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.

Keywords: Cancer, Childhood cancer, nutritional status, iron deficiency, Vitamin

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 range**s** 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,

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

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).

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).

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).

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.

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.

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-Mari**é** 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.

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Conflict of interest

None.

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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