Physical impairments, activity limitations, and participation restrictions of childhood acute lymphoblastic leukemia survivors: A PETALE cohort study

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May 15, 2023

Abstract

Background: Long-term musculoskeletal complications represent a growing burden for survivors of childhood acute lymphoblastic leukemia (cALL). This study aimed to describe impairments, activity limitations, and participation restrictions of survivors of cALL at highest risk for late morbidity (PETALE cohort). Procedure: This retrospective study, using cross-sectional observational data from the PETALE cohort, included a subgroup of survivors who presented extreme phenotypes of late effects. Participants completed bilateral hip magnetic resonance imaging (MRI), assessment of maximal isometric muscle strength (MIMS), range of motion (ROM), Near Tandem Balance (NTB), 6-Minute Walk Test (6MWT), Five Time Sit-to-Stand Test (FTSST)), and quality of life (QOL). Descriptive statistics and regression analyses were performed. Results: 97 survivors were included in this study. The selected survivors (24.2 $\pm$ 6.7 years old) trended toward lower scores for most outcomes compared to available expected values referenced from a healthy population except for QOL. Thirteen participants (14.6%, 18 hips) had hip ON (53.8% male). Female survivors had hip ON with higher severity score (66.7% female vs. 22.2% male). Survivors with hip ON had reduced hip external rotation ROM compared to those without ($p<0.05$). Relationships were found between MIMS and ROM outcomes, and with 6MWT. Our multiple linear regression model explained 27.6% of the variance of the 6MWT. Conclusions: Although they reported QOL in the range of healthy peers, long-term cALL survivors at highest risk for late morbidity had clinically significant impairments and activity limitations. These data are in keeping with the frailty phenotype described in childhood cancer survivors.

TITLE PAGE

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[1] Some of the results presented in this paper have previously been published as meeting abstracts:

- Physical impairments and activity limitations of childhood acute lymphoblastic leukemia survivors: A PETALE cohort study. 10th International Conference on Children's Bone Health, July 2-5, 2022. https://asbmr.onlinelibrary.wiley.com/doi/abs/10.1002/jbm4.10676
- Physical impairments and activity limitations of childhood acute lymphoblastic leukemia survivors: A PETALE cohort study. SIOP 2021. October 21-24, 2021. https://onlinelibrary.wiley.com/toc/15455017/2021/68/S5

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Word count:

a) Abstract : 249 words

b) Main Text *(excludes title page, abstract, Conflicts of Interest, Acknowledgments, References, Tables, Figures, and Legends)*: 3 492 words

Number of:

- Tables: 3
- Figures: 3
- Supporting information files: 0

Short running title: Long-term outcomes of survivors of the PETALE cohort

Keywords: childhood acute lymphoblastic leukemia, survivor, functional outcome, osteonecrosis, neuromusculoskeletal

Abbreviation table:

Abbreviation	Full term or phrase
6MWT	6-Minute Walk Test
cALL	Childhood acute lymphoblastic leukemia
FTSST	Five Time Sit-to-Stand Test
HHD	Hand-held dynamometer
HRR	High risk of relapse
HRQOL	Health-related quality of life
ICF	International Classification of Functioning, Disability and Health
LMHR	Late morbidity high-risk
MIMS	Maximal isometric muscle strength
MIMT	Maximal isometric muscle torque
MRI	Magnetic resonance imaging
NMSK	Neuromusculoskeletal
NTB	Near Tandem Balance
ON	Osteonecrosis
PedsQL	Pediatric Quality of Life Inventory
PedsQL – MFS	Pediatric Quality of Life Inventory - Multidimensional Fatigue Scale
QOL	Quality of life
ROM	Range of motion
WHO-5	World Health Association Well-Being Index – 5

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Procedure: This retrospective study, using cross-sectional observational data from the PETALE cohort, included a subgroup of survivors who presented extreme phenotypes of late effects. Participants completed bilateral hip magnetic resonance imaging (MRI), assessment of maximal isometric muscle strength (MIMS), range of motion (ROM), Near Tandem Balance (NTB), 6-Minute Walk Test (6MWT), Five Time Sit-to-Stand Test (FTSST)), and quality of life (QOL). Descriptive statistics and regression analyses were performed.

Results: 97 survivors were included in this study. The selected survivors (24.2 ± 6.7 years old) trended toward lower scores for most outcomes compared to available expected values referenced from a healthy population except for QOL. Thirteen participants (14.6%, 18 hips) had hip ON (53.8% male). Female survivors had hip ON with higher severity score (66.7% female vs. 22.2% male). Survivors with hip ON had reduced hip external rotation ROM compared to those without ($p<0.05$). Relationships were found between MIMS and ROM outcomes, and with 6MWT. Our multiple linear regression model explained 27.6% of the variance of the 6MWT.

Conclusions: Although they reported QOL in the range of healthy peers, long-term cALL survivors at highest risk for late morbidity had clinically significant impairments and activity limitations. These data are in keeping with the frailty phenotype described in childhood cancer survivors.

Introduction

Childhood acute lymphoblastic leukemia (cALL) is the most frequent type of pediatric cancer [1,2]. Each year in Canada, 1000 children and adolescents get diagnosed with cALL[2,3]. The development of risk-based treatment protocols has contributed to reach a survival rate over 90%, which indicates more adults are now survivors of cALL [2,4].

Although the survival rate has improved, this young population continues to experience physical and mental health issues [5]. Contemporary treatment regimen toxicities have led to multiple late adverse effects [5-7]. While children and adolescents with cALL might survive over five years without disease relapse, most of them will experience at least one chronic condition [5]. The most prevalent morbidities include, but are not limited to, disorders affecting musculoskeletal, endocrine, and neurological systems [5]. The spectrum of neuromusculoskeletal (NMSK) impairments can range from muscle weakness to vertebral fractures and osteonecrosis (ON) and have been associated with poor functional outcomes [5,8-12]. According to the International Classification of Functioning, Disability and Health (ICF) definitions, survivors of cALL are at risk for long-term NMSK impairments, activity limitations, and participation restrictions [13].

ON is one of the most debilitating bone impairments associated with cALL [14,15]. This complication is characterized by an alteration in blood supply causing bone necrosis involving low mineral bone density and hypercoagulopathy [16]. Age at diagnosis (> 10 years old), treatment (radiotherapy, corticosteroids, asparaginase), female sex and body mass index have been identified as contributors to ON [16-23]. ON incidence varies widely between studies ranging from 1.8%-71.8% depending on the definition of ON (symptomatic, asymptomatic), treatment protocol (corticosteroid doses), outcome measures (self-reported, imaging), studied sample (± 10 years old at diagnosis) or timing

of assessment (under treatment, off-treatment) [16,17,20,23-27]. The timing and outcome of ON are also highly unpredictable. It can occur from two months from diagnosis to over five years after and evolve from complete resolution to severe deterioration [20,27]. The most frequent sites affected are weight-bearing joints mainly hips and knees [15,20,22,24,28]. Lesions are more likely to be multifocal (bilateral) and affect multiple sites (different bones) [27]. When ON occurs at the articular surfaces of long bone epiphysis, bone deformity and joint destruction causing chronic pain can ensue [24]. ON symptoms interfering with function can persist over five years in 60% of affected patients [27]. Furthermore, hip ON represents an important proportion (18%) of health problems requiring hip arthroplasty in young adults [29,30].

Neuromuscular and cardiorespiratory late adverse effects can also contribute to physical impairments and activity limitations of survivors of cALL. Indeed, neuromuscular impairments such as muscle weakness and limited range of motion are described among childhood cancer survivors' studies [8,10,31-33]. Chemotherapy induced peripheral neuropathy and immobility are some of the causes identified[34-36]. Cardiorespiratory impairments including limited exercise capacity are also largely documented in the literature and are related but not limited to doxorubicin treatment[37]. Inactivity during and after treatment is a common factor for neuromuscular and cardiorespiratory impairments[38]. These long-term complications contribute to the frailty phenotype described in this population[39,40].

Overall, the spectrum of NMSK morbidities of cALL survivors can impact function and affect quality of life. A better understanding of these physical impairments, activity limitations, and participation restrictions would serve to optimize screening and management of these long-term complications and help support this growing population

of young adult. The main objectives of this study were to: 1) describe the impairments, activity limitations, and participation restrictions related to the long-term NMSK sequelae of survivors of cALL from the PETALE cohort at highest risk for late morbidity; 2) assess the relationships between these impairments, activity limitations, and participation restrictions; and 3) among the impairment variables, identify those that best explain activity limitations. A secondary objective was to compare clinical characteristics and functional outcomes between survivors with and without hip ON.

Methods

Study and participants

This retrospective study is based on cross-sectional observational data from the PETALE cohort [41]. The PETALE cohort included 246 long-term survivors of cALL (> 5 years post-diagnostic) treated with Dana Farber Cancer Institute protocols from 87-01 to 05-01 who did not relapse or receive hematopoietic stem cell transplant (see Marcoux et al. for detailed protocol) [41]. Our late morbidity high-risk (LMHR) subgroup included survivors from the PETALE cohort with extreme phenotypes of late morbidities (bone, cardiac, metabolic, neuropsychologic, quality of life). High-risk survivors for bone morbidities were participants with extreme bone phenotype (defined as vertebral fracture, low bone mineral density at the lumbar or hip site, ON) or at highest risk for asymptomatic ON. Participants at highest risk for asymptomatic ON were selected if they presented at least one of the following criteria: age at diagnosis > 10 years old; high risk of disease relapse.

Outcomes measures

Participant characteristics

Socio-demographic (age, sex, occupation), anthropometric (weight, height, body mass index) and clinical characteristics (age at diagnosis, time since diagnostic, risk stratification, vincristine and corticosteroid cumulative doses, radiotherapy) data was collected through medical files and questionnaires.

Physical impairments and activity limitations

Hip ON was assessed by magnetic resonance imaging (MRI) by two expert radiologists using the Niinimäki classification system [42]. ON was defined by the presence of a unilateral or bilateral ON of grade II or more. Grade IV and V ON were defined has severe ON considering the presence of a lesion affecting $\geq$ 30% of the articular surface [14,21,25,28,43,44]. Physical impairments and activity limitations were assessed by four expert oncology physiotherapists. Presence (yes or no) and location (back, lower or upper limb) of musculoskeletal pain was documented. Passive range of motion (ROM) of the hip (flexion, extension, abduction, adduction, external rotation, internal rotation) and ankle (dorsiflexion) was measured with a bubble inclinometer (Baseline™) according to a standardized protocol [45-47].

Maximal isometric muscle torque (MIMT) of hip abduction and ankle dorsiflexion), and maximal isometric muscle strength (MIMS) of the knee extension was measured with MEDup™ hand-held dynamometer (HHD) (Atlas Medic™, Québec, Canada) according to a standardized protocol developed by Hébert et al. [48,49]. MIMT and MIMS was measured using a make test in closed chain with proper stabilization and without gravity effect to eliminate the impact of the weight of the segment. The mean of the two closest values

158 from a maximum of three trials was used for the final analysis. Grip strength was
159 measured with a JAMAR™ HHD on both sides in sitting position using the mean of three
160 trials for the final analysis [50].
161 Balance and lower limb proprioception were assessed with the Near Tandem Balance
162 (NTB) with a protocol that includes standardized positioning of the feet [51]. Participants put
163 preferred foot 2.5 cm (great toe to heel) in front and 2.5 cm on the side (heel to fore feet)
164 from the other foot. NTB was performed bare feet and eyes closed. The test ended when
165 the participant was taking a step or after completing 30 seconds. A second trial was
166 authorized when the participants held the position ≤ 5 seconds on the first trial.
167 Functional lower limb strength was measured by the Five Times Sit-to-Stand Test
168 (FTSST). Participants were asked to stand up from sitting position five times without arm
169 support [52,53].
170 Functional capacity was measured by a kinesiologist with the 6-Minute Walk Test (6MWT)
171 in the Phase I of the PETALE study (8-12 months before Phase II). The 6MWT is a sub-
172 maximal exercise where participants are asked to walk the longest distance in six minutes
173 [24,54-57]. The test was performed according to a standardized protocol. Participants had a
174 practice trial. A 10-minute break was given between practice and test trial.
175 Participation restrictions
176 Health-related quality of life (HRQOL) was measured in Phase I with the Pediatric Quality
177 of Life Inventory (PedsQL) Generic Core Scales (4.0 version) questionnaire [58,59]. Fatigue
178 impact on HRQOL was assessed with the self-reported version in French language of the
179 PedsQL - Multidimensional Fatigue Scale (PedsQL – MFS) [59-61]. Well-being was

measured in Phase II with the World Health Organisation Well-Being Index – 5 (WHO-5)[62].

Written informed consent was obtained from all participants or their parent (<18 years old). The study was approved by the institution's ethics review board (2022-3260).

Data analysis

Descriptive statistics such as measures of frequency, central tendency and variability were used to characterize bone morbidities, physical impairments, activity limitations and participation restrictions. Depending on available expected values referenced from a healthy population, a descriptive comparison or z-score calculation was conducted (Wilcoxon sing-rank test to compare median to zero). Appropriate for data distribution, t-tests or Wilcoxon-Mann-Whitney tests and chi-square or Fisher tests for continuous and categorial variables, respectively, were performed to compare survivors with and without hip ON. Socio-demographic, anthropometric and clinical characteristics data were compared between our sample and the PETALE cohort.

Pearson or Spearman tests were used to verify the strength and direction of relationships between clinical characteristics, physical impairments, activity limitations, and participation restrictions variables. Considering control variables, multiple linear regression or generalized model analyses appropriate for the distribution of the dependent variables were used to explain variability of scores obtained during the functional tests (FTSST, 6MWT). Statistical analyses were done through R Software (1.3.1056 version). A significance level of 0.05 was selected as p-value.

Results

The PETALE cohort has been previously described in detail by Marcoux et al [41]. Survivors with high-risk criteria for late morbidities were contacted for further investigations in Phase II (n=124). Reasons for eligible survivors not to participate were refusal (n=11), unknown reason (n=6), no show (n=4), cancellation (n=3), unavailability (n=2) or impossible to reach (n=1). As shown in the Table 3, characteristics of the 97 survivors included in this LMHR sub-study were similar to the overall PETALE cohort except for age at diagnosis, HRR, and cranial radiotherapy in accordance with high-risk criteria.

TABLE 1 Participants' characteristics for PETALE cohort and late morbidity high-risk sub-group.

	PETALE cohort (n=245)		Late morbidity high-risk subgroup (n=97)[1]	
	Mean	SD	Mean	SD
Age at assessment, years	22.1	6.3	23.3	6.8
Age at diagnosis,years	6.7	4.6	8.1	5.1
Time since diagnosis, years	15.5	5.2	15.1	5.7
Sex				
Female, n(%)	125 (51.0)		49 (50.5)	
High risk of relapse, n(%)	132 (53.9)		71 (73.2)	
Cranial radiotherapy, n(%)	145 (59.2)		73 (75.3)	
Vertebral fracture[2], n(%)	55 (22.5)		26 (26.8)	

High risk for bone morbidity[2,3]	158 (64.5)	79 (81.4)[4]

[1]At the time of Phase I; [2]Missing data (n=1); [3]At least one criterion for bone morbidity (vertebral fracture, low bone mineral density at the lumbar or hip site (<2SD), ON, > 10 years old, high risk of disease relapse); [4]Representing 50% of high risk for bone morbidity participants.

Hip ON was identified in 14.6% of survivors who underwent MRI (n=13, 53.8% male) representing a total of 18/26 hips (Fig. 1). Both sides were equally affected (50% right) and slightly more than half the lesions were bilateral (55.6%). No statistical difference between sex was shown in hip ON grade though female survivors tended to present hip ON with higher severity score (Niinimäki grade ≥ 4) than male (66.7% vs. 22.2%).

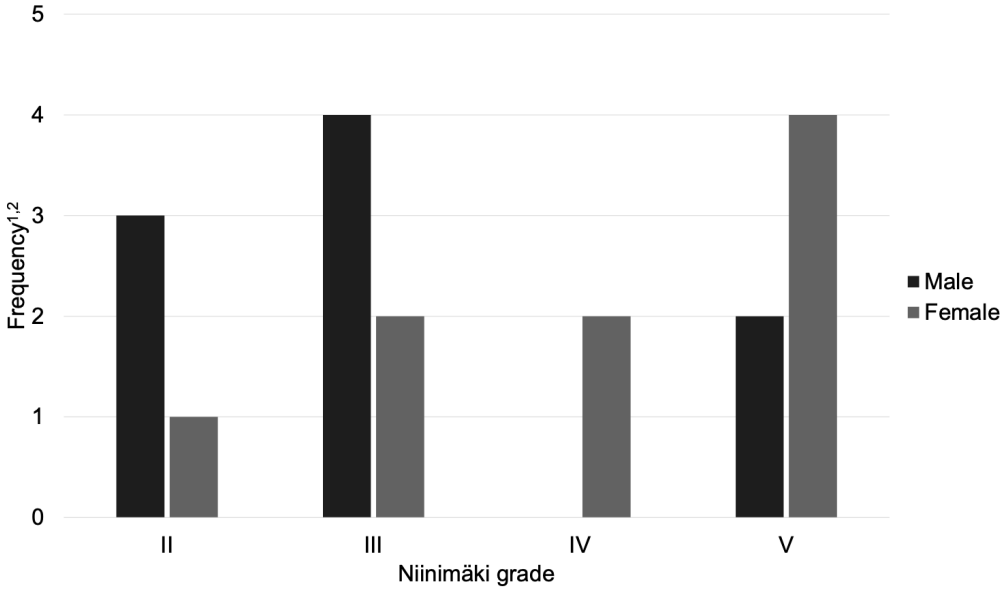

Figure 1 Distribution of hip ON according to Niinimäki grade

[1]Right side hip ON (n=9, 50%; 55.6% female); [2]Bilateral hip ON (n=10, 55.6%; 66.7% female).

Clinical characteristics, impairments, activity limitations, and participation restrictions are shown in Table 2. Descriptive comparisons with available expected values referenced from a healthy population show that survivors tended to have limited passive ROM of the hip (flexion, extension, abduction) and ankle (dorsiflexion) as well as MIMS (knee extension) and MIMT (hip abduction, ankle dorsiflexion) (Fig. 2) [46,48,63-66].

231 TABLE 2 Clinical characteristics, physical impairments, activity limitations, and

232 participation restrictions

	NA n(%)	All participants[1] (n=97)[†]		With ON[2,3] (n=13)		Without ON[2] (n=76)		With ON vs. without ON[2] (p-value)*
		Mean	SD	Mean	SD	Mean	SD	
Age at assessment, year	0	24.2	6.7	25.9	7.4	24.3	6.6	0.478
Age at diagnosis, year	0	8.1	5.1	11.9	5.3	7.6	4.9	**<0.01**
Time since diagnosis, year	0	16.4	5.7	14.5	6.3	17.0	5.7	0.151
Sex								
Female, n(%)	0	49 (50.5)		6 (46.2)		39 (51.3)		0.965
High risk of relapse, n(%)	0	71 (73.2)		13 (100)		52 (68.4)		**<0.05**
Vertebral facture	0	26(26.8%)		3(23.1%)		21(27.6%)		0.997
Cranial radiotherapy, n(%)	0	73 (75.3)		11 (84.6)		56 (73.7)		0.620
Vincristine cumulative dose, mg/m^2	3 (3.1)	57.0	14.1	50.5	12.2	57.8	13.8	0.071
Corticosteroid cumulative dose, mg/m^2	3 (3.1)	12303	4984	11202	5054	12493	5088	0.455

Range of motion, °								
Hip flexion								
Right	4 (4.1)	112.8	11.6	111.8	15.7	112.7	11.4	0.854
Left	4 (4.1)	113.3	11.5	108.5	15.3	113.7	11.3	0.371
Hip extension								
Right	4 (4.1)	12.3	7.5	11.7	7.5	12.2	7.7	0.879
Left	4 (4.1)	12.0	7.6	11.0	10.2	12.0	7.3	0.807
Hip abduction								
Right	4 (4.1)	44.9	11.1	34.6	17.8	45.8	8.3	0.073
Left	4 (4.1)	45.4	9.9	38.1	16.2	46.1	8.2	0.120
Hip external rotation								
Right	5 (5.2)	39.8	10.8	31.5	11.6	40.9	9.5	**<0.05**
Left	5 (5.2)	40.0	11.5	32.3	14.5	41.0	10.1	**<0.05**
Hip internal rotation								
Right	5 (5.2)	35.2	12.4	35.0	14.0	35.4	12.4	0.730
Left	5 (5.2)	35.3	11.6	34.3	11.1	35.3	11.6	0.852
Ankle dorsiflexion								
Right	5 (5.2)	11.2	7.2	13.4	7.0	10.8	7.3	0.263
Left	5 (5.2)	10.5	7.2	11.2	5.8	10.4	7.6	0.636
MIMT and MIMS								
Hip abduction MIMT, Nm								
Right	7 (7.2)	49.9	25.3	52.1	34.5	49.9	23.6	0.924
Left	6 (6.2)	51.1	27.3	56.9	34.8	50.1	26.6	0.506

Knee extension MIMS, N								
Right	5 (5.2)	376.0	137.9	336.0	110.9	381.1	135.4	0.382
Left	6 (6.2)	365.9	138.4	333.5	122.7	370.5	137.5	0.524
Ankle dorsiflexion MIMT, Nm								
Right	7 (7.2)	12.8	5.0	13.1	4.7	13.0	5.2	0.870
Left	7 (7.2)	12.0	5.2	12.6	5.6	12.2	5.2	0.881
Grip strength, kg								
Right	3 (3.1)	34.7	10.7	31.6	8.9	35.4	10.8	0.195
Left	3 (3.1)	33.5	11.2	30.9	10.6	34.2	11.2	0.307
Near tandem balance								
Time, second	4 (4.1)	26.1	8.2	25.3	8.6	25.9	8.4	0.820
Success[4], n(%)	4 (4.1)	75 (80.6)		9 (75)		59 (79.7)		1
FTSTT, seconds	4 (4.1)	8.1	2.5	8.6	2.5	8.2	2.6	0.670
6MWT								
Distance, meter	20 (20.6)	621.7	81.3	610.3	57.7	625.4	85.2	0.609
z-score	20 (20.6)	-0.13	1.60	-0.44	0.79	-0.04	1.71	0.518
PedsQL Generic Core Scale 4.0								
Total score	2 (2.1)	80.4	13.8	76.2	13.2	80.9	13.9	0.206
Physical health	2 (2.1)	83.3	17.3	74.8	20.3	84.3	16.8	0.101
Psychosocial health	2 (2.1)	78.9	14.5	76.9	13.8	79.1	14.9	0.506

PedsQL Multidimensional Fatigue Scale								
Total fatigue, %	1 (1.0)	69.3	17.4	67.4	15.3	69.7	18.2	0.763
General fatigue	1 (1.0)	72.7	20.8	66.7	17.8	73.6	21.5	0.208
Rest/sleep fatigue	1 (1.0)	65.8	18.0	63.1	11.5	66.5	18.9	0.507
Cognitive fatigue	1 (1.0)	69.2	22.7	72.4	22.1	68.8	23.8	0.506
WHO-5, %	0	61.1	23.0	66.8	20.2	60.3	24.2	0.389

233 NA: Missing data; 6MWT: 6-Minute Walk Test; FTSTT: Five Time Sit-to-Stand Test;
234 MIMS: Maximal isometric muscle torque (Nm: Newton-meter) or strength (N: Newton);
235 *Chi square test for binary variables, Wilcoxon-Mann-Whitney test for continuous
236 variables; [1]High-risk subgroup; [2]Participants who underwent MRI (n=89); [3]Number of hip
237 ON on each side (n=9); [4]Participants who completed 30 seconds.
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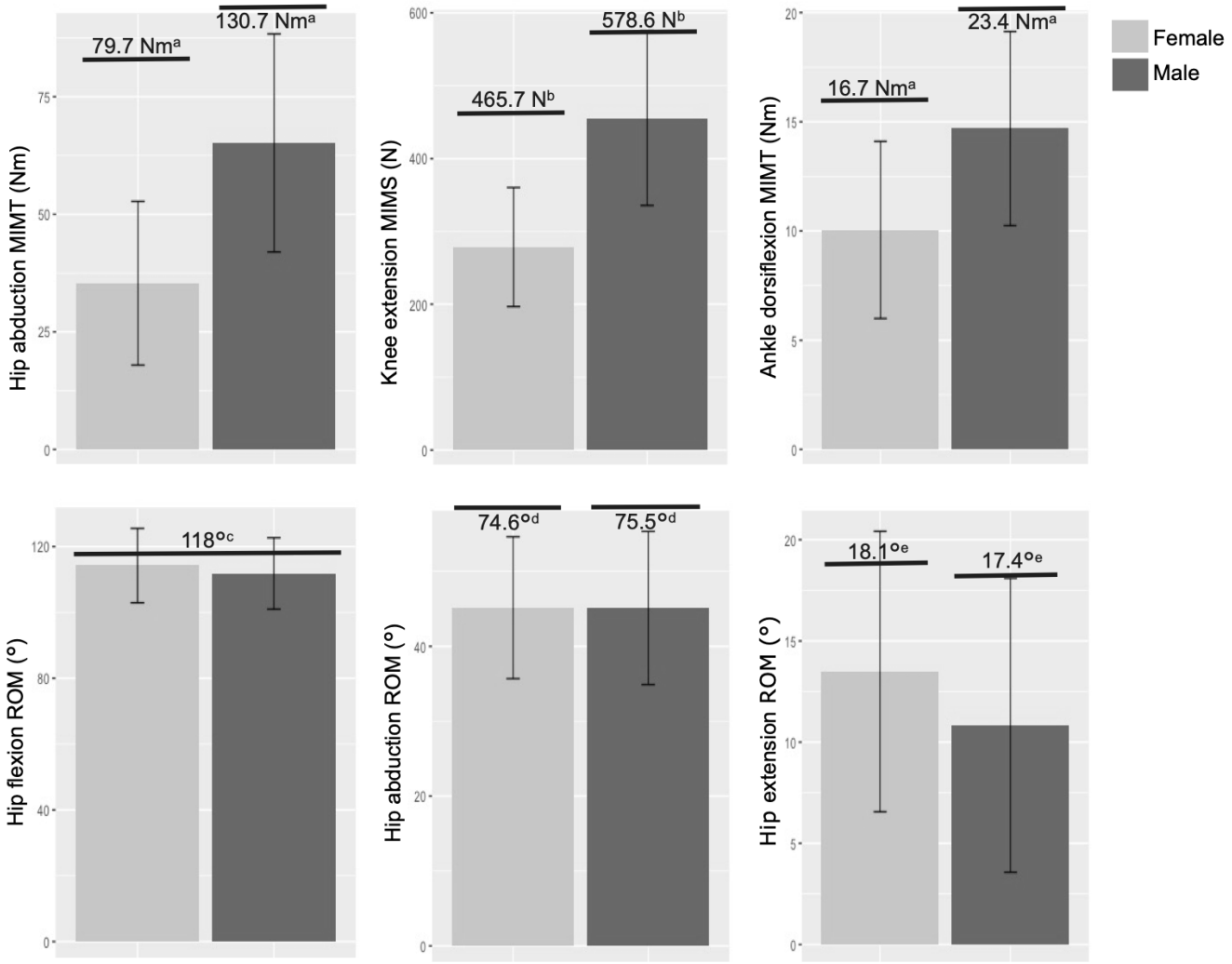

239

240 Figure 2 Physical impairments compared to reference values

241 Mean and SD of the average of both sides (no statistical difference between sides); MIMT:
242 Maximal isometric muscle torque; MIMS: Maximal isometric muscle strength; N: Newton;
243 Nm: Newton-meter; ROM: Range of motion; [a]Lower bond of the 95% confidence interval
244 of the mean values of 17 years old (Hébert et al., 2015); [b]Mean values of the non-
245 dominant side of 20-29 years old (Bohannon et al., 1997); [c]Mean values of 18-35 years
246 old male (Charlton et al., 2015); [d]Mean values of 23.2±1.2 years old in combined unilateral

247 flexion/abduction/external rotation vs. frog leg position (Bagwell et al., 2016). [e]Mean
248 values of 20-44 years old (Soucie et al., 2011).
249
250 Moreover, when z-score were calculated from reference values to compare median to
251 zero (Wilcoxon sing-rank test), grip strength, FTSST et NTB performance were limited
252 ($p<0.001$) [50,51,53,67]. 6MWT performance trended towards lower values but was not
253 statistically significant ($p=0.353$) [68,69]. PedsQL and PedsQL – MFS total scores (p=0.09-
254 0.22) and WHO-5 scores were in the normal range of healthy population values [62,70,71].
255 Pain and self-reported activity limitations are shown in Table 3. Most survivors (blinded
256 from hip MRI outcomes) reported musculoskeletal pain at the time of assessment. The
257 most prevalent location of musculoskeletal pain was in the lower limb (n=31, 33.0%) and
258 the back (n=22, 23.4%). Lower limb pain was located at the knee (n=16, 17.0%), ankle or
259 foot (n=9, 9.6%), and hip (n=6, 6.4%).
260
261 TABLE 3 Pain and self-reported activity limitations

	All participants[1] (n=97)	With ON[2] (n=13)	Without ON[2] (n=76)	With ON vs. without ON[2] (p-value)*
Pain[3]				
Yes, n (%)	50 (53.2%)	6 (50%)	40 (54.1%)	1
Activity limitation[3]				
Yes, n (%)	21 (22.3%)	4 (33.3%)	17 (23.0%)	0.680

[1]All Phase II participants (high-risk subgroup); [2]Participants who underwent MRI (n=89); [3]Missing data (n=3).

Survivors reporting functional limitations had difficulty walking (n=13, 13.8%), climbing stairs, and standing up from a chair (n=7, 7.4%). Walking limitation was reported by the one individual who required a walking aid. Half of the participants reported limping.

When comparing clinical profiles of survivors with and without hip ON, participants with hip ON were significantly older at diagnosis and were all at HRR (Table 4). Half of survivors with hip ON and lower limb musculoskeletal pain (n=6, 50%) located pain specifically at the hip (n=3, 50%). Survivors with hip ON had less hip external rotation ROM compared to those without ($p<0.05$) (Fig. 3). Female survivors with hip ON tended to have more physical impairments, except for hip internal rotation ROM and grip strength, than their male counterparts.

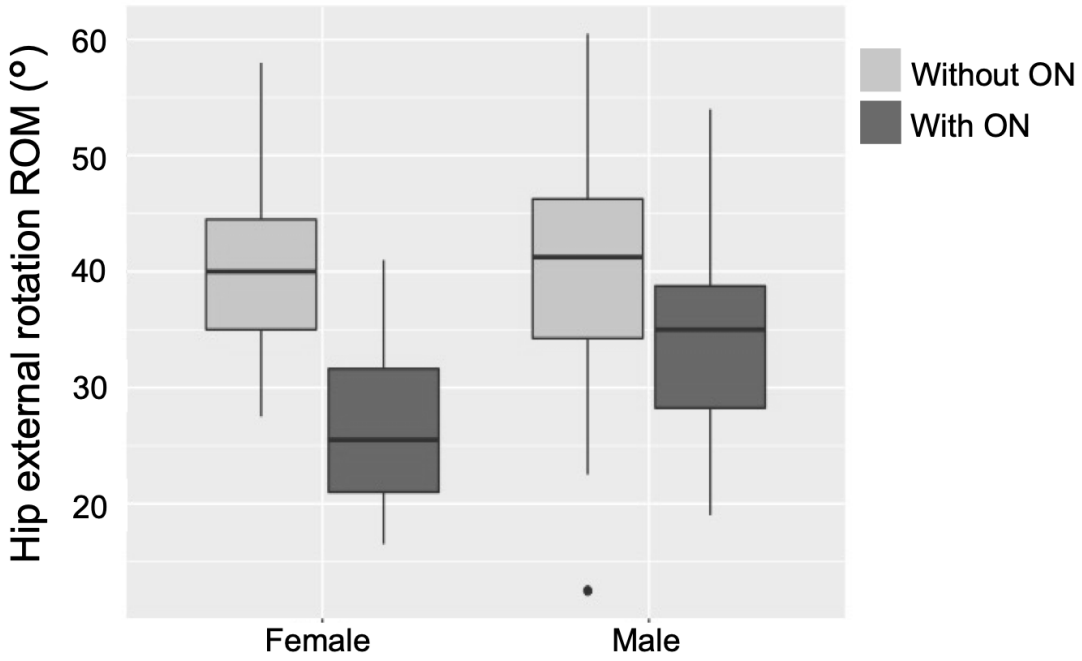

Figure 3 Hip physical impairment in participants with and without hip ON

When all participants were pooled, grip strength was correlated with the following: knee extension MIMS (r=0.70-0.74, p<0.001), hip abduction (r=0.64-0.66, p<0.001) and ankle dorsiflexion MIMT (r=0.40, p<0.001). A correlation was also found between lower limb strength outcomes (hip abduction, knee extension, ankle dorsiflexion) (r=0.35-0.61, p<0.001). Ankle dorsiflexion ROM and MIMT were correlated as well (r=0.32, p<0.01). The 6MWT was correlated with grip strength (r=0.32-0.34, p<0.01), hip abduction MIMT (0.39, p<0.001) and knee extension MIMS (r=0.41, p<0.001). No relationship was found between physical impairments or activity limitations outcomes and cumulative corticosteroids or vincristine doses.

Our multiple linear regression model explained 27.6% of the variance of the 6MWT. Knee extension MIMS (ß=0.27, p<0.01) and body mass index (ß= -5.27, p<0.01) had a

289 statistically significant effect on the 6MWT performance. Our generalized linear models
290 explained 8.13% of the variance of the FTSST. Knee extension MIMS had a statistically
291 significant effect on the FTSTT performance ($p<0.05$) but was not clinically meaningful
292 (0.0079% increase in FTSST for every 1 N of MIMS).
293
294 **Discussion**
295 Our LMHR subgroup of cALL survivors showed important physical impairments and
296 activity limitations regardless of whether they presented hip ON. Most physical impairment
297 and activity limitation outcomes of survivors tended to be lower than their healthy peers.
298 To our knowledge, this is the first study to measure hip ROM in survivors of cALL. Hip
299 (flexion, extension, abduction) and ankle (dorsiflexion) ROM were limited in survivors
300 when compared to available reference values [46,63,72]. This is consistent with previous
301 findings who documented limited active dorsiflexion ROM and its impact on gait and
302 walking capacity [64,65] [8,73]. Furthermore, survivors in our subgroup trended toward lower
303 scores for MIMS (knee extension), MIMT (hip abduction, ankle dorsiflexion), and showed
304 significantly lower grip strength. Moreover, even if the knee extension MIMS might have
305 been overestimated by the HHD placement leading to a shorter lever arm (10 cm vs. 5 cm
306 over the external malleoli), our participants still showed lower knee extension MIMS
307 values compared to reference values[48,66]. These results are in keeping with previous
308 studies involving childhood cancer survivors that described physical impairments such as
309 muscle weakness and limited range of motion [8,10,31-33]. Balance and proprioception as
310 measured by the NTB were also affected in our subgroup. Only 80.6% of participants did
311 successfully complete the test compared with 94% reported by Butler et al. in a young

312 healthy population (20-39 years old) [51]. FTSST performance was significantly lower than
313 age-matched healthy peers. In fact, according to Bohannon et al., our survivors'
314 performance resemble that of an older population (60-79 years old) [53]. This is in keeping
315 with Hayek et al. who reported a prevalence of 4.6% frailty among survivors of leukemia
316 compared to 2.2% among their siblings [74]. Authors suggest that their data seem to
317 highlight an accelerated aging process related to cancer treatment exposure [40,74,75].
318 Although PETALE survivors showed important physical impairments and activity
319 limitations, participation restriction outcomes were similar to those expected from a
320 healthy population. This could be explained by the positive health perception described in
321 long-term survivors [76,77]. However, DeFeo et al. described lower QOL scores on physical
322 domains of the Medical Outcomes Study 36-Item Health Survey Questionnaire (SF-36) in
323 long-term survivors of cALL including survivors with an history of ON [24]. In our cohort,
324 Lamore et al. reported unmet needs in terms of access and continuity of care of survivors
325 with bone complications[78]. Relationship between HRQOL, physical impairments, activity
326 limitations, and unmet needs in our subgroup remains unclear.
327 Hip ON incidence in our subgroup was similar to Inaba et al. who reported 12% of
328 participants in their cohort with hip ON at the end of treatment [28]. Kaste et al. reported an
329 higher cumulative incidence of hip ON of 21.7 ± 1.9% after completion of therapy (4 years
330 post-diagnosis) [21]. To our knowledge, no study has screened for hip ON with MRI in a
331 long-term cohort (> 5 years post-diagnosis) of survivors of cALL regardless of the history
332 of ON or the presence of symptoms[22]. Incidence of hip ON in the PETALE cohort might in
333 fact be underestimated since half of participants considered at high risk of bone morbidity
334 did not take part in Phase II for project resources issues.

Our data also support the evidence that hip ON is often asymptomatic. In contrast with Winkel et al., even if half the participants with hip ON in our study did not report hip pain, they presented important physical impairments [27]. Indeed, external rotation of the hip was significantly limited in our participants with hip ON. DeFeo et al. did not find statistical difference in lower limb function outcome between survivors with and without ON, but they did not measure specific hip outcome although it was the second most affected site[24]. Identification of this physical impairment is interesting from a clinical point of view as physiotherapists may help screen asymptomatic hip ON with a standardized ROM assessment of the hip. Since hip impairment can be associated with referred pain and that knee pain was prevalent in our subgroup, our data might also underestimate symptomatic ON[79].

While incidence of hip ON was similar for both sexes, female survivors of cALL seem to present hip ON with higher severity score. Oeffinger et al. also reported that female long-term survivors of cancer including cALL were 1.5 times more likely to suffer from any severe condition (Common Terminology Criteria for Adverse Events v.3 grade $\geq$ 3)[80]. Knowing that severe hip ON is more likely to progress, our data suggest that female survivors might be at higher risk to develop debilitating ON [21,44].

Correlations were found between some physical impairment outcomes especially regarding MIMS, MIMT and grip strength. A relationship between these outcomes and 6MWT was also found. No significant relationship was observed between corticosteroids and vincristine dose and any physical impairment outcome. As reported by van de Velde et al., few studies did find correlation between vincristine dose and severity of chemotherapy induced peripheral neuropathy but results are still controversial and genetic

factors could play a important role [81]. Indeed, Nadeau et al. found a strong association with skeletal muscle function and specific genetic variants[82]. Our multiple linear regression model explained a low proportion of the variance of the 6MWT. This can be related to the fact that we did not have lower limb strength outcomes available from other important muscle groups in the sagittal plane (hip extensors and flexors, ankle plantiflexors)[83,84]. Nevertheless, our model was able to explain more than a quarter of 6MWT performance variance. We were also able to show a significant effect of knee extension MIMS on walking capacity. Knee extensor muscles are involved in the stance phase in both a concentric and eccentric manner, which could potentially impact gait efficacy[84]. Our generalized linear model explained a smaller variance of the FTSST. This can be explained by the lack of other anti-gravity muscle groups studied that are involved in the sit-to-stand motion (trunk and hip extensors)[85].

Limitations of our study need to be ackownledged. First, this is a retrospective study from cross-sectional data. Onset of hip ON could therefore not be determined. Survivors who may have experienced hip ON in the past and have fully recovered are unknown. Furthermore, since treatment protocols are constantly evolving, our data might not be applicable to recent cALL survivors treated with newer protocols. Moreover, our single-center LMHR subgroup and ethnically homogeneous sample (mostly white French Canadians) limits generalizability. A larger and more multicultural sample would help define this complex population. Nevertheless, our results still describe the physical impairments, activity limitations, and participation restrictions of an important group of survivors of cALL representing the majority of the PETALE cohort.

The small sample size also limited bivariate analyses when comparing participants with and without ON especially when looking into sex differences. Missing data also may have limited the power of our multiple linear analyses results.

Survivor outcome data was compared to available expected values referenced from a healthy population due to lack of a control group. Reference values for some outcome measures of physical impairments (MIMS, ROM) are currently lacking in the literature [86]. Therefore, the interpretation of our results must be modulated by the fact that our reference values were selected from limited available data with the most comparable (but not exact) standardized protocole and age groups.

Moreover, the most prevalent pain location reported by survivors was in the knee. Knowing that the knee is one of the most frequent sites of ON and that lesions are often multifocal, future studies should consider knee MRI.

Our findings support the hypothesis that long-term survivors of cALL have greater physical impairments and activity limitations compared to available expected reference values from a healthy population. There are important NMSK late adverse effects in long-term survivors of cALL and the hip joint is directly affected. Sex differences emerged but need to be validated in a larger cohort. Physiotherapy assessment could help identify hip ON in the asymptomatic phase leading to earlier intervention and prevention of further joint morbidity. These data support the frailty phenotype described in childhood cancer survivors. Additional prospective research to characterize the clinical NMSK phenotype of long-term cALL survivors is warranted.

Conflict of Interest statement

None to declare

Acknowledgements

We extend our thanks to the participants and their families for agreeing to be part of this study.

Financial Support: This study was supported by the Canadian Institute of Health Research, Sainte Justine University Health Center Foundation, Ontario Institute for Cancer Research, Pediatric Oncology Group of Ontario, The Hospital for Sick Kids Foundation, The Canadian Cancer Society, The Terry Fox Foundation, The Cancer Research Society (La Société de Recherche sur le Cancer), Université de Montréal (École de réadaptation, Études supérieures et post-doctorales), and Ordre professionnel de la physiothérapie du Québec.

Special Contributions: Data collection and clinical expertise: Jutras M, Lapointe C, Condé A, Pilon J.

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700 **Legends**

701 Figure 1 Distribution of hip ON according to Niinimäki grade

702 Figure 2 Physical impairments compared to reference values

703 Figure 3 Hip physical impairment in participants with and without hip ON