Long-term kidney complications in childhood leukemia survivors: a study from the Childhood and Adolescent Leukemia (LEA) project

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Abstract

Acute leukemias represent the first cause of cancer in children. Their prognosis has improved significantly due to remarkable advances in therapeutic management, despite the risk of long-term consequences, especially for patients who underwent allogenic hematopoietic stem cell transplantation (aHSCT). Through the Leukemia in Children and Adolescents (LEA) long-term follow-up cohort (*clinicaltrials gov. Identifier: NCT01756599*), we conducted a French national multicenter prospective study on the occurrence and risk factors of chronic kidney disease (CKD), differentiating glomerular and tubular dysfunctions, corresponding to the NephroLEA project. Among the 1,676 patients included, the median age at evaluation was 15.8 (interquartile range [IQR], 11.3-20.5) years, with a median follow-up of 9.2 (IQR, 5.8-13.9) years. aHSCT was performed on 343 (20.6%) patients, half of whom have undergone the procedure after achieving second or greater remission. A higher percentage of children among transplanted patients had diastolic and systolic blood pressure above the 95th, with 13.7% *versus* 5.2% (P=3x10^{-3}) and 15% *versus* 6.5% (P=9x10^{-2}), respectively. A total of 187 patients (11.1%) had a mild CKD (i.e., eGFR

between 75 and 90 mL/min/1.73 m^2), while 3% (N=50) exhibited mild to severe CKD (eGFR <75 mL/min/1.73 m^2). Notably, no patient reached kidney failure. Twenty-one patients (1.3%) had decreased glomerular filtration rate associated with tubular impairment. The principal risk factors for developing CKD were aHSCT and leukemia relapse. In conclusion, CKD represents a long-term risk for patients who relapsed and/or underwent aHSCT. These patients could benefit from nephroprotection advice to further improve their long-term outcomes, which is becoming a public health issue.

Introduction

Acute leukemias (AL) are the leading cause of cancer in children in developed countries.[1] Thanks to improved stratification of these hematologic diseases, based on enhanced clinical, biological and therapeutic knowledge, remarkable progress has been made in their therapeutic management. The overall survival rate has risen to approximately 85-90% for acute lymphoblastic leukemia (ALL)[2] and 60-70% for acute myeloid leukemia (AML).[3] These favorable outcomes have been achieved despite the cumbersome and toxic nature of current chemotherapy regimens. Furthermore, although dramatic overall result enhancement over decades, allogenic hematopoietic stem cell transplantation (aHSCT) remains the treatment of choice for (very) high-risk hematological malignancies.[4,5] All these treatments, however, can induce various toxicities and complications in the short, medium or long term. With current high cure rates, long-term survivors of childhood leukemia now represent a growing population, and these long-term side-effects have become a major public health issue. One significant post-treatment complication is kidney dysfunction.[6] While short-term acute renal failure has been extensively studied,[7-15] there is a lack of data from large, homogeneous cohorts of patients treated for childhood leukemia, particularly regarding the risk of developing chronic kidney disease (CKD) and/or tubular impairment.[16-21] Over time, kidney impairment may develop in patients without predisposing kidney failure, impacting long-term outcomes and subsequent quality of life. It may also represent an additional cardiovascular risk factor,[22-24] alongside the well-documented occurrence of metabolic syndrome in this population.[25,26] Therefore, these patients may benefit from education on general nephroprotective measures.

According to the international definitions, CKD is characterized by a reduced glomerular filtration rate (GFR) under 90 mL/min/1.73 m² in children and below 60 mL/min/1.73 m² in adults, and/or a urinary albumin-to-creatinine ratio (ACR) above 3 mg/mmol, and/or other morphological or electrolyte abnormalities due to tubular disorders.[27] Moreover, glomerular lesions and tubular impairment result from different toxic mechanisms and may lead to non-comparable long-term sequelae. Thus, we decided to systematically study the long-term renal function in a significant and homogeneous cohort of patients treated during childhood for acute lymphoblastic or myeloblastic leukemia, either with chemotherapy alone or intensified with aHSCT. This study was made possible by the French LEA (Leukemia in Children and Adolescents) patient cohort, established in 2004. The aim of this national multicenter prospective cohort is to evaluate the medium- and long-term outcomes of patients treated for acute leukemia in childhood, since January 1980. The participation rate in the LEA cohort, comprising patients treated for childhood leukemia across 18 French pediatric hematology centers, is around 80%.[27] Our main objective was to report the occurrence of CKD and its risk factors in the NephroLEA cohort, based on the presence of glomerular and/or tubular abnormalities.

Methods

Patients

From March 2019 to February 2022, we included all patients who underwent a long-term follow-up evaluation in the LEA program (*clinicaltrials gov. Identifier: NCT01756599*) (*Online Supplementary Figure S1*). The LEA project is a national French cohort initiated in 2004 to assess long-term health of patients treated during childhood or adolescence for AL after 1980. Follow-up begins 1 year after completion of chemotherapy for AML or aHSCT, and 2 years after the completion of chemotherapy for ALL. Clinical examinations are conducted at predefined intervals: every 2 years until the age of 20 and at least 10 years of complete remission (CR), and every 4 years thereafter. Late effects are detected through medical examination and adequate additional tests (biological and radiological) by physicians.[28]

Clinical data related to AL were obtained from the LEA database, including patient demographics, AL subtype, CR status (including any relapse), details of aHSCT procedures (i.e., conditioning regimen, donor type, source of stem cells, and graft-*versus*-host disease (GVHD) grading, if any. All patients (or their parents or legal guardians) provided written informed consent. The study was approved by the Comité de Protection des Personnes Sud Méditerranée V Ethics Review Board (opinion n° 2012-A00984-39), and conducted in compliance with the General Data Protection Regulation.

Clinical definition and specimen collection

Blood pressure was measured three times on the right arm, with the patient lying down or seated calmly. The lowest

systolic and diastolic results were recorded, as recommended.[29] Arterial hypertension was defined as a systolic or diastolic blood pressure (SBP or DBP, respectively) above the 95th percentile for children under 15 years, or SBP >140 mmHg and/or DBP >90 mmHg for older children and adults.[29]

Blood samples for creatinine (Cr), sodium (Na), potassium (K), bicarbonates (HCO_3), calcium (Ca), phosphate (Ph), magnesium (Mg), uric acid, glucose, as well as urine samples for Cr, Na, K, Ca, Ph, Mg, uric acid, glucose, β2-microglobulinuria, and albuminuria were collected either at time of medical examination or from local laboratories. This allowed evaluation of glomerular (estimated GFR [eGFR] and ACR) and tubular functions. Tubular function was assessed using formulas for electrolytes (E) reabsorption rates: (E_urine/E_plasma)/(Cr urine/Cr plasma) x100 (%), as well as tubular maximum Ph reabsorption per glomerular filtration rate (TmP/GFR), and urinary Ca/Cr and Mg/Cr ratios.[30] For patients under 25 years old, eGFR was calculated using the Chronic Kidney Disease in Children U25 equation (eGFR-CKiDU25).[31] For patients older than 25 years at evaluation, the CKD-EPI equation was employed.[32,33] Plasma Cr measurements were standardized according to National Institute of Standards and Technology recommendations.

According to Kidney Disease Improving Global Outcomes (KDIGO) guidelines,[27,34] CKD was defined as GFR <90 mL/min/1.73 m^2. CKD staging followed classical GFR stratification: (i) stage 1 for normal renal function (GFR ≥90 mL/min/1.73 m^2), (ii) stage 2 for mild renal dysfunction (60 ≤ GFR <90 mL/min/1.73 m^2), (iii) stage 3 for moderate renal dysfunctions, subdivided into 3a (45 ≤ GFR <60 mL/min/1.73 m^2) and 3b (30 ≤GFR <45mL/min/1.73 m^2), and (iv) stage 4 for severe renal dysfunction (GFR <30 mL/min/1.73 m^2). To refine the definition of CKD in younger patients (<40 years), we further subdivided the stage 2 into two subclasses: stage 2a (75≤ GFR <90 mL/min/1.73 m^2) and stage 2b (60 ≤ GFR <75 mL/min/1.73 m^2), as proposed by Delanaye *et al.*[35]

Albuminuria was expressed as ACR in a spot urine sample. Microalbuminuria was defined as ACR between 3-30 mg/mmol, and macroalbuminuria as ACR >30 mg/mmol. Tubular renal disorders were characterized by metabolic acidosis (bicarbonates <18 mmol/L) and/or a renal phosphate wasting (hypophosphatemia for age 36 and a low age-adjusted TmP/GFR).[37]

Statistical analysis

Statistical analysis was performed using SPSS 20.0 ® (SPSS Inc., Chicago, IL, USA). Qualitative data were expressed as counts and percentages. Quantitative data were presented as median (minimum-maximum). Continuous variables, such as age at leukemia diagnosis, age at last evaluation, and follow-up duration, were categorized at the median and interquartile range (IQR). Fisher's exact tests were used to compare qualitative variables, while the Student's *t* test or the Mann-Whitney U test was employed for quantitative variables. A *P* value <0.05 was considered statistically significant.

Results

Patients' demographics

The NephroLEA cohort included a total of 1,772 patients, of whom 1,676 patients were eligible with available Cr-based eGFR data. Demographic and clinical features are detailed in Table 1. The median age at AL diagnosis was 4.5 years (IQR, 2.7-8.7), with a median follow-up of 9.2 years (IQR, 5.8-13.9). The cohort consisted of 52.8% (N=885) male patients. The most common diagnosis was ALL (84.5%, N=1,416), with 90% (N=1276) achieving first CR. aHSCT was

Table 1. Patient demographic data and clinical characteristics at baseline.

Variables	Whole population N=1,676
Median age at evaluation, years (IQR)	15.8 (11.3-20.5)
Median age at diagnosis, years (IQR)	4.5 (2.7-8.7)
Median follow-up, years (IQR)	9.2 (5.8-13.9)
Sex: male, N (%)	885 (52.8)
Body surface area, m^2 (IQR)	1.5 (1.2-1.7)
Body mass index, kg/m^2 (IQR)	19.7 (17-23)
Acute leukemia subtype	
ALL, N (%)	1,416 (84.5)
CR1	1,276 (90.0)
Relapse (≥ CR2)	140 (10.0)
AML, N (%)	260 (15.5)
CR1	223 (85.8)
Relapse (≥ CR2)	37 (14.2)
Complete remission status, N (%)	
CR1	1,498 (89.4)
Relapse (≥ CR2)	178 (10.6)
aHSCT, N (%)	343 (20.6)
Median age at 1st aHSCT, years (IQR)	8.4 (0.5-11.3)
Complete remission status at aHSCT, N (%)	
CR1	190 (55.4)
Relapse (≥ CR2)	153 (44.6)
Conditioning regimen, N (%)	
Myeloablative: TBI	199 (58.0)
Myeloablative: Bu	144 (42.0)
Donor type/stem cell source, N (%)	
Sibling related donor	97 (30.1)
Unrelated donor	225 (69.9)
Bone marrow/peripheral stem cells	264 (77.0)
Cord blood	79 (23.0)
GVHD, N (%)	153 (44.6)

aHSCT: allogenic hematopoietic stem cell transplantation; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; BMI: body mass index; Bu: busulfan; CR: complete remission; GVDH: graft-*versus*-host disease; IQR: interquartile range; TBI: total body irradiation.

performed in 343 patients (20.6%), half of whom underwent the procedure in CR2 or beyond. Among patients receiving HSCT, 219 (63.8%) were treated for ALL and 124 (36.2%) for AML. One-third of transplanted individuals had sibling-related donors. All aHSCT recipients underwent myeloablative conditioning, with total body irradiation (TBI) included in 58% (N=199) of the regimens for children. The median age at NephroLEA screening was 15.8 years (IQR, 11.3-20.5). Clinical abnormalities during physical examination were observed in 1.7% (N=28) of patients, including edema and/or elevated blood pressure. A small proportion of patients received medications: 23 patients received antihypertensive treatment, ten were on anti-diabetic drugs, four were treated with lipid-lowering medications, and three received nephroprotection therapy (angiotensin-converting enzyme inhibitor or angiotensin receptor antagonists). Patients who underwent aHSCT exhibited a trend toward a higher median DBP compared with non-aHSCT (69 mmHg [IQR, 61-78] *vs.* 68 mmHg [IQR, 60-74]; *P*=0.1) (Table 2), although no significant difference in the median SBP was observed (*P*=0.6). These results were supported by an increased percentage of children with DBP above the 95th in the aHSCT group (13.7% *vs.* 5.2%; *P*=0.003) (Table 2). Furthermore, aHSCT patients were older (17 *vs.* 15.6 years; *P*=0.002), lighter (48 *vs.* 52.5 kg; *P*=0.006), and had a trend toward shorter height (157 *vs.* 160 cm; *P*=0.07). These findings were corroborated by significantly smaller body surface area (BSA) in aHSCT patients compared with others (1.45 m^2 [IQR, 1.2-1.7] *vs.* 1.53 m^2 [IQR: 1.2-1.7]; *P*=0.001) (Table 2).

Evaluation of long-term glomerular function after acute leukemia treatment during childhood

In the entire cohort, 85.9% (N=1,439) of patients exhibited normal eGFR (CKD stage 1), with a mean eGFR of 111.8 mL/min/1.73 m^2 [IQR, 102.3-123.9]). Additionally, 11.1% of patients displayed a slight decrease in eGFR (CKD stage 2a), while 3% (N=50) were categorized as CKD stage 2b-4. Notably, only one patient was classified as CKD stage 4, with an eGFR of 26.3 mL/min/73 m² (Table 2). No cases of kidney failure were observed. Among patients classified in CKD stage 1, 10.5% (N=124) demonstrated abnormal albuminuria. Of these, 9.6% (N=113) had only microalbuminuria, while 0.9% (N=11) presented with macroalbuminuria.

Evaluation of long-term tubular function after childhood acute leukemia treatment

Plasma electrolyte levels were within normal ranges and comparable across all patients, except for chloride, uric acid and Ph levels. aHSCT patients had significantly lower TmP/GFR (1.03 [IQR, 0.89-1.23] mmol/L compared with others (1.15 [IQR, 0.97-1.33] mmol/lL; *P*<0.001) and higher uric acid levels (283 [IQR, 230.2-369.5] μmol/L *vs.* 258 [IQR, 217-304.2] μmol/L; *P*<0.001) (Table 3). A greater

Table 2. Long-term glomerular function after acute leukemia treatment during childhood.

Variables	All patients		Non-aHSCT		aHSCT		*P*
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	
Age, years	1,676	15.8 (11.3-20.5)	1,322	15.5 (10.9-20)	343	17 (12.8-22.6)	$2x10^{-3}$
Sex, male, N (%)	1,676	-	1,322	679 (51.4)	343	199 (58.0)	$3x10^{-2}$
Weight, Kg	1,647	52 (37-64.1)	1,300	52.5 (37-65)	336	48 (36-60.6)	$6x10^{-3}$
Size, cm	1,676	160 (143.2-169)	1,322	160 (143-170)	343	157 (145-165)	$7x10^{-2}$
BSA	1,647	1.5 (1.2-1.7)	1,300	1.5 (1.2-1.7)	336	1.45 (1.2-1.7)	$1x10^{-3}$
BMI	1,676	19.7 (17-23)	1,322	19.9 (17.2-23)	343	19 (16.4-23)	$4x10^{-2}$
Systolic BP, mmHg	1,537	112 (103-121)	1,204	112 (104-121)	323	112 (102-122)	0.6
Diastolic BP, mmHg	1,537	68 (60-75)	1,204	68 (60-74)	323	69 (61-78)	0.1
High SBP, N (%)*	520	-	381	25 (6.5)	131	15 (11.4)	$9x10^{-2}$
High DBP, N (%)#	520	-	381	20 (5.2)	131	18 (13.7)	$3x10^{-3}$
eGFR, mL/min/1.73m^2							
CKD stage 1	1,439	111.8 (102.3-123.9)	1,165	111.3 (102-122.7)	264	114.9 (104.2-127.4)	$2x10^{-2}$
CKD stage 2a	187	84.4 (81.3-87.1)	128	84.8 (81.7-87.2)	58	84 (80.7-86.9)	0.4
CKD stage 2b	41	71.3 (65.4-73)	26	71.6 (68.9-73.1)	15	67 (61.1-72)	0.2
CKD stage 3a	7	56.7 (47.9-57.2)	3	55.1 (47.9-NA)	4	56.9 (49.1-59.1)	1
CKD stage 3b	1	43.5 (43.5-43.5)	-	-	1	43.5 (43.5-43.5)	-
CKD stage 4	1	26.3 (26.3-26.3)	-	-	1	26.3 (26.3-26.3)	-
ACR <3, mg/mmol	1,345	0.8 (0.4-1.5)	1078	0.8 (0.4-1.4)	257	1 (0.6-2.1)	$<1x10^{-3}$
Microalbuminuria, N (%)	-	140 (10.5)	-	97 (9)	-	43 (16.7)	$2x10^{-3}$
Macroalbuminuria, N (%)	-	12 (0.9)	-	10 (0.9)	-	2 (0.8)	-

ACR: albumin-to-creatinine ratio; aHSCT: allogenic hematopoietic stem cell transplantation; BMI: body mass index; BP: blood pressure; BSA: body surface area; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; IQR: interquartile range; NA: not available; SBP: systolic blood pressure. *Systolic blood pression above the 95th percentile; #diastolic blood pression above the 95th percentile.

Table 3. Long-term electrolytes, and uric acid rates, and tubular function after acute leukemia treatment during childhood.

Variables	All patients		Non-aHSCT		aHSCT		*P*
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	
Blood							
Cr µmol/L	1,676	54 (42-68)	1,322	53 (42-67)	343	56 (42-71)	0.08
Sodium, mmol/L Ref 136-145	1,667	140 (138-141)	1,315	140 (138-141)	341	140 (138-141)	0.8
Potassium, mmol/L Ref 3.5-4.8	1,667	4 (3.8-4.1)	1,315	4 (3.8-4.1)	341	3.98 (3.79-4.2)	0.8
Chlor, mmol/L	1,446	160 (104-203)	1,149	162 (106-208.5)	286	143 (98-186.2)	0.02
Bicarbonate, mmol/L Ref 22-29	1,389	24.8 (23-26)	1,108	25 (23-26)	272	24 (23-25)	0.07
Ca, mmol/L Ref 2.1-2.5	1,673	2.4 (2.35-2.47)	1,320	2.41 (2.35-2.47)	342	2.43 (2.38-2.5)	<0.001
Phosphate, mmol/L N depending on age	1,606	1.21 (1.03-1.4)	1,270	1.23 (1.04-1.4)	325	1.16 (1-1.35)	0.001
Magnesium, mmol/L Ref 0.7-0.9	1,522	0.84 (0.8-0.87)	1,199	0.84 (0.8-0.88)	313	0.83 (0.78-0.87)	0.1
Uric acid, µmol/L N depending on age and sex	1,448	262.8 (218-317.2)	1,142	258 (217-304.2)	296	283 (230.2-369.5)	<0.001
High uric acid level, N (%)	-	122 (8.5)	-	70 (6.1)	-	52 (17.6)	<0.001
Tubular parameters							
Tmp/GFR, mmol/L N depending on age	1,230	1.12 (0.9-1.3)	990	1.15 (0.97-1.33)	231	1.03 (0.89-1.23)	<0.001
Low TmP/GFR, abnormal, N (%)	-	110 (8.9)	-	75 (7.6)	-	32 (13.9)	0.004
Ca/Cr, mmol/mmol Ref <0.7	1,301	0.23 (0.1-0.4)	1,048	0.2 (0.1-0.4)	243	0.2 (0.13-0.43)	0.6
Elevated Ca/Cr, N (%) Ref >0.7	-	62 (4.8)	-	44 (4.2)	-	18 (7.4)	0.04
β2microG/Cr, mg/mol Ref <40.7	977	10 (7-17.6)	753	10 (6.9-16.4)	220	12.6 (7.8-21.7)	<0.001
Abnormal β2microG/Cr, N (%)	-	66 (6.8)	-	36 (4.8)	-	30 (13.6)	<0.001
EF glucose Ref <0.1%	1,580	4.8 (4.4-5.2)	1,256	4.8 (4.4-5.14)	314	4.81 (4.5-5.2)	0.1
«Tubular dysfunction», N (%)	-	278 (20.5)	1,088	212 (19.5)	269	66 (24.5)	0.08

AHSCT: allogenic hematopoietic stem cell transplantation; β2microG: β2microglobulin; Ca: calcium; Cr: creatinine; EF glucose: excretion fraction of glucose; IQR: interquartile range; TmP/GFR: tubular maximum phosphate reabsorption per glomerular filtration rate.

proportion of aHSCT patients exhibited abnormal uric acid values (17.6% *vs*. 6.1%; *P*<0.001) (Table 3).

Similarly, Ph levels were slightly but significantly lower in the aHSCT group, with a higher percentage of decreased TmP/GFR (13.9% *vs*. 7.6%; *P*=0.004) (Table 3). aHSCT patients also had significantly elevated β2-microglobulin/Cr ratios (12.6 [IQR, 7.8-21.7] mg/mol *vs*. 10 [IQR, 6.9-16.4] mg/mol; *P*<0.001).

There was a trend toward more frequent "tubular signs" (low bicarbonatemia [<18 mmol/L] and/or a renal Ph wasting) among transplanted patients (24.5 % *vs*. 19.5%, *P*=0.08). Overall, 19.1% (N=320) of the cohort exhibited at least one tubular or glomerular abnormality, whereas 80.9% (N=1356) were classified as CKD stage 1 without tubular dysfunction. Among the remaining patients, 1.3% (N=21) were classified as CKD stage 2a-4 with tubular dysfunction, 4.9% (N=83) displayed normal GFR but exhibited tubular impairment, and 12.9% (N=216) were classified as CKD stage 2a-4 without tubular dysfunction (Tables 2, 3).

Risk factors for developing chronic kidney disease in all NephroLEA cohort

The analysis identified leukemia relapse (*P*<0.0001) and aHSCT (*P*<0.0001) as significant risk factors for long-term CKD (Table 4). Older age at evaluation (≥15.8 years; *P*<0.0001) was associated with higher incidence of CKD ≥2a. TBI and older patients were significant risk factors for tubular dysfunction (*P*=0.003 and *P*<0.0001, respectively) (Table 5).

Chronic kidney disease risk factors in subgroups

Among aHSCT patients, TBI was not a significant risk factor for CKD (*P*=0.4). However, relapse (*P*=0.03) and older age at evaluation remained significant (*P*=0.03 and *P*=0.04, for thresholds of 15.8 and 4.6 years, respectively) (Table 6). In patients who did not undergo aHSCT, age at evaluation (*P*=0.01)

Table 4. Chronic kidney disease risk factors for all the NephroLEA cohort according to risk factors.

Risk factors	CKD stage 1 eGFR >90 mL/min/1.73m² N (%)	CKD stage 2a 90< eGFR >75 mL/min/1.73m² N (%)	CKD stage 2b - 4 eGFR <75 mL/min/1.73m² N (%)	*P*
Total patients, N=1,676	1,439 (85.9)	187 (11.1)	50 (3)	
Sex				0.02
Female, N=791	660 (83.4)	101 (12.8)	30 (3.8)	
Male, N=885	779 (88)	86 (9.7)	20 (2.3)	
Acute leukemia				
ALL, N=415	1,217 (86)	155 (11)	43 (3.0)	0.8
AML, N=260	221 (85)	32 (12.3)	7 (2.7)	
aHSCT				$7.6.\ 10^{-7}$
No, N=1,322	1,165 (88.1)	128 (9.7)	29 (2.2)	
Yes, N=343	264 (77)	58 (16.9)	21 (6.1)	
Relapse				$3.3x10^{-5}$
No, CR1, N=1,488	1,292 (86.8)	162 (10.9)	34 (2.2)	
Yes, ≥CR2, N=177	137 (77.4)	24 (13.6)	16 (9.0)	
Age at evaluation, years				$3.5x10^{-5}$
≤15.8	751 (89.6)	66 (7.9)	21 (2.5)	
>15.8	688 (82.1)	121 (14.4)	29 (3.5)	
Age at diagnosis, years				0.2
≤ 4.6	731 (87.2)	86 (10.3)	21 (2.5)	
>4.6	7.8 (84.5)	101 (12.1)	29 (3.5)	
Follow-up, years				0.1
≤9.2	727 (86.8)	82 (9.8)	29 (3.5)	
>9.2	712 (85)	105 (12.5)	21 (2.5)	

eGFR: estimated glomerular filtration rate; aHSCT: allogenic hematopoietic stem cell transplantation; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CKD: chronic kidney disease; CR: complete remission; TBI: total body irradiation.

and sex (*P*<0.0001) were identified as significant risk factors for CKD ≥2a (Table 7). Notably, only 24 non-aHSCT patients experienced relapse, with three classified as CKD ≥2a.

Discussion

The increasing survival rates among children with AL have raised concerns regarding the long-term effects of the disease and its treatments, particularly for patients who have undergone aHSCT. Acute nephrotoxicity is a known side effect of several treatments used for malignant hemopathies, such as high-dose methotrexate, aminoglycoside or vancomycin as empirical antibiotherapy, and anti-calcineurin for GVHD prevention in grafted patients. However, evidence regarding the long-term effects of these treatments on kidney function in a homogeneous, large cohort of children treated during childhood for malignant hemopathies remains unknown. Consequently, the Cochrane meta-analysis recommends enrolling this category of patients in long-term follow-up programs to monitor blood pressure and renal function.[27,34,38] To our knowledge, the NephroLEA study is the largest and most comprehensive national prospective study to evaluate the prevalence of CKD among long-term survivors (>9 years) of pediatric ALL and AML treated with chemotherapies alone and/or with aHSCT. This study uniquely differentiates between glomerular and tubular dysfunctions and identifies risk factors for kidney function impairment in these specific long-term survivors.

The majority of patients in the NephroLEA cohort were treated for ALL with chemotherapies alone, including high-dose methotrexate and anthracyclines. Most patients also received empirical antibiotic therapy during the intensive treatment phase, such as aminoglycosides and/or vancomycin, to manage febrile neutropenia. These patients generally maintained normal long-term kidney function (CKD stage 1), with a median eGFR of 112 mL/min/1.73 m^2 (IQR, 102-124), without evidence of tubular dysfunction. Consequently, routine long-term nephrology follow-up may not be necessary for these patients. These findings align with those of Stotter *et al.*,[19] who reported no significant association between high-dose methotrexate and a decline in eGFR over time (*P*=0.07).

For patients with high-risk disease or relapse, aHSCT remains the treatment of choice following complete remission.[39,40] Our team recently reported that this procedure is associated with long-term CKD in a retrospective tertiary monocentric study.[6] These findings are confirmed by the NephroLEA cohort, where aHSCT emerged as the principal

risk factor for CKD development CKD (*P*<0.0001), including glomerular dysfunction and a tendency for increased tubular dysfunction. Similarly, Pelletier *et al*. reported an adverse long-term prognosis for adult aHSCT patients with CKD, including an increased risk of mortality.[17]

TBI is mandatory in the conditioning regimen for aHSCT to increase treatment success for ALL patients.[41,42] It has been identified as a risk factor for kidney injury in various pediatric studies.[13,14,43-45] However, within the aHSCT population only, TBI was not a significant risk factor (*P*=0.4). This observation aligns with our previous publication[6] and contrasts with findings from Abboud *et al*.,[44] who reported a higher cumulative incidence of CKD for adults than children in a mixed cohort of 148 patients, with TBI being an associated risk factor. Conversely, Frisk *et al*. found no difference in eGFR between individuals who underwent TBI and controls.[46] In the NephroLEA cohort, leukemia relapse (*P*=0.03), the use of "conventional" second-line chemotherapies (or more), calcineurin inhibitors for aGVHD prevention, and repeated infections (including viral infections) had a greater impact on long-term kidney function than the specific type of conditioning regimen used.

One of the major long-term complications of aHSCT reported by the LEA cohort is the occurrence of metabolic syndrome.[25,26,47,48] This complication, associated with long-term kidney dysfunction, could amplify the risk of cardiovascular disease in these long-term cancer survivors.[22-24] Florido *et al*.[49] reported a heightened risk of cardiovascular disease in adult cancer survivors (hazard ratio (HR)=2.7 [IQR, 2.04-3.59]; mean age: 54.5 years) compared to controls. This risk is exacerbated by hypertension, as observed with elevated DBP in aHSCT patients in NephroLEA cohort. In line with our results, Hsiao *et al*. reported that arterial hypertension was most common among patients who received aHSCT, with or without TBI.[50]

In our cohort, no patient had progressed to kidney failure at a median age of 15 years. However, Calderon-Margalit *et al*. highlighted that a history of pediatric CKD, regardless its aetiology, significantly increases the risk of kidney failure in later life.[51] Dieffenbach *et al*.,[18] identified key risk factors for kidney failure, including nephrectomy, irradiation exceeding 15 Gy, and high doses of anthracyclines, or ifosfamide. Effective management of hypertension and diabetes, when present, can decelerate the progression of kidney dysfunction.

Within our homogeneous hematological cohort, 3% of patients had an eGFR <75 mL/min/1.73 m^2, similar to findings from the Dutch Childhood Cancer Survivor Study, where 3.7% of survivors had an eGFR <60 mL/min/1.73 m^2 at a median age of 32 years, 5 years after diagnosis.[16] The cumulative impact of previous treatment and aging likely contribute to glomerular dysfunction over time, explaining why older patients in our cohort exhibited higher risk of developing CKD. With aging, the reduction in nephron numbers induces compensatory hypertrophy of the remaining nephrons, leading to glomerulosclerosis and a progressive decline in the eGFR. This process could partially explain the increased CKD risk observed in older patients within our cohort. Consequently, lifelong monitoring of glomerular function is strongly recommended for survivors exposed to high-risk factors, alongside adherence to standard nephroprotective measures.

Tubular dysfunction remains an under-researched area in the long-term follow-up of pediatric AL survivors, including aHSCT recipients. In our study, "tubular impairment" was defined as low bicarbonate levels (<18 mmol/L) and/or renal Ph wasting. Similar to glomerular dysfunction, we observed a trend towards a higher prevalence of tubular disease among transplanted patients compared to non-transplanted patients (24.5% *vs*. 19.5%; *P*=0.08). While most plasma electrolyte levels were normal, abnormalities in uric acid, Ph and Mg were noted, particularly among aHSCT recipients. This contrasts with our earlier findings, where Ca reabsorption rated differed between subgroups.[6] In the NephroLEA cohort, 83 patients (5.3%) exhibited tubular impairement with normal eGFR, while

Table 5. Tubular disease risk factors for all the NephroLEA cohort. Tubular dysfunction is defined by metabolic acidosis and/or phosphate wasting.

Risk factors	No tubular disease N (%)	Tubular disease N (%)	*P*
Sex			
Female	517 (80.7)	124 (19.3)	0.4
Male	571 (78.7)	155 (21.3)	
Acute leukemia			0.8
ALL	924 (79.4)	239 (20.6)	
AML	163 (80.3)	40 (19.7)	
aHSCT			0.07
No	876 (80.5)	212 (19.5)	
Yes	203 (75.5)	66 (24.5)	
TBI			0.003
No	968 (80.7)	231 (19.3)	
Yes	107 (69.9)	46 (30.1)	
Relapse			0.2
No, CR1	972 (80)	243 (20)	
Yes, ≥CR2	107 (75.4)	35 (24.6)	
Age at evaluation, years			$7.6x10^{-10}$
≤15.8	513 (73.1)	189 (26.9)	
>15.8	575 (86.5)	90 (13.5)	
Age at diagnosis, years			0.02
≤4.6	532 (77.1)	158 (22.9)	
>4.6	556 (82.1)	121 (17.9)	
Follow-up, years			$3.6x10^{-4}$
≤9.2	536 (75.8)	171 (24.2)	
>9.2	552 (83.6)	108 (16.4)	

aHSCT: allogenic hematopoietic stem cell transplantation; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CKD: chronic kidney disease; CR: complete remission; TBI: total body irradiation.

Table 6. Chronic kidney disease risk factors for the allogenic hematopoietic stem cell transplantation patents of the NephroLEA cohort.

Risk factors	CKD stage 1 eGFR >90 mL/min/1.73 m² N (%)	CKD stage 2a 90< eGFR >75 mL/min/1.73 m² N (%)	CKD stage 2b - 4 eGFR <75 mL/min/1.73 m² N (%)	*P*
Total patients, N=343	264 (77)	58 (16.9)	21 (6.1)	
Sex				0.9
Female, N=144	111 (77)	25 (17.4)	8 (5.6)	
Male, N=199	153 (76.9)	33 (16.6)	13 (6.5)	
Acute leukemia				0.2
ALL, N=219	163 (74.4)	39 (17.8)	19 (15.3)	
AML, N=24	101 (81.5)	17 (7.8)	4 (3.2)	
TBI				0.4
No, N=171	109 (63.7)	27 (15.8)	35 (20.5)	
Yes, N=199	153 (76.9)	31 (15.6)	15 (7.5)	
Relapse				0.03
No, CR1, N=190	148 (77.9)	36 (19)	6 (3.1)	
Yes, ≥ CR2, N=153	116 (75.8)	22(14.4)	15 (9.8)	
Type of donor				0.09
Sibling related donor, N=97	70 (72.2)	23 (23.7)	4 (4.1)	
Unrelated, N=225	176 (78.2)	32 (14.2)	17 (7.6)	
GVHD				0.8
No, N=56	45 (80.4)	8 (14.3)	3 (5.3)	
Yes, N=153	116 (75.8)	27 (17.6)	10 (6.6)	
Age at evaluation, years				0.003
≤ 15.8, N=147	126 (85.7)	15 (10.2)	6 (4.1)	
>15.8, N=196	138 (70.4)	43 (22)	15 (7.6)	
Age at diagnosis, years				0.04
≤ 4.6, N=142	119 (83.8)	17 (12)	6 (4.2)	
>4.6, N=201	145 (72.1)	41 (20.4)	15 (7.5)	
Age at 1st HSCT, years				0.004
≤ 8.4, N=170	144 (84.7)	19 (11.2)	7 (4.1)	
>8.4, N=170	118 (69.4)	38 (22.4)	14 (8.2)	
Follow-up, years				0.8
≤9.2, N=161	125 (77.7)	25 (15.5)	11 (6.8)	
>9.2, N=182	139 (76.4)	33 (18.1)	10 (5.5)	

aHSCT: allogenic hematopoietic stem cell transplantation; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CKD: chronic kidney disease; CR: complete remission; GVDH: graft-*versus*-host disease; eGFR: estimated glomerular filtration rate; TBI: total body irradiation.

197 patients (12.5%) were classified with CKD stage 2a-4 without tubular dysfunction.

These findings suggest a shift in the pattern of tubular damage over time. Subclinical tubulopathy may have a more insidious impact than CKD, as it is harder to detect and interpret. It may also play a putative role in the complex process of growth and bone metabolism for these growing children and adolescents, especially post-aHSCT.

In conclusion the NephroLEA cohort highlights that the aHSCT-specific population is at a significantly higher risk of developing CKD, particularly among patients older than 15 years at time of evaluation. This major long-term side effect may exacerbate cardiovascular risk factors, compounded by the well-documented prevalence of metabolic syndrome in this population of long-term transplanted survivors. Kidney-related side effects, including glomerular dysfunction or more insidious tubular dysfunction, potentially impact growth and overall health. To mitigate these risks, targeted education on general nephroprotective measures is essential. Recommendations include maintaining a diet controlled in sodium and proteins, achieving a normal BMI, engaging in regular physical activity, avoiding non-steroidal anti-inflammatory medications, and abstaining from tobacco exposure. These measures should be supported by regular medical monitoring, including annual blood pressure screenings with prompt therapeutic management in case of elevated SBP and/or DBP. Additionally, urinary ACR should be assessed at least every 5 years, as per nephrology guidelines. Implementing

Table 7. Chronic kidney disease risk factors for the patients of the NephroLEA cohort without allogenic hematopoietic stem cell transplantation.

Risk factors	CKD stage 1 N (%)	CKD stage 2a N (%)	CKD stage 2b-4 N (%)	*P*
Sex				
Female	546 (84.9)	75 (11.7)	22 (3.4)	5.10^{-6}
Male	619 (91.2)	53 (7.8)	7 (1.0)	
Acute leukemia				
ALL	1,045 (88.1)	115 (9.7)	26 (2.2)	1
AML	119 (88.1)	13 (9.6)	3 (2.2)	
Relapse				
No	1,144 (88.1)	126 (9.7)	28 (2.2)	0.6
Yes	21 (87.5)	2 (8.3)	1 (4.2)	
Age at evaluation, years				
≤ 15.8	623 (90.4)	51 (7.4)	15 (2.2)	0.01
>15.8	542 (85.6)	77 (12.2)	14 (2.2)	
Age at diagnosis, years				
≤ 4.6	609 (87.9)	69 (10.0)	15 (2.2)	0.9
>4.6	556 (88.4)	59 (9.4)	14 (2.2)	
Follow-up, years				
≤ 9.2	596 (89)	56 (8.4)	18 (2.7)	0.1
> 9.2	569 (87.3)	72 (11)	11 (1.7)	

aHSCT: allogenic hematopoietic stem cell transplantation; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CKD: chronic kidney disease.

these nephroprotective measures could improve global outcomes of post-leukemia survivors and address the growing public health challenge posed by the increasing number of cancer survivors, particularly those who have undergone aHSCT.

Disclosures

No conflicts of interest to disclose.

Contributions

CD, GM and LD designed research. CD, PS, MDT, MP, VG, SD, MP, DP, JHD, PC, ST, JK, AT, IP, YR, AB, PA and GM performed research. JB, PA and LD contributed analytical tools. CD, PS, ZH, JB, GM and LD analyzed data. CD, PS, ZH, MDT, MP, VG, SD, MP, DP, JHD, PC, ST, JK, AT, IP, YR, AB, PA, JB, GM and LD wrote the paper. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data-sharing statement

We accept to share the anonymous clinical data issued from this publication.

References

1. Clavel J, Goubin A, Auclerc MF, et al. Incidence of childhood leukaemia and non-Hodgkin's lymphoma in France: National Registry of Childhood Leukaemia and Lymphoma, 1990-1999. Eur J Cancer Prev. 2004;13(2):97-103.
2. Domenech C, Suciu S, De Moerloose B, et al. Dexamethasone (6 mg/m2/day) and prednisolone (60 mg/m2/day) were equally effective as induction therapy for childhood acute lymphoblastic leukemia in the EORTC CLG 58951 randomized trial. Haematologica. 2014;99(7):1220-1227.
3. Creutzig U, Zimmermann M, Bourquin J-P, et al. Randomized trial comparing liposomal daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: results from Study AML-BFM 2004. Blood. 2013;122(1):37-43.
4. Leung W, Campana D, Yang J, et al. High success rate of hematopoietic cell transplantation regardless of donor source in children with very high-risk leukemia. Blood. 2011;118(2):223-230.
5. Pession A, Masetti R, Rizzari C, et al. Results of the AIEOP AML 2002/01 multicenter prospective trial for the treatment of children with acute myeloid leukemia. Blood. 2013;122(2):170-178.
6. da Silva Selistre L, Renard C, Bacchetta J, et al. Teenagers and young adults with a past of allogenic hematopoietic stem cell transplantation are at significant risk of chronic kidney disease. Pediatr Nephrol. 2022;37(6):1365-1375.
7. Malyszko J, Kozlowska K, Kozlowski L, Malyszko J.

Nephrotoxicity of anticancer treatment. Nephrol Dial Transplant. 2017;32(6):924-936.
8. Tsurusawa M, Gosho M, Mori T, et al. Statistical analysis of relation between plasma methotrexate concentration and toxicity in high-dose methotrexate therapy of childhood nonHodgkin lymphoma. Pediatr Blood Cancer. 2015;62(2):279-284.
9. Kwatra NS, Meany HJ, Ghelani SJ, Zahavi D, Pandya N, Majd M. Glomerular hyperfiltration in children with cancer: prevalence and a hypothesis. Pediatr Radiol. 2017;47(2):221-226.
10. Perazella MA. Onco-nephrology: renal toxicities of chemotherapeutic agents. Clin J Am Soc Nephrol. 2012;7(10):1713-1721.
11. Ruggiero A, Ferrara P, Attinà G, Rizzo D, Riccardi R. Renal toxicity and chemotherapy in children with cancer. Br J Clin Pharmacol. 2017;83(12):2605-2614.
12. Skinner R. Nephrotoxicity of cancer treatment in children. Pediatric Health. 2010;4(5):519-538.
13. Krishnappa V, Gupta M, Manu G, Kwatra S, Owusu O-T, Raina R. Acute kidney injury in hematopoietic stem cell transplantation: a review. Int J Nephrol. 2016;2016:5163789.
14. Kizilbash SJ, Kashtan CE, Chavers BM, Cao Q, Smith AR. Acute kidney injury and the risk of mortality in children undergoing hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2016;22(7):1264-1270.
15. Isoda T, Ito S, Kajiwara M, Nagasawa M. Successful high-dose methotrexate chemotherapy in a patient with acute lymphocytic leukemia who developed acute renal failure during the initial treatment. Pediatr Int. 2007;49(6):1018-1019.
16. Kooijmans ECM, van der Pal HJH, Pluijm SMF, et al. The Dutch Childhood Cancer Survivor Study (DCCSS)-LATER 2 kidney analysis examined long-term glomerular dysfunction in childhood cancer survivors. Kidney Int. 2022;102(5):1136-1146.
17. Pelletier K, Côté G, Madsen K, et al. Chronic kidney disease, survival and graft-versus-host-disease-free/relapse-free survival in recipients of allogeneic hematopoietic stem cell transplant. Clin Kidney J. 2022;15(8):1583-1592.
18. Dieffenbach BV, Liu Q, Murphy AJ, et al. Late-onset kidney failure in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Eur J Cancer. 2021;155:216-226.
19. Stotter BR, Chan C, Chanchlani R. Late kidney effects of childhood cancer and cancer therapies. Adv Chronic Kidney Dis. 2021;28(5):490-501.e1.
20. Warady BA, Abraham AG, Schwartz GJ, et al. Predictors of rapid progression of glomerular and nonglomerular kidney disease in children and adolescents: the Chronic Kidney Disease in Children (CKiD) cohort. Am J Kidney Dis. 2015;65(6):878-888.
21. Kumar R, Reed S, Stanek JR, Mahan JD. Defining kidney outcomes in children with acute lymphoblastic leukemia in the modern era. Pediatr Nephrol. 2022;37(9):2119-2126.
22. Shroff R. Reducing the burden of cardiovascular disease in children with chronic kidney disease: prevention vs. damage limitation. Pediatr Nephrol. 2021;36(8):2537-2544.
23. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32(5 Suppl 3):S112-119.
24. Mitsnefes MM. Cardiovascular disease in children with chronic kidney disease. J Am Soc Nephrol. 2012;23(4):578-585.
25. Saultier P, Auquier P, Bertrand Y, et al. Metabolic syndrome in long-term survivors of childhood acute leukemia treated without hematopoietic stem cell transplantation: an L.E.A. study. Haematologica. 2016;101(12):1603-1610.
26. Oudin C, Berbis J, Bertrand Y, et al. Prevalence and characteristics of metabolic syndrome in adults from the French childhood leukemia survivors' cohort: a comparison with controls from the French population. Haematologica. 2018;103(4):645-654.
27. Kidney Disease: improving global outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2024;105(Suppl 4):S117-S314.
28. Berbis J, Michel G, Baruchel A, et al. Cohort Profile: the French Childhood Cancer Survivor study for leukaemia (LEA cohort). Int J Epidemiol. 2015;44(1):49-57.
29. Bouhanick B, Sosner P, Brochard K, et al. Hypertension in children and adolescents: a position statement from a panel of multidisciplinary experts coordinated by the French Society of Hypertension. Front. Pediatr. 2021;9:680803.
30. Matos V, Van Melle G, Boulat O, Markert M, Bachman C, Guignard JP. Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. J Pediatr. 1997;131(2):252-257.
31. Pierce CB, Muñoz A, Ng DK, Warady BA Furth SL, Schwartz GJ. Age- and sex-dependent clinical equations to estimate glomerular filtration rates in children and young adults with chronic kidney disease. Kidney Int. 2021;99(4):948-956.
32. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.
33. Ng DKS, Schwartz GJ, Jacobson LP, et al. Universal GFR determination based on two time points during plasma iohexol disappearance. Kidney Int. 2011;80(4):423-430.
34. Stevens PE, Levin A; Kidney disease: improving global outcomes chronic Kidney Disease Guideline Development Work group members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 Clinical Practice Guideline. Ann Intern Med. 2013;158(11):825-830.
35. Delanaye P, Jager KJ, Bökenkamp A, et al. CKD: a call for an age-adapted definition. J Am Soc Nephrol. 2019;30(10):1785-1805.
36. Adeli K, Higgins V, Trajcevski K, White-Al Habeeb N. The Canadian laboratory initiative on pediatric reference intervals: a CALIPER white paper. Crit Rev Clin Lab Sci. 2017;54(6):358-413.
37. Derain Dubourg L, Aurelle M, Chardon L, Flammier S, Lemoine S, Bacchetta J. Tubular phosphate handling: references from child to adulthood in the era of standardized serum creatinine. Nephrol Dial Transplant. 2022;37(11):2150-2156.
38. Kooijmans EC, Bökenkamp A, Tjahjadi NS, et al. Early and late adverse renal effects after potentially nephrotoxic treatment for childhood cancer. Cochrane Database Syst Rev. 2019;3(3):CD008944.
39. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016;34(36):4381-4389.
40. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. 2018;378(5):439-448.
41. Peters C, Dalle J-H, Locatelli F, et al. Total body irradiation or chemotherapy conditioning in childhood ALL: a multinational, randomized, noninferiority phase III study. JCO. 2021;39(4):295-307.

42. Willasch AM, Peters C, Sedláček P, et al. Myeloablative conditioning for allo-HSCT in pediatric ALL: FTBI or chemotherapy? A multicenter EBMT-PDWP study. Bone Marrow Transplant. 2020;55(8):1540-1551.
43. Piñana JL, Valcárcel D, Martino R, et al. Study of kidney function impairment after reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation. A single-center experience. Biol Blood Marrow Transplant. 2009;15(1):21-29.
44. Abboud I, Porcher R, Robin M, et al. Chronic kidney dysfunction in patients alive without relapse 2 years after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2009;15(10):1251-1257.
45. Watanabe Nemoto M, Isobe K, Togasaki G, et al. Delayed renal dysfunction after total body irradiation in pediatric malignancies. J Radiat Res. 2014;55(5):996-1001.
46. Frisk P, Arvidson J, Neveus T. Glomerular and tubular function in young adults treated with stem-cell transplantation in childhood. Pediatr Nephrol. 2010;25(7):1337-1342.
47. Saultier P, Oudin C, Michel G. Metabolic syndrome among leukemia survivors: still delineating the risk. Metab Syndr Relat Disord. 2017;15(6):263-265.
48. Lopez R, Plat G, Bertrand Y, et al. Testosterone deficiency in men surviving childhood acute leukemia after treatment with hematopoietic stem cell transplantation or testicular radiation: an L.E.A. study. Bone Marrow Transplant. 2021;56(6):1422-1425.
49. Florido R, Daya NR, Ndumele CE, et al. Cardiovascular disease risk among cancer survivors: the Atherosclerosis Risk In Communities (ARIC) study. J Am Coll Cardiol. 2022;80(1):22-32.
50. Hsiao W, Lapite A, Faig W, et al. Long-term kidney and cardiovascular complications in pediatric cancer survivors. J Pediatr. 2023;255:89-97.e1.
51. Calderon-Margalit R, Golan E, Twig G, et al. History of childhood kidney disease and risk of adult end-stage renal disease. N Engl J Med. 2018;378(5):428-438.