such an algorithm (see Fig. 3) could be included in the IMCI manual if it is feasible, practical, and easy to understand and implement at primary care level.

Declaration. None.

Acknowledgements. Nivethan Chetty, my husband, who supported and encouraged me all through this journey. Sathianathan Coopoosamy, for always believing in me. Thelvathie Moodaley, my hakka, who started this process with me, supported me but unfortunately passed on before this article was published. This article is dedicated to you and three other angels in heaven, my late mummy, my ma and my Uncle Thumbie. These three people started this journey with me but unfortunately are not here to see the end result, but I know they are watching over me from heaven. This is all for you. I wouldn't be where I am and the person I am without the foundation you laid for me and the values you instilled in me. I am grateful for the unconditional love, support and concern I received from you throughout my life. Lastly, Indrani Naidoo, for her love and support and all that she did for me during my final year of reg time.

Author contributions. LC: literature review, protocol write-up, data collection, data analysis, graphs, dissertation write-up, article write-up and corrections. JS: protocol review, data analysis, article review. DTR: conceptualisation. FEO: dissertation and article review. AB: conceptualisation, literature review, protocol review, data analysis, dissertation write-up and article review.

Funding. None.

Conflicts of interest. None.

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Accepted 7 February 2023.

Appendix F: Nutrition related research and congress abstracts as co-author

(2019-2022)

A COLLABORATIVE EDUCATION MODEL FOR ADVANCING NUTRITIONAL CARE IN AFRICA

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Poster viewing at the 54th Congress of the International Paediatric Oncology Society conference. Barcelona, Spain, September 2022

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Background and Aims

The SIOP Global Health nutrition committee (2017) administered a survey among Pediatric Oncology Units (POUs) located in Africa to determine the existing nutritional services and unmet needs. The most common reported barrier was a lack of education in nutritional assessment and intervention. A 2022 survey of Ghanaian POUs found that 90% of POUs were merely at levels 1-2 in terms of nutrition capacity. A partnership between World Child Cancer (WCC) and the International Initiative for Nutrition and Paediatrics (IIPAN) aims to increase nutritional knowledge among clinicians caring for children with cancer in Ghana.

Methods

WCC and IIPAN held a five-day nutritional workshop in Accra, Ghana, from 7 to 11 March 2022. Attendees included paediatric oncologists, paediatricians, dieticians, nutritionists, nursing staff, and WCC personnel. The first three days addressed theory and clinical practice, followed by a two-day practical exercise at Korle Bu Teaching and Greater Accra Regional Hospitals in Accra. A standardized questionnaire was completed by all participants to test pre-training and post-training knowledge.

Results

Seventy-four percent of participants felt they were 'very knowledgeable' after the course, compared to 10% prior, and 92% felt they could use the knowledge daily. Participants reported that hospital practical sessions (30%), determining nutritional requirements (23%) and performing anthropometry (18%) were the most beneficial aspects of the training. The mean test grade post-training was 77%. Several barriers were identified that would preclude incorporation into clinical practice, namely lack of resources (32%), additional training needs (18%), and non-supporting colleagues (10%). Almost all participants reported they would benefit from longer training, more on-site training, and more opportunities for subsequent/ongoing training.

Conclusion

This workshop successfully improved knowledge about nutrition in pediatric oncology. Future planning with WCC, IIPAN, and SIOP Global Nutrition Committee will involve addressing the barriers to incorporate nutritional assessment and interventions into clinical practice in pediatric oncology units.

CHANGES IN ANTHROPOMETRICAL STATUS AND BODY COMPOSITION OF PAEDIATRIC CANCER PATIENTS DURING INTENSIVE ONCO-CHEMOTHERAPY

Ilde-Marié Kellerman[1] , Reneé Blaauw[1] , Judith Schoeman[2,3] , Mariana Kruger[3]

Poster viewing at the 54th Congress of the International Paediatric Oncology Society conference. Barcelona, Spain, October 2021

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Background and Aims:

Children with cancer require adequate nutritional support to prevent malnutrition. This study investigated the impact of intensive onco-chemotherapy on anthropometrical status and body composition during the first six months of treatment.

Methods:

Anthropometrical status and body composition were measured at diagnosis, prior to the initiation of chemotherapy utilising standardised protocols and validated S10 InBody bio-electrical impedance (BIA) mobile unit. Baseline values for all variables were compared to consecutive monthly follow-up measurements to plot changes over time during the first six months. $p < 0.05$ indicated statistical significance.

Results

Forty-three newly diagnosed children (median age 4years, range 0.3–15 years; 51% male) participated in the study. There were 53% haematological malignancies (n = 23) and 47% solid tumours (n = 20). Prevalence of malnutrition varied among anthropometrical variables, with under-nutrition 14% (mid-upper arm circumference; MUAC), over-nutrition 9.3% (body mass index; BMI) and stunting 7.1% at diagnosis. MUAC recognised only 14% of patients with actual underlying muscle store depletion as per BIA (41.8%). Chemotherapy exposure acutely

exacerbated existing nutritional depletion during the first two months after diagnosis for all variables except fat mass (FM), with contrary effects on cancer type, as haematological malignancies had rapid increases in weight, BMI and FM. All patients had a clinically significant, acute loss of skeletal muscle mass during this period. Catch-up growth was achieved for all cancer types with a significant increase in weight (chi2 = 40.43, $p < 0.001$), height (chi2 = 53.79, $p < 0.001$), BMI (chi2 = 16.32, $p < 0.005$)), fat-free mass (chi2 = 23.69, $p < 0.003$) and skeletal muscle mass (chi2 = 24.19, $p < 0.001$) after six months.

Conclusions

Children with cancer are vulnerable for the development of acute malnutrition with body composition alterations during the first two months onco-chemotherapy treatment. Monthly anthropometry and BIA (body composition) measurements assist in implementation of timely nutritional interventions to prevent malnutrition.

Prevalence of malnutrition in patients with solid tumours at cancer diagnosis in Pediatric Oncology Units in South Africa

J Schoeman [1], I Kellerman[2], R Uys [1] G Naidu [3], B Rowe [3], J du Plessis [4], M Herholdt [5], K Thomas [6], B Van Emmenes [6], R Matthew [6], E J Ladas [7], P C Rogers [8], M Kruger [1]

Oral presentation at the 53rd Congress of the International Paediatric Oncology Society, virtual conference. Hawaii. October 2021

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Introduction:

In Africa, more than 45% of children diagnosed with cancer are classified as malnourished based on body mass index (BMI), or 59% when mid-upper arm circumference (MUAC) is included. This study aims to determine prevalence of malnutrition in children diagnosed with a solid tumour in South Africa.

Methods:

Children from five South African pediatric oncology units (POUs) diagnosed with a solid tumour had their nutritional assessment done by measuring height/length, weight, BMI and MUAC within 72h after diagnosis between October 2018 and December 2020. Z-scores for height-for-age (H/A), weight-for-age (W/A), BMI-for-age (BMI/A) were determined with WHO AnthroPlus 2007; MUAC with MUAC growth charts (<5 years WHO 2007; >5 years Mramba 2017). Two standard deviations (≤-2SD) below normal defined malnutrition (≤-2SD MUAC/A), stunting (≤-2SD H/A), underweight (≤-2 W/A) and wasting (≤-2SD BMI/A). Frequencies and correlations were calculated using SPSS v27 statistical software.

Results:

A hundred and seventy-nine (179) patients were included with an M: F ratio of 1:0.9. The median age was 3.8 years (range 0.3 to 15.3 years; mean 5.1 years). The majority (68%) had advanced disease (29% stage 3, 39% stage 4). Malnutrition was present in 24% (n=42) of children measured by MUAC, while 17% (n=31) were stunted, 12% (n=22), wasted, and 9% (n=14) underweight. There was a significant correlation between MUAC and both underweight ($p<0.000$) and wasting ($p<0.008$). Wasting correlated with the UNICEF MUAC colour band ($p=0.003$) and had a trend towards significant association with the province of residence ($p<0.008$) and gestational age at birth ($p<0.087$). Underweight patients had a trend towards significant association with advanced disease ($p<=0.091$) and gestational age at birth ($p<0.098$).

Conclusions:

Children with solid tumours in South Africa were less malnourished (24%) than reported by other African countries. MUAC is a sensitive measurement as it is independent of a large tumour burden.

Agreement of predictive equations and measured resting energy expenditure in children with cancer.

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Poster viewing at International Dietetics Congress, Virtual congress, cape Town, South Africa. Conference. October 2021

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Introduction:

Provision of adequate energy and protein requirements in the paediatric oncology population is key to prevent malnutrition and its detrimental effect on event-free survival. There is no consensus regarding the estimation of energy expenditure in this setting. This study aimed to determine whether existing predictive equations used as standard of care in paediatric nutrition can accurately predict the resting energy expenditure (REE) of newly diagnosed children with cancer.

Methods:

REE was measured at diagnosis utilising the validated InbodyS10 Bioelectrical Impedance Analysis (BIA) mobile unit and compared to three predictive equations (Schofield 1985, WHO 1985 and the RDA 1989). Agreement and accuracy of these equations were tested by determining bias and agreement rates, which were graphically displayed using the Bland Altman plot. Statistical significance was 5%.

Results:

Forty-three newly diagnosed children with median age 4 years (range 0.3 - 15 years) were measured at diagnosis prior to initiation of chemotherapy. Significant differences were found between REE (mean±SD) as determined by BIA 719.53±206.29kcal/day, WHO1985 889.75±323.31kcal/day, Schofield1985 899.62±336.10kcal/day and RDA

1647.67±481.06kcal/day (p<0.001). Overestimation of REE by 23.6% (WHO 1985), 25.0% (Schofield 1985), and 129.0% (RDA 1989) were noted. Significant proportionate bias was described in all three equations (p<0.001), with the WHO 1985 equation (-170.2±149.0kcal/day) lower than both the Schofield 1985 (-180.1±145.7kcal/day) and RDA (-928.1±324.8kcal/day) equations.

Conclusions:

Existing predictive energy equations (Schofield 1985, WHO 1985 and the RDA 1989) are inaccurate in predicting resting energy expenditure in newly diagnosed children with cancer by overestimating measured energy requirements between 23.6 – 129%.

THE PREVALENCE OF VITAMIN DEFICIENCIES IN CHILDREN DIAGNOSED WITH CANCER IN TWO PAEDIATRIC ONCOLOGY UNITS IN SOUTH AFRICA

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Poster viewing at the virtual conference's 53rd Congress of the International Paediatric Oncology Society. Canada, October 2020

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Background:

Recent South African (SA) studies reported that 66% of children have vitamin D deficiency (VDD), while 43.6% have vitamin A deficiency.

Aim:

This study investigated the serum levels of vitamins A, D, B12 and folate in SA children diagnosed with cancer in relation to poverty, hunger and province of residence.

Methods:

Serum blood tests for vitamins A, D, B12 and folate were done on admission at two SA paediatric

oncology units at cancer diagnosis between October 2018 and March 2020. Families were interviewed, and poverty- and hunger-related questionnaires were completed.

Results:

Interim analysis of 170 patients documented VDD prevalence of 46%; while deficiencies of folate, vitamin A, and B12 were 34%; 25% and 11%, respectively. VDD was significantly higher in poorer provinces, Mpumalanga (45%) and Western Cape (WC) (36%) compared with Gauteng (18%) (p=0.048); and in males (72%) versus females (27%) (p=0.023). Significant lower serum levels of vitamin B12 were found in children from Mpumalanga (50%) (p=0.013), specifically children ⩽ 5 years of age (58%) (p=0.020), in the Leukaemia/Lymphoma (LL) patient group (58%) versus Solid Tumour (ST) patient group (41%) (p=0.024). Folate deficiency was significantly increased in those >5 years of age (78%) (p=0.00)), the LL patient group (67%) compared to ST patient group (33%) (p=0.002), with a trend towards significance for Mpumalanga province (61%) (p=0.083). The category '>50% risk for poverty' was associated with decreased vitamin A- (70%; (p=0.016)) and vitamin D levels (66%, (p=0.022)). Patients categorised as 'Hunger' in hunger scale questionnaire' (64%) were significantly associated with folate deficiency (p=0.006).

Conclusion:

Nearly half the children had significant VDD. Another quarter had deficiencies for vitamins A, B12 and folate which were also significantly associated with poorer province of residence, young age, a more than 50% risk for poverty, hunger and underlying cancer diagnosis. Outcomes associated with these deficiencies will be evaluated.

Prevalence of malnutrition at cancer diagnosis in Paediatric Oncology Units in South Africa

J Schoeman [1], I Kellerman[2], R Uys 1G Naidu [3] , B Rowe [3], J du Plessis [4,] M Herholdt [5], K Thomas [6], B Van Emmenes [6], R Matthew [6] , E J Ladas [7], P C Rogers [8], M Kruger [1]

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Introduction:

In Africa, 55%- 60% of children diagnosed with cancer are classified as malnourished based on body mass index (BMI), with the prevalence increasing to 74% when mid-upper arm circumference (MUAC) is included. MUAC is more sensitive in the assessment of nutritional status in children with cancer; therefore, MUAC should be an essential factor in nutritional assessment. This study aims to determine prevalence of malnutrition in children at cancer diagnosis and the specificity of MUAC as single screening measure of malnutrition.

Methods:

All children diagnosed with cancer between 3 months and 15 years were measured for height/ length, weight, BMI and MUAC within 72h after diagnosis between October 2018 and September 2020 at five Paediatric Oncology Units in South Africa. Z-scores for height-for-age (H/A), weight-for-age (W/A), BMI-for-age (BMI/A) were determined with WHO AntroPlus 2007, MUAC with MUAC growth charts (<5 years WHO 2007; >5 years Mramba 2017). Two standard deviations (<-2SD) below normal used to classify malnutrition in this study group. SPSS version 25 used for frequencies and correlations.

Results:

This is an interim analysis with 283 newly diagnosed children assessed at diagnosis, with an M: F ratio of nearly 1:1(51,6% (n=146) boys, 48,4% (n=137) girls). The age range is 0.3 to 15.7 years (mean 6.2 years). More than half (56.2%) were diagnosed with solid tumours, and 43.8% leukaemia/lymphoma. Malnutrition was present in 21.1% (n=60) of children with MUAC, while 6.9% (n=15) wasted (⩽-2BMI/A); 14.5% (n=40) stunted (⩽-2H/A) and 7.4% (n=16/216) underweight (⩽-2 W/A). There is a significant association between MUAC ⩽ -2 SD, wasting (p=0.00); underweight (p=0.00) but not stunting (p=0.511)

Conclusions:

Compared to other African countries, fewer children with cancer were malnourished at diagnosis, and MUAC indicated a higher percentage, potentially due to its independence of large tumour burden, and can be used as a single screening measure of malnutrition.

Prevalence of malnutrition at cancer diagnosis in Paediatric Oncology Units in South Africa

J Schoeman [1], I Kellerman[2], R Uys 1G Naidu [3] , B Rowe [3], J du Plessis [4,] M Herholdt [5], K Thomas [6], B Van Emmenes [6], R Matthew [6] , E J Ladas [7], P C Rogers [8], M Kruger [1]

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Introduction:

In Africa, 55%- 60% of children diagnosed with cancer are classified as malnourished based on body mass index (BMI), with the prevalence increasing to 74% when mid-upper arm circumference (MUAC) is included. MUAC is more sensitive in the assessment of nutritional status in children with cancer; therefore, MUAC should be an essential factor in nutritional assessment. This study aims to determine prevalence of malnutrition in children at cancer diagnosis and the specificity of MUAC as single screening measure of malnutrition.

Methods:

All children diagnosed with cancer between 3 months and 15 years were measured for height/ length, weight, BMI and MUAC within 72h after diagnosis between October 2018 and September 2020 at five Paediatric Oncology Units in South Africa. Z-scores for height-for-age (H/A), weight-for-age (W/A), BMI-for-age (BMI/A) were determined with WHO AntroPlus 2007, MUAC with MUAC growth charts (<5 years WHO 2007; >5 years Mramba 2017). Two standard deviations (<-2SD) below normal used to classify malnutrition in this study group. SPSS version 25 used for frequencies and correlations.

Results:

This is an interim analysis with 283 newly diagnosed children assessed at diagnosis, with an M: F ratio of nearly 1:1(51,6% (n=146) boys, 48,4% (n=137) girls). The age range is 0.3 to 15.7 years (mean 6.2 years). More than half (56.2%) were diagnosed with solid tumours, and 43.8% leukaemia/lymphoma. Malnutrition was present in 21.1% (n=60) of children with MUAC, while 6.9% (n=15) wasted (⩽-2BMI/A); 14.5% (n=40) stunted (⩽-2H/A) and 7.4% (n=16/216) underweight (⩽-2 W/A). There is a significant association between MUAC ⩽ -2 SD, wasting (p=0.00); underweight (p=0.00) but not stunting (p=0.511)

Conclusions:

Compared to other African countries, fewer children with cancer were malnourished at diagnosis, and MUAC indicated a higher percentage, potentially due to its independence of large tumour burden, and can be used as a single screening measure of malnutrition.

THE PREVALENCE OF HOUSEHOLD FOOD INSECURITY AFFECTING CHILDREN DIAGNOSED WITH CANCER IN TWO PAEDIATRIC ONCOLOGY UNITS IN SOUTH AFRICA

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Poster viewing at the 51st Congress of the International Paediatric Oncology Society, Lyon, France October 2019

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Background:

Food insecurity is defined as the lack of nutritionally adequate, safe and sufficient amounts of food for all household members, which is a major cause of malnutrition in developing countries. Families cope with food insecurity by decreasing the variety of foods they buy for the household, as well as portion sizes. In 2015 UNICEF reported that 70% of households in informal settlements in South Africa (SA) suffered food insecurity. The prevalence of food insecurity of children diagnosed and treated for cancer in SA is unknown.

Methods:

The Household Hunger Scale (HHS) consists of eight "Yes/No" questions and is used to determine food security or child hunger. Five or more "yes" responses indicate food insecurity. The family of each newly diagnosed child with cancer family was interviewed with the HHS questionnaire within 72h after diagnosis from 1 Oct 2018. The study is ongoing until December 2020**.**

Results:

The interim analysis includes the responses of parents of 51 patients, but as the study is ongoing, will include more in future. The majority of families (74.5%; 38/51) rely on limited number of food types to feed their children. A further 62.7% (32/51) run out of money to buy food during the month, while 58.8% (30/51) of the caregivers eat less than they should, and 52.9% (27/51) cut the size of their meals due to inadequate money to buy food. The final score indicated that 52.9% (27/51) have a risk for hunger, while 25.5% (13/51) of patients have food shortages, and only 21.6% (11/51) have food security at home.

Conclusion:

The high percentage of newly diagnosed children with cancer that are at risk for food insecurity at home is of great concern. Interventions are needed to ensure adequate nutrition for children during cancer treatment.

Appendix G: Paediatric Oncology related research and congress abstracts as co-author (2019-2022)

DETERMINING THE TRUE INCIDENCE OF NEUROBLASTOMA IN SOUTH AFRICA

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Poster viewing at the 52nd Congress of the International Paediatric Oncology Society, virtual conference; Hawai. October 2021.

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ABSTRACT

Background and aims

According to the Surveillance, Epidemiology, and End Results (SEER) Program, the incidence of neuroblastoma (NB) in the USA is 10.5/ million children. The reported South African incidence (2015) is 2.7/ million children, based on the South African Children's Tumour Registry (SACTR), a clinical data-based registry, while there also a national pathology registry (SA-NCR) in South Africa. The aim is to determine the true incidence of NB in South Africa based on both registries and reported cases from the paediatric oncology units.

Methods

A probabilistic linkage study was conducted using the data from cases of patients diagnosed with NB between 2000 and 2016 in nine paediatric oncology units in SA, registry data of NB cases during this period requested from the SACTR and the SA – NCR.

Results

There were 463, 312 and 603 cases identified from respectively the hospital-based records, SA-NCR and SACTR, respectively. After excluding duplicates (n=148) and patients with insufficient data (n=14) for linking, 824 cases were included for linking. Only 329 records (39.9%) matched between these respective registries. The SA-NCR and SACTR reported between 23 – 51 cases per annum and 18 – 57 cases per annum, respectively. The SA-NCR incidence for children under 15 years varied between 1.5-2.8/ million children and was between 1.74-2.6 cases/million children in the SACTR was. Both registries reported incidences less than the SEER Program. A probabilistic record linkage from all the sourced data resulted in a combined incidence of 2.9 cases/ million children.

Conclusions

South Africa still reported a lower incidence of NB than the SEER Program. The reasons for a lower incidence are not clear but are either due to a true lower incidence or underdiagnoses of NB cases. Underdiagnoses may be due to spontaneous regression of tumours or deaths before the diagnosis of NB.

Outcome comparison of 2 Retinoblastoma treatment protocols for developing countries as per SIOP-PODC recommendations

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Oral presentation at the 50th Congress of the International Paediatric Oncology Society, Lyon, France. October 2019.

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Introduction:

Members of the International Society of Paediatric Oncology (SIOP) and Paediatric Oncology in Developing Countries (PODC) provided recommendations for graduated-intensity treatment of children with retinoblastoma in developing countries.

Aim:

The study aim was to compare the outcome of children treated with 2 SIOP-PODC recommended retinoblastoma treatment protocols respectively in South Africa and Cameroon.

Methods:

All children diagnosed with retinoblastoma between 2012 and 2016, treated in 6 paediatric oncology units (POUs) in South Africa (SA) and 2 POUs in Cameroon (CA) were included (n=281). Treatment involved in South Africa (upper middle-income country) local intraocular therapy, or chemotherapy and/or surgery and/or radiotherapy for more extensive disease versus local intraocular therapy or combination chemotherapy and/or surgery in Cameroon (low income country). The SA chemotherapy protocol included Vincristine, Carboplatin and Etoposide. The CA chemotherapy protocol included Vincristine, Adriamycin and Cyclophosphamide. Survival data presented is for 12-month follow-up unless otherwise specified, Chi-square and p-values for Log Rank Mantel-Cox.

Results:

The 12-month survival in SA was 78.2% (100 of 127) and 59.2% (45 of 76) in CA (Chi-Square = 9.277, p=0.002), which was significantly affected by stage. All stage 0 patients had a 100% survival in SA (27/27)and CA (2/2). SA patients had a better survival for all other stages compared to CA patients except stage IV: Stage I – SA 92.7% (51/55) versus 58.8% (10/17) in CA (Chi-Square = 13.391, p=0.000); Stage II – SA 100% (14/14) versus 75% in CA (9/12) in CA (Chi-Square = 3.833, p=0.050); Stage III – SA 70% (7/10) versus CA 40% (2/5) (Chi-Square = 1.207, no survival difference). Stage IV CA patients however, had a better 12-month survival of 66% compared to SA with only 10%. The differences in survival between the stages might indicate the difficulty in staging children in CA, with only one dedicated pathologist and not all histology reviewed.

Conclusion:

The SIOP-PODC recommendations for graduated-intensity treatment protocols in different settings in developing countries had an acceptable overall survival after 12 months.

Report of first national collaborative treatment protocol of Retinoblastoma in South Africa – An interim analysis

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Poster viewing at the 49th Congress of the International Paediatric Oncology Society, Kyota, Japan, October 2018.

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Introduction:

Collaborative treatment protocols improve the overall survival of children with cancer.

Aim:

To determine the outcome of children treated with a standard national treatment protocol for retinoblastoma in South Africa.

Methods:

All specialists, involved in retinoblastoma care, participated in the development of a national treatment protocol (2009-2011), based on the SIOP-PODC retinoblastoma guideline for high income countries (HIC). Treatment involved local therapy for intraocular disease,

chemotherapy and/or surgery and/or radiotherapy for more extensive disease. Five of nine existing pediatric oncology units (POUs) initiated treatment in January 2012.

Results:

One hundred and eighty-seven patients were included in the interim data analyses. The median age was 28.0 months (range 0-159.0 months; IQR 16.0-40.0). Male/female ratio was 1.4:1. Fifty-two patients (29%) had bilateral disease. Nearly half (61 patients; 49%) had advanced disease. For the interim analysis with 1 year post treatment survival data overall survival was 71%, but 75% if excluding absconding patients (6%). Children with limited disease had overall survival (OS) of 81% versus advanced disease 51%.

Conclusion:

In comparison to a previous published single South African unit study mean age was younger (28 months versus 35 months) and OS improved from 43% to 71%. A national retinoblastoma treatment protocol was feasible in South Africa with improved overall survival.