TITLE PAGE

Title: Physical impairments, activity limitations, and participation restrictions of childhood acute lymphoblastic leukemia survivors: A PETALE cohort study[1]

Authors: Annie Brochu[1,2], Dahlia Kairy[2,3], Nathalie Alos[1,2], Caroline Laverdière[1,2], Daniel Sinnett[1,2], Serge Sultan[1,2], Daniel Curnier[1,2], Marie-Claude Miron[1,2], Ramy El-Jalbout[1,2], Melissa Fiscaletti[1,2*], Luc J. Hébert[4,5*]

Affiliations :

1. Sainte Justine University Hospital and Research Center
2. Université de Montréal
3. Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal
4. Université Laval
5. Centre for Interdisciplinary Research in Rehabilitation and Social Integration

* Contributed equally to senior authorship

[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

Corresponding author contact:

Annie Brochu

3175, chemin Côte-Sainte-Catherine, H3T 1C5

Montréal, Québec, Canada

Phone : +1-514-345-4931 #7054

Fax : +1-514-345-4746

Email : annie.brochu@outlook.com

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

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 ± 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%).

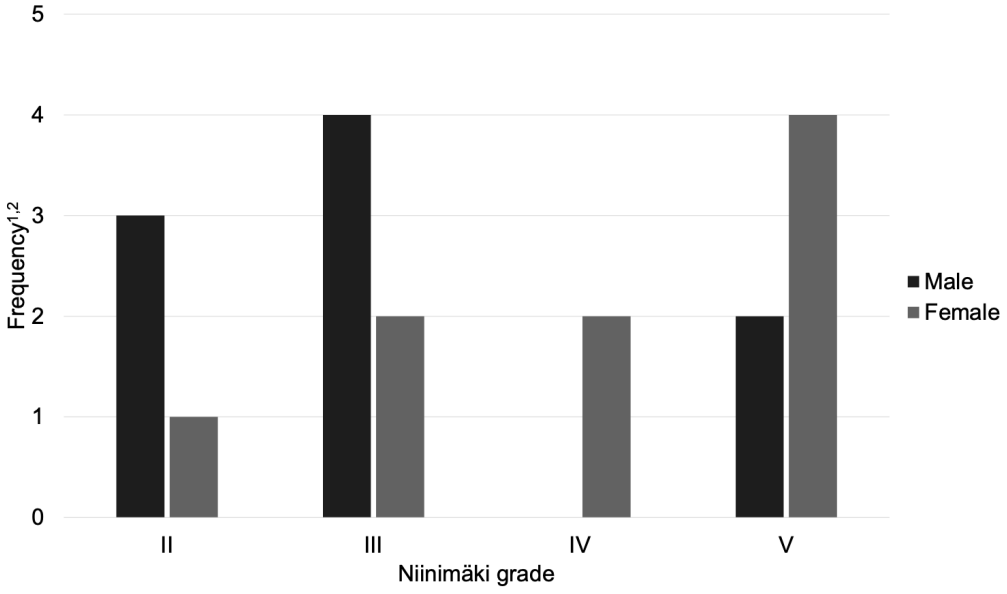


Figure 1 Distribution of hip ON according to Niinimäki grade

[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

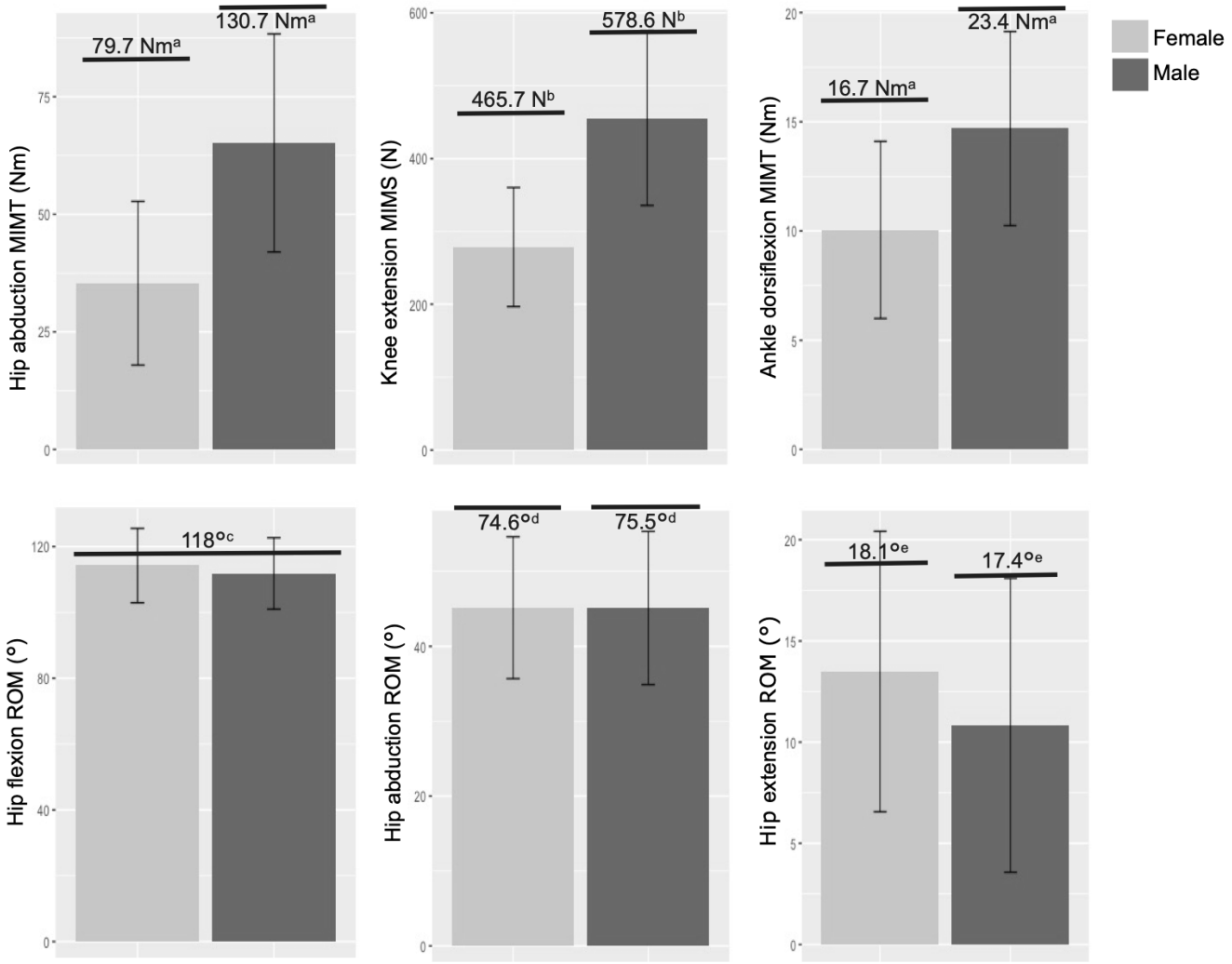
	NA n(%)	All participants[1] (n=97)[†]		With ON[2,3] (n=13)		Without ON[2] (n=76)		With ON vs. without ON[2] (p-value)*
		Mean	SD	Mean	SD	Mean	SD	
Age at assessment, year	0	24.2	6.7	25.9	7.4	24.3	6.6	0.478
Age at diagnosis, year	0	8.1	5.1	11.9	5.3	7.6	4.9	**<0.01**
Time since diagnosis, year	0	16.4	5.7	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.
238



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.

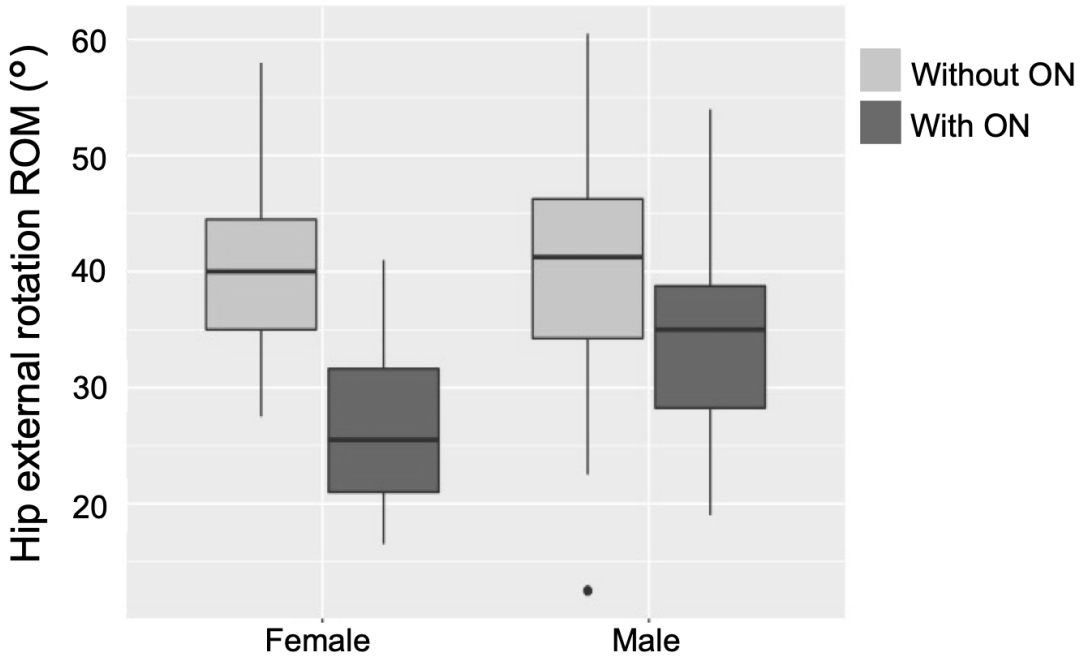


Figure 3 Hip physical impairment in participants with and without hip ON

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.

References

1. Pui C-H, Robison LL, Look AT. Acute lymphoblastic leukaemia. *The Lancet*. 2008/03/22/ 2008;371(9617):1030-1043. doi:https://doi.org/10.1016/S0140-6736(08)60457-2
2. Les principales causes de décès, population totale, selon le groupe d'âge (Tableau 13-10-0394-01). Statistique Canada. Updated January 23, 2022. Accessed January 23, 2022. https://www150.statcan.gc.ca/t1/tbl1/fr/tv.action?pid=1310039401&pickMembers%5B0%5D=2.21&pickMembers%5B1%5D=3.1&cubeTimeFrame.startYear=2015&cubeTimeFrame.endYear=2019&referencePeriods=20150101%2C20190101.
3. Ellison LF, Xie L, Sung L. Tendances de la survie au cancer chez les enfants au Canada, 1992 à 2017. Statistiques Canada. February 17, 2021. Accessed October 20, 2021. Disponible: https://www150.statcan.gc.ca/n1/fr/pub/82-003-x/2021002/article/00001-fra.pdf?st=40FobZ_a.
4. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med*. Jun 25 2009;360(26):2730-41. doi:10.1056/NEJMoa0900386
5. Mulrooney DA, Hyun G, Ness KK, et al. The changing burden of long-term health outcomes in survivors of childhood acute lymphoblastic leukaemia: a retrospective analysis of the St Jude Lifetime Cohort Study. *Lancet Haematol*. Jun 2019;6(6):e306-e316. doi:10.1016/s2352-3026(19)30050-x

6. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. *J Clin Oncol*. Apr 20 2014;32(12):1218-27. doi:10.1200/jco.2013.51.1055
7. Ness KK, Hudson MM, Jones KE, et al. Effect of Temporal Changes in Therapeutic Exposure on Self-reported Health Status in Childhood Cancer Survivors. *Ann Intern Med*. 2017;166(2):89-98. doi:10.7326/M16-0742
8. Ness KK, Hudson MM, Pui C-H, et al. Neuromuscular impairments in adult survivors of childhood acute lymphoblastic leukemia: associations with physical performance and chemotherapy doses. *Cancer*. 2012;118(3):828-38. doi:https://dx.doi.org/10.1002/cncr.26337
9. Ness KK, Baker KS, Dengel DR, et al. Body composition, muscle strength deficits and mobility limitations in adult survivors of childhood acute lymphoblastic leukemia. *Pediatric blood & cancer*. 2007;49(7):975-81.
10. Rodwin RL, Chen Y, Yasui Y, et al. Longitudinal evaluation of neuromuscular dysfunction in long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer Epidemiology Biomarkers & Prevention*. 2021:cebp.0154.2021. doi:10.1158/1055-9965.EPI-21-0154
11. Tonning Olsson I, Alberts NM, Li C, et al. Pain and functional outcomes in adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort study. *Cancer*. 2021;127(10):1679-1689. doi:https://doi.org/10.1002/cncr.33303
12. Barr RD, Inglis D, Athale U, Jaworski M, Farncombe T, Gordon CL. Bone health in long-term survivors of pediatric acute lymphoblastic leukemia. An assessment by peripheral quantitative computed tomography. *Pediatr Blood Cancer*. Jul 15 2021:e29218. doi:10.1002/pbc.29218
13. Classification internationale du fonctionnement, du handicap et de la santé : CIF. Organisation mondiale de la santé. Classification internationale du fonctionnement, du handicap et de la santé [En ligne]. Genève (CH): Organisation mondiale de la santé; 2001 [cité le 24 janvier 2022]. Disponible: https://apps.who.int/iris/bitstream/handle/10665/42418/9242545422_fre.pdf?sequence=1&isAllowed=y.
14. Inaba H, Varechtchouk O, Neel MD, et al. Whole-joint magnetic resonance imaging to assess osteonecrosis in pediatric patients with acute lymphoblastic lymphoma. *Pediatr Blood Cancer*. Aug 2020;67(8):e28336. doi:10.1002/pbc.28336
15. Kadan-Lottick NS, Dinu I, Wasilewski-Masker K, et al. Osteonecrosis in Adult Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. *Journal of Clinical Oncology*. 2008;26(18):3038-3045. doi:10.1200/jco.2007.14.9088
16. Rao SS, El Abiad JM, Puvanesarajah V, Levin AS, Jones LC, Morris CD. Osteonecrosis in pediatric cancer survivors: Epidemiology, risk factors, and treatment. *Surg Oncol*. Mar 2019;28:214-221. doi:10.1016/j.suronc.2019.02.001
17. Kawedia JD, Kaste SC, Pei D, et al. Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia. *Blood*. 2011;117(8):2340-2347. doi:10.1182/blood-2010-10-311969
18. Barr RD, Sala A. Osteonecrosis in children and adolescents with cancer. *Pediatr Blood Cancer*. Feb 2008;50(2 Suppl):483-5; discussion 486. doi:10.1002/pbc.21405
19. Elmantaser M, Stewart G, Young D, Duncan R, Gibson B, Ahmed SF. Skeletal morbidity in children receiving chemotherapy for acute lymphoblastic leukaemia. *Archives*

of disease in childhood. 2010;95(10):805-9. doi:https://dx.doi.org/10.1136/adc.2009.172528
20. Mattano LA, Jr., Sather HN, Trigg ME, Nachman JB. Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2000;18(18):3262-72.
21. Kaste SC, Pei D, Cheng C, et al. Utility of early screening magnetic resonance imaging for extensive hip osteonecrosis in pediatric patients treated with glucocorticoids. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(6):610-5. doi:https://dx.doi.org/10.1200/JCO.2014.57.5480
22. Kadan-Lottick NS, Dinu I, Wasilewski-Masker K, et al. Osteonecrosis in adult survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. Jun 20 2008;26(18):3038-45. doi:10.1200/jco.2007.14.9088
23. Padhye B, Dalla-Pozza L, Little D, Munns C. Incidence and outcome of osteonecrosis in children and adolescents after intensive therapy for acute lymphoblastic leukemia (ALL). *Cancer medicine*. 2016;5(5):960-7. doi:https://dx.doi.org/10.1002/cam4.645
24. DeFeo BM, Kaste SC, Li Z, et al. Long-Term Functional Outcomes Among Childhood Survivors of Cancer Who Have a History of Osteonecrosis. *Phys Ther*. Feb 11 2020;doi:10.1093/ptj/pzz176
25. Kaste SC, Karimova EJ, Neel MD. Osteonecrosis in children after therapy for malignancy. *AJR Am J Roentgenol*. May 2011;196(5):1011-8. doi:10.2214/ajr.10.6073
26. Burger B, Beier R, Zimmermann M, Beck JD, Reiter A, Schrappe M. Osteonecrosis: a treatment related toxicity in childhood acute lymphoblastic leukemia (ALL)--experiences from trial ALL-BFM 95. *Pediatric blood & cancer*. 2005;44(3):220-5.
27. te Winkel ML, Pieters R, Hop WC, et al. Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia. *J Clin Oncol*. Nov 1 2011;29(31):4143-50. doi:10.1200/jco.2011.37.3217
28. Inaba H, Cao X, Chang JY, et al. Incidence of hip and knee osteonecrosis and their associations with bone mineral density in children with acute lymphoblastic leukaemia. *British Journal of Haematology*. 2020;189(4):e177-e181. doi:10.1111/bjh.16589
29. Mereddy PKR, Sunderamoorthy D. Avascular necrosis of the femoral head 8 years after posterior hip dislocation. *Injury*. 2008/07// 2008;39(7):823. doi:10.1016/j.injury.2008.02.021
30. Lavernia CJ, Sierra RJ, Grieco FR. Osteonecrosis of the femoral head. *J Am Acad Orthop Surg*. Jul-Aug 1999;7(4):250-61. doi:10.5435/00124635-199907000-00005
31. Akyay A, Olcay L, Sezer N, Atay Sonmez C. Muscle strength, motor performance, cardiac and muscle biomarkers in detection of muscle side effects during and after acute lymphoblastic leukemia treatment in children. *J Pediatr Hematol Oncol*. Nov 2014;36(8):594-8. doi:10.1097/MPH.0000000000000067
32. Hoffman MC, Mulrooney DA, Steinberger J, Lee J, Baker KS, Ness KK. Deficits in physical function among young childhood cancer survivors. *J Clin Oncol*. Aug 1 2013;31(22):2799-805. doi:10.1200/jco.2012.47.8081
33. Barr R, Nayiager T, Gordon C, Marriott C, Athale U. Body composition and bone health in long-term survivors of acute lymphoblastic leukaemia in childhood and adolescence: the protocol for a cross-sectional cohort study. *BMJ open*. 2015;5(1):e006191. doi:https://dx.doi.org/10.1136/bmjopen-2014-006191

34. Ness KK, Jones KE, Smith WA, et al. Chemotherapy-related neuropathic symptoms and functional impairment in adult survivors of extracranial solid tumors of childhood: results from the St. Jude Lifetime Cohort Study. *Arch Phys Med Rehabil*. Aug 2013;94(8):1451-7. doi:10.1016/j.apmr.2013.03.009
35. Rodwin. Peripheral motor and sensory neuropathy and associated outcomes in long-term survivors of childhood cancer. Working group. 2019;
36. Jain P, Gulati S, Seth R, Bakhshi S, Toteja GS, Pandey RM. Vincristine-induced neuropathy in childhood ALL (acute lymphoblastic leukemia) survivors: prevalence and electrophysiological characteristics. *Journal of child neurology*. 2014;29(7):932-7. doi:https://dx.doi.org/10.1177/0883073813491829
37. Caru M, Samoilenko M, Drouin S, et al. Childhood Acute Lymphoblastic Leukemia Survivors Have a Substantially Lower Cardiorespiratory Fitness Level Than Healthy Canadians Despite a Clinically Equivalent Level of Physical Activity. *Journal of Adolescent and Young Adult Oncology*. 2019/12/01 2019;8(6):674-683. doi:10.1089/jayao.2019.0024
38. Ho S, Betz G, Marchese V. Exploring pulmonary function and physical function in childhood cancer: A systematic review. *Critical Reviews in Oncology/Hematology*. 2021/04/01/ 2021;160:103279. doi:https://doi.org/10.1016/j.critrevonc.2021.103279
39. Ness KK, Armstrong GT, Kundu M, Wilson CL, Tchkonia T, Kirkland JL. Frailty in childhood cancer survivors. *Cancer*. 2015;121(10):1540-1547. doi:10.1002/cncr.29211
40. Ness KK, Krull KR, Jones KE, et al. Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime cohort study. *J Clin Oncol*. Dec 20 2013;31(36):4496-503. doi:10.1200/jco.2013.52.2268
41. Marcoux S, Drouin S, Laverdiere C, et al. The PETALE study: Late adverse effects and biomarkers in childhood acute lymphoblastic leukemia survivors. *Pediatric blood & cancer*. 2017;64(6)doi:https://dx.doi.org/10.1002/pbc.26361
42. Niinimäki T, Niinimäki J, Halonen J, Hänninen P, Harila-Saari A, Niinimäki R. The classification of osteonecrosis in patients with cancer: validation of a new radiological classification system. *Clinical Radiology*. 2015/12/01/ 2015;70(12):1439-1444. doi:https://doi.org/10.1016/j.crad.2015.08.011
43. Portera MV, Karol SE, Smith C, et al. Osteonecrosis is unrelated to hip anatomy in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer*. Jul 2017;64(7)doi:10.1002/pbc.26407
44. Karimova EJ, Rai SN, Howard SC, et al. Femoral head osteonecrosis in pediatric and young adult patients with leukemia or lymphoma. *J Clin Oncol*. Apr 20 2007;25(12):1525-31. doi:10.1200/jco.2006.07.9947
45. Bolduc N, Roy S, Blouin C. *Bolduc N, Roy S, Blouin C. Le protocole d'utilisation de l'inclinomètre. Québec (CA): Institut de réadaptation en déficience physique de Québec; 2009*. Institut de réadaptation en déficience physique de Québec; 2009.
46. Charlton PC, Mentiplay BF, Pua Y-H, Clark RA. Reliability and concurrent validity of a Smartphone, bubble inclinometer and motion analysis system for measurement of hip joint range of motion. *Journal of Science and Medicine in Sport*. 2015/05/01/ 2015;18(3):262-267. doi:https://doi.org/10.1016/j.jsams.2014.04.008
47. Clapis PA, Davis SM, Davis RO. Reliability of inclinometer and goniometric measurements of hip extension flexibility using the modified Thomas test. *Physiotherapy Theory and Practice*. 2008/01/01 2008;24(2):135-141. doi:10.1080/09593980701378256

48. Hebert LJ, Maltais DB, Lepage C, Saulnier J, Crete M. Hand-Held Dynamometry Isometric Torque Reference Values for Children and Adolescents. *Pediatr Phys Ther*. Winter 2015;27(4):414-23. doi:10.1097/pep.0000000000000179
49. Hebert LJ, Maltais DB, Lepage C, Saulnier J, Crete M, Perron M. Isometric muscle strength in youth assessed by hand-held dynamometry: a feasibility, reliability, and validity study. *Pediatr Phys Ther*. Fall 2011;23(3):289-99. doi:10.1097/PEP.0b013e318227ccff
50. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil*. Feb 1985;66(2):69-74.
51. Butler AA, Menant JC, Tiedemann AC, Lord SR. Age and gender differences in seven tests of functional mobility. *Journal of NeuroEngineering and Rehabilitation*. 2009/07/30 2009;6(1):31. doi:10.1186/1743-0003-6-31
52. Medina-Mirapeix F, Vivo-Fernández I, López-Cañizares J, García-Vidal JA, Benítez-Martínez JC, del Baño-Aledo ME. Five times sit-to-stand test in subjects with total knee replacement: Reliability and relationship with functional mobility tests. *Gait & Posture*. 2018/01/01/ 2018;59:258-260. doi:https://doi.org/10.1016/j.gaitpost.2017.10.028
53. Bohannon RW, Bubela DJ, Magasi SR, Wang Y-C, Gershon RC. Sit-to-stand test: Performance and determinants across the age-span. *Isokinet Exerc Sci*. 2010;18(4):235-240. doi:10.3233/IES-2010-0389
54. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-minute walking tests in respiratory disease. *Br Med J (Clin Res Ed)*. May 29 1982;284(6329):1607-8. doi:10.1136/bmj.284.6329.1607
55. Bartels B, de Groot JF, Terwee CB. The six-minute walk test in chronic pediatric conditions: a systematic review of measurement properties. *Phys Ther*. Apr 2013;93(4):529-41. doi:10.2522/ptj.20120210
56. Schmidt K, Vogt L, Thiel C, Jager E, Banzer W. Validity of the six-minute walk test in cancer patients. *Int J Sports Med*. Jul 2013;34(7):631-6. doi:10.1055/s-0032-1323746
57. Hartman A, Hop W, Takken T, Pieters R, van den Heuvel-Eibrink M. Motor performance and functional exercise capacity in survivors of pediatric acute lymphoblastic leukemia. *Pediatr Blood Cancer*. Mar 2013;60(3):494-9. doi:10.1002/pbc.24243
58. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer*. Apr 1 2002;94(7):2090-106. doi:10.1002/cncr.10428
59. Robert RS, Paxton RJ, Palla SL, et al. Feasibility, reliability, and validity of the Pediatric Quality of Life Inventory ™ generic core scales, cancer module, and multidimensional fatigue scale in long-term adult survivors of pediatric cancer. *Pediatr Blood Cancer*. Oct 2012;59(4):703-7. doi:10.1002/pbc.24099
60. Tomlinson D, Hinds PS, Ethier MC, Ness KK, Zupanec S, Sung L. Psychometric properties of instruments used to measure fatigue in children and adolescents with cancer: a systematic review. *J Pain Symptom Manage*. Jan 2013;45(1):83-91. doi:10.1016/j.jpainsymman.2012.02.010
61. Christen S, Roser K, Mulder RL, et al. Recommendations for the surveillance of cancer-related fatigue in childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *J Cancer Surviv*. Dec 2020;14(6):923-938. doi:10.1007/s11764-020-00904-9

62. Topp CW, Østergaard SD, Søndergaard S, Bech P. The WHO-5 Well-Being Index: A Systematic Review of the Literature. *Psychotherapy and Psychosomatics*. 2015;84(3):167-176. doi:10.1159/000376585
63. SOUCIE JM, WANG C, FORSYTH A, et al. Range of motion measurements: reference values and a database for comparison studies. *Haemophilia*. 2011;17(3):500-507. doi:https://doi.org/10.1111/j.1365-2516.2010.02399.x
64. Gilchrist L, Tanner L. Gait Patterns in Children With Cancer and Vincristine Neuropathy. *Pediatr Phys Ther*. Spring 2016;28(1):16-22. doi:10.1097/pep.0000000000000208
65. Wright MJ, Halton JM, Barr RD. Limitation of ankle range of motion in survivors of acute lymphoblastic leukemia: a cross-sectional study. *Medical and pediatric oncology*. 1999;32(4):279-82.
66. Bohannon RW. Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. *Arch Phys Med Rehabil*. Jan 1997;78(1):26-32. doi:10.1016/s0003-9993(97)90005-8
67. Mathiowetz V, Wiemer DM, Federman SM. Grip and pinch strength: norms for 6- to 19-year-olds. *Am J Occup Ther*. Oct 1986;40(10):705-11. doi:10.5014/ajot.40.10.705
68. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. *J Cardiopulm Rehabil*. Mar-Apr 2001;21(2):87-93. doi:10.1097/00008483-200103000-00005
69. Ulrich S, Hildenbrand FF, Treder U, et al. Reference values for the 6-minute walk test in healthy children and adolescents in Switzerland. *BMC Pulmonary Medicine*. 2013/08/05 2013;13(1):49. doi:10.1186/1471-2466-13-49
70. Varni JW, Limbers CA. The PedsQL™ Multidimensional Fatigue Scale in young adults: feasibility, reliability and validity in a University student population. *Quality of Life Research*. 2008/02/01 2008;17(1):105-114. doi:10.1007/s11136-007-9282-5
71. Varni JW, Limbers CA. The PedsQL 4.0 Generic Core Scales Young Adult Version: feasibility, reliability and validity in a university student population. *J Health Psychol*. May 2009;14(4):611-22. doi:10.1177/1359105309103580
72. Bagwell JJ, Bauer L, Gradoz M, Grindstaff TL. THE RELIABILITY OF FABER TEST HIP RANGE OF MOTION MEASUREMENTS. *Int J Sports Phys Ther*. 2016;11(7):1101-1105.
73. Beulertz J, Bloch W, Prokop A, et al. Limitations in Ankle Dorsiflexion Range of Motion, Gait, and Walking Efficiency in Childhood Cancer Survivors. *Cancer Nurs*. Mar-Apr 2016;39(2):117-24. doi:10.1097/ncc.0000000000000256
74. Hayek S, Gibson TM, Leisenring WM, et al. Prevalence and Predictors of Frailty in Childhood Cancer Survivors and Siblings: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol*. Jan 20 2020;38(3):232-247. doi:10.1200/jco.19.01226
75. Ness KK, Kirkland JL, Gramatges MM, et al. Premature Physiologic Aging as a Paradigm for Understanding Increased Risk of Adverse Health Across the Lifespan of Survivors of Childhood Cancer. *Journal of Clinical Oncology*. 2018/07/20 2018;36(21):2206-2215. doi:10.1200/JCO.2017.76.7467
76. Yallop K, McDowell H, Koziol-McLain J, Reed PW. Self-reported psychosocial wellbeing of adolescent childhood cancer survivors. *Eur J Oncol Nurs*. Dec 2013;17(6):711-9. doi:10.1016/j.ejon.2013.06.007
77. Weinstein AG, Henrich CC, Armstrong GT, et al. Roles of positive psychological outcomes in future health perception and mental health problems: A report from the

667 Childhood Cancer Survivor Study. *Psychooncology*. Dec 2018;27(12):2754-2760.
668 doi:10.1002/pon.4881
669 78. Lamore K, Bourdeau C, Alos N, et al. Contributing Factors of Unmet Needs Among
670 Young Adult Survivors of Childhood Acute Lymphoblastic Leukemia with Comorbidities.
671 *Journal of Adolescent and Young Adult Oncology*. 2021/08/01 2020;10(4):462-475.
672 doi:10.1089/jayao.2020.0090
673 79. Khan AM, McLoughlin E, Giannakas K, Hutchinson C, Andrew JG. Hip
674 osteoarthritis: where is the pain? *Ann R Coll Surg Engl*. Mar 2004;86(2):119-21.
675 doi:10.1308/003588404322827518
676 80. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic Health Conditions in Adult
677 Survivors of Childhood Cancer. *New England Journal of Medicine*. 2006;355(15):1572-
678 1582. doi:10.1056/NEJMsa060185
679 81. van de Velde ME, Kaspers GL, Abbink FCH, Wilhelm AJ, Ket JCF, van den Berg
680 MH. Vincristine-induced peripheral neuropathy in children with cancer: A systematic
681 review. *Critical Reviews in Oncology/Hematology*. 2017/06/01/ 2017;114:114-130.
682 doi:https://doi.org/10.1016/j.critrevonc.2017.04.004
683 82. Nadeau G, Ouimet-Grennan E, Aaron M, et al. Identification of genetic variants
684 associated with skeletal muscle function deficit in childhood acute lymphoblastic leukemia
685 survivors. *Pharmgenomics Pers Med*. 2019;12:33-45. doi:10.2147/pgpm.S192924
686 83. Riley PO, Croce UD, Casey Kerrigan D. Propulsive adaptation to changing gait
687 speed. *Journal of Biomechanics*. 2001/02/01/ 2001;34(2):197-202.
688 doi:https://doi.org/10.1016/S0021-9290(00)00174-3
689 84. Spinoso DH, Bellei NC, Marques NR, Navega MT. Quadriceps muscle weakness
690 influences the gait pattern in women with knee osteoarthritis. *Advances in Rheumatology*.
691 2018/08/31 2018;58(1):26. doi:10.1186/s42358-018-0027-7
692 85. Tully EA, Fotoohabadi MR, Galea MP. Sagittal spine and lower limb movement
693 during sit-to-stand in healthy young subjects. *Gait & Posture*. 2005/12/01/ 2005;22(4):338-
694 345. doi:https://doi.org/10.1016/j.gaitpost.2004.11.007
695 86. Morin M, Duchesne E, Bernier J, Blanchette P, Langlois D, Hébert LJ. What is
696 Known About Muscle Strength Reference Values for Adults Measured by Hand-Held
697 Dynamometry: A Scoping Review. *Archives of Rehabilitation Research and Clinical*
698 *Translation*. 2021/12/07/ 2021:100172. doi:https://doi.org/10.1016/j.arrct.2021.100172

699

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