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Nutritional status at diagnosis and its relationship with survival and relapse in Mexican children with acute lymphoblastic leukemia: a retrospective study

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Abstract

Background & aims Childhood acute lymphoblastic leukemia (ALL) is a malignancy with varying survival rates across countries with low, middle, and high income. The assessment of nutritional status (NS) using anthropometric indicators has been explored for its potential relationship on treatment outcomes. This study analyzed a 3-year retrospective cohort of Mexican pediatric patients with ALL, exploring the association between NS at diagnosis and relapse/mortality.

Methods Retrospective observational study. Medical records from 252 pediatric patients with ALL were included; anthropometric indicators (Z-scores) of body weight, height, mid-upper arm circumference (MUAC), and triceps and subscapular skinfolds (TSF and SSF, respectively) measurements were used to assess NS. The relapse/mortality data were collected from medical records. Kaplan-Meier (KM) functions and Cox regression models were performed to evaluate the effect of indicators on survival, relapse, and event (death or disease relapse).

Results Patients with malnutrition showed a significantly lower survival rate according to their BMI (76% vs 63%, $p=0.049$), while relapses were higher in the group with TSF < -2 SD (41% vs 12%, $p=0.007$). Patients with stunting and TSF < -2 SD showed a higher risk of mortality (HR:6.214, 95%CI: 1.372 to 28.154; HR:2.91, 95%CI: 1.27 to 6.68, respectively), while in patients with higher MUAC Z-score showed a decrease in the mortality risk (HR:0.85, 95%CI:0.73 to 1.00).

Conclusions The nutritional status assessed by anthropometric measurements was a strong predictor of survival and relapse outcomes 3y post/diagnosis in this cohort of pediatric patients with ALL.

Keywords ALL, Acute lymphoblastic leukemia, Childhood ALL, Survival rate, Nutritional status, BMI, body mass index

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Introduction

Acute lymphoblastic leukemia (ALL) is the most prevalent hematological malignancy (HM) among the pediatric population worldwide, accounting for approximately one third of all cancer cases in this age group [1–5]. The past decades have witnessed significant advancements in treatment strategies for pediatric ALL, leading to substantially improved survival outcomes. Current data indicates that approximately 90% of affected children in high-income countries (HIC) and approximately 50% in low- and middle-income countries (LMIC) can achieve long-term survival [3–6], regardless of the similarity between the oncological treatments used. Despite the advancements, there is a growing recognition that not all pediatric ALL patients respond uniformly to treatment. Survival outcomes remain influenced by multiple factors (e. g. age, comorbidities, treatment tolerance, ALL immunophenotype, income, adverse events), some of which are yet to be fully elucidated [1, 3–5, 7–10].

Among the determinants of pediatric patients with ALL prognoses, the nutritional status at the time of diagnosis has emerged as an area of increasing interest [7, 10–12, 6, 13–15]. Anthropometric measurements, such as body weight, height, arm circumference, and skinfold thickness provide quantifiable indicators of an individual's nutritional health and overall physiological development [6, 7, 10, 12–17]. These measurements are commonly collected at the time of diagnosis and at follow-up visits, and in this case, measurements did not increase the cost of attention, since hospital nutrition staff took part, and readily available equipment was used.

While some research showed a potential link between malnutrition and lower survival rates [7, 6, 18–20], results vary widely among cancer types and treatment approaches [7, 6, 19–21]. There is still little to no data on how nutritional status directly affects the likelihood of relapse [7, 10, 12, 17]. To elucidate the precise mechanisms and possible variations in this connection, more research is required [11, 6, 15, 17, 22–24]. Particularly in Mexico, López-Facundo et al. [18] found that in children with ALL, the presence of obesity increased the risk of relapse (Odds Ratio (OR): 3.6; CI 95%: 1.7–7.6) and death (OR: 3.4; CI 95%: 1.51–7.48) and limited survival (52%) at 77 months after diagnosis. According to data from the Mexican National Health and Nutrition Survey (ENSANUT 2023), 6.7% of children under 5 years are affected by overweight/obesity [25], while in school-age children and adolescents (5–19 years) this condition affects about 30.5 – 44.3% of the population [25]. Malnutrition (expressed as thinness and overweight/obesity) in Mexican children is exacerbated by the lack of access to nutritious foods and the high intake of processed foods and added sugars [26, 27].

In pediatric patients with ALL, non-relapse mortality (NRM) involves deaths related to treatment complications or infections [2, 28–30], and the nutritional status of these patients plays a crucial role in both treatment-related and infection-related outcomes [15, 30, 31, 7, 32, 33]. Malnourished patients experience prolonged periods of neutropenia due to chemotherapy, leading to immunosuppression and a higher risk of infections [15, 30, 7, 31–33]. Also, nutritional status has been shown to be an independent risk factor for increased NRM, including infection-related deaths [15, 30, 31, 7, 32, 33]. Both undernutrition and obesity can negatively impact immune function and the body's capacity to recover from the treatment regimens used in ALL [19, 34–36].

This retrospective study investigates the association between the nutritional status of Mexican pediatric patients with ALL at the time of diagnosis using anthropometric indicators and the 3-year (36 months) disease relapse and survival rate, treated in a low budget public hospital for low-income population without health insurance.

Methods

Study design

This is a retrospective-observational study. Patients aged 1 to 18 years with newly diagnosed ALL from 2017 to 2023 were included. As part of the hospital protocol, the initial nutritional screening was performed after the patient's diagnosis and before receiving their first inpatient chemotherapy dose. Patients were treated on the St. Jude Total XV [37] and MAS-ALL 18 [38] (Mexico in Alliance with St. Jude) protocols at the Division of Pediatric Hematology and Oncology of the Hospital Civil de Guadalajara "Dr. Juan I. Menchaca" in Mexico (a public hospital for people without health insurance and limited resources) were included. Approval of the study was granted by the Hospital's Bioethics Committee (register number: 00021). The investigators complied with applicable requirements of the declaration of Helsinki [39].

A total of 322 patients' records of the Nutrition Unit were reviewed, seventy were excluded due to incomplete anthropometric data ($n=55$) or having comorbidities ($n=15$) that altered body composition (thyroid gland disease, Down syndrome, among others), leaving a total of 252 included records.

Clinical variables/data of interest that have been reported in the literature related to survival and relapse (age at diagnosis, ALL immunophenotype, treatment protocol, survival/relapse status, white blood cells count, central nervous system infiltration, minimal residual disease at day 14, and cause of death) [40, 41] were collected from the patients' electronic medical record. Anthropometric data (weight, height, mid-upper arm

circumference, tricipital and subscapular skinfold) were extracted from the records of the Nutrition Unit to calculate the respective anthropometric indicators, as described below.

Classification and treatment

Leukemia phenotyping was used to classify patients into standard- and high-risk groups, with T-cell phenotype considered high-risk [1]. Modified St. Jude Total Therapy XV treatment protocol consisted of induction with vincristine, prednisone, daunorubicin and nine doses of L-asparaginase, cyclophosphamide, cytarabine and oral mercaptopurine followed by consolidation with high-dose methotrexate (2.5 and 5 g/m^2 dose depending on risk group) with oral mercaptopurine and 104 weeks of maintenance with a multi drug rotation of vincristine, dexamethasone, cyclophosphamide plus cytarabine, mercaptopurine and methotrexate. The standard-risk group patients received maintenance with daily oral mercaptopurine, weekly methotrexate and monthly pulses of vincristine plus prednisone. Central nervous system therapy with triple intrathecal methotrexate, cytarabine and hydrocortisone is administered weekly during induction, biweekly on consolidation, monthly on first year of maintenance and every eight weeks on second year until the end of treatment. The MAS-ALL 18 treatment consisted of similar induction with only six doses of L-asparaginase, no administration of cyclophosphamide, cytarabine and mercaptopurine. Consolidation consisted of high dose methotrexate with 2 g/m^2 in 4-h infusion for the standard-risk patients and 5 g/m^2 in 24-h for the high-risk patients group. Maintenance was administered in similar way on standard- and high-risk as Modified St. Jude Total Therapy XV. CNS (central nervous system) treatment was applied every eight weeks on maintenance but with a reduced number of doses (13 doses vs 18 when compared to Modified St. Jude Total Therapy XV).

Patients who were diagnosed and started treatment before October 2020 were treated with the Modified St. Jude Total Therapy XV, whereas the MAS-ALL 18 protocol was used for those treated at later times.

Anthropometric indicators

Body mass index (BMI/age) was calculated from weight and height using the standard formula [42]:

$$\mathrm{BMI} = \mathrm{weight}\ (\mathrm{kg})/\mathrm{height}^2\ \left(\mathrm{m}^2\right) \tag{1}$$

The World Health Organization Anthro software (WHO Anthro [43] for < 5 years and AnthroPlus [44] for ≥ 5 years) was used to calculated and classify the BMI/age, results were expressed as Z-scores [42] specific for age and sex (Supplemental Table S1) [42].

The anthropometric indicators for mid-upper arm circumference (MUAC), triceps (TSF) and subscapular skinfolds (SSF), arm muscle (AMA) and fat area (AFA) Z-scores were calculated for age and sex using reference cutoff points from healthy population (Supplemental Table S1) [45–48] (Supplemental Table S1).

The AMA and AFA were derived from TSF and MUAC measurements with the following Eqs [48]:

$$\mathrm{AMA} = (\mathrm{MUAC} - \pi \times \mathrm{TSF})^2 \div 4\pi \tag{2}$$

$$\text{Upper arm area (AA)} = (\pi \div 4) \times \mathrm{D}^2 \tag{3}$$

$$\text{Diameter (D)} = \mathrm{MUAC} \div \pi \tag{4}$$

$$\mathrm{AFA} = \mathrm{AA} - \mathrm{AMA} \tag{5}$$

Z-scores for MUAC [47], TSF, SSF, AMA, and AFA [48] were calculated using the lambda-mu-sigma (LMS) coefficients [49] that are specific to the nearest completed month or one-half year of age.

$$\mathrm{Z-score\ (SD)} = \left[\mathrm{X} \div \mathrm{M})^{\mathrm{L}} - 1\right] \div \mathrm{S} \times \mathrm{L} \tag{6}$$

X = MUAC (cm), TSF (mm), SSF (mm), AMA (cm^2), or AFA (cm^2); *S* = coefficient of variation; *L* = Box-Cox power transformation of the objective function; *M* = median for each reference data [49].

Events were defined as the presence of death or relapse of the disease.

Statistical methods

The distribution of the study variables was assessed using descriptive statistics and frequency tables. Overall survival was estimated using the Kaplan–Meier method, with the log-rank test [50]. Bivariate and Multivariate analysis were conducted using the Cox proportional hazards model [51] to estimate the death and relapse risk factors. The proportionality of the hazard ratios assumption was verified by plotting the Schoenfeld residuals against time.

For the Multivariate stepwise analysis, variables that satisfied the proportional hazard assumptions (bivariate analysis with a p-value < 0.05) [50, 51] were included in the prediction model. The cumulative survival proportion and hazard ratio (HR), with a 95% confidence interval (CI) were reported. A p-value < 0.05 was considered statistically significant. All statistical analysis were performed using SPSS Statistics for Windows, Version 25.0

(IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) [52].

Results

This retrospective study analyzed 252 medical records of pediatric patients with ALL, of whom 45.2% ($n=114$) were girls. Most patients had pre-B ALL immunophenotype (90.5%, $n=228$) and were < 120 months old at diagnosis (70.2%, $n=177$), with a median age of 67.5 months (IQR: 92.5). After 3 years of the patient's diagnosis, 14.11% ($n=35$) presented disease relapse and 32.4% ($n=79$) event (relapse or death) (Table 1).

Table 2 summarizes the anthropometric indicators at diagnosis. According to BMI, patients' nutritional status was classified as 7.5% ($n=19$) thinness, 85.3% ($n=215$) normal, and 7.1% ($n=18$) overweight/obesity The median of MUAC (Z-score) and AMA (Z-score) at diagnosis were below the recommended cut-off points for the healthy reference population (MUAC −1.41 SD, IQR: 2.44; AMA −1.19 SD, IQR: 1.89). The medians of all other anthropometric indicators (height/age, TSF, SSF and AFA Z-scores) were within the healthy range.

The Log-rank Kaplan-Meier test was performed to assess the variables that influenced survival (Table 3), disease relapse (Supplemental Table S2), and event (Supplemental Table S3) at 36 months from diagnosis. The overall survival rate at 36 months post-diagnosis was 74%, indicating that nearly three-quarters of the patient cohort remained alive three years after receiving the initial diagnosis. Age at diagnosis (≥ 120 months), immunophenotype (T-cell), disease relapse, and malnutrition categorized by BMI/age were associated with lower survival ($p<0.05$) (Table 3 and Fig. 1). The CNS-3 status has been reported as a clinically relevant variable in the prognosis of pediatric patients with ALL [9, 24, 53–57]. Despite not reaching statistical significance in this study ($p=0.050$). From a clinical and biological perspective, CNS involvement in ALL is a marker of more aggressive disease, as leukemic infiltration into the central nervous system (CNS) may create an anatomical and physiological barrier that limits the efficacy of systemic treatments [9, 24, 53–57].

For the relapse analysis (Supplemental Table S2), CNS-3 status and a TSF Z-score <−2 SD showed higher disease relapse ($p<0.05$) (Supplemental Table S2). Furthermore, the age at diagnosis (≥ 120 months) and CNS-3 status group were associated with higher ($p<0.05$) event proportion at 36 months (Supplemental Table S3).

The bivariate Cox regression analysis was performed to assess the variables that influenced the risk of death, disease relapse, and event (Table 4) at 36 months from diagnosis. The age at diagnosis (≥ 120 months) (Hazard Ratio (HR): 3.21, 95%CI: 1.96 to 5.24, $p<0.001$), disease

Table 1 Patient characteristics

Patient characteristics	Median (IQR)	% (n)
Sex		
Male		54.8% (138)
Female		45.2% (114)
Age (months) at diagnosis		
< 120	67.5 (92.5)	70.2% (177)
≥ 120		29.8% (75)
WBC (cells/μL) at diagnosis		
< 50 000		74.3% (107)
≥ 50 000		25.7% (37)
CNS-3 at diagnosis		
Yes		6.5% (16)
No		93.5% (230)
Remission day		
≤ 14		88.4% (168)
> 14		11.6% (22)
MRD		
≥ 0.01%		10.2% (18)
< 0.01%		89.8% (159)
Relapse at 36 months		
Yes		14.1% (35)
No		85.9% (213)
Relapse site		
BM		68.6% (24)
CNS		14.3% (5)
Mixed		17.1% (6)
ALL Immunophenotype		
Pre-B		90.5% (228)
T		9.5% (24)
Treatment protocol		
TOTAL XV		69.8% (176)
MAS-ALL		30.2% (76)
Status at 36 months from diagnosis		
Survival		73.8% (180)
Death		26.2% (64)
Causes of death		
Septic shock		54.7% (35)
Neutropenic colitis		14.1% (9)
Other (pancreatitis, intracranial hemorrhage, pulmonary hemorrhage, multiple organ failure)		31.2% (20)
Event at 36 months (relapse or death)		
Yes		32.4% (79)
No		67.6% (165)

IQR Interquartile range, *WBC* White blood cells, *CNS-3* Central nervous system (WBC count is ≥ 5/mL with blasts in the cerebrospinal fluid), *MRD* Minimal residual disease at day 14 (% leukemic cells detected), *BM* Bone marrow, *ALL* Acute lymphoblastic leukemia

Table 2 Anthropometric indicators at diagnosis

Patient characteristics	Median (IQR)	% ($n = 192$)
Height/age (Z-score)	-0.31 (1.39)	
Severely stunted (< -3)		1.2% (3)
Stunted (≥ -3 to < -2)		2.4% (6)
Normal (≥ -2)		96.4% (243)
Stunted		
Yes (< -2)		3.6% (9)
No (≥ -2)		96.4% (243)
BMI/age (Z-score)	-0.24 (1.81)	
Thinness (< -2)		7.5% (19)
Normal (≥ -2 to < +2)		85.3% (215)
Overweight and obese (≥ +2)		7.1% (18)
Malnutrition		
Yes (< -2, ≥ +2)		14.7% (37)
No (≥ -2 to < +2)		85.3% (215)
MUAC/age (Z-score)	-1.41 (2.44)	
Normal (≥ -1)		41.6% (104)
Mild malnutrition (≥ -2 to < -1)		20.8% (52)
Moderate malnutrition (≥ -3 to < -2)		20.4% (51)
Severe malnutrition (< -3)		17.2% (43)
Malnutrition		
Yes (< -1)		58.4% (146)
No (≥ -1)		41.6% (104)
TSF/age (Z-score)	-0.74 (1.37)	
Decreased subcutaneous fat (< -2)		7% (17)
Normal (≥ -2 to < +2)		90.9% (220)
Increased subcutaneous fat (≥ +2)		2% (5)
SSF/age (Z-score)	-0.55 (1.45)	
Decreased subcutaneous fat (< -2)		5.5% (13)
Normal (≥ -2 to < +2)		92.8% (218)
Increased subcutaneous fat (≥ +2)		1.7% (4)
AMA/age (Z-score)	-1.19 (1.67)	54.8% (132)
Decreased (< -1)		45.2% (109)
Normal No (≥ -1)		
AFA/age (Z-score)	-0.97 (1.83)	48.1% (116)
Decreased (< -1)		51.9% (125)
Normal (≥ -1)		

BMI Body mass index, *MUAC* Mid-upper arm circumference, *TSF* Triceps skinfold, *SSF* Subscapular skinfold, *AMA* Arm muscle area, *AFA* Arm fat area

relapse (HR: 2.33, 95%CI: 1.36 to 3.98, $p=0.002$) and T-cell ALL immunophenotype (HR: 1.97, 95%CI: 1.01 to 3.87, $p=0.049$) showed an increased risk of mortality at 36 months after the diagnosis of ALL. Furthermore, the patients' higher MUAC (Z-score) at diagnosis showed a decrease in the risk of relapse (HR: 0.85, 95%CI: 0.73 to 1.00, $p=0.049$), while the patients' group with a decreased TSF (<−2 SD) was associated with a higher risk of disease relapse (HR: 2.91, 95%CI: 1.27 to 6.68, $p=0.012$) (Table 4). The children diagnosed at ≥120 months showed an increased event risk (HR: 2.39, 95%CI: 1.53 to 3.72, $p<0.001$).

To assess the association between each of the variables and the survival time, disease relapse, and event, a multivariate Cox regression analysis was performed with the forward stepwise selection method (Table 5). The presence of disease relapse and H/A (<−2SD) increased the risk of death. A CNS-3 status and minimal residual disease (MRD) at day 14 (≥0.01% leukemic cells detected in bone marrow) showed an increased risk for relapse, while a higher MUAC Z-score was associated with a decreased risk of relapse. Furthermore, CNS-3 status increased the risk of event, while a higher BMI Z-score reduced the risk of event.

Discussion

A retrospective cohort of 252 Mexican pediatric patients with ALL with a low socioeconomic status and without health insurance was analyzed to obtain a comprehensive understanding of the patient characteristics and factors that could influence survival and disease relapse. Our results show that the age at diagnosis (≥120 months), immunophenotype (T-cell), minimal residual disease (MRD) with ≥0.01% leukemic cells, and disease relapse were significantly associated with lower survival rates, higher risk of death and of presenting an event, all of which have been previously reported in the literature, highlighting the crucial role of these variables [4, 9, 24, 53–59]. In this study, the analyzed population showed a 3-year survival rate of 74%, which is lower than the average reported in HIC (80–90%) [3–5, 60–62] but higher than observed in LMIC (40–60%) [3, 30, 63–65].

The results of the present study showed a significant association ($p<0.05$) between anthropometric indicators at diagnosis and survival, as well as risk of relapse, contrary to the report by earlier studies [11, 6, 13, 15–17, 23]. Survival rate was lower for children who were malnourished according to their BMI/age (Table 3 and Fig. 1), while a significant increased risk of mortality was found for patients with stunting (H/A <−2SD group) (Table 5). Patients with a TSF <−2 SD at diagnosis presented a higher risk for relapses (Table 2), and those with a higher Z-score for MUAC showed a reduction in the risk of relapse (Table 5).

Adipose tissue plays a crucial role in regulating inflammation and immune responses [66, 67]. An altered (increase or decrease) fat mass may worsen the side effects of chemotherapy, increase susceptibility to infections, and hinder recovery, thereby elevating the risk of relapse [66, 67]. TSF is commonly used as a proxy for subcutaneous fat reserves, and a decrease in TSF may indicate depleted fat stores [48, 66, 67]. Furthermore, TSF is a cost-effective and easily applicable measurement

Table 3 Log-rank Kaplan-Meier test for survival at 36 months from diagnosis

Variable	(n)	Cumulative survival proportion	Mean survival (95% CI)	*p*-value
Overall survival	244	0.74	29.3 (27.7 to 30.9)	N/A
Event survival	244	0.68	28.9 (27.3 to 30.6)	
Age at diagnosis (months)				
< 120	174	0.83	31.6 (29.9 to 33.3)	< 0.000*
≥ 120	70	0.51	23.7 (20.1 to 27.3)	
CNS-3				
Yes	16	0.56	23.3 (15.8 to 30.8)	0.050
No	228	0.75	29.7 (28.1 to 31.4)	
Immunophenotype				
Pre-B	220	0.76	29.7 (28.1 to 31.4)	0.041*
T	24	0.58	25.2 (18.6 to 31.8)	
Treatment protocol				
TOTAL XV	172	0.69	28.5 (26.5 to 30.5)	0.213
MAS-ALL	72	0.86	27.2 (25.1 to 29.4)	
WBC (cells/μL)				
< 50 000	107	0.77	29.3 (26.9 to 31.8)	0.113
≥ 50 000	37	0.62	29.4 (25.3 to 33.5)	
MRD				
≥ 0.01%	18	0.61	29.2 (23.5 to 34.9)	0.111
< 0.01%	159	0.79	30.8 (28.9 to 32.6)	
Relapse				
No	210	0.79	29.3 (27.5 to 31.1)	0.001*
Yes	34	0.44	30.2 (26.9 to 33.5)	
Remission day				
≤ 14	168	0.83	32.5 (31.1 to 33.9)	0.197
> 14	22	0.73	31.8 (27.6 to 35.9)	
Sex				
Female	112	0.73	28.7 (26.2 to 31.2)	0.703
Male	132	0.74	29.9 (27.7 to 30.9)	
Height/age				
Stunted (< −2)	9	0.78	27.9 (18.4 to 37.4)	0.799
Normal (≥ −2)	235	0.74	29.4 (27.7 to 31.1)	
BMI/age (Z-score)				
Thinness (< −2)	18	0.61	25.5 (17.9 to 33.1)	0.145
Normal (≥ −2 to < + 2)	209	0.76	29.9 (28.3 to 31.7)	
Overweight/Obese (≥ + 2)	17	0.65	25.2 (17.8 to 32.7)	
Malnutrition				
Yes (< −2, ≥ + 2)	35	0.63	25.4 (20.1 to 30.7)	0.049*
No (≥ −2 to < + 2)	209	0.76	29.9 (28.3 to 31.7)	
MUAC/age (Z-score)				
Malnutrition (< −1 Z)	142	0.76	30.2 (28.3 to 32.2)	0.395
Normal (≥ −1 Z)	100	0.70	27.9 (25.1 to 30.7)	
TSF/age (Z-score)				
Decreased subcutaneous fat (< -2)	17	0.71	32.4 (27.8 to 36.9)	0.932
Normal (≥ -2)	218	0.74	29.3 (27.6 to 31.1)	
SSF/age (Z-score)				
Decreased subcutaneous fat (< −2)	13	0.92	35.4 (34.4 to 36.5)	0.153
Normal (≥ −2)	215	0.73	28.9 (27.7 to 31.1)	

Table 3 (continued)

Variable	(n)	Cumulative survival proportion	Mean survival (95% CI)	*p*-value
AMA/age (Z-score)				
Decreased (< −1)	129	0.76	30.7 (28.6 to 32.7)	0.462
Normal (≥ −1)	105	0.71	28.1 (25.4 to 30.6)	
AFA/age (Z-score)				
Decreased (< −1)	114	0.76	29.7 (27.3 to 32.1)	0.615
Normal (≥−1)	120	0.72	29.3 (26.9 to 31.6)	

CI Confidence interval, *CNS-3* Central nervous system (WBC count is ≥ 5/mL with blasts in the cerebrospinal fluid), *WBC* White blood cells, *MRD* Minimal residual disease at day 14 (% leukemic cells detected), *MUAC* Mid-upper arm circumference, *BMI* Body mass index, *TSF* Triceps skinfold, *SSF* Subscapular skinfold, *AMA* Arm muscle area, *AFA* Arm fat area

* *p*-value < 0.05

in routine clinical practice, providing valuable information about nutritional status and body composition [48, 66, 67]. It also enables monitoring changes over time and allows for the adjustment of medical-nutritional interventions [48, 66, 67].

The prevalence of overweight/obesity of 7.1% (median age of 67.5 months) observed in our study population is within the range reported for the Mexican pediatric population from 5 to 19 years (6.7 – 44.3%) [25], but lower than the average of the global pediatric population of 8.5% [68]. As reported in previous studies [1–3, 8, 9, 24, 54–56, 59], our results confirm the association of a higher BMI Z score at diagnosis and a lower the risk for adverse events (like death or disease relapse) during the first three years (Table 5). The prevalence of stunting (3.6%, $n=9$) was lower than reported for the Mexican pediatric population (16.2%) [25]. However, a higher prevalence of thinness was found (7.5%) compared to the national average (3.5%) [25], which could be related to the adverse effects/symptoms (e.g. fever, persistent fatigue, weakness, frequent infections, unintentional weight loss) that occur prior to diagnosis [12, 30, 69–73], leading to acute weight loss [51].

Malnutrition is associated with increased mortality. This relationship is multifaceted, encompassing impaired immune function (low BMI and lean body mass increase the susceptibility to infections), reduced tolerance to chemotherapy (less capacity to metabolize drugs/treatments, higher risk of side effects, and organ dysfunction such as liver and kidney damage), and compromised recovery (prolonged neutropenia, compromised wound healing, and prolonged tissue recovery) [17, 23, 28, 74].. On the other hand, an increased body fat has also been linked to these side-effects, therefore, body fat may play a dual role in pediatric patients with ALL and their tolerance/response to treatment [17, 28, 74, 23]. Thus, it is crucial to monitor the nutritional status closely, especially as Mexico is experiencing a rapid rise in childhood obesity due to factors like urbanization, dietary changes, and reduced physical activity [27, 51].

In our study we reported a high prevalence of malnutrition (58.4%) identified by MUAC (according to the cut-off points recommended by the WHO and the cited authors) [42–44, 47, 68, 75]. This significantly exceeds the global target of MUAC malnutrition prevalence below 5% [42]. The MUAC measurement holds relevance in pediatric oncology [13, 14, 16, 46], especially in the context of patients upon hospital admission [76]. Relying exclusively on weight-based values for nutritional assessment can be misleading, given the fluid dynamics and possible changes in body weight resulting from intravenous fluid delivery, organomegaly and tumor masses [11, 77, 78]. The MUAC measurement has been considered an economical, low-cost, and non-invasive approach [76]. The International Society of Pediatric Oncology (SIOP) recommends MUAC to assess nutritional status in children with cancer, as it is reliable and unaffected by tumor mass, giving an objective evaluation of lean tissue mass, regardless of fluid condition [13, 14]. It reduces confounding effects, allowing a more accurate assessment of nutritional status in pediatric patients with ALL [13, 14, 76].

Furthermore, the high prevalence of low arm muscle area (54.8%) and arm fat area (48.1%) reported in our patients are alarming. This could be linked to deficiencies in both protein and overall energy intake, leading to muscle wasting [79–81] and insufficient fat reserves [3, 66, 67]. Also, the onset and progression of ALL are typically followed by a series of inflammatory reactions in the body, which are mediated by numerous cytokines and immune cells [1, 82–85]. These inflammatory mechanisms not only contribute to the pathogenesis of the disease but also have a significant impact on the host's metabolic environment [1, 82–85]. One prominent outcome is a shift in body composition, which is characterized by a decrease in muscle mass [30, 86–91].

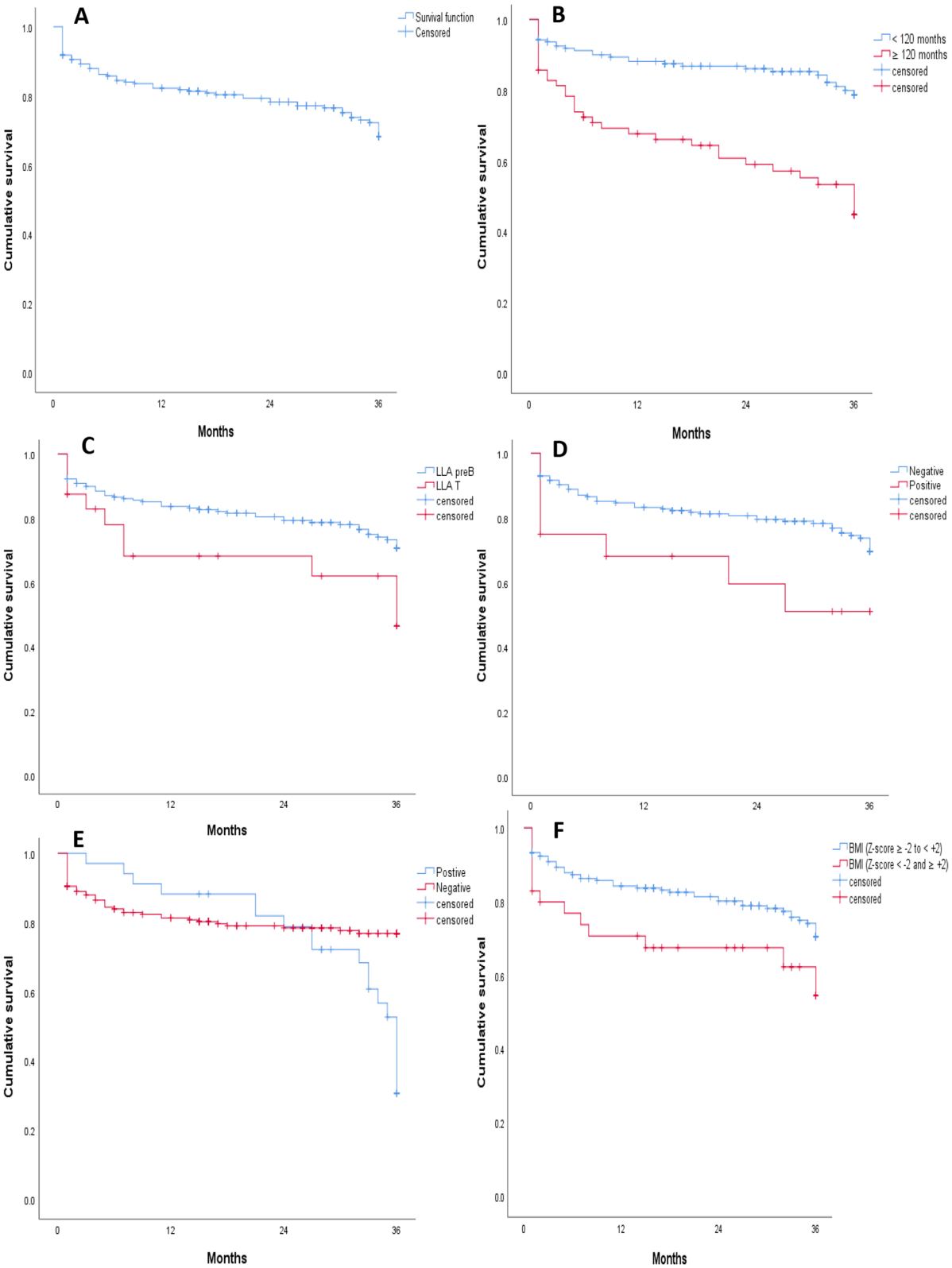

Fig. 1 Childhood cancer survival, according to **A**) Overall survival, **B**) Age at diagnosis, **C**) Immunophenotype, **D**) CNS-3, **E**) Relapse, and **F**) BMI. CNS-3: central nervous system; BMI: body mass index. The "X" axis represents time in months from diagnosis, and the "Y" axis represents the estimated survival proportion

Table 4 Bivariate Cox regression analysis of independent variables affecting 36 months survival, relapse, and event

Variables	Survival		Event		
	B	Hazard ratio (95% CI)	B	Hazard ratio (95% CI)	B	Hazard ratio (95% CI)
Age at diagnosis (months) ≥ 120 Age at diagnosis (months)	1.165 0.008	3.21 (1.96 to 5.24)* 1.01 (1.01 to 1.01)*	0.352 0.001	0.34 (0.69 to 2.92) 1.01 (0.99 to 1.01)	0.869 0.006	2.39 (1.53 to 3.72)* 1.01 (1.00 to 1.01)*
MUAC (Z-score) MUAC (< -1 Z-score)	0.060 0.210	1.06 (0.92 to 1.22) 1.23 (0.75 to 2.01)	-0.159 0.137	0.85 (0.73 to 1.00) 1.15 (0.58 to 2.26)*	0.062 -0.130	1.03 (0.91 to 1.16) 0.88 (0.56 to 1.37)
H/A (Z-score) H/A (< -2 Z-score)	-0.012 0.180	0.99 (0.79 to 1.23) 1.19 (0.29 to 4.91)	0.043 -3.028	1.04 (0.75 to 1.45) 1.19 (0.29 to 4.91)	-0.008 0.059	0.99 (0.81 to 1.21) 1.06 (0.26 to 4.33)
BMI (Z-score) BMI (< -2, ≥ +2 Z-score)	-0.052 0.593	0.95 (0.79 to 1.13) 1.81 (0.98 to 3.33)	-0.097 0.172	0.91 (0.71 to 1.17) 1.19 (0.42 to 3.38)	-0.067 0.471	0.94 (0.80 to 1.10) 1.60 (0.90 to 2.86)
SSF (Z-score) SSF (< -2 Z-score)	0.140 -1.32	1.15 (0.92 to 1.43) 0.27 (0.37 to 1.93)	0.020 0.029	1.02 (0.76 to 1.37) 1.03 (0.25 to 4.31)	0.116 -0.845	1.12 (0.92 to 1.38) 0.43 (0.11 to 1.75)
TSF (Z-score) TSF (< -2 Z-score)	0.070 0.039	1.07 (0.87 to 1.32) 1.04 (0.42 to 2.60)	-0.155 1.067	0.86 (0.69 to 1.01) 2.91 (1.27 to 6.68)*	0.004 0.308	1.00 (0.84 to 1.20) 1.36 (0.65 to 2.83)
AMA (Z-score) AMA (< -1 Z-score)	0.043 -0.185	1.04 (0.88 to 1.23) 0.83 (0.50 to 1.37)	-0.096 0.514	0.91 (0.75 to 1.10) 1.67 (0.82 to 3.43)	0.039 -0.114	1.04 (0.90 to 1.21) 0.89 (0.57 to 1.40)
AFA (Zscore) AFA (< -1 Z-score)	0.086 -0.128	1.09 (0.91 to 1.31) 0.88 (0.53 to 1.46)	-0.140 0.180	0.87 (0.70 to 1.09) 1.20 (0.61 to 2.35)	0.020 -0.037	1.02 (0.87 to 1.20) 0.96 (0.61 to 1.51)
CNS-3 status	0.753	2.12 (0.97 to 4.66)	1.006	2.74 (0.96 to 7.77)	0.703	2.02 (0.97 to 4.19)
WBC (≥50 000 cells/μL)	0.513	1.67 (0.87 to 3.21)	0.642	1.90 (0.79 to 4.59)	0.240	1.27 (0.68 to 2.38)
Relapse (Yes)	0.844	2.33 (1.36 to 3.98)*	-	-	-	-
MRD (< 0.01%)	-0.643	0.53 (0.23 to 1.19)	-0.610	0.54 (0.19 to 1.58)	-0.367	0.69 (0.31 to 1.54)
Remission (≥14 day)	0.570	1.77 (0.73 to 4.27)	0.378	1.46 (0.50 to 4.22)	0.220	1.25 (0.53 to 2.94)
Sex (Female)	0.094	1.01 (0.67 to 1.79)	-0.604	0.55 (0.26 to 1.14)	0.000	1.00 (0.64 to 1.56)
Immunophenotype (T-ALL)	0.679	1.97 (1.01 to 3.87)*	0.414	1.51 (0.53 to 4.29)	0.445	1.56 (0.80 to 3.03)
Treatment protocol (Total XV)	0.428	1.54 (0.77 to 3.07)	-0.997	0.37 (0.12 to 1.15)	0.057	1.06 (0.58 to 1.95)

CI confidence interval, *MUAC* mid-upper arm circumference, *BMI* body mass index, *TSF* triceps skinfold, *SSF* subscapular skinfold, *AMA* arm muscle area, *CNS-3* central nervous system (WBC count is ≥ 5/mL with blasts in the cerebrospinal fluid), *WBC* white blood cells, *MRD* minimal residual disease at day 14 (% leukemic cells detected)

*: *p*-value <0.05

Pro-inflammatory cytokines like IL-6 and TNF-α regulate catabolic pathways that increase muscle protein breakdown and suppress adipogenesis [1, 82–85]. Furthermore, disruption of insulin-like growth factor-1 signaling (a major regulator of muscle growth and maintenance) worsens muscle wasting in the context of ALL-related inflammation [1, 82–85]. Fat metabolic changes accompany muscle loss, defined by increased lipolysis and decreased adipocyte development, resulting in adipose tissue depletion [30, 86–91].

Our results highlight the role of nutritional status at diagnosis and its relationship to survival and disease relapse in Mexican pediatric patients with ALL. While the impact of nutritional status by anthropometric indicators on the feasibility and tolerability of treatment regimens has been reported in some studies [7, 10, 6, 11, 12, 15, 16, 22–24], the association with survival outcomes needs further consideration of other variables, including genetic, environmental, treatment, and illness-related parameters such as changes in body composition throughout the disease and after the treatment completion.

The difference in clinical outcomes when compared with HIC may be due to the influence of contextual factors on pediatric ALL outcomes [4, 5, 8, 9, 59, 92], such as limited access to advanced therapies, supportive care, and the potential impact of socio-economic factors on treatment adherence and follow-up care [4, 5, 8, 9, 38, 76], which have been reported previously [2–5, 24, 53, 56, 60–62].

Table 5 Multivariate Cox regression analysis of independent variables affecting 36 months survival, relapse, and event

Survival					Relapse				Event			
Variable		**B**	**SE**	**Hazard ratio (95% CI)**	**Variable**	**B**	**SE**	**Hazard ratio (95% CI)**	**Variable**	**B**	**SE**	**Hazard ratio (95% CI)**
Step 1	Relapse	1.49	0.41	4.43 (1.98 to 9.90)*	CNS-3	3.11	0.89	22.4 (3.94 to 127.8)*	CNS-3	1.16	0.76	4.81 (1.09 to 21.3)*
Step 2	Relapse	1.63	0.43	5.09 (2.20 to 11.8)*	CNS-3	3.27	0.89	26.3 (4.54 to 152.5)*	CNS-3	1.66	0.76	5.26 (1.18 to 23.4)*
	H/A (<−2 Z)	1.83	0.77	6.21 (1.37 to 28.2)*	MRD	1.12	0.57	3.06 (0.99 to 9.40)	BMI/age (Z-score)	−0.28	0.12	0.76 (0.59 to 0.96)*
Step 3	-	-	-	-	CNS-3	3.38	0.91	29.4 (4.99 to 173.2)*	-	-	-	-
	-	-	-	-	MRD	1.39	0.60	4.04 (1.24 to 13.1)	-	-	-	-
	-	-	-	-	MUAC/age (Z-score)	−0.20	0.10	0.815 (0.67 to 0.99)	-	-	-	-

CI Confidence interval, *H/A* height/age, *CNS-3* central nervous system, *MRD* Minimal residual disease at day 14 (≥ 0.01% leukemic cells detected), *MUAC* Mid-upper arm circumference, *BMI* Body mass index

*p-value < 0.05

Several studies in HIC have reported associations between nutritional status and treatment outcomes in pediatric patients with cancer, emphasizing the importance of personalized nutritional interventions [4, 5, 7–9, 6, 12, 17, 22, 23, 59, 92]. Investigations should not only focus on the diagnosis of nutritional status by anthropometric indicators, but it is also necessary to elucidate the relevance of body composition (specifically, the fat and fat-free mass) [67, 71, 86–90, 93] at the time of diagnosis and trough treatment on survival and the risk of relapse in patients with ALL [49, 54, 67, 72–75, 77, 78].

In Mexico, the survival rate of pediatric oncology patients varies significantly (43.7 to 74.7%, 5-year survival rate) between different health care centers [60, 62]. Particularly in our public hospital in Guadalajara, the reported survival rates are higher than the national average (61.8%, 5-year survival rate) [60, 62]. This difference could be related to the coordinated work of a multidisciplinary team made up of oncologists, hematologists, dietitians, psychologists and other specialists, providing complete and personalized treatment to each patient. However, even with this effort, survival rates of HIC have not been reached.

Additionally, it is important to consider the type of population evaluated in this study and the factors that may contribute to survival. The patients analyzed in this study come from uninsured households with limited access to healthy food in quantity and quality, many may have had nutritional deficiencies at the time of diagnosis, which probably affected their body composition and nutrient status, which have been reported to have implications on treatment tolerance and recovery [10, 12, 13, 6, 7, 11, 15, 19, 30, 65, 69, 77, 79, 94–97]. Factors such as treatment abandonment, lack of access to medications, and economic and social barriers also play a crucial role in the survival of these patients [3, 19, 34, 54, 64, 67, 98, 99]. Understanding and addressing these problematic situations is essential to design strategies to improve the quality of treatment and increase survival rates in the pediatric ALL population.

It's crucial to acknowledge the limitations of our study, including the retrospective nature, the reliance on traditional anthropometric measurements, and that the anthropometric evaluations were made by different members of the nutrition unit over time. Additionally, the time range of one month after diagnosis should be considered when patients were evaluated, which may mean that some already received treatment in the outpatient clinic (prednisone). However, regarding the administration of prednisone, effects on body composition and weight have been reported until after one month of treatment [100, 74, 67, 101].

Limited information was available through hard-copy and electronic medical records regarding NRM, thus, exploring the association between nutritional status and infection-related mortality was not possible. Furthermore, in developing countries, the lack of reagents to perform tests on variables of interest is a consistent problematic. In addition, the transition from physical to electronic records can sometimes lead to the loss of documents or information in data records, which makes it difficult to collect information in retrospective studies. Designing and implementing a systematic operating procedure for data collection and registry in medical records is strongly recommended, especially for hospitals where hard-copy records are used.

In addition to the information discussed, the authors recommend the systematic evaluation in routine clinical nutrition practice suggested by the Pan American Health Organization in pediatric patients with cancer [95]. The evaluation should include anthropometric measurements like height, weight, TSF, MUAC, and WC, and body composition analysis when feasible using bioelectrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DXA) [30, 67, 71, 86–88, 90, 102, 103]. Additionally, biochemical exams should be conducted to evaluate liver and renal function, lipid and glucose profiles, serum protein concentrations, and micronutrient levels. Dietary intake assessments, including both macronutrient and micronutrient intake as well as dietary patterns, are also relevant to identify changes in food consumption. Incorporating these assessments into routine clinical practice can enhance the monitoring of relapse risk and improve survival outcomes in pediatric patients with ALL. By identifying and addressing nutritional deficiencies early in the treatment process, healthcare professionals can implement timely interventions that may reduce the risk of complications and positively influence long-term prognosis. Furthermore, the implementation of standardized evaluation techniques ensures consistency and efficiency in the data documentation, enables better comparisons across studies and contributes to the creation of evidence-based guidelines for nutritional management in cancer.

In conclusion, our study enhances the understanding of childhood ALL in the Mexican population, emphasizing the influence of the age at diagnosis, the immunophenotype, MRD, disease relapse, BMI, MUAC, and TSF as significant variables for survival and relapse. The discrepancy between the results reported worldwide regarding the relationship of anthropometric indicators with survival and relapse needs to be investigated in greater depth at the time of diagnosis, during and after treatment; in addition to using techniques to measure body composition (deuterium dilution, body volume/BOD POD, dual x-ray absorptiometry/DXA) that evaluate more sensitive parameters, such as total body water, fat mass, fat-free mass, and bone mineral content.

Abbreviations

ALL	Acute lymphoblastic leukemia
NS	Nutritional status
BMI	Body mass index
MUAC	Mid upper arm circumference
TSF	Triceps skinfold
SSF	Subscapular skinfold
AMA	Upper arm muscle area
AFA	Arm fat area
CNS	Central nervous system
MRD	Minimal residual disease
BM	Bone marrow
HIC	High-income countries
LMIC	Low- and middle-income countries
WBC	White blood cells

Supplementary Information

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Supplementary Material 1. Table S1 Anthropometric indicators classification (Z-score).

Supplementary Material 2. Table S2 Log-rank Kaplan-Meier test for relapse at 36 months from diagnosis.

Supplementary Material 3. Table S3 Log-rank Kaplan-Meier test for event at 36 months from diagnosis.

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Authors'contributions
The authors' responsibilities were as follow: AEGL collected the information, performed the database creation and data analysis, and wrote the manuscript; KS, VLT, HR, ECT, and SG supervised, wrote, and edited the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was evaluated and approved by the Research and Ethics Committee of the Civil Hospital of Guadalajara "Dr. Juan I. Menchaca" (Comité de ética en investigación del Hospital Civil de Guadalajara "Dr. Juan I. Menchaca" / CONBIOETICA-14-CEI-008-20161212) with the register number 00021. The requirement for informed consent was waived due to the retrospective nature of the study and the use of anonymized data. The study was also registered and approved by the Jalisco State Health Secretary (register number: 0410/20HCJIM/2020).
The investigators complied with applicable requirements of the declaration of Helsinki [39].

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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