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Nutritional status at diagnosis is related to clinical outcomes in children and adolescents with cancer: A perspective from Central America

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ABSTRACT

Background: The prevalence of malnutrition in children may exceed 50% in countries with limited resources. The aims of this study were to assess nutritional status at diagnosis in children and adolescents with cancer, and to correlate it with clinical outcomes in the Spanish speaking countries of Central America that formed the AHOPCA (Asociacion de Hemato-Oncologia Pediatrica de Centro America) consortium.

Methods: Patients aged 1–18 years, diagnosed with cancer between 1st October 2004 and 30th September 2007, were eligible for study. Weight (kg) and height or length (m), mid upper arm circumference – MUAC and triceps skin fold thickness – TSFT were measured and their Z-scores or percentiles were calculated. Three categories of nutritional status were defined according to these parameters.

Results: A total of 2954 new patients were enrolled; 1787 had all anthropometric measurements performed and 1513 also had measurements of serum albumin. By arm anthropometry 322/1787 patients (18%) had moderate nutritional depletion and 813/1787 patients (45%) were severely depleted. Adding serum albumin, the proportion classified as severely depleted rose to 59%. Malnourished children more often abandoned therapy and their event free survival was inferior to that of other children.

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Conclusions: Arm anthropometry in children with cancer is a sensitive measure of nutritional status. Since malnutrition at diagnosis was related to important clinical outcomes, an opportunity exists to devise simple, cost-effective nutritional interventions in such children that may enhance their prospects for survival.

1. Introduction

The great majority of children with cancer live in developing countries, where the prevalence of malnutrition (undernutrition) in this age group may exceed 50%.[1] Malnutrition is often related to other factors, such as socioeconomic disadvantage,[2] and is not restricted to countries with limited resources.[3] Poor nutritional status can influence the course of malignant disease and the prospects for survival. Some authors have described decreased tolerance of chemotherapy, associated with altered metabolism of antineoplastic drugs, increased infection rates and poor clinical outcome. However, the relationship between malnutrition and morbidity/mortality is still controversial[4–10] and, with present knowledge, it is not possible to reach a definitive conclusion. Assessment of nutritional status in itself is difficult because there is currently no clinical 'gold standard'.[11]

An opportunity to study this phenomenon in detail is provided by the collaboration established among the six Spanish speaking countries of Central America – Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, Panama – plus the Dominican Republic in the form of a consortium of investigators focused on the challenges of cancer in childhood: AHOPCA (Asociacion de Hemato-Oncologia Pediatrica de Centro America). Since 1998 AHOPCA members have met once a year to discuss and update common protocols, and to elaborate further strategies for cooperation. A registry for clinical epidemiology was also established in which AHOPCA members report routinely on all cases of newly diagnosed cancers in children less than 18 years of age. As an additional AHOPCA meeting, a workshop on nutrition was organised in Guatemala City[12] with the goal of performing a study on nutritional status at diagnosis in children and adolescents with cancer. To this end, an algorithm for assessment of nutritional status was generated and adopted by all the countries of AHOPCA.

The primary aims of this study were:

(1) to determine the prevalence and severity of malnutrition at diagnosis in children and adolescents with cancer;
(2) to correlate nutritional status at diagnosis with clinical outcomes – abandonment of therapy, relapse of disease and death.

It was postulated that a high proportion of children with cancer in Central America are malnourished at diagnosis and that poor nutritional status compromises clinical outcomes. The member nations of AHOPCA meet the definition of low income countries,[13] and their economic disadvantage is reflected in their population age distribution (Table 1).

2. Patients and methods

This was a prospective study of newly diagnosed patients with cancer, aged 1–18 years, between 1st October 2004 and 30th September 2007. Patients were excluded from the study if assessment of nutritional status was performed more than 48 h after the beginning of chemotherapy. The following data were collected at diagnosis and recorded on a study data form prepared in the POND (Pediatric Oncology Networked Database) system. POND was developed by the International Outreach Program of St. Jude Children's Research Hospital's International Outreach Education Group and is provided as a free service. AHOPCA members use POND as a tool for clinical epidemiology and report routinely on selected demographical and clinical data for newly diagnosed children

Table 1 – Demographic and economic data pertaining to the countries of AHOPCA.

Country	Total population (thousands)[a]	Population <18 years (thousands)[a]		Population <15 years (thousands)[b]		GNI per capita (US$)[a]
Costa Rica	4468	1482	33%	1162	26%	5560
Dominican Republic	9760	3788	38%	3026	31%	3550
El Salvador	6857	2696	39%	2400	35%	2850
Guatemala	13,354	6588	49%	5208	39%	2440
Honduras	7106	3257	45%	2700	38%	1600
Nicaragua	5603	2441	43%	1849	33%	980
Panama	3343	1181	35%	969	29%	5510
Total (mean)	50,491	21,433	42/43%[c]	17,314	33/35%[c]	3,213/2,900[c]

[a] From the State of the World's Children 2009 http://www.unicef.org/publications/index.htm.
[b] Data from the US Census Bureau, Population Division/International Programs Center, http://www.census.gov/cgi-bin/ipc/agggen.
[c] Weighted mean.

Table 2 – Expected number of children with cancer in the countries of AHOPCA.

Country	Annual Registrations in POND (<15 years of age)	Expected[a] Registrations in POND-1 (<15 years of age)	Expected[a] Registrations in POND-2 (<15 years of age)	O/E ratio-1	O/E ratio-2
Costa Rica	120	116	145	1.03	0.82
Dominican Republic	76	303	378	0.25	0.20
El Salvador	185	240	300	0.77	0.61
Guatemala	265	521	651	0.50	0.40
Honduras	168	270	338	0.62	0.49
Nicaragua	175	185	231	0.94	0.75
Panama	34	97	121	0.35	0.28
Total (mean)	1023	1732	2164	0.68[b]	0.54[b]

O/E, observed/expected.

[a] Based on average incidence estimates of 100 (POND-1) and 125 (POND-2) per million per year (Ref. 18) (from Howard et al, Cancer 2008; 112:461–72).

[b] Weighted mean.

with cancer. Data quality is checked each year, before the AHOPCA meeting, by SOPHOLIC (Statistical Office for Pediatric Hemato-Oncology in Low Income Countries) of the Università di Milano-Bicocca, Monza, Italy. Information on clinical outcomes was updated at January 2009.

2.1. *Demographic data*

Name, gender, ethnicity, date of birth, date of diagnosis and type of cancer (according to the International Classification of Childhood Cancer[14]) were registered. Observed:expected ratios of incident cancer cases were generated for children diagnosed before age 15 years on the basis of published population age distributions[15] and with two different putative incidence rates derived from experience in developing countries[16] (Table 2).

2.2. *Anthropometric assessments*

Weight (kg) and height or length (m) were measured – from which body mass index (BMI) – weight/height,[2] weight-for-height (WFH) and their Z-scores or percentiles were calculated on all subjects. The results of weight, height and BMI were compared with CDC (Centers for Disease Control and Prevention) normative data in children.[17] BMI-for-age defines underweight as less than the 15th centile and less than the 5th centile was taken to represent severe malnutrition. The WFH results, based on the methods of the CDC and the World Health Organization (WHO), are limited to children 5 years of age and younger, and so cannot be used for the entire population under study. Consequently these results will not be reported here. We also calculated weight as a percentage of ideal weight for height, age and gender, based on the method of McLaren and Read[18] which, since we chose to report height/weight data in the current manuscript only as BMI, are not shown in this paper.

Mid upper arm circumference – MUAC – was measured to the nearest 1 mm. The mid-point of the dependant right upper arm was determined, between the olecranon process of the ulna and the acromial process of the scapula with the forearm held at a right angle and a mark was made at this point. A paper measuring tape was passed around the arm at the mark. The measurement was repeated twice and the mean of the three measurements was used for analysis. The results were compared with age and gender matched norms.[19] Triceps skin fold thickness – TSFT – was measured using a Harpenden caliper (John Bull British Indicators, LTD., made in England) to the nearest 0.2 mm at the same level of the site used for the MUAC. Lifting the skin and fat away from underlying muscle tissue with one hand and applying the caliper blades to either side of this fold of skin, the reading was determined 2–3 s after the full pressure of the jaws of the caliper had been exerted. The measurement was repeated twice within 1 mm of the previous one and the mean of the 3 measurements was used for analysis. The results were compared with age and gender matched norms.[19] All the measurements were undertaken by only one or two observers in each country. The observers were trained and methods were standardised at the nutrition workshop in Guatemala City.[12] MUAC and TSFT can be considered as surrogate measures of lean and fat mass[11] respectively, and were used with serum albumin to define the following categories of nutritional status based on an algorithm developed at St. Jude Children's Research Hospital[20]:

ADEQUATELY NOURISHED

Albumin > 3.5 g/dl and TSFT > 10th percentile and MUAC > 10th percentile

INADEQUATELY NOURISHED

– Severely depleted

Albumin < 3.2 g/dl or TSFT < 5th percentile or MUAC < 5th percentile

– Moderately depleted

The remaining subjects.

2.3. *Treatment-related mortality*

Causes of death were classified as haemorrhage, infection, progressive disease and other – the last including hematologic toxicity.

This study fulfilled the requirements of the Research Ethics Board of McMaster University and Hamilton Health Sciences.

2.4. Statistical analysis

Statistical evaluation included descriptive statistics on children enrolled in the study; chi square tests to compare the distribution of nutritional status among classes of diagnosis; Cochran-Armitage trend tests to estimate if the percentages of the main events (death, relapse, abandonment) increase according to worsening of the nutritional status; estimation of the event free survival (EFS) according to Kaplan–Meier with Greenwood standard error (SE); comparison of EFS between groups with different nutritional status performed using the log-rank test; estimation of hazard ratios by nutritional status, according to the Cox model stratified by country, to control for the heterogeneity by country; and the evaluation of the goodness-of-fit of the model was performed using the log-likelihood test. EFS time was defined as time to the following events: relapse, abandonment of therapy, death, second malignant neoplasm, whichever occurred first. Abandonment of therapy was defined as 'Missing four or more consecutive weeks of treatment or follow-up while still on theraspy'.[21] To exclude the potential bias caused by the incomplete capture of all cases, the analyses on the outcomes were performed a second time excluding those countries with a very low observed/expected ratio (Panama and Dominican Republic). Statistical evaluation was performed by SOPHOLIC and carried out with SAS, version 9.1 (SAS Institute, Cary, NC).

3. Results

A total of 2954 new patients in the pre-determined age range were enrolled in POND during the study period; 1787 had all anthropometric measurements performed, and 1513 of this group (85%) also had measurements of serum albumin. The median age at diagnosis was 6.8 years (interquartile range (IQR): 3.8–10.6 years) and 56.4% were male. Only a small proportion ($n = 61$, 3.4%, median age = 15.8 years, IQR: 15.4–16.3 years) of patients was 15 years of age or older.

Among the 1787 patients, 1353 (75.7%) were mestizo (an indigenous/Caucasian mixture), 178 (10%) were indigenous, 130 (7.3%) were mulatto (an indigenous/Black mixture), 44 (2.5%) were Caucasian, 22 (1.2%) were Black, one person was Asiatic and the ethnicity of the remaining 59 (3.3%) was not recorded. The indigenous population in Central America is composed of Mayan and related groups; and in Guatemala approximately 26% is Mayan. Demographic data on the 1167 patients who were not enrolled were very similar to the data on the enrolled patients; median age was 7.0 years (IQR: 3.5–11.1 years), 58.5% were male, the median age of the small proportion (5.2%) of children older than 15 years was 16.0 years (IQR: 15.3–16.8 years). The most common race was mestizo (82.9%), followed by Caucasian 93 (8.0%), mulatto 41 (3.5%), indigenous 28 (2.4%) and black 10 (0.9%). Race was missing in 28 patients (2.4%).

The 2954 cancer diagnoses and the 1787 patients enrolled in the study are described by country and disease in Table 3. Diseases were clustered according to the following groups – acute lymphoblastic leukaemia (ALL); other leukaemias and myelodysplastic syndromes; lymphomas; and solid tumours – for further analyses.

Table 4 shows the data on weight, height and BMI in the 1677 patients who were 2–18 years of age. Overall, according to the BMI based classification, 28% of the patients were underweight and this varied significantly by category of disease (overall chi square test: $p = 0.02$). Fewer than 20% were severely malnourished.

Using only arm anthropometric values (MUAC, TSFT) to categorise nutritional status, 18% of patients were moderately depleted, 45% of patients were severely depleted and there was minimal added value to the inclusion of percent IBW (Table 5A). By contrast, there was considerable added value to the inclusion of serum albumin in the categories of nutritional status (Table 5B). Although the proportion of subjects who were moderately depleted remained very similar, the proportion classified as severely depleted rose considerably to 59% when albumin was considered. Not surprisingly, the

Table 3 – Recruitment to the nutritional study versus POND registration by disease in the countries of AHOPCA.

Diagnosis	Number of patients recruited to the study over the number registered in POND[a]								
	Costa Rica	Dominican Republic	El Salvador	Guatemala	Honduras	Nicaragua	Panama	Total	%
ALL	102/134	78/98	191/216	300/329	8/261	174/202	17/35	870/1275	68.2
APL	2/3	3/5	5/6	13/17	0/5	3/7	0/0	26/43	60.5
AML	21/23	22/30	25/32	32/36	1/31	28/37	1/4	130/193	67.4
HD	5/34	9/11	24/32	68/72	2/61	23/35	4/9	135/254	53.1
NHL	4/31	15/21	31/38	39/42	2/34	21/49	4/8	116/223	52.0
Brain tumours	3/38	0/0	35/64	35/48	0/7	10/38	1/11	84/206	40.8
Neuroblastoma	1/4	4/7	15/17	6/7	0/6	3/6	1/2	30/49	61.2
Wilms tumour	5/11	13/18	21/26	14/14	2/31	11/25	1/3	67/128	52.3
Bone tumours	0/10	0/0	16/20	51/58	1/20	15/32	2/6	85/146	58.2
Retinoblastoma	1/7	4/5	8/18	48/58	0/22	7/20	1/5	69/135	51.1
Soft tissue sarcomas	4/13	9/10	11/13	26/31	2/12	9/18	1/3	62/100	62.0
Others	4/27	8/11	27/41	54/56	0/17	19/48	1/2	113/202	55.9
Total	152/335	165/216	409/523	686/768	18/507	323/517	34/88	1787/2954	60.5
%	45.4	76.4	78.2	89.3	3.6	62.5	38.6	60.5	

[a] Only patients 1–18 years old.

Table 4 – Weight, height and body mass index (BMI).[a]

Disease group	Weight Z score	Height Z score	BMI for [b] age centile	BMI <15th[b] age centile	BMI <5th[b] age centile
ALL	–0.73 (–11.44, 4.16)	–0.88 (–9.67, 8.40)	45.8 (0.0, 100.0)	25.0	14.4
Other leukaemias + MDS	–1.02 (–4.14, 2.36)	–1.05 (–6.35, 2.31)	32.7 (0.0, 99.2)	34.0	19.3
Lymphomas	–1.17 (–6.87, 2.76)	–1.31 (–6.27, 3.31)	39.9 (0.0, 99.9)	27.8	18.3
Solid tumours	–0.98 (–12.18, 4.51)	–0.99 (–6.77, 3.90)	44.4 (0.0, 99.9)	31.8	20.6
Total	–0.86 (–12.18, 4.51)	–0.97 (–9.67, 8.40)	41.6 (0.0, 100.0)	28.0	17.1

ALL, acute lymphoblastic leukaemia.
MDS, myelodysplastic syndrome.
[a] Range and median values.
[b] Ages 2–18 years ($n = 1677$).

Table 5A – Distribution of children by category of nutritional status using 2 (TSFT, MUAC) or 3 (TSFT, MUAC, IBW) indicators.

TSFT, MUAC, IBW	TSFT, MUAC			Total (%)
	Adequate	Moderately depleted	Severely depleted	
Nutritional status classification according to:				
Adequate	592	0	0	592 (33.1)
Moderately depleted	60	322	0	382 (21.4)
Severely depleted	0	0	813	813 (45.5)
Total (%)	652 (36.5)	322 (18.0)	813 (45.5)	1787

Table 5B – Distribution of children by category of nutritional status using 2 (TSFT, MUAC) or 3 (TSFT, MUAC, albumin) indicators.

TSFT, MUAC, albumin	TSFT, MUAC			Total (%)
	Adequate	Moderately depleted	Severely depleted	
Classification according to:				
Adequate	344	0	0	344 (22.8)
Moderately depleted	90	183	0	273 (18.0)
Severely depleted	114	86	696	896 (59.2)
Total (%)	548 (36.2)	269 (17.8)	696 (46.0)	1513

further inclusion of percent IBW provided minimal added value (data not shown). The overall proportion of subjects who were severely malnourished ranged from 56% in solid tumours to 69% in leukaemias other than ALL ($p = 0.002$). Among the 1513 children in whom nutritional status was evaluated according to arm anthropometry and serum albumin, BMI was unavailable in 93 because of age. In the remaining 1420 children, the BMI was less than the 5th centile in 3.9%, 6.2% and 24.4% of those classified as adequately nourished ($n = 331$), moderately depleted ($n = 257$) and severely depleted ($n = 832$) respectively.

As measured conventionally, by BMI greater than the 95th percentile, among the adequately nourished group ($n = 344$), 42 (12%) were obese. For comparison, using an unconventional metric based on arm anthropometry (MUAC or TSFT greater than the 95th percentile and serum albumin greater than 3.5 g/l), 29 (8%) patients in this group were obese. There was a significant association between these two measures of obesity (chi square test $p < 0.001$).

According to the results of tests for trend (Table 6), significantly higher mortality rates (for patients with solid tumours and the study sample as a whole) and frequency of abandonment (for patients with ALL and solid tumours and the study sample as a whole) were related to the degree of malnutrition. Although there was a suggestion of more fatal toxicity, mostly hematologic, with more severe malnutrition (0.0%, 10.0% and 14.7% in adequately nourished, moderately depleted and severely depleted patients in the 'other leukemias and MDS' category respectively), the absolute numbers (0, 1 and 5 patients) were too small to allow statistical evaluation.

There was no correlation between nutritional status and relapse rate.

Table 6 – Distribution of children by category of nutritional status using 3 (TSFT, MUAC, albumin) indicators and outcome.

Nutritional status by disease classification	First event N (%)			No. of patients	% 2-year EFS (SE) Log-rank test *p*-value	HR ($CI_{95\%}$) Log-likelihood test *p*-value
	Death	Relapse	Abandonment			
ALL						
Adequate	17 (8.9)	28 (14.7)	11 (5.8)	191 (24.1)	68.7 (3.9)	1
Moderately depleted	19 (12.8)	15 (10.1)	17 (11.5)	148 (18.7)	67.1 (4.1)	1.24 (0.84–1.84)
Severely depleted*	46 (10.1)	72 (15.9)	58 (12.8)	454 (57.2)	60.8 (2.5)	1.35 (0.99–1.84)
Total	82 (10.3)	115 (14.5)	86 (10.8)	793	$p = 0.080$	$p = 0.161$
Trend test	$p = 0.802$	$p = 0.481$	$p = 0.012$			
Other leukaemias + MDS						
Adequate	8 (38.1)	4 (19.0)	0 (0.0)	21 (14.3)	45.8 (11.3)	1
Moderately depleted	10 (40.0)	10 (40.0)	2 (8.0)	25 (17.0)	12.0 (6.5)	1.89 (0.90–4.00)
Severely depleted	34 (33.7)	30 (29.7)	10 (9.9)	101 (68.7)	25.6 (4.5)	1.44 (0.75–2.75)
Total	52 (35.4)	44 (29.9)	12 (8.2)	147	$p = 0.086$	$p = 0.231$
Trend test	$p = 0.587$	$p = 0.613$	$p = 0.153$			
Lymphomas						
Adequate	3 (10.0)	2 (6.7)	3 (10.0)	30 (14.8)	72.3 (8.4)	1
Moderately depleted	1 (2.6)	2 (5.3)	4 (10.5)	38 (18.7)	79.1 (7.1)	0.63 (0.23–1.76)
Severely depleted[a]	22 (16.3)	9 (6.7)	24 (17.8)	135 (66.5)	57.5 (4.5)	1.70 (0.81–3.58)
Total	26 (12.8)	13 (6.4)	31 (15.3)	203	$p = 0.020$	$p = 0.014$
Trend test	$p = 0.114$	$p = 0.915$	$p = 0.190$			
Solid tumours						
Adequate	20 (19.6)	11 (10.8)	7 (6.9)	102 (25.6)	59.4 (5.6)	1
Moderately depleted	16 (25.8)	9 (14.5)	11 (17.7)	62 (16.7)	40.6 (6.8)	1.9 (1.19-3.04)
Severely depleted	82 (41.4)	21 (10.6)	33 (16.7)	198 (55.7)	25.8 (3.6)	3.01 (2.08-4.35)
Total	118 (31.9)	41 (11.1)	51 (13.8)	370	$p < 0.001$	$p < 0.001$
Trend test	$p < 0.001$	$p = 0.771$	$p = 0.043$			
Total						
Adequate	48 (14.0)	45 (13.1)	21 (6.1)	344 (22.7)	65.0 (2.9)	1
Moderately depleted	46 (16.8)	36 (13.2)	34 (12.5)	273 (18.1)	57.3 (3.2)	1.29 (0.86–1.94)
Severely depleted[b]	184 (20.5)	132 (14.7)	125 (14.0)	896 (59.2)	48.4 (1.8)	1.64 (1.19–2.27)
Total	278 (18.4)	213 (14.1)	180 (11.9)	1513	$p < 0.001$	$p = 0.005$
Trend test	$p = 0.006$	$p = 0.407$	$p < 0.001$			

[a] There was 1 second malignant neoplasm (SMN).
[b] There were 2 SMN.

In all four clusters of disease, malnourished children more often abandoned therapy and the trend was significant in those with ALL and solid tumours, while a significant trend in the association between nutritional status and death was observed only in patients diagnosed with a solid tumour. EFS was significantly different in the three levels of nutritional status ($p < 0.001$); 65% of adequately nourished children were alive without any adverse event while only 48% of the severely depleted children were alive and free of any event at 2 years from diagnosis (Table 6). EFS by disease cluster was significantly different in children with solid tumours and lymphomas in whom 2-year EFS in those who were severely depleted nutritionally was approximately 26% and 58% respectively, compared with 2-year EFS in adequately nourished children in these disease clusters of approximately 59% and 72% respectively. Results obtained with a Cox model stratified by country, to adjust indirectly for heterogeneity, showed similar EFS; only solid tumours were significantly different by nutritional status. The results of the sensitivity analysis, excluding countries with very low observed/expected ratios, did not highlight strong differences with the results on the overall study population (Table 7).

4. Discussion

All methods for clinical assessment of nutritional status have limitations, especially in children with cancer, since there is currently no clinical 'gold standard'.[11] The CDC and most recent WHO methods, based on weight-for-height, are valid only for pre-school age children. A recent review of the WHO standards, with respect to severe acute malnutrition in the developing country setting, has been published.[22] BMI is a valid measure of nutritional status across a wide age range of childhood and adolescence[23] and population-based data are available from a large study sample in another Latin American context (Brazil).[24] Another approach is to use percent IBW, but all measures of nutritional status that rely on weight are problematic in children with cancer in whom

Table 7 – Distribution of children by category of nutritional status using 3 (TSFT, MUAC, Albumin) indicators and outcome (Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua).

Nutritional status by disease classification	First event N (%)			No. of patients	% 2-year EFS (SE) Log-rank test p-value	HR ($CI_{95\%}$) Log-likelihood test p-value
	Death	Relapse	Abandonment			
ALL						
Adequate	11 (6.2)	24 (13.6)	9 (5.1)	177	72.9 (3.9)	1
Moderately depleted	14 (10.1)	14 (10.1)	16 (11.5)	139	69.8 (4.1)	1.56 (0.70–3.49)
Severely depleted[a]	30 (7.4)	60 (14.7)	56 (13.8)	407	63.9 (2.5)	1.16 (0.57–2.33)
Total	55 (7.6)	98 (13.6)	81 (11.2)	723	$p = 0.04$	$p = 0.533$
Trend test	$p = 0.802$	$p = 0.533$	$p = 0.003$			
Other leukaemias + MDS						
Adequate	7 (35.0)	4 (20.0)	0 (0.0)	20	48.1 (11.8)	1
Moderately depleted	7 (36.8)	9 (47.4)	1 (5.3)	19	10.5 (7.0)	1.33 (0.45–3.98)
Severely depleted	21 (25.0)	30 (35.7)	7 (8.3)	84	28.4 (5.2)	0.78 (0.31–1.96)
Total	35 (28.5)	43 (35.0)	8 (6.5)	123	$p = 0.07$	$p = 0.497$
Trend test	$p = 0.267$	$p = 0.366$	$p = 0.171$			
Lymphomas						
Adequate	1 (3.7)	2 (7.4)	3 (11.19)	27	76.9 (8.3)	1
Moderately depleted	1 (2.9)	2 (5.7)	4 (11.4)	35	77.4 (7.6)	0.78 (0.05–12.54)
Severely depleted	18 (15.3)	7 (5.9)	22 (18.6)	118	59.7 (4.8)	4.78 (0.63–36.04)
Total	20 (11.1)	11 (6.1)	29 (16.1)	180	$p = 0.04$	$p = 0.020$
Trend test	$p = 0.028$	$p = 0.814$	$p = 0.236$			
Solid tumours						
Adequate	20 (20.0)	10 (10.0)	7 (7.0)	100	59.6 (5.7)	1
Moderately depleted	16 (28.1)	7 (12.3)	10 (17.5)	57	40.8 (7.2)	2.06 (1.06–4.01)
Severely depleted	72 (39.1)	20 (10.9)	30 (16.3)	184	27.8 (3.8)	3.50 (2.11–5.81)
Total	108 (31.7)	37 (10.9)	47 (13.8)	341	$p < 0.001$	$p < 0.001$
Trend test	$p < 0.001$	$p = 0.861$	$p = 0.041$			
Total						
Adequate	39 (12.4)	40 (12.4)	18 (5.9)	324	67.8 (2.9)	1
Moderately depleted	38 (15.2)	32 (12.89)	27 (12.4)	250	59.4 (3.3)	1.45 (0.93-2.28)
Severely depleted[a]	141 (17.8)	117 (14.8)	111 (14.5)	793	51.1 (1.9)	1.80 (1.26-2.57)
Total	218 (16.0)	189 (13.8)	156 (12.1)	1367	$p < 0.001$	$p = 0.003$
Trend test	$p = 0.016$	$p = 0.255$	$p < 0.001$			

[a] There was 1 second malignant neoplasm (SMN).

Table 8 – Comparisons of rates (%) of malnutrition in children with cancer by weight-for-height (WFH) and arm anthropometry (TSFT/MUAC).

Country	Ref No.	Number of subjects	WFH	TSFT	MUAC	TSFT + MUAC
England	25	100	5	23	20	n/a
Turkey	27	62	3	30	29	27
India[a]	28	25	48[b]	48	36	n/a
Morocco	29	100	33	50	39	n/a
Malawi	30	118	17[c]	n/a	n/a	59
Current study		1787	12[d]	19	40	46

n/a, not available.
[a] ALL only.
[b] Less than 90th centile.
[c] Prevalent stunting.
[d] Only on 1044.

10% of the body weight or more may be comprised of tumour.[25] Although there are several ways to calculate IBW,[25] percent IBW[26] may both under- and over-estimate the severity of malnutrition in children with a chronic disease.[27] More generically, there may be a systematic problem in applying normative data generated in North American and Western

European populations to children in Central America who may be constitutionally of shorter stature.[13]

There are a small number of published studies in which the nutritional status of children with cancer at diagnosis has been assessed by measures based on weight and height with comparisons to arm anthropometry.[25,28–31] These are summarised in Table 8. Additionally, there were two presentations at the annual meeting of the International Society of Pediatric Oncology (SIOP) in 2008 that addressed this issue. One from Macedonia, on 45 patients, reported that measures based on weight and height did not distinguish patients from healthy controls, but MUAC and TSFT 'were significantly less than reference and control values'.[32] The other from South Africa, on 346 patients, did not report the comparison of measures of nutritional status.[33] The present study is on a number of children greater by an order of magnitude than in any of these reports and it demonstrates that arm anthropometry is a more sensitive indicator of malnutrition than a measure, BMI, based on weight and height. A strong plea has been made for the use of arm anthropometry to assess nutritional status in children with cancer.[34] Given the human health care resource restrictions in these countries, it is a remarkable accomplishment that so many of the eligible subjects had arm anthropometry and the great majority of them had additional measures of serum albumin.

Evidently, combination of measures will increase the proportion of children who are classified as malnourished, e.g. reaching almost 90% in the study from India.[29] The original AHOPCA algorithm[12] used percent IBW, weight loss, serum albumin, MUAC and TSFT (i.e. both values for arm anthropometry had to be less than pre-determined thresholds). The algorithm has evolved with progressive simplification, using arm anthropometry, from MUAC *and* TSFT to MUAC *or* TSFT failing to meet threshold values. While this increases the total proportion of patients who are malnourished and, even more, the fraction who are severely depleted, this potential over-estimation offers the prospect of effective intervention for a greater number of children; a similar argument for such liberalisation has been advanced by a group of investigators engaged in a study of more than 50,000 pre-school aged children in the impoverished Saharan country of Niger.[22]

We recognise that, in children with cancer, there are numerous causes of hypoalbuminemia.[35] These include acute and chronic inflammation/infection, severe liver or renal disease, intravascular volume overload, zinc deficiency and even the use of asparaginase. Assessment of these factors must be considered in individual patients. Although pre-albumin has been proposed as a better indicator of nutritional status, because of its shorter half-life, there are imperfections with this measure also.[11]

Although MUAC and TSFT are independent of ethnicity[19] and, unlike weight, are not influenced by large tumour masses, this study is limited by the absence of local normative data, as could be provided by corresponding arm anthropometry in siblings. Furthermore, such measures on children in the general population of developing countries, that are an essential requisite,[36] could be compared with estimates of body composition, such as are provided by dual energy X ray absorptiometry.[37,38]

Further limitations of this study relate to the various cell sizes of the study subjects. Even though the total population was large, it was also heterogeneous and cancer-related factors could not be analysed. The prevalence and severity of nutritional depletion may vary considerably by specific tumour type, e.g. within the aggregated category of solid tumours. Again there were only 25 subjects in the other 'leukaemias and MDS' category who were moderately depleted. Moreover, malnutrition may be confounded by other components of socio-economic disadvantage[3] which is linked negatively to several components of cancer control, ranging from access to care through adherence to therapy to long-term follow-up.[39]

Obesity can be considered also as a problem in countries with limited resources due to 'junk food' consumption, often a manifestation of poverty. In the setting of this study, only a small number of children were demonstrably obese. Although they were not a target of research, this issue should be kept in mind in future studies.

Most studies report a negative impact of malnutrition on the prospect for survival in children with cancer; but not all,[11] including one[10] involving subjects from a country (El Salvador) contributing to the present study. However, such a relationship has face validity, reflected in the heightened risk of infection in under-nourished patients[11] and the increased toxicity of chemotherapy in malnourished children with cancer.[40] In our study, we show a clear decreasing trend in EFS from adequately nourished to severely malnourished children. Of course it is expected that children with the greatest burden of disease will have the poorest nutritional status.

The lack of a statistically significant association between malnutrition and treatment-related mortality mirrors experience in Central America confined to children with ALL.[41] However, the association between hematologic toxicity and malnutrition is well recognised, as exemplified in a recent report from Malawi on children being treated for Burkitt lymphoma.[42]

In conclusion, it is clear that malnutrition is prevalent among children with cancer in Central America, as elsewhere in the developing world, and it can be associated with adverse oncological outcomes. Recognising that malnutrition may be only a part of socio-economic disadvantage,[3] an opportunity exists to devise simple, cost-effective nutritional interventions that will diminish the morbidity burden of under-nourishment in children with malignant disease in low income countries where most of them live, so contributing to enhanced prospects for their survival. As stated by Dr. Jan Van Eys[43] 'Nutrition should be viewed for what it is: supplying the most basic needs of children. No child has died from being fed appropriately, but many die of starvation. The practice of paediatric oncology should not add to that statistic'.

Conflict of interest statement

None declared.

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