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Original Article

Long-Term Complications in Pediatric Leukemia Survivors: A Cross-Sectional Study

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Abstract

Background: Survival rates for pediatric leukemia have improved dramatically with advances in medical care. However, long-term complications may develop after treatment and adversely affect survivors' quality of life. This study aimed to evaluate long-term complications in children who had recovered from leukemia.

Methods: In this cross-sectional study, 115 children with leukemia who had completed treatment at least one year prior to enrollment were evaluated. Comprehensive assessments included laboratory tests, imaging studies, bone density measurements, and hormonal evaluations.

Results: Among the 115 survivors (62.6% boys), significant long-term complications were identified across multiple organ systems. Overall, 57% of participants had at least one abnormal finding among the evaluated systems. Endocrine dysfunction was the most common abnormality, detected in nearly half of the patients. Low bone mass was observed in 23.1% (15/65) of the assessed patients. More than half of the participants (53%) had vitamin D deficiency. Thyroid dysfunction occurred in 6.1% of patients (six with hypothyroidism and one with hyperthyroidism). One patient had diabetes mellitus, and 12 patients (10.4%) had abnormal lipid profiles. Pituitary dysfunction was observed in 8.7% (10/115) of patients. Psychiatric disorders and learning disabilities were identified in 19 patients (16.5%). Eight patients (8.4%) had transfusion-related iron overload. Multivariable logistic regression analysis showed that serum ferritin >200 ng/mL was associated with a higher risk of low bone mass (odds ratio: 14.2, 95% CI: 1.1–178.8, P = 0.039).

Conclusion: Long-term complications are common among pediatric leukemia survivors, particularly affecting bone health, endocrine function, and cognitive or learning abilities. Systematic surveillance and early intervention are essential to optimize long-term outcomes and quality of life.

Keywords:

Leukemia
Pediatric
Long-term complications
Survivors

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1. INTRODUCTION

Leukemia is the most common pediatric malignancy, accounting for approximately 30% of all childhood cancers (1, 2). Advances in risk-adapted chemotherapy and supportive care have improved 5 years overall survival (OS) rates to >90% for acute lymphoblastic leukemia (ALL) and 65–70% for acute myeloid leukemia (AML) in developed countries (3, 4). Similar improvements have been observed in developing countries such as Iran, where 8 years OS rates of 81% and 63.5% have been reported for pediatric ALL and AML, respectively (5). Consequently, there is a rapidly growing population of childhood cancer survivors, estimated at over 500,000 in the United States alone (6). With this increase, considerable attention has shifted to the burden of long-term treatment-related complications that may impair quality of life.

1.1. The burden of late effects

Survivors of pediatric cancers have substantially higher risks of chronic health conditions compared with the general population, with more than 95% developing at least one chronic complication and 80% experiencing severe or life-threatening conditions by age 45 (7, 8). Late effects arise from chemotherapy-and radiotherapy-related damage to multiple organ systems and may manifest years after completion of therapy. Key complications include cardiomyopathy and heart failure following anthracycline exposure or chest irradiation; growth hormone deficiency, thyroid disorders, and metabolic syndrome; low bone mass (LBM) and increased fracture risk; cognitive impairment and academic difficulties; gonadal dysfunction and infertility, particularly after treatment with alkylating agents or pelvic irradiation; as well as depression, anxiety, and reduced health related quality of life (9-15).

1.2. Bone health in pediatric leukemia survivors

Bone health is a major concern, as childhood and adolescence are critical periods for peak bone mass acquisition. Antileukemic treatment may disrupt this process through direct effects on bone cells, glucocorticoid-induced bone loss, endocrine dysfunction, nutritional deficiencies, and physical inactivity. Several studies have demonstrated significantly lower bone mineral density (BMD) Z scores in survivors compared with healthy controls, with increased risk of persistent deficits and fractures extending into adulthood (16-18).

1.3. Endocrine, genitourinary, and other key late effects

Endocrine disorders—including thyroid, pituitary, and gonadal dysfunction—are highly prevalent and may adversely affect growth, pubertal development, metabolism, and fertility (19). Genitourinary complications, such as gonadal failure and structural abnormalities, can also occur following chemotherapy or radiotherapy and require long term surveillance (11, 20). In addition, neurocognitive, psychosocial, and cardiometabolic late effects collectively contribute to the overall morbidity burden in this population.

1.4. Gaps in knowledge and the Iranian context

Despite robust data from industrialized countries, comprehensive regional evidence, particularly from low- and middle-income settings such as Iran, remains limited. Differences in treatment protocols, genetic background, environmental exposures, healthcare infrastructure, and cultural factors underscore the need for locally relevant data. In Iran, while risk factors for childhood leukemia have been investigated (21), information regarding the prevalence, patterns, and determinants of long-term complications among pediatric leukemia survivors is still scarce.

1.5. Study objectives

- Primary objective: To determine the prevalence and patterns of long-term complications across different organ systems in Iranian pediatric leukemia survivors, with a particular focus on detailed evaluation of bone health.
- Secondary objective: To identify clinical and treatment-related variables associated with these complications.

2. MATERIALS AND METHODS

This cross-sectional study was conducted in a tertiary outpatient oncology clinic in Shiraz, Iran, in 2025. Patients with a confirmed diagnosis of acute leukemia who had completed therapy at least 12 months prior to enrolment were included. All patients were examined by a pediatric oncologist. Medical files were reviewed, and demographic and paraclinical data were collected. Demographic variables included age at diagnosis, sex, type of leukemia, body mass index (BMI), and duration off-therapy. Clinical and paraclinical evidence of organ dysfunction—including cardiac, genitourinary, gastrointestinal, endocrine, and neuropsychiatric abnormalities—was systematically evaluated. All assessments had been performed within the

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preceding 6 months. When necessary, patients or their caregivers were contacted to complete missing evaluations.

2.1. Cardiac assessment

All patients were evaluated by a pediatric cardiologist for clinical signs of congestive heart failure. Electrocardiography and echocardiography findings were reviewed for dysrhythmias, systolic or diastolic dysfunction, and moderate to severe valvular abnormalities, compared with baseline (pre-treatment) studies.

2.2. Genitourinary assessment

Evaluations included blood urea nitrogen, serum creatinine, sodium, potassium, and uric acid levels; urinalysis; kidney and urinary bladder (KUB) ultrasonography; and testicular ultrasonography. Glomerular filtration rate (GFR) was calculated using the modified Schwartz formula:

GFR (mL/min/1.73 m^2) = 0.413 × height (cm) / serum creatinine (mg/dL)

Chronic kidney disease (CKD) was defined as:

1. GFR < 60 mL/min/1.73 m^2 persisting for more than 3 months, or
2. Presence of markers of kidney damage, including: a) urinary albumin/creatinine ratio > 30 mg/g, b) glomerular hematuria, c) electrolyte imbalance attributable to tubular dysfunction, d) structural abnormalities on imaging (polycystic kidney, renal scarring, or reflux nephropathy), e) pathological findings on kidney biopsy.

2.3. Gastrointestinal assessment

Liver function tests (LFTs), serum amylase, serum lipase, and abdominal ultrasonography were reviewed for liver and pancreatic injury. Abnormal liver tests were defined as transaminase levels > 2 times the upper limit of normal or direct bilirubin > 2 mg/dL. Ultrasonography was evaluated for parenchymal liver disease and fatty liver.

2.4. Endocrine assessment

2.4.1. Thyroid function

Thyroid-stimulating hormone (TSH) and free thyroxine (free T4) were measured. Overt hypothyroidism was defined as elevated TSH with low free T4; subclinical hypothyroidism as elevated TSH with normal free T4; and hyperthyroidism as suppressed TSH with elevated free T4.

2.4.2. Mineral and electrolyte balance

Serum calcium, phosphorus, and magnesium were measured. Hypocalcemia, hypercalcemia, hypophosphatemia, and hypomagnesemia were defined using age-specific reference ranges.

2.4.3. Pituitary function

Serum cortisol, adrenocorticotropic hormone (ACTH), insulin-like growth factor 1 (IGF 1), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin were measured and interpreted according to standardized pediatric reference values.

2.4.4. Glucose and lipid profile

Fasting blood glucose and lipid parameters—including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides—were assessed after at least 8 hours of fasting. Hyperglycemia and dyslipidemia were defined based on international pediatric guidelines.

2.4.5. Bone mineral density (BMD) and body composition

BMD and body composition were evaluated using dual-energy X-ray absorptiometry (DEXA). BMD Z scores were calculated, and low bone mass (LBM) was defined as a Z score ≤ −2.0 at the lumbar spine, femoral neck, or whole body. BMI was categorized as underweight, normal weight, overweight, or obese according to World Health Organization age- and sex-specific percentiles.

2.5. Neuropsychiatric assessment

A pediatric neurologist evaluated all patients for peripheral neuropathy, seizure disorders, and focal neurological deficits. Cognitive and behavioral status were assessed using age-appropriate standardized questionnaires and clinical interviews. Patients with suspected psychiatric disorders were referred to a pediatric psychiatrist for diagnostic evaluation, including assessment for anxiety, depression, attention deficit/hyperactivity disorder, and learning disabilities.

2.6. Additional measurements

Patients with abnormalities in at least one organ system were categorized as having "any-organ abnormality." Serum ferritin was measured to identify transfusion-related iron overload (defined as > 200 ng/mL), and serum 25-hydroxyvitamin D [25(OH)D] was measured to detect vitamin D deficiency (defined as < 30 ng/mL).

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2.7. Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of Shiraz University of Medical Sciences (Code: IR.SUMS.REC.1403.489). Written informed consent was obtained from all participants or their legal guardians prior to enrollment.

2.8. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA). Quantitative variables are expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]) based on the normality of distribution, which was assessed using the Kolmogorov–Smirnov test. Categorical variables are presented as frequencies and percentages. To compare categorical variables, the Chi-square test or Fisher's exact test was employed. Continuous variables were compared using the independent t-test or the Mann–Whitney U test, as appropriate. Univariate analyses were performed to identify factors associated with organ abnormalities and low bone mass. Variables with a P-value < 0.30 in the univariate analysis were included in multivariable logistic regression models. A P-value < 0.05 was considered statistically significant.

3. RESULTS

3.1. Patient Characteristics

The study included 115 pediatric leukemia survivors, of whom 72% were boys. The median (IQR) age at diagnosis was 8 (6–10) years. The most common diagnosis was B cell acute lymphoblastic leukemia (B ALL) (85.2%), followed by T cell acute lymphoblastic leukemia (T ALL) (10.4%) and acute myeloid leukemia (AML) (4.4%).

More than half of the patients (53%) had vitamin D deficiency. Transfusion-related iron overload (serum ferritin > 200 ng/mL) was detected in eight patients (8.4%). Overall, 66 patients (57.4%) had at least one organ abnormality.

3.2. Endocrine and Metabolic Complications

Endocrine abnormalities were the most common organ dysfunctions and were identified in nearly half of the patients.

3.3. Thyroid Function

Thyroid function abnormalities were detected in seven patients (6.1%), including hypothyroidism in six patients (5.2%) and hyperthyroidism in one patient (0.9%).

3.4. Mineral and Electrolyte Status

Laboratory evaluation revealed hypocalcemia (< 8.5 mg/dL) in two patients (1.7%), hypercalcemia (> 11.5 mg/dL) in one patient (0.9%), and hypophosphatemia (< 3.5 mg/dL) in one patient (0.9%).

3.5. Pituitary Function

Pituitary hormone abnormalities were identified in ten patients (8.7%).

3.6. Glucose and Lipid Profile

One patient (0.9%) had fasting hyperglycemia (142 mg/dL). Hypertriglyceridemia (> 250 mg/dL) was detected in two patients (1.7%), and elevated LDL cholesterol (> 100 mg/dL) was observed in ten patients (8.7%).

3.7. Bone Mineral Density and Body Composition

Bone mineral density (BMD) was assessed in 65 patients, of whom 15 (23.1%) had low bone mass (LBM). Most patients had a normal body mass index (44.1%), whereas approximately 20% were overweight or obese (**Table 1**).

3.8. Genitourinary Complications

3.8.1. Glomerular Filtration Rate

Twenty-three patients (20%) had mildly reduced GFR (< 90 mL/min/1.73 m^2); however, none met the diagnostic criteria for chronic kidney disease.

3.8.2. KUB and Testicular Ultrasonography

Abnormal findings were observed in seven patients (6.1%), five of which were attributed to disease-related complications. The identified abnormalities included varicocele (2 cases), urethral stricture (1 case), retractile testis (1 case), undescended testis (1 case), combined hydrocele and varicocele (1 case), and renal stones (2 cases).

3.9. Gastrointestinal Complications

Liver function tests showed elevated alanine aminotransferase (ALT) in one patient (0.9%) (98 IU/L). Other liver enzymes, as well as serum amylase and lipase levels, were within normal limits. Abdominal ultrasonography revealed fatty liver (grade I–III) in eight patients (7%).

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Table 1. Demographic and clinical characteristics of the study population (n=115)

Variables	N (%)
Age at diagnosis(y), median (IQR)	8.0 (6.0-10.0)
Sex (male)	72 (62.6)
Diagnosis	
• B-ALL	98 (85.2)
• T-ALL	12 (10.4)
• AML	5 (4.4)
Duration of off treatment (m), median (IQR)	48.5 (26.5-75.0)
Body mass index (kg/m2), median (IQR)	20.0 (16.7-24.0)
Body mass index (kg/m2), (n=93)	
• < 18.5	34 (36.6)
• 18.5-24.9	41 (44.1)
• 25-29.9	13 (14.0)
• ≥ 30	5 (5.4)
Bone mineral densitometry Z score (mean± SD)	
• Subtotal	-1.05 ± 1.34
• Spine (L1-L4)	-0.85 ± 1.15
• Femur neck	-0.69 ± 1.33
Low bone mass (yes), (n=65)	15 (23.1)
Pituitary dysfunction (yes)	10 (8.7)
25(OH) vitamin D (ng/mL), median (IQR)	28.4 (24.1-36.3)
25(OH) vitamin D (ng/mL), (n=100)	
< 30	53 (53)
≥ 30	47 (47)
Ferritin (ng/mL), median (IQR)	62.0 (40.0-103.6)
Ferritin (ng/mL), (n=95)	
≤ 200	87 (91.6)
>200	8 (8.4)
Genitourinary abnormalities	5 (4.3)
Cardiac abnormalities	4 (3.5)
Gastrointestinal abnormalities	8 (7.0)
Endocrine abnormalities	57 (49.6)
Neuropsychiatric abnormalities	19 (16.5)
Any organ abnormality	66 (57.4)

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia

3.10. Cardiac Complications

All patients were evaluated by a pediatric cardiologist, and no cases of heart failure were detected. Echocardiographic abnormalities—including mild left ventricular hypertrophy, mild left ventricular dilatation, and moderate mitral valve regurgitation—were reported in four patients (3.5%). No cases of cardiac dysrhythmia were identified.

3.11. Neuropsychiatric Findings

Neurological examinations revealed no cases of peripheral neuropathy, epilepsy, or focal neurological deficits. However, 19 patients (16.5%) had cognitive or behavioral abnormalities and were referred to a pediatric psychiatrist. Diagnosed conditions included anxiety, depression, and attention deficit/hyperactivity disorder. In addition, 16 patients (13.9%) were reported to have learning disabilities, particularly difficulties in mathematics that resulted in academic failure.

3.12. Factors Associated with Low Bone Mass

Chi-square analysis demonstrated a significant association between BMI categories and LBM (P = 0.005) (**Table 2**). Adjusted residual analysis indicated that LBM was

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Table 2. Univariate analysis of variables associated with low bone mass in pediatric leukemia survivors.

Variables	Osteoporosis		
	Yes (%)	No (%)	P value
Sex			0.37
• Male	19.5	80.5	
• Female	29.2	70.8	
Diagnosis			0.64
• B-ALL	25	75	
• T-ALL	22.2	77.8	
• AML	0	100	
BMI classification (kg/m2)			0.005
< 18.5	52.9	47.1	
18.5-24.9	14.3	85.7	
25-29.9	0	100	
≥ 30	50	50	
BMI categorized*			0.053
Normal	14.3	85.7	
Abnormal	37	63	
Ferritin (ng/dL)			0.004
≤ 200	14	84	
>200	80	20	
25(OH) vitamin D (mg/dL)			0.58
< 30	20	80	
≥ 30	26.1	73.9	
Age at diagnosis (y), mean difference (95% CI)		0.8 (-2.0 to 3.7)	0.56
Duration of off treatment (m) Mean difference (95%CI)		9.2 (-9.3 to 27.8)	0.32
Calcium (mg/dL) Mean difference (95%CI)		0.04 (-0.2 to 0.3)	0.75
Phosphorus (mg/dL) Mean difference (95%CI)		-0.2 (-0.6 to 0.2)	0.36

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; BMI: body mass index
*Normal BMI refers to values of 18.5-24.9 kg/m^2

significantly overrepresented in the underweight group (adjusted residual = +3.1), while the frequency of individuals without osteoporosis in this group was significantly lower than expected (adjusted residual = −3.1). No other BMI category showed significant deviations from expected frequencies.

Patients with transfusion related iron overload (ferritin > 200 ng/mL) were also more likely to have LBM (P = 0.004). Patients with neuropsychiatric abnormalities had a longer duration since treatment discontinuation compared with those without such complications (mean difference = 16.4 months, 95% CI: 1.6–31.1, P = 0.03) **(Table 3)**. No other complications showed significant associations with the evaluated variables in univariate analyses **(Table 4)**.

3.13. Multivariable Analysis

Multivariable logistic regression analysis showed that ferritin levels > 200 ng/mL were associated with an approximately 14-fold increased odds of LBM in pediatric leukemia survivors (OR = 14.25, 95% CI: 1.13–178.85, P = 0.039). No other organ dysfunctions were independently associated with the evaluated covariates **(Table 5)**.

4. DISCUSSION

This cross-sectional study evaluated long-term complications among 115 pediatric leukemia survivors and demonstrates a substantial burden of late effects across multiple organ systems. The findings add important evidence to the survivorship literature and represent one of the first systematic assessments of long-term complications among childhood leukemia survivors in Iran.

One of the most notable findings was the high prevalence of endocrine dysfunction (49.6%), the presence of at least one organ abnormality in nearly 60% of survivors, vitamin D deficiency in more than half of the cohort (53%), low bone mass (LBM) in 23% of patients, and psychiatric or

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Table 3. Univariate analysis of variables associated with neuropsychiatric abnormalities in survivors of pediatric leukemia.

Variables	Neuropsychiatric abnormalities		
	Yes (%)	No (%)	P value
Sex			0.07
• Male	22.2	77.8	
• Female	9.3	90.7	
Diagnosis			0.55
• B-ALL	17.3	82.7	
• T-ALL	25	75	
• AML	0	100	
BMI*			0.78
Normal	19.5	80.5	
Abnormal	17.3	82.7	
Bone mineral densitometry			0.44
Within expected range for age	6.7	93.3	
Below expected range for age	16	84	
Ferritin (ng/mL)			0.79
≤ 200	16.1	83.9	
>200	12.5	87.5	
25(OH) vitamin D (mg/mL)			0.28
< 30	13.2	86.8	
≥ 30	21.3	88.7	
Age at diagnosis (y), mean difference (95% CI)		-1.1 (-3.2 to 1.0)	0.301
Duration of off treatment (m) mean difference (95% CI)		-16.4 (-31.1 to -1.6)	0.03

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; BMI: body mass index
*Normal BMI refers to BMI of 18.5-24.9 kg/m^2

Table 4. Univariate analysis of variables associated with any organ abnormalities in survivors of childhood leukemia

Variables	Any organ abnormalities		
	Yes (%)	No (%)	P value
Sex			0.29
• Male	61.1	38.9	
• Female	51.2	48.8	
Diagnosis			0.77
• B-ALL	58.2	41.8	
• T-ALL	58.3	41.7	
• AML	40	60	
Ferritin (ng/dL)			0.13
≤ 200	54.0	46	
>200	87.5	12.5	
25(OH) vitamin D (mg/dL)			0.46
< 30	56.6	43.4	
≥ 30	63.8	36.2	
Age at diagnosis (y), mean difference (95% CI)		-0.6 (-2.2 to 0.93)	0.43
Duration of off treatment (m) mean difference (95% CI)		0.001 (-11.4 to 11.4)	1.0

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia

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Table 5. Multivariable logistic regression of covariates associated with osteoporosis, neuropsychiatric abnormalities, and any organ abnormalities

Variables	Odds ratio (95% CI)	P value
Osteoporosis		
Ferritin (ng/mL)		0.039
≤ 200	Reference	
>200	14.25 (1.13 to 178.85)	
Body mass index*		0.105
Normal	Reference	
Abnormal	0.22 (0.03 to 1.36)	
Neuropsychiatric abnormalities		
Sex		0.141
Female	Reference	
Male	2.81 (0.71 to 11.07)	
Duration of off treatment (m)	1.01 (0.99 to 1.03)	0.094
25(OH) vitamin D (mg/dL)		0.124
≥ 30	Reference	
< 30	0.41 (0.13 to 1.28)	
Any organ abnormalities		
Sex		0.649
Female	Reference	
Male	1.22 (0.52 to 2.88)	
Ferritin (ng/mL)		0.106
≤ 200	Reference	
>200	5.83 (0.69 to 49.57)	

*Normal body mass index refers to values of 18.5-24.9 kg/m2

learning problems affecting approximately one-fifth of survivors. Collectively, these results underscore the need for comprehensive, long-term, multisystem surveillance in this population.

Bone health emerged as a major area of concern. Since approximately 90% of peak bone mass is acquired by the end of adolescence, disruptions during this critical period may increase the risk of low BMD, osteoporosis, and fractures later in life (22, 23). Previous studies, including a meta-analysis by Cummings et al. and the St. Jude Lifetime Cohort Study, have similarly reported reduced BMD among survivors of childhood ALL (24, 25). Several mechanisms likely contribute to impaired bone health in these patients. Methotrexate can inhibit osteoblast proliferation and promote osteoblast apoptosis, while glucocorticoids cause dose dependent bone loss through decreased bone formation, enhanced resorption, and impaired calcium metabolism (26-28). Additional factors—such as treatment related endocrine dysfunction, physical inactivity, and inadequate nutrition—may further exacerbate bone deficits (29-32).

A key finding of this study was the strong association between elevated ferritin (> 200 ng/mL) and markedly increased odds of LBM, with survivors demonstrating a fourteen-fold higher risk. Hyperferritinemia may reflect iron overload or inflammation, both of which negatively influence bone metabolism. Excess iron has been shown to inhibit osteoblast differentiation, promote osteoclast activity through oxidative stress, and interfere with type I collagen synthesis and hydroxyapatite crystal formation (33, 34). Pro inflammatory cytokines such as IL-6 and TNF-α, commonly elevated in states of high ferritin, can further shift bone remodelling toward resorption (35). These mechanisms provide biologic plausibility for the observed association and highlight the importance of monitoring iron status in survivorship care.

Vitamin D deficiency was highly prevalent and exceeded rates reported in many Western cohorts, although it is consistent with patterns observed in the Iranian general population. Limited sun exposure, high air pollution levels, and reduced outdoor activity may contribute to this deficiency (36, 37). Given the critical role of vitamin D in calcium absorption and bone mineralization, routine screening and supplementation may represent effective, modifiable strategies to improve bone health in this vulnerable population.

Endocrine abnormalities were the most common organ system dysfunctions identified. Thyroid disorders occurred in 6.1% of survivors, predominantly hypothyroidism, consistent with prior survivorship studies. Such dysfunction may arise from direct treatment effects, hypothalamic pituitary axis injury, or immune mediated mechanisms (38).

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Pituitary dysfunction was observed in 8.7% of patients, further highlighting the sensitivity of the hypothalamic–pituitary axis to chemotherapy and cranial-directed therapies. Growth hormone deficiency is one of the most frequently reported late endocrine effects and may contribute to short stature, altered body composition, and impaired bone density, reinforcing the importance of regular endocrine surveillance (39).

Genitourinary complications were also observed, predominantly among males. Chemotherapeutic agents, particularly alkylating agents, may impair germinal epithelium and disrupt spermatogenesis (40, 41). Structural abnormalities such as varicocele or undescended testis, identified in this cohort, may further compromise future fertility. Although fewer abnormalities were identified among female survivors, the risk of ovarian insufficiency remains well recognized, particularly after alkylating agent exposure or pelvic irradiation (42).

Despite the high prevalence of vitamin D deficiency, serum calcium and phosphorus levels were largely preserved, suggesting activation of compensatory mechanisms such as secondary hyperparathyroidism. However, persistent deficiency may eventually contribute to progressive bone loss, supporting the need for appropriate monitoring and intervention.

Neuropsychiatric abnormalities were detected in approximately 20% of survivors, consistent with existing literature showing elevated rates of attention deficits, executive dysfunction, learning disabilities, anxiety, and depression. Contributing mechanisms may include neurotoxic effects of chemotherapeutic agents—especially high dose methotrexate and intrathecal therapy—as well as prolonged school absence and treatment related psychosocial stress (43-45). These complications may have long-term consequences for educational attainment and quality of life; therefore, integrating neurocognitive and psychological assessment into survivorship programs is essential.

Overall, our findings align with data from large international cohorts such as the Childhood Cancer Survivor Study (CCSS) and European survivorship studies, which report increased risks of endocrine, skeletal, and reproductive complications (7, 8, 25, 46, 47). Differences in prevalence between our cohort and Western populations may reflect variations in treatment regimens, genetic susceptibility, environmental exposures, and the high baseline rate of vitamin D deficiency in Iran.

Several strengths enhance the value of this study, including its structured evaluation of multiple organ systems and its contribution to survivorship data from a region where such research is limited. Nevertheless, the study is subject to several limitations. The cross-sectional design precludes causal inference and prevents assessment of temporal trends. Some evaluations were not performed for all patients, which may introduce selection bias. The single-center setting limits generalizability, and the lack of an age-matched healthy control group restricts interpretation of conditions with high background prevalence. Longer-term longitudinal studies are needed to better characterize the trajectory of late effects and identify modifiable risk factors.

In conclusion, this study demonstrates a substantial burden of long-term complications among pediatric leukemia survivors, particularly involving bone health, vitamin D status, endocrine function, and neuropsychiatric outcomes. These findings highlight the need for structured survivorship programs with systematic, multisystem monitoring. Early detection and proactive management of late effects may significantly improve long-term health and quality of life in the growing population of childhood cancer survivors.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Ethical statement

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1403.489).

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