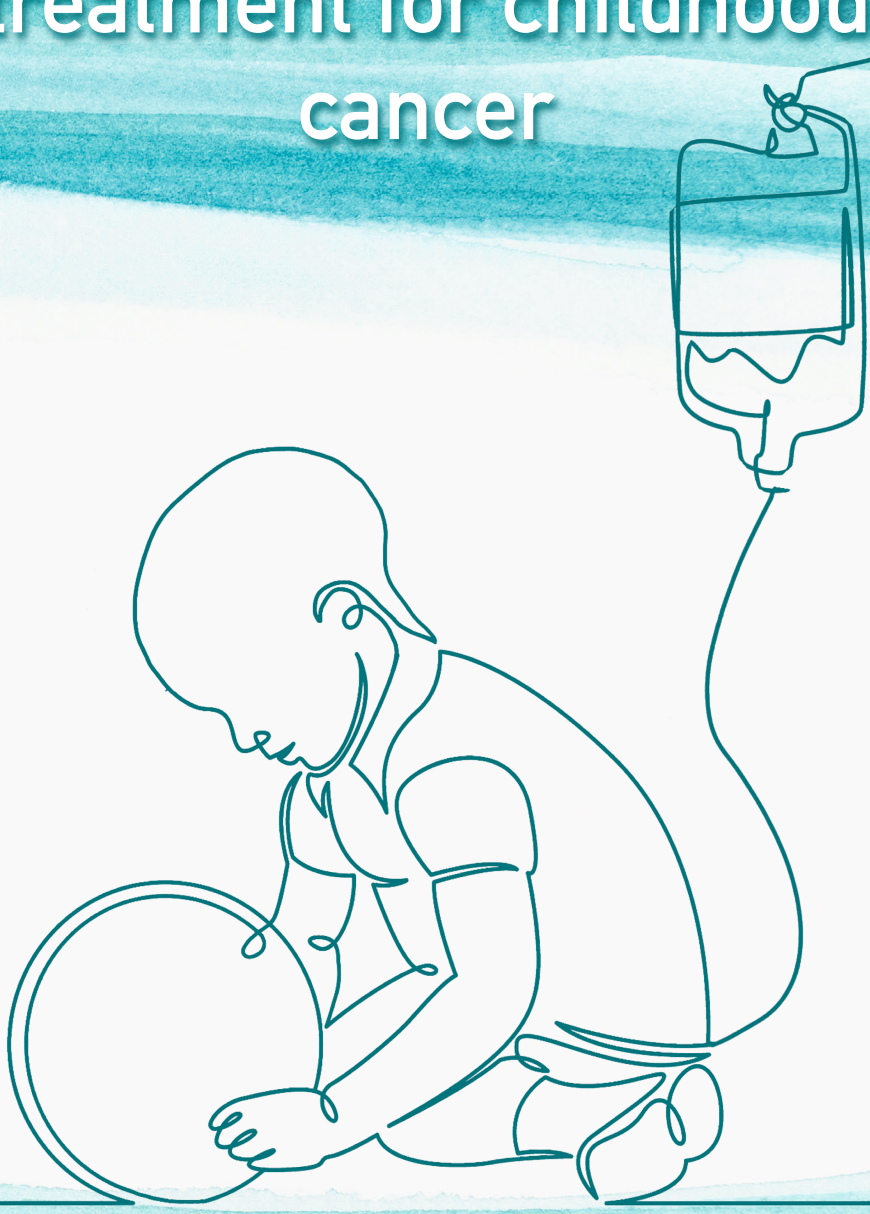
Musculoskeletal vulnerability and physical frailty during and after treatment for childhood cancer



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Musculoskeletal vulnerability and physical frailty during and after treatment for childhood cancer

Musculoskeletale en fysieke kwetsbaarheid tijdens en na de behandeling voor kinderkanker

(met een samenvatting in het Nederlands)

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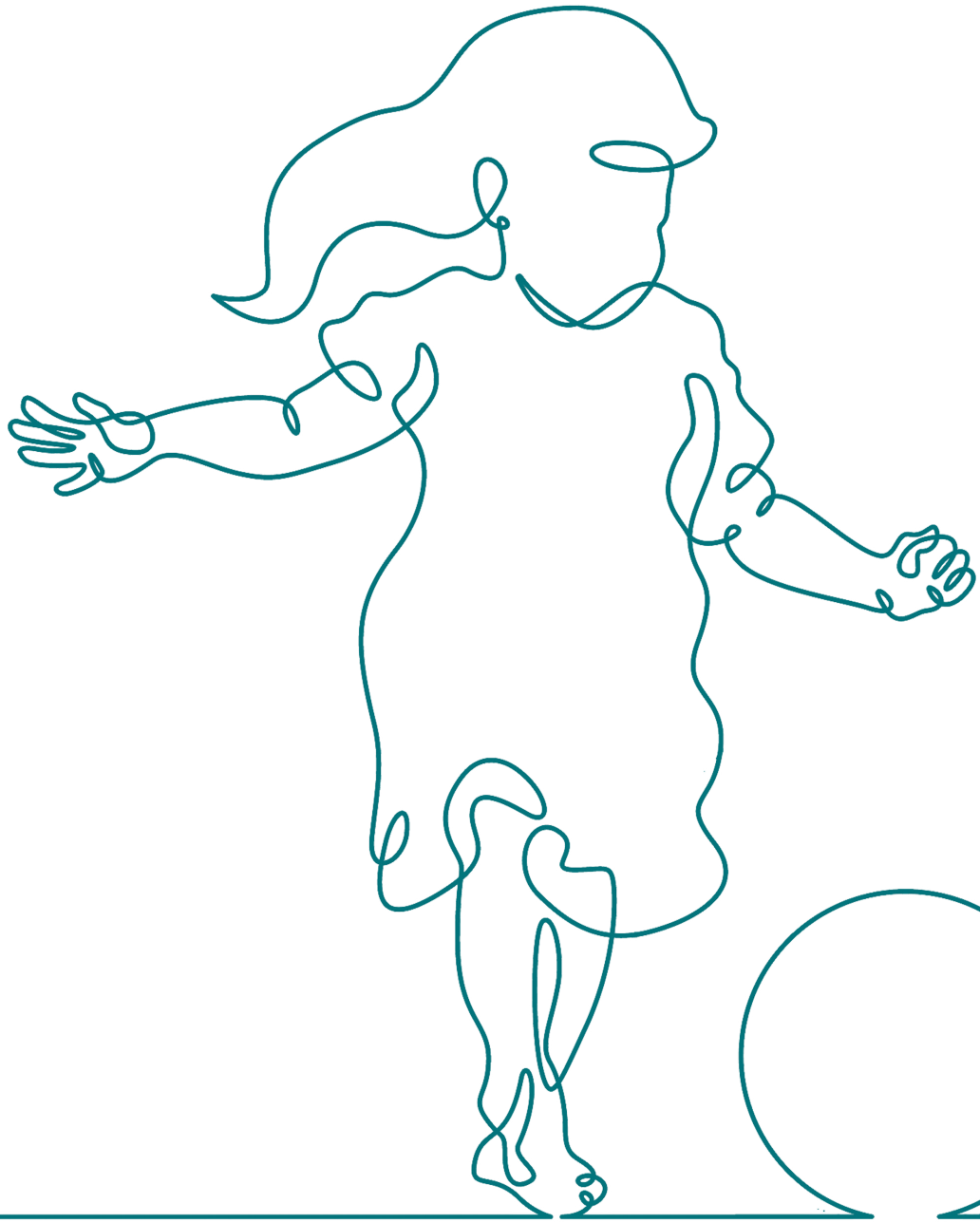
CONTENT

If there is a chance that something is wrong, there is an equal chance that things are right.



General introduction

Childhood cancer

In the Netherlands, 550-600 children below the age of 19 are yearly diagnosed with cancer[1], and it remains the leading cause of death due to disease in children.[2] The most common type of childhood cancer is leukemia, which represents about one third of all childhood cancer diagnoses. Central nervous system tumors are the second most common diagnosed tumors (21%). Substantial progress in stratification of risk groups, treatment modalities and supportive care strategies have been made over the past decades and resulted in a current 5-year overall survival rate of approximately 83% between 2010-2020 (Figure 1).[3] As survival rates are improving, there is a growing population of childhood cancer survivors. However, survival is often accompanied by short-term and long-term side effects, resulting from the cancer itself and/or its treatment.[4] In the following paragraphs the types of cancer, leukemia in particular, that are comprised in this thesis are described.

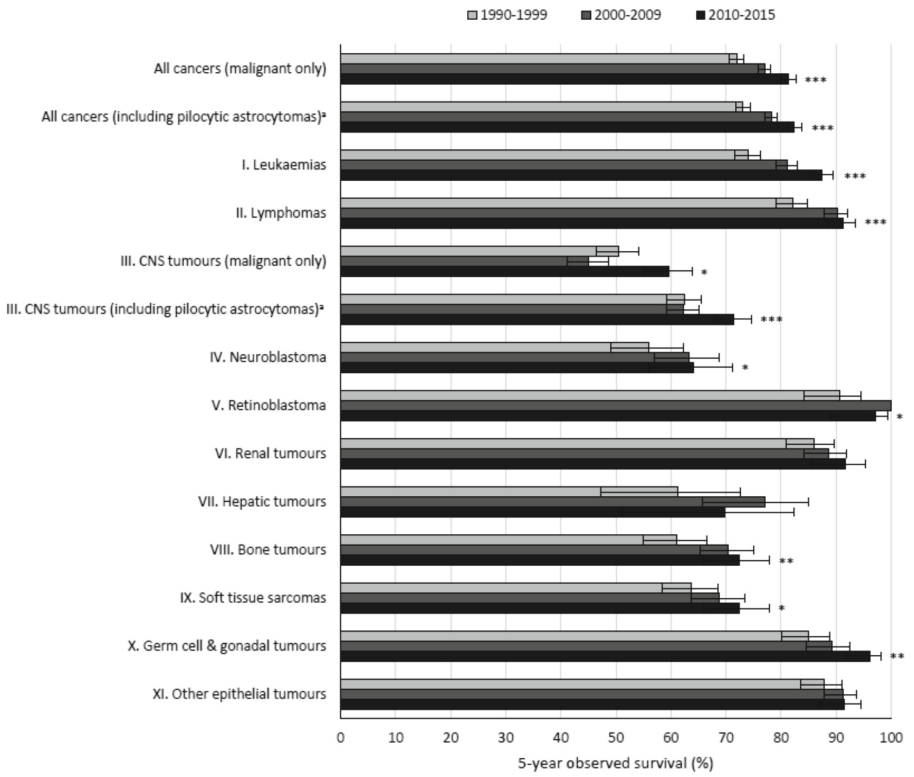


Figure 1. Overview of the 5-year observed survival of childhood and young adolescent cancer in the Netherlands by diagnostic group 1990-2015. Adapted from Schulten et al, *European Journal of Cancer 2021*.

Acute lymphoblastic/myeloid leukemia
In leukemia, a disruption of hematopoiesis (the formation of mature blood cells) occurs. Immature blood cells are hampered by differentiation arrest, and malignant cells subsequently start proliferating uncontrollably replacing the normal blood cells in the bone marrow. This results in a decrease in the number of normal mature blood cells, which causes symptoms such as anemia, fatigue, poor infection control, weight loss or hemorrhage.[5,6] During childhood, acute leukemias are the most frequent types of cancer. Approximately 80% suffers from acute lymphoblastic leukemia (ALL), and 15% from acute myeloid leukemia (AML).

In the Netherlands, about 120 children are diagnosed with ALL each year, with an incidence peak between the ages of 2-6 years. Advances in treatment strategies and supportive care have resulted in a 5-year survival rate of over 90%.[7,8] In children with ALL, musculoskeletal pain[9], proximal muscle weakness, decreased exercise capacity and limited walking distance are commonly present, often already at diagnosis.[10] Since the 1970's, children with ALL have been treated according to the national protocols designed by the Dutch Childhood Oncology Group (DCOG). Treatment protocols all include a 2-3 year chemotherapy schedule, which generally consists of four phases: induction phase, consolidation phase, intensification phase and lastly the maintenance phase.[11]

Each year approximately 25 Dutch children are diagnosed with AML, with a peak incidence in children 0-4 years of age and 10-14 years of age. In recent years, the 5-year survival rate has improved reaching 70%. Current treatment according to DCOG protocol, takes approximately six months and consists of 4 or 5 block of intensive combination chemotherapy.[12]

Both ALL and AML patients with a high risk of recurrence, may undergo allogenic stem cell transplantation (SCT). After intensive high-dose chemotherapy and/or radiotherapy, patients receive an infusion of hematopoietic stem cells to restore their bone marrow.

Neuroblastoma
A neuroblastoma originates from neural crest derived cells and can develop anywhere in the sympathetic nervous system: 65% occurs within the abdomen, especially in the adrenal medulla, sympathetic ganglia and paraganglia. Yearly, approximately 25 children in the Netherlands are diagnosed with neuroblastoma. The median age at diagnosis is 17 months, 37% of patients are diagnosed in infancy and 90% before the age of five. Patients are treated according to the DCOG protocol, based on risk stratification and

stage of the disease. Treatment is multi-modally and consists generally of a combination of chemotherapy, radiotherapy and surgery. Neuroblastoma is an extremely heterogeneous disease with a broad clinical outcome varying from spontaneous regression without any therapy, to highly aggressive metastatic disease despite treatment. The reported survival rates therefore vary widely between 70-90% and 25-50%.[13]

Wilms tumor
Renal tumors account for approximately 5% of all childhood cancer diagnoses. In the Netherlands, 30-35 children are diagnosed with a renal tumor each year. Wilms tumor is by far the most common renal tumor in children, and the majority occurs in children before the age of four. Children with Wilms tumor are treated according to the Internarial Society of Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG) protocol[14], which includes 4-weeks preoperative chemotherapy followed by a surgical resection of the tumor as well as the adjacent kidney. In selected patients with a small tumor, nephron-sparing surgery can be performed. Following resection, postoperative treatment consists of chemotherapy and in some cases radiotherapy, depending on tumor stage and histological subtype. This current therapy regimen has led to an overall survival rate of 90%.

Pediatric brain tumors
Central nervous system (CNS) tumors are the second most common malignancy in children. In the Netherlands, approximately 120 children per year are diagnosed with a brain tumor. CNS tumors are categorized according to tumor morphology and primary site of origin. The majority of pediatric brain tumors (60%) occur in the posterior fossa (infratentorial), the other 40% occurs in the cerebral hemispheres of the brain. The type of pediatric brain tumor is age-dependent. Between ages 0-4, medulloblastoma and other embryonal tumors (arising from fetal cells in the brain) are the most common. Between ages 5-9, the most common tumor tends to be pilocytic astrocytoma. Malignant gliomas are most commonly diagnosed in children aged 10-15. Treatment for a pediatric brain tumor may include neurosurgery, radiotherapy, chemotherapy or a combination of these approaches. The 5-year survival rate is about 75% for all CNS tumors, but subgroup variations are considerable, as treatments and prognoses vary widely based on age, tumor location, size, histology, and staging.[15]

In order to appreciate the impact of cancer and its treatment on the musculoskeletal system and physical functioning of children, it is necessary to firstly be aware of normal physical development and secondly of side effects of treatment.

Normal physical development in children

Bone development

The process of bone formation (ossification) begins around the third month of fetal life and continues until peak bone mass is achieved between the ages of 20 to 30 years (Figure 2).[16] During childhood the most rapid periods of bone growth occur in infancy, toddlerhood and around puberty. Bone provides structural support for musculature and enables movement, protects of organs, metabolic functions and is a reservoir for calcium and phosphate.[17]

Bone consists of cortical and trabecular compartments. Cortical bone constitutes the shaft of long bones and the outer shell of flat bones. As it is formed of concentric rings of bone, it is particularly adapted to oppose bending strain. Trabecular bone is located inside flat bones such as the vertebrae as well as at the ends of long bones and mainly offers resistance to compressive loads.[17]

Bone remodeling persists throughout life. Osteoblasts are the bone-forming cells while osteoclasts resorb bone to initiate the process. The trabecular bone compartment is the metabolically active part of bone where bone remodeling takes place, which involves the removal of mineralized bone by osteoclasts followed by the formation of bone matrix through osteoblasts. Bone modeling is a distinct process that is needed for increasing thickness and describes the process in which bones are continuously shaped by osteoblasts and osteoclasts.[18]

Bone strength is determined by bone geometry, cortical thickness and porosity, trabecular bone morphology and intrinsic properties of bony tissue.[19] It is strongly influenced by locomotion, and early life mobility contributes directly to bone health in childhood and adulthood.[20] Bone mineral density reflects the amount of calcium, phosphate, and other minerals in a certain volume of bone. Measurement of bone mineral density provides an indirect measure of bone strength, and is a crucial component in the diagnosis of osteoporosis and fracture risk.[21,22]

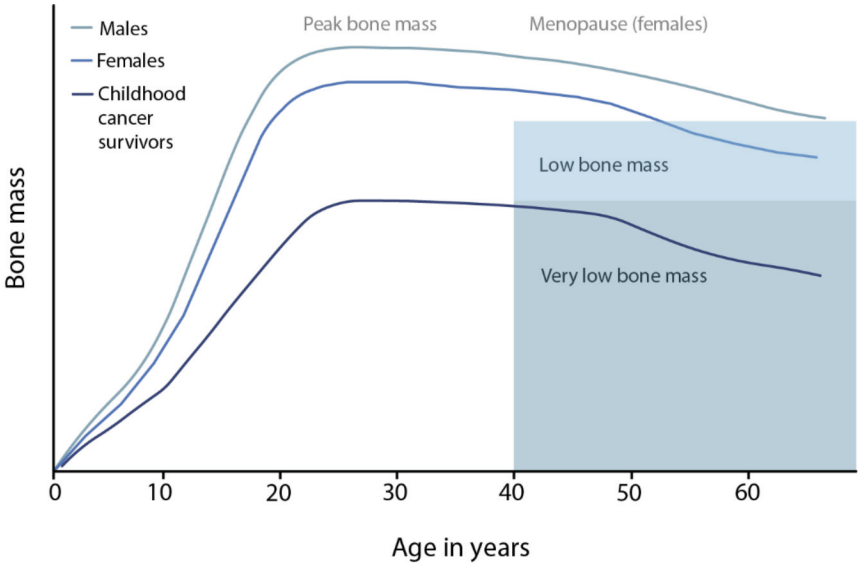


Figure 2. The course of bone mass during life. Adapted from *Van Atteveld, 2023*.

Muscle development

The human body contains 600 anatomical distinguishable muscles accounting for 40% of total body mass in adults. Muscle tissue consists of muscle fibers and these are all formed during fetal development. The formation of new muscle fibers is termed myogenesis, which is a differentiation process where multipotent stem cells are converted into destined muscle cells.[23] Postnatal muscle development is mainly due to the increase in muscle fiber size; new muscle fibers will only be generated to replace injured muscle fibers. Muscle fiber area doubles from the age of five onwards and maximal area is reached in mid-twenties, followed by aging atrophy.[24]

There are three types of muscle tissue: smooth, cardiac and striated.[25] In this thesis, the latter type is particularly important. Striated muscle fibers have a cylindrical shape with blunt ends in bundles (fasciculi) and are connected by tendons to the moving parts of the skeleton (skeletal muscles).[26] They are responsible for moving and stabilizing the skeleton, under conscious control. Striated muscle fibers can be distinguished into three types: I, IIA and IIB. Type-I fibers have a high activity of oxidative enzymes (aerobic metabolism) and are used for low power contractions and prolonged effort. Type II-A fibers have fast contractions and primarily have an aerobic metabolism, but because they may switch to anaerobic metabolism (glycolysis) they fatigue earlier compared to type-I fibers. Type II-B fibers have a low activity of oxidative enzymes and mainly have an anaerobic metabolism, with glucose being the primary source

of energy. This fiber type fatigues quickly and is used for short but powerful contractions.[25]

Appendicular skeletal muscle (muscle mass of the upper and lower extremities) accounts for >75% of total body skeletal muscle and is the primary portion of skeletal muscle involved in ambulation and physical activities.[27]

The musculoskeletal (bone and muscle) system is the underlying necessary component of physical functioning.

Physical functioning

Physical functioning describes the ability of a child to physically perform daily physical activities and is an important aspect of a child's overall development.[28] Attaining physical functions encompasses motor performance, as well as strengthening of the musculoskeletal system and increasing exercise capacity. This thesis focuses primarily on motor performance and muscle strength.

Development of motor performance starts during early fetal life and continues during infancy, with series of gross movements of variable speed and amplitude involving all parts of the body but lacking distinctive orientation (also termed 'general movements').[29] Around 3-4 months post-term age, these general movements are gradually replaced by goal-directed coordinated movements of the arms and legs, and postural control.[30] This subsequently leads to the ability to sit independently around 5–8 months, to stand without support at 9–13 months and to walk independently at 10-14 months (*10-90 percentile ranges of the WHO Multicentre Growth Reference Study Group*).[31] In general, by the age of 5-6 years children are improving higher motor competence skills, such as adequate accelerating and slowing down during running, skipping, jumping, balancing on one foot and riding a bike independently.[32] Thereafter, physical function development is increasingly focused on muscle strength, coordination and exercise capacity.

Muscle strength is essential for the execution of daily physical and sport activities. The following factors of strength can be recognized: isometric, explosive and dynamic strength.[33] Isometric strength is the maximal voluntary force produced against an external resistance without change in muscle length, for example during arm wrestling. Explosive strength or power is the ability of the muscles to release force in the shortest possible time, for example during jumping or skipping. Dynamic strength (also functional strength) is the force generated by repetitive contractions of the muscle, for example during push-ups or squats.

Motor performance and muscle strength are essential for engagement in physical activities. However, this development can be threatened by severe disease and its treatment affecting the musculoskeletal system, which in turn has serious consequences for physical functioning ability. Childhood cancer is such a disease.

Impact of childhood cancer (treatment) on the musculoskeletal system and physical functioning

Treatment for childhood cancer is intensive and leads to several short- and long-term side effects. The type and severity of side effects differ between patients, depending on dosage and type of anti-cancer agent, genetic susceptibility and environmental and personal factors (e.g. socio-economic status, family structure, lifestyle habits).

During treatment patients are prone to side effects such as general malaise, gastrointestinal problems with consequent malnutrition, pain, increased infection risk, and prolonged hospitalizations including periods of compromised mobility. In addition to these side-effects that are an indirect negative influence on physical functioning, chemotherapeutic agents also affect the musculoskeletal system directly (such as glucocorticoids inducing muscle atrophy). Side effects are sometimes so severe that treatment has to be adjusted or even discontinued, and can lead to musculoskeletal impairments with negative consequences for motor development, functional independence and physical fitness in the short and long term.

The improved prognosis of childhood cancer treatment has been accompanied by the occurrence of late treatment-related complications such as organ dysfunction, musculoskeletal, psychosocial and cognitive problems. On average 17 years after completion of treatment, 75% of childhood cancer survivors experience one or more severe side effect of which 40% is physically disabling.[4]

In this thesis, the following side-effects related to the musculoskeletal system and impaired physical function in children with cancer and childhood cancer survivors are of importance: bone fragility, muscle impairments, sarcopenia, frailty, fatigue and limited participation (Figure 3).

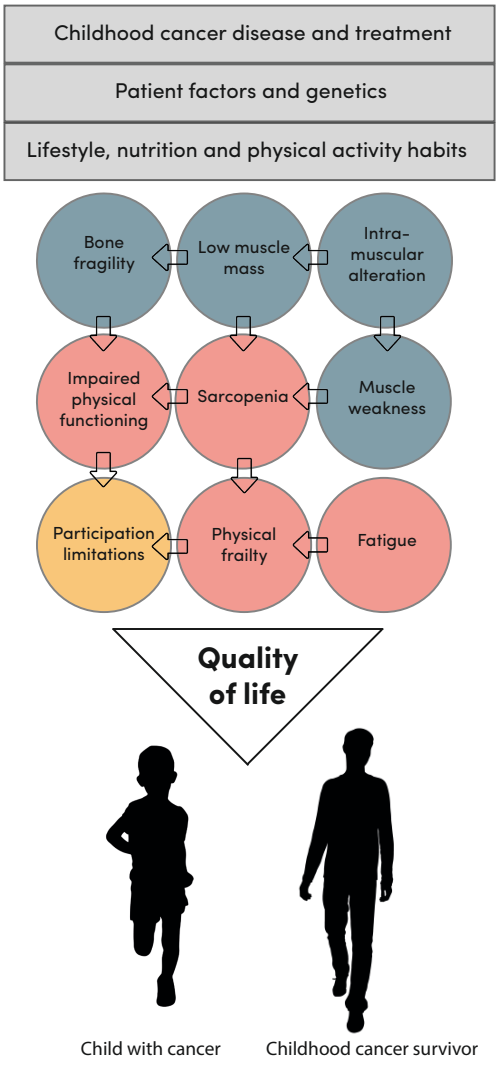


Figure 3. The damaging effect of childhood cancer and its treatment, and personal and environmental factors, with the consequential impairments (blue circles), vulnerability states (red circles) and participation limitations (yellow circle) which affect quality of life in children during treatment and in childhood cancer survivors.

Bone fragility

Both childhood cancer and its treatment may affect normal bone physiology leading to bone fragility, a silent condition that increases fracture risk, which is further enhanced by low bone mineral density and microarchitecture deterioration of bone tissue.[34]

Bone fragility in pediatric cancer patients has been investigated most extensively in children with ALL. In newly diagnosed patients, bone fragility occurs due to increased osteoclast bone resorption resulting from cytokines released by leukemic cells. During therapy, administration of glucocorticoids (e.g. dexamethasone) influences bone remodeling, causing an imbalance between osteoblast and osteoclast activity leading to bone loss.[35,36] Other chemotherapeutic agents such as asparaginase and methotrexate may additionally contribute to bone mineral density decline by impairing osteoblast function.[37] Moreover, malnutrition and immobilization (reduction of weight-bearing activities) which are common during intensive treatment, may induce or exaggerate bone decline. Due to bone fragility, children have a 6-fold greater fracture risk during ALL treatment compared to peers.[38]

In the DCOG-ALL9 cohort, symptomatic vertebral and non-vertebral fractures were reported in 1.5% of children at diagnosis and the cumulative incidence of symptomatic fractures at three years after diagnosis was 18%.[39] *Te Winkel et al* showed that the skeletal state at ALL diagnosis plays an important role in the further development of bone fragility[39], as lumbar spine bone mineral density (LSBMD) at ALL diagnosis was associated with the occurrence of fractures during and shortly after therapy.[36,39]

Muscle impairments

Intensive treatment with chemotherapy, radiation and other drugs (e.g. glucocorticoids) during crucial physiological development make childhood cancer patients prone to muscle impairments. To exemplify, glucocorticoids are frequently used in the treatment of childhood cancer, since they are the cornerstone in treatment of lymphoid leukemia and lymphoma, as well as crucial in reducing brain swelling in neurological patients and diminishing graft-versus-host disease in stem cell transplant patients. However, glucocorticoids have a degenerative effect on skeletal muscle inducing muscle atrophy[40,41], with consequences for muscle mass, strength and function. Another agent, vincristine is frequently used in the treatment of various pediatric hematological and solid cancers. A commonly occurring side-effect of vincristine is peripheral neuropathy, which is a mixed sensory, motor and autonomous neuropathy mainly affecting the longer peripheral nerves. Symptoms include paresthesia, numbness and tingling, loss of proprioception, pain and leads to profound muscle weakness with walking difficulties.[42]

Altered muscle mass, intramuscular quality, impaired strength and function have been reported in childhood cancer patients during therapy[10,43-45], but standardization for unambiguity in the different impairments and their measurements has not yet been defined. This is partly explained by

limited access to muscle tissue samples (intramuscular) and to difficulties surrounding noninvasive approaches for muscle imaging. However, to increase understanding of (intra)muscular alterations in children with cancer, an easy non-invasive imaging technique would be of value to identify patients with a risk of deterioration.

Sarcopenia

Sarcopenia is usually known as age-related muscular deterioration, and is currently defined by the European Working Group on Sarcopenia in Older People as the presence of both low muscle mass and low muscle strength.[46] However, over the last decade it is shown that sarcopenia is a progressive and generalized skeletal muscle disorder associated with increased adverse health outcomes and mortality, not only in the elderly but in adults with various diseases as well.[46,47] Moreover, recent studies described this muscle disorder in chronically ill children and found associations between sarcopenia and post-colectomy complications in ulcerative colitis patients[48], as well as increased perioperative length of stay, ventilator dependency, and readmissions in children after liver transplantation.[49]

In pediatric cancer patients, sarcopenia is a relatively understudied condition, and causal factors and consequences have not been elucidated.[50] However, previous studies indicate the necessity of awareness of this phenomena during treatment. In children with ALL, muscle mass loss has been associated with the number and duration of hospital admissions[51], occurrence of invasive fungal infections[52], and even with impaired survival.[53] Moreover, impaired muscle strength has been associated with poor quality of life.[10] These phenomena also occur in solid tumor patients, a decrease in muscle mass was observed in children during treatment for a renal tumor.[54] Besides, low muscle mass and strength persisted 2-9 years after treatment for high-risk neuroblastoma.[55] To timely identify patients at risk of sarcopenia, simple but valid screening methods are needed, to facilitate interventions to prevent deterioration towards seriously impaired physical functioning.

Physical frailty

Compared to sarcopenia, frailty is a more extended state of vulnerability. The two components of sarcopenia are both also components of the frailty phenotype, in which three or more of the following criteria have to be present: low muscle mass, muscle weakness, fatigue, slow walking speed, and low physical activity. Therefore, a patient may be sarcopenic but not frail and vice versa, depending on the number and type of frailty components that are present (Figure 4).

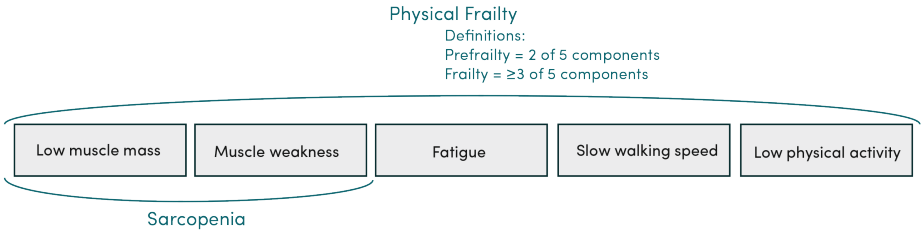


Figure 4. The definition of the sarcopenia and physical frailty phenotype and the components addressing the phenotype. (*created by E.J. Verwaaijen*)

The frailty phenotype was first described in older adults as a state of exaggerated vulnerability and poor resolution of homeostasis following a stressor event.[56] In the elderly, frailty is independently predictive of deteriorating mobility and disability, falling, hospitalization, and death.[57] However, frailty has also found to be highly prevalent among critically- and chronically-ill adults[58], and has shown a serious negative impact on clinical outcomes in adult cancer patients.[59] Two large American studies have shown that long-term childhood cancer survivors are frail at a younger age compared with controls.[8,60] In addition, it was shown that frailty increases the risk of a chronic medical condition and death, which underscores the importance of this phenotype in childhood cancer survivors.

The frailty phenotype has also been found in pediatric patients. In patients aged 5-17 years with end stage liver disease 64% was frail.[61] Moreover, in patients with chronic kidney disease (6-19 years) the frailty phenotype was associated with an increased risk of severe infections and hospitalizations.[62] The frailty components have been separately reported as side effects of cancer treatment[10,43,52,63-65], but currently the phenotype itself has not yet been investigated in pediatric cancer patients.

Cancer-related fatigue

In addition to its share in the frailty phenotype, cancer-related fatigue in itself is one of the most frequently reported side effects after treatment for childhood cancer.[66] It is defined by the National Comprehensive Cancer Network as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or as exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.[67] Increased levels of fatigue are reported in 24% of childhood cancer survivors, compared to 13.5% in sibling-controls.[68] This is a concern because fatigue may have a distinct negative effect on the ability of childhood cancer patients to develop their full potential, as it impacts school performance and engaging in social

activities and sports. Therefore, the coherence between fatigue, impaired physical functioning and participation ability in children with cancer, as well as potential risk factors, deserves attention.

Impaired daily life participation

Participation in daily life plays an important role in a child's development and helps facilitate a healthy transition into adulthood.[69] Participation is defined by the World Health Organization as 'involvement in a life situation', such as engaging in social interactions or taking on a role in sports or academia. Participation ability in childhood cancer survivors may be seriously threatened by the influence of musculoskeletal impairments and limited physical functioning with consequent diminished involvement in daily life activities. Only one previous study investigated participation ability specifically, in survivors of childhood retinoblastoma (malignant eye tumor) and found that a selected group of survivors participated less in daily activities.[70] Thus far, studies investigating the prevalence and risk factors of participation restrictions in childhood cancer survivors have not been pursued.

Assessment of bone fragility, muscle impairments, sarcopenia and frailty, physical functioning

In the following paragraphs gold standard assessments and the measurement instruments relevant for this thesis are described.

Bone fragility: measurement of bone mineral density and fractures

Dual-energy X-ray absorptiometry (DXA) is the gold standard for bone mineral density assessment. The transmission of low-dose X-rays with high- and low-energy photons is used to measure the density of bones and other tissues (e.g. fat and lean mass). The posterior-anterior lumbar spine and total body are typically measured in children.[71] Bone mineral density is then compared with normative values, and expressed as a Z-score. A Z-score represents the number of standard deviations that bone mineral density (BMD) differs from age- and sex-matched normative means. A value of ≤1 and ≤2 is considered low BMD and very low BMD, respectively. When there is a decrease in the amount and thickness of bone tissue, or when the structure and strength of bone diminishes, it is known as osteoporosis.[72] The diagnosis of osteoporosis in children requires the presence of both a clinical significant fracture history and very low bone mineral density.[73] A clinically significant fracture history is defined as a vertebral compression fracture, long bone fracture of the lower extremities or two or more long bone fractures of the upper extremities.

Muscle impairments: measurement of muscle mass, intramuscular alterations and strength

The assessment of muscle mass and muscle structure alterations has several challenges. The current gold standard for such muscle assessment is magnetic resonance imaging (MRI) or diagnostic computed tomography (CT).[74] These techniques can provide images, which are then used for manual segmentation of different muscle structures needed to calculate muscle mass, a time consuming procedure which can only be performed by experienced radiologists. For the assessment of (appendicular) muscle mass, DXA examination is a valid technique and has availability of Dutch normative values from the age of four years old. The disadvantage of these techniques is that they are not routinely used in standard follow-up of most pediatric cancer patients, are time-consuming, patients need to be transferred to the radiology department, younger children need sedation for such assessments, and CT is unsuitable due to radiation exposure. Therefore these techniques are too burdensome to be used as a simple muscle assessment in clinical care.

An non-imaging technique, bio-electrical impedance analysis (BIA) is a method where a weak electric current flows through the body in order to calculate impedance (resistance) of the body. As most body water is stored in muscle, a more muscular body will lead to lower impedance. BIA is a safe, cost-efficient, and quick method. The downside is that most devices are not portable nor validated in young children, and normative values are only available for a limited number of outcomes, age groups and ethnicities. Moreover, since BIA is not an imaging technique it cannot provide information on muscle structure alterations (intramuscular aspects), but can only estimate muscle mass. Nevertheless, the Tanita MC-780 BIA analyzer (used in this thesis) has shown excellent test-retest reliability[75], and showed high significant correlations (≥0.85) for body composition values in children and adolescents when compared to DXA.[76]

In addition, an emerging imaging technique is muscle ultrasound, which may be suitable to estimate both muscle quantity (size) and quality (intramuscular aspects) in children[77], and may therefore offer a promising role in muscle impairment assessment. Ultrasound is easy available in clinic and has been used for musculoskeletal tissue research in both adults and children.[78,79] To date, the utility of muscle ultrasound in the assessment of muscle impairments in children with cancer has not been studied.

The assessment of muscle strength handheld dynamometry is commonly used. In this thesis, isometric strength by assessing handgrip strength (upper extremity) and dynamically for hip-flexion and knee-extension strength (lower

extremity) are used in the sarcopenia and frailty assessments. Handgrip strength is widely considered as an indicator for overall muscle strength in adults[80] and children.[81] However, it is not a direct measure of the major locomotive muscle groups in the legs[82] and lower limb muscle weakness seems to occur more often than upper limb weakness in children with cancer.[83]

Screening for sarcopenia

The European Working Group on Sarcopenia recommends the use of the SARC-F as a case-finding tool for sarcopenia in the elderly.[46] The SARC-F is a quick self-report score including five questions addressing muscular strength, ability to walk, to rise from a chair, to climb stairs and the occurrence of falls (Figure 5).[84] The SARC-F has shown to be a valid and consistent instrument for detecting sarcopenia in the elderly[85] and in adult cancer patients.[86] Previous meta-analyses showed that the SARC-F has low to moderate sensitivity (27%-39%) and high specificity (86%-91%), which indicates it has strong ability to exclude patients without high risk of sarcopenia.[87,88] A SARC-F cut-off of ≥4 score has been defined as probable sarcopenia in the elderly. Higher SARC-F scores have been associated with (re)hospitalizations and early mortality, demonstrating the importance of screening for sarcopenia using this tool.[85,87] To date the utility of the SARC-F has not been studied in a pediatric (oncology) setting.

Component	Question	Scoring
Strength	How much difficulty do you have in lifting and carrying 10 pounds?	None = 0 Some = 1 A lot or unable = 2
Assistance in walking	How much difficulty do you have walking across a room?	None = 0 Some = 1 A lot or unable = 2
Rise from a chair	How much difficulty do you have transferring from a chair to bed?	None = 0 Some = 1 A lot or unable = 2
Climb stairs	How much difficulty do you have climbing a flight of 10 stairs?	None = 0 Some = 1 A lot or unable = 2
Falls	How many times have you fallen in the past year?	None = 0 1-3 falls = 1 4 or more falls = 2

Figure 5. The SARC-F questionnaire. Adapted from Malmstrom and Morley. *Journal of Post-Acute and Long-Term Care Medicine,* 2013.

Assessment of physical functioning, sarcopenia and frailty components
Relevant aspects of physical functioning are generally considered to be walking ability, rising from the floor, stair walking, experienced fatigue and physical activity levels.

For the assessment of walking ability several tests are available. In this thesis, the six-minute walking test (6MWT), the timed up and go test (TUG) and the ten meter walk test (10MWT) are used. The 6MWT is a submaximal test generally used to evaluate functional walking capacity by measuring the distance an individual can walk in 6 minutes. The test closely reflects activities of daily life and may provide valuable information regarding the pulmonary, cardiovascular and neuromuscular systems, in both adult and pediatric populations.[89] The TUG is a timed functional test in which the individual has to stand up from a chair, walk 3 meters, turn around, walk back and sit down. The test was originally developed to assess functional mobility in in frail elderly, but has over time been generalized to other populations including pediatric patients.[90] Lastly, the 10MWT is a commonly used rapid measure to assess walking speed in meters per second over a 10 meter distance. The test is mostly employed to determine safety of functional mobility, gait patterns and balance in both adults[91] and children.[92]

To assess the ability of rising from the floor in children, the time to rise from the floor test (TRF) is generally performed.[93] During this test the child is asked to sit in cross-legged position on the floor and to get up as fast as possible. The time and degree of support needed to rise from the floor is measured. To assess stair walking ability, the stair climbing test or timed up and down the stairs test, can be used in adult[94] and pediatric populations.[95] The test measures functional strength, balance and agility through ascending and descending a flight of stairs independently.

Fatigue in the pediatric population can be dimensionally assessed using the Dutch version of the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale.[96] This questionnaire is designed specifically to measure fatigue in pediatric patients[97], has been previously used in children with cancer[98] and is used in the research of this thesis.

Scope and outline of this thesis

The general aim of the research projects in this thesis is to develop and validate simplified tools to identify musculoskeletal impairments in children with cancer, to establish risk factors and their occurrence for sarcopenia and frailty during maintenance treatment for ALL, as well as the occurrence of frailty-related

problems, fatigue and participation ability in survivors of childhood cancer. This knowledge may enhance timely identification of and intervention for childhood cancer patients at risk of musculoskeletal impairments.

In **Chapter 2**, a prediction model to identify children at risk of low lumbar spine bone mineral density at ALL diagnosis, as an important indicator for bone fragility is presented. The model is developed on a national cohort of Dutch ALL patients and externally validated on a Canadian multicenter cohort. In **Chapter 3**, the adaptation of SARC-F questionnaire to a pediatric version is described and its diagnostic accuracy for identification of hemato-oncology patients with sarcopenia determined. Moreover, a clinically useful cut-off point is defined. In **Chapter 4,** the utility of muscle ultrasound in children during ALL treatment was studied. Subsequently, it was determined whether ultrasound outcomes of muscle size and muscle quality were associated with skeletal muscle mass, muscle strength and physical performance. **Chapter 5** describes the protocol of a national prospective study in which the acute effect of dexamethasone on sarcopenia and frailty during maintenance therapy for ALL is studied, as well as prognostic factors for developing frailty. In **Chapter 6** some of the findings of this prospective study are described. In **Chapter 7,** the occurrence and determinants of frailty in a cohort of very long-term survivors of acute myeloid leukemia, neuroblastoma and Wilms tumor are described. In **Chapter 8**, the severity of fatigue-related problems, risk factors and the association with participation restrictions in pediatric brain tumor survivors are studied. Finally, the results of this thesis are discussed in **Chapter 9**.

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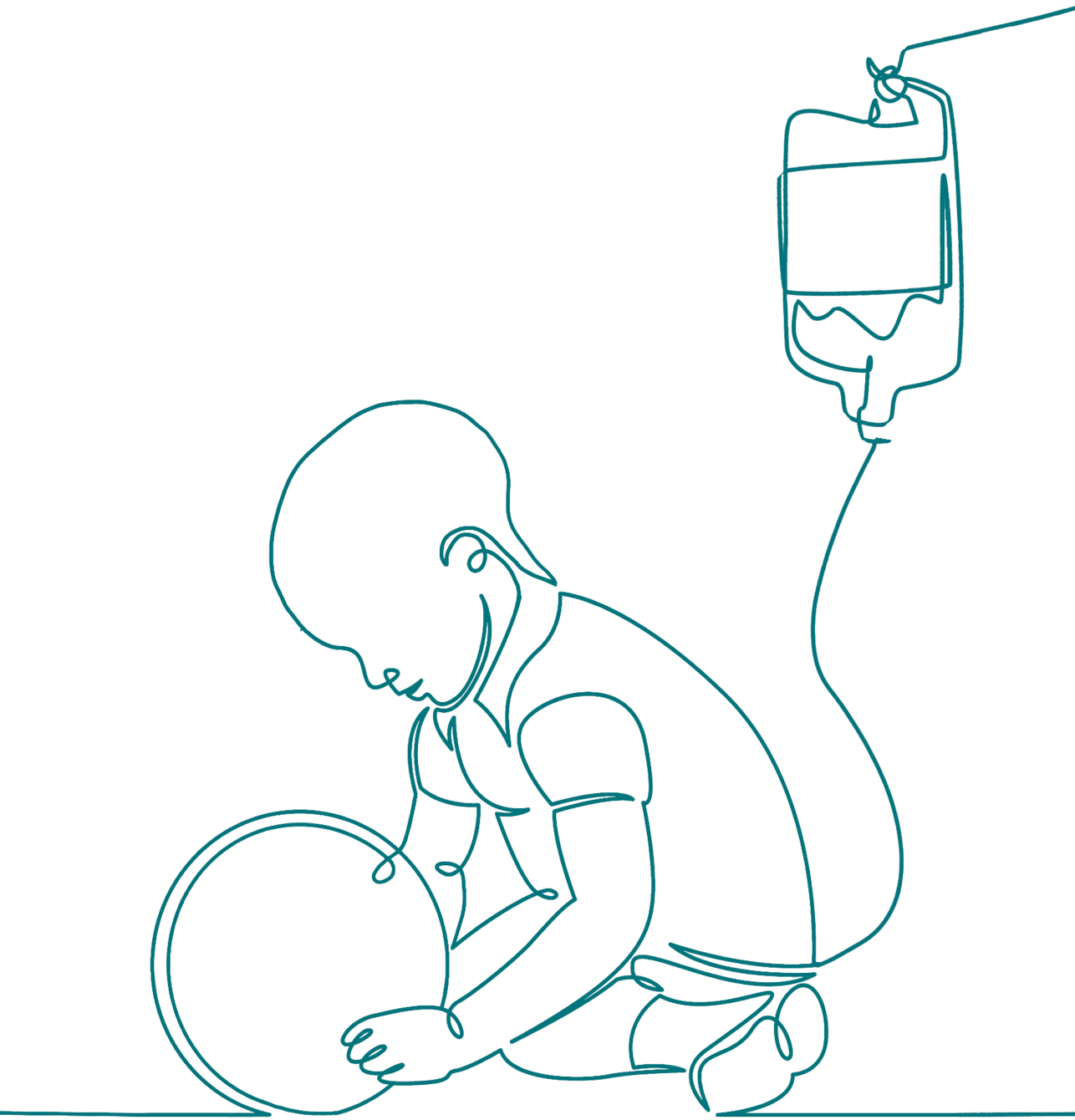

A validated risk prediction model for bone fragility in children with acute lymphoblastic leukemia

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Abstract

Although bone fragility may already be present at diagnosis of pediatric acute lymphoblastic leukemia (ALL), routine performance of dual-energy X-ray absorptiometry (DXA) in every child is not universally feasible. The aim of this study was to develop and validate a risk prediction model for low lumbar spine bone mineral density (LS BMD Z-score ≤-2.0) at diagnosis, as an important indicator for fracture risk and further treatment-related BMD aggravation.

Children with ALL (4-18 years), treated according to the Dutch Childhood Oncology Group protocol (DCOG-ALL9; model development; n=249) and children from the Canadian STeroid-Associated Osteoporosis in the Pediatric Population cohort (STOPP; validation; n=99) were included in this study. Multivariable logistic regression analyses were used to develop the prediction model and to confirm the association of low LS BMD at diagnosis with symptomatic fractures during and shortly after cessation of ALL treatment. Receiver operating characteristic area under the curve (AUC) was used to assess model performance.

The prediction model for low LS BMD at diagnosis using weight (β=-0.70) and age (β=-0.10) at diagnosis revealed an AUC of 0.71 (95% CI=0.63-0.78) in DCOG-ALL9 and 0.74 (95% CI=0.63-0.84) in STOPP, and resulted in correct identification of 71% of the patients with low LS BMD. We confirmed that low LS BMD at diagnosis is associated with LSBMD at treatment cessation (OR=5.9; 95% CI=3.2-10.9) and with symptomatic fractures (OR=1.7; 95% CI=1.3-2.4) that occurred between diagnosis and 12 months following treatment cessation. In meta-analysis, LS BMD at diagnosis (OR=1.6, 95% CI=1.1-2.4) and the six-month cumulative glucocorticoid dose (OR=1.9, 95% CI=1.1-3.2) were associated with fractures that occurred in the first year of treatment.

In summary, a prediction model for identifying pediatric ALL patients with low LS BMD at diagnosis, as an important indicator for bone fragility, was successfully developed and validated. This can facilitate identification of future bone fragility in individual pediatric ALL patients.

Introduction

Acute Lymphoblastic Leukemia (ALL) is the most prevalent pediatric cancer across the globe. Advances in treatment strategies and supportive care have resulted in a 5-year survival rate of about 90% in developed countries.[1-3] With this, there is growing attention to adverse health effects including bone fragility resulting in low-trauma fractures, which can occur at diagnosis, during therapy, and also in the years after therapy cessation. Bone fragility in ALL occurs due to increased osteoclast bone resorption resulting from cytokines released by leukemic cells, as well as by treatment factors (glucocorticoids and malnutrition) and related comorbidities such as osteonecrosis and consequent immobilization.[4-12]

Children have a sixfold greater fracture risk during ALL treatment compared to peers.[10] In the Dutch Childhood Oncology Group protocol (DCOG-ALL9) cohort, symptomatic vertebral and nonvertebral fractures were reported in 1.5% of children at diagnosis and the cumulative incidence of symptomatic fractures at three years was 18%.[5] The Canadian STeroid-associated Osteoporosis in the Pediatric Population (STOPP) Consortium reported a vertebral fracture prevalence (including symptomatic and asymptomatic vertebral fractures) of 16% at diagnosis.[7-9] Over 6 years, the cumulative incidence went on to be 33% for vertebral and 23% for nonvertebral fractures.[7]

The skeletal state at ALL diagnosis plays an important role in the further development of bone fragility during and shortly after therapy. In both of the aforementioned studies, lower lumbar spine bone mineral density (LS BMD) Z-scores and prevalent vertebral fractures at ALL diagnosis were associated with future fractures (vertebral and nonvertebral).[5,7] However, routinely performing dual-energy X-ray absorptiometry (DXA) and spine radiographs in each newly diagnosed child may be undesirable and/or universally unfeasible because of patient burden, lack of DXA availability, or for socioeconomic reasons.

Nevertheless, osteoporotic fractures are a concern, because they lead to adverse health outcomes including pain, loss of height due to vertebral deformity, and (transient) disability.[5,6,9,13] Early identification of patients at risk of fractures is important to facilitate individual management during or following therapy, because it may support clinical decision-making, including whether it is reasonable to perform a DXA scan.

Therefore, the primary aim of this study was to develop and validate a risk prediction model to identify children with low LS BMD at diagnosis of ALL, as

an important indicator of fracture risk and further treatment-related BMD aggravation, during treatment and 12 months following treatment cessation. The secondary aim was to confirm the relevance of LS BMD at diagnosis in the early identification of children with treatment-related bone fragility.

Patients and methods

Study population

DCOG-ALL9 cohort (model development)

Model development was based on an already-reported subsample of a prospective national longitudinal study on bone-toxicity in 751 children with ALL.[5] Children were treated according to the DCOG-ALL9 protocol and enrolled in six centers across The Netherlands between 1997 and 2004.[14] In that study, LS BMD was measured by DXA at diagnosis, after 32 weeks, after 2 years (at cessation of treatment), and 1 year after treatment cessation. All types of symptomatic fractures that were suspected clinically were subsequently confirmed on plain radiographs at each centre. The criteria for defining vertebral fractures were not prespecified, but relied on the expert opinion of pediatric radiologists. For the current study, children between 4 and 18 years of age at diagnosis (due to normative data spanning this age range) with at least one available LS BMD measurement at ALL diagnosis or at treatment cessation were eligible. However, only those patients that had DXAs carried out on Hologic scanners were included in the current study, with raw results and age- and gender-matched Z-scores generated by the local site machine according to the manufacturers' reference data at each site. In the absence of machine cross-calibration, we were unable to pool results from different machines; therefore, DXAs performed on Lunar scanners (24%) were not included in this analysis. Calcium and vitamin D intake was advised based on the recommended required daily dietary intake. Children receiving bisphosphonates were excluded. Further exclusion criteria were Down syndrome and congenital diseases affecting the locomotor system.[5]

STOPP cohort (model validation)

The validation cohort consisted of a subsample of the STOPP cohort, in which a total of 186 children with ALL were enrolled through oncology clinics in 10 pediatric hospitals across Canada from 2005 to 2007.[7-9] Children were treated according to Children's Oncology Group (nine sites) or the Dana-Farber Cancer Institute (one site) protocols. In general, the duration of treatment was 2.5 years for girls and 3.5 years for boys. Children underwent LS BMD assessments within 30 days of chemotherapy initiation, every 6 months for the first 4 years, and then annually for 2 more years. Hologic and Lunar DXA scans were analyzed

centrally by a single DXA technologist. DXA machines at different study sites were cross-calibrated using a spine phantom that was circulated prestudy and annually. All LS BMD raw values were converted to Hologic units prior to generation of age- and gender-matched Z-scores.[7] Symptomatic nonvertebral fractures were confirmed on radiographs by a certified expert pediatric radiologist at each site. Symptomatic and asymptomatic vertebral fractures were identified on spine radiographs at baseline and annually following a central, triple read process by certified pediatric radiologists using the Genant semiquantitative method.[7,9,15] Only symptomatic fractures were included in this study, however, to align with the DCOG-ALL9 cohort's methods. Similar to the DCOG-ALL9 cohort, children participating were between 4 and 18 years of age with at least one available LS BMD at diagnosis and/or at treatment cessation. Children were excluded if they had received bisphosphonates, or if they had calcium and/or vitamin D supplementation that exceeded the dietary reference intake for age.[9]

Outcome definitions

Our previous studies showed that LS BMD Z-scores at diagnosis predicted fractures during and shortly after treatment cessation.[5,7] Hence the primary outcome for the risk prediction model was low LS BMD at diagnosis. LS BMD raw results were expressed as age- and gender-matched Z-scores.[5,9] The model was developed to predict LS BMD Z-scores ≤ -2 (referred to as 'low LS BMD'). Selection of candidate predictors for low LS BMD Z-scores at diagnosis was based on our previous findings and included sex, age, height, and weight Z-scores at diagnosis of ALL.[5,7]

To confirm the importance of LS BMD at diagnosis (for predicting treatment-related fractures and low LS BMD), we performed multivariable analyses with 'low LS BMD at therapy cessation' and '≥ one symptomatic fracture that occurred during and within 12 months following treatment cessation' as endpoints. For the latter purpose, three separate fracture outcome measures were performed: one for all symptomatic fractures, one for symptomatic 'major osteoporotic fractures', and one for 'major osteoporotic fractures' including recurrent distal extremity fractures (referred to as extended major osteoporotic fractures). Major osteoporotic fractures were defined according to the expert opinion of the co-authors and included vertebral, humerus, femur, tibia, and fibula fractures.[16] Extended major osteoporotic fractures included the aforementioned plus single radius, single ulna, and two or more finger or toe fractures. The degree of fracture trauma was not quantified in DCOG-ALL9, therefore, for both cohorts all fractures, whether high-impact or low-impact, were included.

The following prognostic variables based on associations in previous studies were included: sex, age, weight, height or body mass index (BMI) Z-scores, LS BMD Z-scores at diagnosis and glucocorticoid doses.[4,5,7-9,17-20] Glucocorticoid doses were converted to prednisone equivalents, and were based on the intended doses for the DCOG-ALL9 cohort, and on actual doses for the STOPP cohort (Supplemental Table 1).

In addition, because of homogeneity in the intended glucocorticoid doses in the DCOG-ALL9 cohort, we performed multivariable pooled cohort analyses with DCOG-ALL9 and STOPP combined in order to increase statistical power. Potential associations between the 6-month cumulative glucocorticoid dose and fractures that occurred in the first year of therapy were explored. Furthermore, we assessed potential associations between the cumulative glucocorticoid dose at cessation of therapy, and the endpoints 'low LS BMD at therapy cessation' and 'fractures that occurred during and within 12 months following treatment cessation'.

Statistics

Characteristics at baseline were summarized using mean and standard deviation (SD) for normally distributed continuous data, and count and percentage for categorical data. To compare the difference between the development and validation cohorts, two-sample t-tests or $\chi 2$ tests were used.

Patients' characteristics between those with and without missing LS BMD values were compared using either the two sample t-test, Mann-Whitney U or $\chi 2$ test, as appropriate. Predictive mean matching using the Multiple Imputation Chained Equations (MICE) package was used to impute the missing data.[21] Complete case analyses were performed to assess the robustness of prediction models despite imputed data.

A logistic regression-based risk prediction model was developed by combining the as few accessible predictors as possible and achieving as high predictive capacity as possible. Multicollinearity of predictors was not taken into account because it does not affect the overall fit of the model.[22] All candidate predictors were entered simultaneously into a multivariable logistic regression model, using the stepwise backward elimination procedure. Final estimates were pooled from the five imputed datasets using MICE technique[21,23], and were presented as betacoefficients (β) with standard errors (SEs) in log odds and odds ratios (OR) with confidence intervals (CIs). The results derived from the Dutch DCOG-ALL9 cohort were externally validated using data from the Canadian STOPP cohort.

To determine the discriminative ability of the model, receiver operating characteristic (ROC) curve analysis was used to calculate the area under the ROC curve (AUC) and 95% CI. The AUC explains the model's capability of distinguishing between children with and without high risk of the outcome. The AUC value lies between 0.5 to 1, where 0.5 suggests no discrimination, 0.5 to 0.7 = poor discrimination, 0.7 to 0.8 = acceptable discrimination, 0.8 to 0.9 = excellent discrimination, > 0.9 = outstanding discrimination.[24] Hosmer-Lemeshow Goodness-of-fit tests were used to compare the predicted probability to the true probability in the sample, a p-value >0.05 means sufficient calibration of the model.[24]

Results

Cohort characteristics

DCOG-ALL9 cohort (model development)

Of the 751 children treated according to the DCOG-ALL9 protocol, 275 were younger than 4 years at diagnosis, and 21 subjects were excluded because of preexisting conditions interfering with LS BMD. DXA scans at relevant time points were unavailable for 128 children, and 78 children were measured on a Lunar scanner, leaving 249 evaluable children available for the prediction model development (Figure 1).

Baseline characteristics (sex, age, BMI and risk group) of children included in the current study with complete data on LS BMD at diagnosis (n = 219) were not different from those with imputed LS BMD values (n = 30), without DXA examinations (n = 128), and from those who were measured using a Lunar scanner (n = 78) ($p \geq 0.1$).

Children with complete (n = 179), and imputed (n = 70) LS BMD values at treatment cessation did not differ with respect to sex, age, BMI and LS BMD Z-scores at baseline. However, children with missing values were more often treated according to the high-risk protocol (43% versus 23%, $p < 0.01$), an observation which may reflect the greater numbers of nonresponders, and adverse events, in high-risk patients. Characteristics of the children from DCOG-ALL9 with complete LS BMD values are listed in Supplemental Table 2.

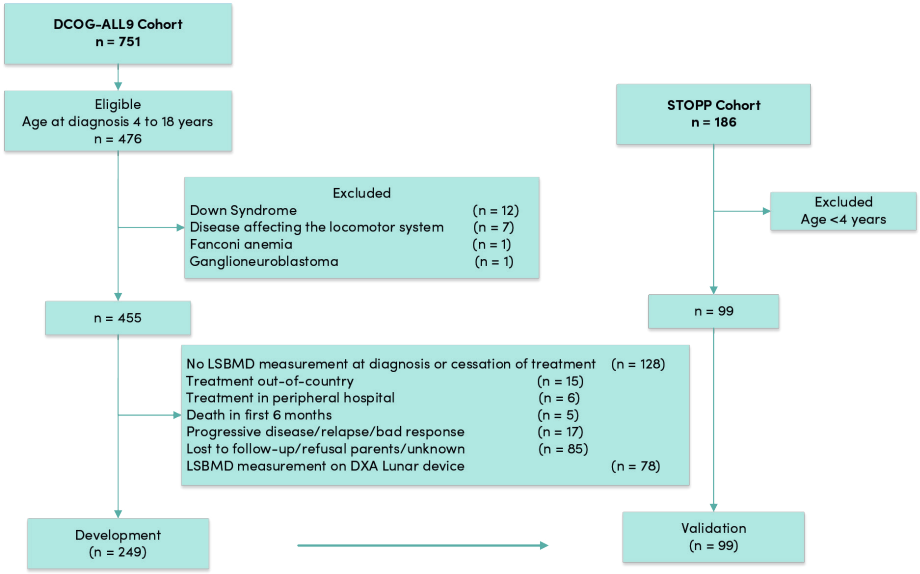

Figure 1. Flow diagram of study participants. Abbreviations: DCOG-ALL9 = Dutch Childhood Oncology Group ALL9 ; STOPP = STeroid-associated Osteoporosis in the Pediatric Population; LS BMD= lumbar spine bone mineral density; DXA = dual-energy x-ray absorptiometry.

STOPP Cohort (model validation)

Of the 186 children enrolled in the STOPP study, 87 were excluded because of young age (<4 years), leaving 99 children available for model validation.

Baseline characteristics of the two cohorts were comparable with regard to sex, age, height and LS BMD Z-scores, but children in the DCOG-ALL9 cohort had lower weight and BMI Z-scores ($p < 0.01$) compared to children in the STOPP cohort (Table 1). Forty-four symptomatic vertebral and nonvertebral fractures (35 during treatment, nine within 12 months after treatment) were recorded in the DCOG-ALL9 cohort, and 33 (30 during treatment, three within 12 months after treatment cessation) in the STOPP cohort. LS BMD Z-scores ≤ -2 were observed in 24.1% and 27.3% at diagnosis, and in 35.7% and 16.2% at cessation of treatment, in the DCOG-ALL9 and STOPP cohorts, respectively. The pooled cumulative glucocorticoid dose (in both cohorts combined) after 6 months of therapy was 2371 ± 543 mg/m^2 (Mean ± SD), and the cumulative dose was 8556 ± 1,953 mg/m^2 at cessation of therapy.

Table 1. Child characteristics at ALL diagnosis

	DCOG-ALL9 Cohort (n = 249)	STOPP Cohort (n = 99)	
Characteristic	**Mean (SD; range)**	**Mean (SD; range)**	***P****
Age, years	7.6 (3.5; 4.0 to 16.6)	8.4 (3.7; 4.0 to 16.6)	0.07
Height, Z-score	0.03 (1.1; -3.6 to 3.1)	0.23 (1.23; -3.23 to 3.15)	0.16
Weight, Z-score	-0.15 (1.1; -3.2 to 3.3)	0.36 (1.16; -2.82 to 3.18)	<0.01
BMI, Z-score	-0.25 (1.1; -4.2 to 2.6)	0.44 (1.36; -4.55 to 3.59)	<0.01
LSBMD, Z-score	-1.1 (1.1; -4.1 to 2.4)	-1.13 (1.41; -5.17 to 2.76)	0.84
	No. (%)	**No. (%)**	
Sex			0.64
Female	91 (36.5)	35 (45.5)	
Male	158 (63.5)	54 (54.6)	
LSBMD Z-score			0.27
≤-2.0	60 (24.1)	27 (27.3)	
>-2.0	189 (75.9)	72 (72.7)	

**P*-values at two-sample t-test and chi-square test
Abbreviations: DCOG-ALL9 = Dutch Childhood Oncology Group ALL9; STOPP = STeroid-Associated Osteoporosis in the Pediatric Population; BMI = Body Mass Index, LSBMD = lumbar spine bone mineral density

Risk prediction model for low LS BMD at ALL diagnosis

Two predictors of low LS BMD Z-scores at ALL diagnosis were identified and included in the model: lower weight Z-scores (OR 2.0; 95% CI, 1.5-2.8) and lower age (OR = 1.1; 95% CI, 1.0-1.2). The prediction model revealed an AUC of 0.71 (95% CI, 0.63- 0.78), indicating that 71% of the children with low LS BMD Z-scores at diagnosis can be correctly identified. This was successfully validated in the STOPP cohort, in which an AUC of 0.74 (95% CI, 0.63-0.84) was observed (Table 2).

Similar findings were obtained when the analysis was restricted to the complete cases only; including DCOG-ALL9 patients without imputed values of LS BMD (AUC 0.69; 95% CI, = 0.61-0.77), confirming robust imputations. We subsequently developed an online calculator for the probability of low LS BMD at ALL diagnosis for an individual patient, which is available at http://lsbmd-risk-calculator.azurewebsites.net/(Figure 2). The probability equation is presented in Supplemental Table 3.

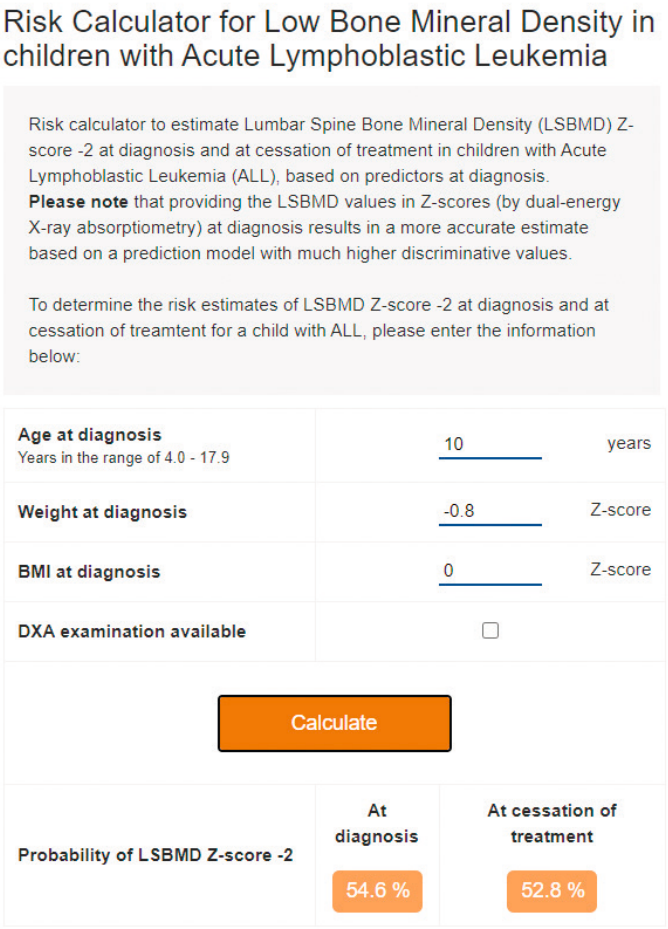

Figure 2. Online risk calculator to estimate the risk of low LS BMD at diagnosis and at cessation of treatment for an individual child with ALL. Clinical applicability (https://lsbmd-risk-calculator.azurewebsites.net/). The use of the models in clinical practice can be shown using the following fictitious case description. A 10-year-old newly diagnosed child with ALL, with a weight Z-score at diagnosis of -0.8. The risk of having low LS BMD Z-scores at that time-point is 54.6% and the risk of having low LS BMD at the cessation of treatment is 52.8%.

Confirmation of the association of baseline LS BMD Z-scores with LS BMD at cessation of therapy and with fractures that occurred between diagnosis and 12 months following treatment cessation

Multivariable analyses showed that lower weight Z-scores (OR 2.0; 95% CI, 1.4-2.8) and higher age (OR 1.3; 95% CI, 1.2-1.5) at diagnosis, were associated with low LS BMD at cessation of treatment. Adding 'LS BMD Z-scores at diagnosis' (lower LS BMD Z-scores: OR 6.2; 95% CI, 3.2-12.1) to the multivariable model

in addition to age (older age: OR 1.7; 95% CI, 1.4-1.9) and BMI Z-scores (lower BMI Z-scores: OR 1.6; 95% CI, 1.0-2.5) at diagnosis enhanced the diagnostic accuracy even further (Table 3).

The association of low LS BMD Z-scores at ALL diagnosis with symptomatic fractures (OR 1.8; 95% CI, 1.3-2.6), the subsample of major osteoporotic fractures (OR 1.6; 95% CI, 1.1-2.4), and the extended major osteoporotic fractures (OR 2.0; 95% CI, 1.3-2.9) that occurred during and within 12 months following treatment cessation was also confirmed (Table 3). The results were successfully validated in the STOPP cohort and consistent findings were generated when the analyses were restricted to the nested cohort of cases with complete data of DCOG-ALL9.

Association of glucocorticoids with low LS BMD and symptomatic fractures (in pooled data of DCOG-ALL9 and STOPP)

Multivariable analyses showed that higher cumulative glucocorticoid dose within the first 6 months of therapy (OR 1.9; 95% CI, 1.1-3.3, for every gram increase), and lower LS BMD Z-scores at diagnosis (OR 1.6; 95% CI, 1.1 to 2.4) were associated with symptomatic fractures (vertebral and non-vertebral) that occurred in the first year of therapy.

Higher cumulative glucocorticoid dose at cessation of therapy (OR 1.5; 95% CI, 1.2- 2.0, for every gram increase), lower LS BMD Z-scores at diagnosis (OR 7.9; 95% CI, 4.8-13.1) and higher age at diagnosis (OR 1.6; 95% CI, 1.4-1.8) were associated with low LS BMD at cessation of therapy, in the pooled dataset (Table 4).

Table 2. Prediction model for low LSBMD at ALL diagnosis; stepwise multivariable logistic regression analysis; backward elimination of potential predictors in DCOG-ALL9 cohort and validation on STOPP cohort

	Initial model (DCOG-ALL9)			Final model (DCOG-ALL9)				Validation (STOPP)
	β	SE	P	β	SE	P	AUC (95% CI)	AUC (95% CI)
Low LSBMD at diagnosis							0.71 (0.63, 0.78)	0.74 (0.63, 0.84)
β_0	-0.58			-0.61				
Weight at diagnosis, Z-score	-0.81	0.24	0.0007	-0.70	0.17	<0.0001		
Age at diagnosis, years	-0.10	0.05	0.03	-0.10	0.05	0.03		
Height at diagnosis, Z-score	0.13	0.21	0.55					
Sex (boy vs girl)	-0.04	0.33	0.89					

Abbreviations: ALL = Acute lymphoblastic leukemia; DCOG-ALL9 = Dutch Childhood Oncology Group ALL9; STOPP = STeroid-associated Osteoporosis in the Pediatric Population; LSBMD = lumbar bone mineral density; AUC = Area under the curve; No = number of children, $\beta_{0,}$ = intercept; β = regression coefficient; SE = standard error

Table 3. The importance of low LSBMD Z-scores at diagnosis for future bone fragility by multivariable logistic regression analysis in DCOG-ALL9 cohort and validation on STOPP cohort

	Initial model (DCOG-ALL9)			Final model (DCOG-ALL9)				Validation (STOPP)
	β	SE	P	β	SE	OR (95% CI)	C-index (95% CI)	C-index (95% CI)
Low LSBMD at treatment cessation							0.78 (0.72, 0.84)	0.74 (0.60, 0.88)
β_0	5.26			-3.25				
Age at diagnosis, years	0.26	0.05	<0.0001	0.28	0.05	1.32 (1.2 to 1.5)		
Weight at diagnosis, Z-score	-0.99	0.24	<0.0001	-0.68	0.17	0.51 (0.4 to 0.7)		
Total glucocorticoid doses, g/m^2 [I]	-0.96	0.40	0.02					
Height at diagnosis, Z-score	0.38	0.21	0.07					
Sex (boy vs girl)	0.13	0.32	0.68					
Low LSBMD at treatment cessation							0.93 (0.89, 0.96)	0.88 (0.80, 0.97)
β_0	13.6			-7.65				
LSBMD at diagnosis, Z-score	-2.55	0.37	<0.0001	-1.83	0.34	0.16 (0.08 to 0.3)[II]		
Age at diagnosis, years	0.59	0.09	<0.0001	0.51	0.08	1.67 (1.4 to 1.9)		
Body mass index at diagnosis, Z-score	-0.65	0.22	0.004	-0.44	0.23	0.64 (0.4 to 1.0)		
Total glucocorticoid doses, g/m^2	-2.51	0.65	0.0001					
Sex (boy vs girl)	-1.02	0.46	0.03					

Table 3. *Continued.*

	Initial model (DCOG-ALL9)			Final model (DCOG-ALL9)			Validation (STOPP)	
	β	**SE**	**P**	**β**	**SE**	**OR (95% CI)**	**C-index (95% CI)**	**C-index (95% CI)**
Symptomatic fractures							0.68 (0.59, 0.78)	0.63 (0.51, 0.74)
β_0	-3.23			-1.93				
LSBMD at diagnosis, Z-score	-0.62	0.17	0.0004	-0.59	0.18	0.55 (0.4 to 0.8)[III]		
Weight at diagnosis, Z-score	0.26	0.23	0.05	0.32	0.17	1.37 (1.0 to 1.9)		
Sex (boy vs girl)	-0.61	0.36	0.09					
Height at diagnosis, Z-score	0.10	0.22	0.65					
Age at diagnosis, years	0.02	0.05	0.63					
Total glucocorticoid doses, g/m^2	0.12	0.48	0.80					
Major osteoporotic fractures[VI]							0.65 (0.51, 0.78)	0.56 (0.42, 0.71)
β_0	-6.67			-3.16				
LSBMD at diagnosis, Z-score	-0.59	0.25	0.02	-0.45	0.22	0.64 (0.4 to 0.9)[IV]		
Weight at diagnosis, Z-score	0.40	0.33	0.22					
Sex (boy vs girl)	-0.58	0.51	0.26					
Age at diagnosis, years	0.05	0.07	0.50					
Total glucocorticoid doses, g/m^2	0.37	0.72	0.61					
Height at diagnosis, Z-score	-0.14	0.31	0.66					

Table 3. *Continued.*

	Initial model (DCOG-ALL9)			Final model (DCOG-ALL9)				Validation (STOPP)
	β	**SE**	**P**	**β**	**SE**	**OR (95% CI)**	**C-index (95% CI)**	**C-index (95% CI)**
Extended major osteoporotic fractures[VII]							0.70 (0.61, 0.80)	0.62 (0.46, 0.72)
β_0	-1.36			-0.25				
LSBMD at diagnosis, Z-score	-0.71	0.20	0.0003	-0.67	0.19	0.51 (0.4 to 0.7)[V]		
Sex (boy vs girl)	-0.76	0.39	0.06	-0.71	0.39	0.49 (0.2 to 1.1)		
Weight at diagnosis, Z-score	0.38	0.25	0.13	0.34	0.19	1.4 (1.0 to 2.0)		
Age at diagnosis, years	0.04	0.06	0.45					
Total glucocorticoid doses, g/m^2	-0.14	0.51	0.78					
Height at diagnosis, Z-score	-0.04	0.24	0.86					

[I] Glucocorticoid doses showed an inverse effect based on the risk group therapy and were therefore not included in the final model
[II] Corresponds with lower LSBMD Z-scores at diagnosis increases odds for low LSBMD at therapy cessation (OR: 6.2; 95%CI: 3.2 to 12.1)
[III] Corresponds with lower LSBMD Z-scores at diagnosis increases odds for symptomatic fractures (OR: 1.8; 95%CI: 1.3 to 2.6)
[IV] Corresponds with lower LSBMD Z-scores at diagnosis increases odds for major osteoporotic fractures (OR: 1.6; 95%CI: 1.1 to 2.4)
[V] Corresponds with lower LSBMD Z-scores at diagnosis increases odds for extended major osteoporotic fractures (OR: 2.0; 95%CI: 1.3 to 2.9)
[VI] Includes symptomatic vertebral, humerus, femur, tibia, and fibula fractures
[VII] Includes symptomatic vertebral, humerus, femur, tibia, fibula, single radius, single ulna, and ≥2 finger/toe fractures

Abbreviations: ALL = Acute lymphoblastic leukemia; DCOG-ALL9 = Dutch Childhood Oncology Group ALL9; STOPP = STeroid-associated Osteoporosis in the Pediatric Population; LSBMD = lumbar bone mineral density; AUC = Area under the curve ; No = number of children, $\beta_{0,}$ = intercept; β = regression coefficient; SE = standard error, OR = Odds Ratio, CI = Confidence interval

Table 4. Multivariable logistic regression analyses in the pooled cohorts of DCOG-ALL9 and STOPP (N=348)

	Initial model			Final model			
	β	**SE**	**P**	**β**	**SE**	**OR (95% CI)**	**C-index (95% CI)**
Symptomatic fractures occurred in the first year of therapy							0.69 (0.58, 0.80)
β_0	-5.31			-4.96			
LSBMD at diagnosis, Z-score	-0.58	0.21	**0.005**	-0.48	0.19	0.62 (0.4 to 0.9)[I]	
Six-month glucocorticoid dose, g/m^2	0.69	0.28	**0.01**	0.65	0.28	1.9 (1.1 to 3.2)	
Sex (boy vs girl)	-0.61	0.47	0.19				
Age at diagnosis, years	0.05	0.07	0.42				
BMI at diagnosis, Z-score	0.09	0.19	0.63				
Symptomatic fractures occurred during therapy or until 12 months after cessation							0.63 (0.55, 0.70)
β_0	-2.69			-1.72			
LSBMD at diagnosis, Z-score	-0.44	0.12	**0.0002**	-0.38	0.11	0.68 (0.5 to 0.9)[II]	
BMI at diagnosis, Z-score	0.30	0.12	**0.01**	0.27	0.11	1.3 (1.1 to 1.6)	
Age at diagnosis, years	0.05	0.04	0.21				
Total glucocorticoid dose, g/m^2	0.08	0.07	0.22				
Sex (boy vs girl)	-0.35	0.28	0.22				

Table 4. *Continued.*

	Initial model			Final model			
	β	**SE**	**P**	**β**	**SE**	**OR (95% CI)**	**C-index (95% CI)**
Low LSBMD at therapy cessation							0.92 (0.89, 0.95)
β_0	-12.9			-12.5			
LSBMD at diagnosis, Z-score	-2.08	0.26	**<0.0001**	-2.07	0.25	0.13 (0.1 to 0.2)[III]	
Age at diagnosis, years	0.47	0.07	**<0.0001**	0.46	0.07	1.6 (1.4 to 1.8)	
Total glucocorticoid dose, g/m^2	0.56	0.19	**0.003**	0.53	0.18	1.5 (1.2 to 2.0)	
BMI at diagnosis, Z-score	-0.34	0.16	**0.03**				
Sex (boy vs girl)	-0.10	0.37	0.78				

[I] Correspondents with lower LSBMD Z-scores at diagnosis increases odds for symptomatic fractures (OR: 1.6; 95%CI: 1.1 to 2.4)
[II] Correspondents with lower LSBMD Z-scores at diagnosis increases odds for symptomatic fractures (OR: 1.5; 95%CI: 1.2 to 1.8)
[III] Correspondents with lower LSBMD Z-scores at diagnosis increases odds for low LSBMD at therapy cessation (OR: 7.9; 95%CI: 4.8 to 13.1)
Abbreviations: DCOG-ALL9 = Dutch Childhood Oncology Group ALL9; STOPP = STeroid-associated Osteoporosis in the Pediatric Population; LSBMD = lumbar bone mineral density; AUC = Area under the curve; $\beta_{0,}$ = intercept; β = regression coefficient; SE = standard error, OR = Odds Ratio, CI = Confidence interval

Discussion

We developed and successfully validated a risk prediction model for low LS BMD at diagnosis of ALL in children 4 to 18 years of age. Although bone fragility is already present at ALL diagnosis, routine performance of DXA scans in every child is not universally feasible. Our easy-to-use and cross-Atlantic validated prediction method facilitates identifying children at risk for treatment-related aggravation of bone fragility over the course of disease, simply by using their weight Z-scores and age at diagnosis. This model has an acceptable capability of 71% to distinguish between children with and without low LS BMD Z-scores.[24,25] This discriminative ability was in the same range as prediction models for low BMD in adult survivors of childhood cancer.[26]

Our results illustrate that lower weight Z-scores and younger age at diagnosis were most predictive of low LS BMD at diagnosis. Lean children have low BMD more often in the general pediatric population as well.[27] The increased risk of low LS BMD with young age might reflect the effect of ALL lineage (precursor B-ALL versus T-ALL), because younger patients present more often with precursor B-ALL, and it has been shown that patients with precursor B-ALL have lower LS BMD at diagnosis compared to those with T-ALL.[5] It has been suggested that this might be explained by a different interaction between T-cell and B-precursor lymphoblasts and osteoblast-osteoclast homeostasis early in the course of ALL. Also, T-cell ALL shows a more rapid development compared to B-precursor ALL and may therefore have less time to adversely affect the bone.

We found a striking difference in the prevalence of low LS BMD between the DCOG-ALL9 and STOPP cohorts at treatment cessation (36% versus 16%). This may be due to the longer time since the last glucocorticoid treatment (0-1 month in DCOG-ALL9 versus 0.5-1.5 years in the STOPP cohort), which may have allowed LS BMD recovery in some of the children in the STOPP cohort. From previous studies it became apparent that BMD values increase after glucocorticoid treatment discontinuation.[28,29]

Our results also showed that weight and age at diagnosis can estimate the risk of low LS BMD at cessation of treatment with 78% certainty. This risk prediction can be enhanced to 92% by performing DXA and adding the individual LS BMD Z-score to the online calculator. This method facilitates an excellent estimation of bone fragility during the course of therapy which may support clinical decision-making with regard to bone health follow-up. Studies have shown that over time, other factors including genetic susceptibility, glucocorticoid dosages, immobility, and comorbidity (such as osteonecrosis) also become important

determinants of fracture risk and BMD decline during treatment.[12,30,31] Previous findings by the STOPP Consortium showed that average daily glucocorticoid dose predicts both vertebral and long-bone fractures over 6 years following diagnosis.[7]

In the DCOG-ALL9 cohort alone, we found no association between intended glucocorticoid doses and fractures, which appears to have resulted from insufficient power, given the findings of a positive relationship when the Dutch and Canadian cohorts were combined. We observed that lower intended glucocorticoid doses were associated with lower LS BMD at therapy cessation in the DCOG-ALL9 cohort. We propose the following explanation for this somewhat surprising observation. First, we note that the intended glucocorticoid dose in the high-risk protocol (8297 mg/m^2) was lower than in the non-high-risk protocol (9136 mg/m^2), because such a lower glucocorticoid dose, albeit only slightly lower, is a hallmark of the high-risk protocol. At the same time, the high-risk protocol is characterized by more intensive treatment overall (including higher doses of asparaginase and methotrexate), which in turn is typically associated with treatment-related toxicity including malnutrition, more frequent hospitalizations, and longer periods of compromised mobility.[14] In addition, methotrexate has been linked to lower BMD[32,33], and the intended cumulative dose of methotrexate was higher in the high-risk group (13650 versus 8100 mg/m^2). Furthermore, asparaginase increases dexamethasone plasma levels and may thus potentiate the detrimental effects of glucocorticoids on BMD[34]; once again, a higher cumulative dose of asparaginase was administered in the high-risk group (114000 IU/m^2 versus 24000 IU/m^2). Taken together, we hypothesize that the lower BMD in the high-risk group was not driven by lower intended glucocorticoid doses per se, but by the more intensive treatment regimen, which is anticipated to adversely affect BMD development.

When our statistical power was increased by combining DCOG-ALL9 and STOPP data, we confirmed that a higher cumulative glucocorticoid dose was associated with low LS BMD at cessation of therapy. More importantly, the cumulative glucocorticoid dose in the first six months of therapy increased the odds of a symptomatic (vertebral or nonvertebral) fracture in the first year by 1.9.

Although low LS BMD is expected in children with lower weight Z-scores at diagnosis, it is important to realize that the development of obesity during therapy may increase the risk of fractures. In the general population, children with obesity carry a higher risk of extremity fractures compared to normal-weight peers, although the mechanism behind this has not yet been entirely elucidated.[27,35] Fracture risk in obese children may be increased due to failure

to accrue sufficient bone mineral content and BMD relative to the mechanical needs of the skeleton, or due to weight-related clumsiness, postural instability, or impaired gait (rendering these children prone to falls).[27] In children with ALL, glucocorticoid-related obesity in combination with immobilization, reduction in weight-bearing activities, and/or vincristine-induced impaired neuromotor skills may raise the risk of fractures.[36,37]

In this study we used LS BMD because this is the most consistently acquired and frequently reported clinical DXA site in children. LS BMD is feasible in children given the ease of positioning for spine measurements compared to hip and total body; it is also a logical clinical site in this context because the spine is linked to the most extensively available reference data[38,39], and because vertebral fractures are far more common than long bone fractures in pediatric ALL as described by the Canadian STOPP consortium.[7]

A number of limitations of this study need to be mentioned. First, a considerable number of children was excluded from the two cohorts because of missing LS BMD values, and because of the need to harmonize methodologies between the two cohorts; ie lack of machine cross-calibration in DCOG-ALL9 led to inclusion of only children measured on Hologic scanners, and only children with symptomatic vertebral fractures were included in the analyses (due to absence of routine spine imaging in the DCOG-ALL9 cohort). In addition, the degree of trauma was not systematically documented in the DCOG-ALL9 registry, which might have influenced the results because low-trauma fractures would be expected to have stronger associations with osteoporotic fractures. The lack of asymptomatic fracture screening in the DCOG-ALL9 may have also explained the lower number of children with vertebral fractures observed in DCOG-ALL9 compared with the STOPP cohort. This methodological issue also prevented the possibility of predicting vertebral fractures at diagnosis which would have been informative, because the STOPP Consortium has previously shown that prevalent vertebral fractures at diagnosis were associated with future vertebral and nonvertebral fractures.[7]

The consideration that both symptomatic and asymptomatic vertebral fractures at diagnosis are strongly associated with incident low-trauma vertebral and nonvertebral fractures in the 6 years following ALL diagnosis underscores the importance of understanding a child's skeletal status at diagnosis. Peripubertal children with vertebral fractures can be left with permanent vertebral deformity[7], and these have been linked to both height reductions in children with ALL[40], and reduced lung function in postmenopausal women.[41] Recently, it was shown that BMD and back pain history can be used in targeted case-finding to identify children with the highest risk of having vertebral fractures

due to serious illnesses.[42] To this end, our easy-to-use BMD prediction model provides some insight into the baseline prevalent and future skeletal status of the child with ALL, and can be used to decide whether a child should undergo a DXA examination.

Ultimately, the clinical goal is to determine which children should be targeted for osteoporosis prevention or intervention. We expanded this knowledge by delineating the predictors of low BMD at diagnosis in a validated, binational model, and have also shown the importance of BMD on the pathway to bone fragility, which occurs most often in the first 2 years of leukemia therapy. Our study therefore provides critical information about best candidates for any future studies tackling the optimal treatment and prevention of low BMD and subsequent fragility fractures in this context.

In summary, we developed and validated an easy-to-use prediction model for low LS BMD in newly diagnosed pediatric ALL patients, aged 4 to 18 years, an important indicator of future treatment-related fracture risk. This model can support clinicians in identifying children with ALL with a high risk of bone fragility during and following therapy.

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Supplemental Table 1. Prednisone exposure for Dana-Farber vs. Children's Oncology Group and DCOG-ALL9 across risk stratification groups

Prednisone exposure at cessation of treatment*	**Dana-Farber Cancer institute***		**Children's Oncology group***		**DCOG-ALL9****	
	High risk	Standard risk	High risk	Standard Risk	High risk	Non-high risk
Cumulative prednisone (mg/m2)	9,693	8,748	7,307	7,959	8,297	9,138

*Dose 48 months after therapy initiation; **Intended dose 24 months after therapy initiation

Supplemental Table 2. Baseline characteristics of children (DCOG-ALL9 cohort) with complete LSBMD values

	Complete LSBMD at diagnosis (n=219)		**Complete LSBMD at treatment cessation (n=179)**	
Characteristic	**Median (range)**	**No. (%)**	**Median (range)**	**No. (%)**
Age, years	7.8 (4-16.4)		7.5 (4.0-16.4)	
	Mean (SD)		**Mean (SD)**	
Height, Z-score	0.09 (1.1)		0.0 (1.1)	
Weight, Z-score	-0.11 (1.1)		-0.15 (1.1)	
BMI, Z-score	-0.24 (1.1)		-0.22 (1.1)	
LSBMD, Z-score	-1.1 (1.2)		-1.1 (1.2)	
Sex				
Female		81 (37%)		65 (36%)
Male		138 (63%)		114 (64%)

Supplemental Table 2. *Continued.*

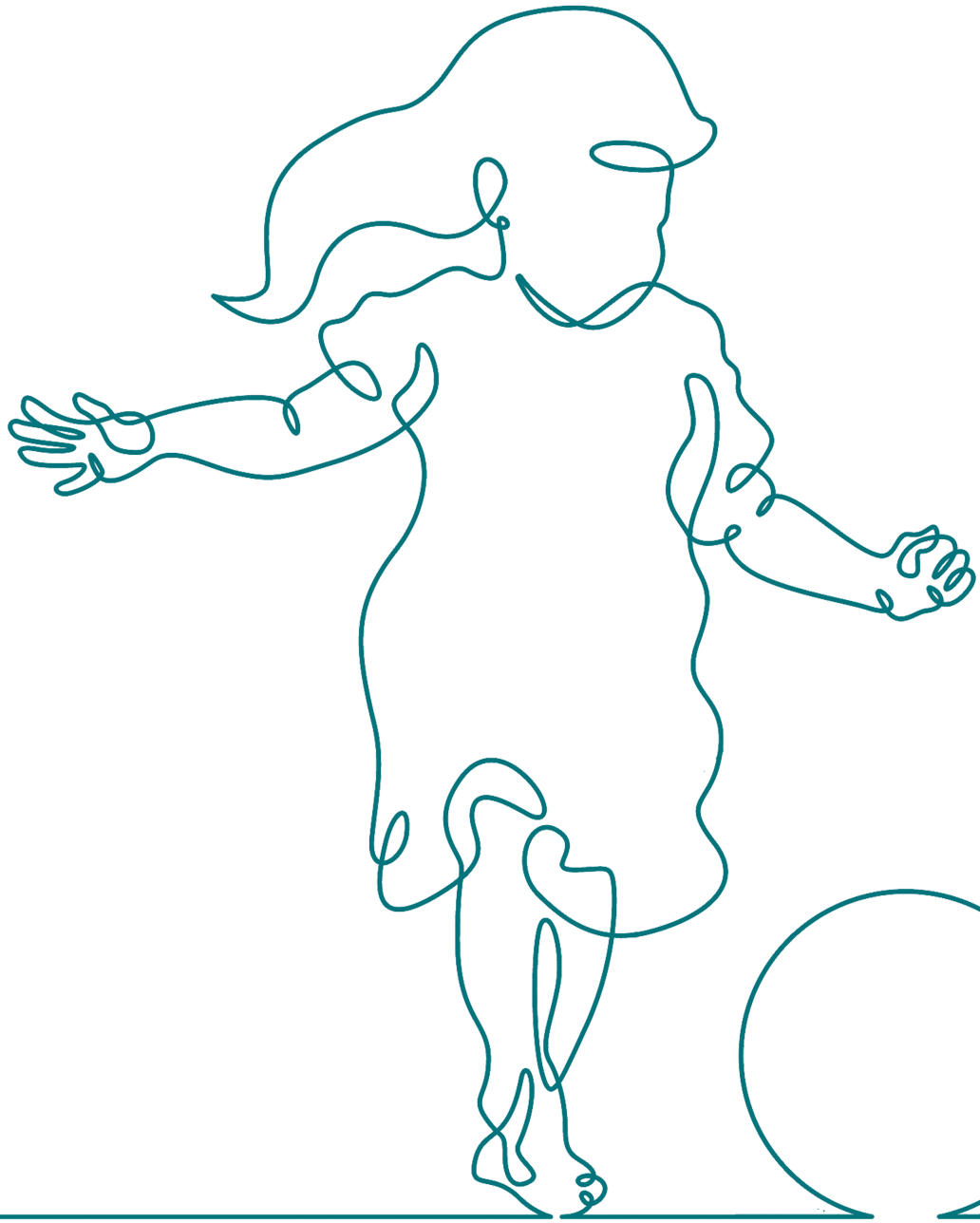
	Complete LSBMD at diagnosis (n=219)		Complete LSBMD at treatment cessation (n=179)	
Characteristic	**Median (range)**	**No. (%)**	**Median (range)**	**No. (%)**
Risk group				
High		63 (29%)		41 (23%)
Non-High		156 (71%)		138 (77%)

Abbreviations: DCOG-ALL9 = Dutch Childhood Oncology Group ALL9; BMI = Body Mass Index; LSBMD = Lumbar spine bone mineral density; SD = standard deviation

Supplemental Table 3. The probability equation to calculate the risk of low LSBMD for an individual child with ALL

$$P\ (\%)\ of\ low\ LSBMD\ at\ diagnosis = \frac{exp(-0.61 - 0.1 * age - 0.7 * weight)}{1 + exp(-0.61 - 0.1 * age - 0.7 * weight)}$$

Abbreviations: P = Probability quantifies the likelihood that an event will occur; exp = exponent, Age in years; Weight in Z-scores



Novel adaption of the SARC-F score to classify pediatric hemato-oncology patients with functional sarcopenia

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Abstract

Sarcopenia in pediatric hemato-oncology patients is undesirable because of the consequences it may have for treatment continuation and outcome, physical abilities and participation in daily life. An easy-to-use screening tool for sarcopenia will facilitate the identification of children at risk who need interventions to prevent serious physical deterioration. In the elderly, the use of the SARC-F score as a case-finding tool for sarcopenia is recommended. The aim of this cross-sectional study was to investigate the accuracy of the pediatric SARC-F (PED-SARC-F) for identifying sarcopenia in pediatric hemato-oncology patients, including the determination of a cut-off point for clinical use.

Patients 3–20 years of age, under active treatment or within 12 months after treatment cessation were eligible. Patients had a physiotherapy assessment including a PED-SARC-F (0–10) and measurements of muscle strength (handheld dynamometry), physical performance (various tests) and/or muscle mass (bio-impedance analysis), as part of the standard of care. Spearman's correlation coefficient ($r_{s)}$ between the PED-SARC-F and physiotherapy outcomes were calculated. Structural sarcopenia was defined as low appendicular skeletal muscle mass (ASMM) in combination with low muscle strength and/or low physical performance. Functional sarcopenia indicated low muscle strength combined with low physical performance. Multiple logistic regression models were estimated to study the associations between the PED-SARC-F and structural/functional sarcopenia. To evaluate which cut-off point provides the most accurate classification, the area under the receiver operating characteristic curve (AUCs), sensitivity and specificity per point were calculated.

In total, 215 assessments were included, 62% were performed in boys and the median age was 12.9 years (interquartile range: 8.5–15.8). The PED-SARC-F scores correlated moderately with the measurements of muscle strength (r_s = −0.37 to −0.47, $p < 0.001$) and physical performance (r_s = −0.45 to −0.66, $p < 0.001$), and weakly with ASMM (r_s = −0.27, $p < 0.001$) . The PED-SARC-F had an AUC of 0.90 (95% confidence interval (CI) = 0.84–0.95) for functional sarcopenia and 0.79 (95% CI = 0.68–0.90) for structural sarcopenia. A cut-off point of ≥5 had the highest specificity of 96% and a sensitivity of 74%.

In conclusion, we adapted the SARC-F to a pediatric version, confirmed its excellent diagnostic accuracy for identifying functional sarcopenia and defined a clinically useful cut-off point in pediatric hemato-oncology patients.

Introduction

Treatment of children with hemato-oncological diseases is often intensive and associated with symptom burdened trajectories which may involve (prolonged) hospitalizations. These children are generally immunocompromised, at higher risk of infections, and prone to malnutrition, general malaise and immobilization. In particular, the administration of glucocorticoids and vincristine contributes to muscle deterioration[1,2] and peripheral neuropathy[3,4], which can aggravate immobilization and consequent loss of muscle mass and strength. This all can lead to seriously impaired physical performance with negative consequences for quality of life.

The combination of decreased muscle strength and muscle mass loss is referred to as sarcopenia: a generalized muscle deficiency.[5,6] Sarcopenia has been associated with increased adverse health outcomes and mortality in adults with various diseases.[6,7] In pediatric cancer patients, sarcopenia is a relatively understudied condition, and its prevalence, causal factors and consequences have not been entirely elucidated.[8] However, studies in children with acute lymphoblastic leukemia (ALL) indicate the necessity of awareness of sarcopenia during therapy.[9-11] Muscle mass loss during ALL therapy was associated with the number and duration of hospital admissions[9], occurrence of invasive fungal infections[10], and even with impaired survival.[11]

The European Working Group on Sarcopenia recommends the use of the SARC-F as a case-finding tool for sarcopenia.[6] The SARC-F is a quick self-report score including five questions addressing muscular strength, ability to walk, rise from a chair, climb stairs and experience of falls.[12] The SARC-F has shown to be a valid and consistent instrument for detecting sarcopenia in the elderly[13] and in adult cancer settings.[14] Previous meta-analyses showed that the SARC-F had low-to-moderate sensitivity and a high specificity for identifying older adults at risk of sarcopenia.[15,16] A cut-off of a score ≥4 has been proposed to detect probable sarcopenia and has been associated with poorer health outcomes.[13]

Based on the results in the elderly population, we implemented a slightly adapted version as part of our clinical physiotherapy care for children with hemato-oncological diseases. However, to our knowledge, the clinical usefulness of the SARC-F had never been investigated in pediatric populations. Therefore, the aim of this project was to determine the accuracy of the pediatric SARC-F (PED-SARC-F) in our (national) single-center pediatric hemato-oncology cohort, using physiotherapy outcome measures. Subsequently, we determined a clinically useful cut-off score of the PED-SARC-F to easily classify children with sarcopenia.

Materials and methods

Study design and patients

In this cross-sectional study, patients between 3 and 20 years of age, under active treatment or within 12 months after the cessation of treatment at the hemato-oncology and stem cell department of the Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands were included. Only patients that had given informed consent to use their data for research purposes were considered; this was approved by the Medical Ethical Committee (MEC-2016-739).

The PED-SARC-F has been implemented as part of the standard physiotherapy assessment since December 2018. Data from assessments performed between that time and January 2021 were retrieved from the electronic patient records and anonymized. Patients had to have an in-patient physiotherapy consultation including the administration of the PED-SARC-F with at least one assessment of muscle strength, physical performance or muscle mass to be included. If a patient had undergone more than one physiotherapy consultation, these could only be included if the assessments happened during different treatment phases (e.g., during intensive chemotherapy and after therapy cessation). Patients with known (motor)developmental or neurological disorders, as well as symptomatic osteonecrosis or bone fractures that resulted in impaired physical functioning, were excluded.

PED-SARC-F

The SARC-F is a short screening tool that encompasses five self-reported questions, which reflect physical changes associated with sarcopenia.[13] For the particular usage in our pediatric oncology population, we slightly adapted the text of the original questions resulting in a pediatric version: the PED-SARC-F (Supplemental figure 1). Parents and/or patients were asked to estimate the difficulties they had observed over the last 2 weeks for each of the four items: 'lifting something heavy', 'walking', 'rising from the floor' and 'climbing stairs' as follows: 0 = no difficulties, 1 = some difficulties, and 2 = a lot of difficulties or unable to perform. The fifth item 'number of falls' was scored as 0 = zero falls, 1 = 1-3 falls and 2 = ≥4 falls. Total scores range from 0-10. Cognitive debriefing was not performed prior to administration.

Physiotherapy assessment

The standard physiotherapy assessment consisted of measuring muscle strength, physical performance, and muscle mass. Not all measurements could be performed in every patient. As the assessment took place as part

of clinical care, it depended on the fitness of the patient and the assessment being a burden.

A total of three different measures of muscle strength with handheld dynamometry (HHD) were performed. Handgrip strength was assessed in a sitting position with the elbow unsupported and flexed at 90° using a Jamar HHD (Sammons Preston, Bolingbrook, Illinois, USA). Hip flexion and knee extension strength were measured with the eccentric break technique protocol in the standardized positions[17] using the MicroFET-2 HHD (Hoggan Health Industries, Salt Lake City, UT, USA). With the break technique, the physiotherapist applies the force needed to overpower the patient who is extending the knee or flexing the hip, thereby eliciting an eccentric contraction from the patient. All HHD measurements were carried out bilaterally, the mean of three repeats was compared to normative values and Z-scores were calculated.[17,18]

Aspects of physical performance were assessed with three different tests. First, the 10 m walk test (10-MWT) was used.[19] The child was asked to walk a marked distance of 10 m at normal pace, independently, without using support. The fastest time in seconds of three tries was scored. Second, the Time to Rise from the Floor test (TRF)[19] was carried out. The child was asked to get up as fast as possible from sitting in a cross-legged position on the floor. Per protocol[19], this test was performed twice, the fastest performance in seconds was scored. Third, the Timed Up and Down Stairs (TUDS) test was performed.[20] The time required to ascend and descend a flight of stairs (10 steps) was measured in seconds.

Muscle mass was measured using bioimpedance analysis (BIA) (Tanita MC-780, Tanita Corporation, Tokyo, Japan). The measurement procedure required the child to stand barefoot on the analyzer and hold a handgrip on each side for approximately 10 seconds. Appendicular skeletal muscle mass (ASMM) was calculated with correction for light indoor clothing. As reference data for Dutch children were unavailable, to estimate Z-scores, we used age and sex-specific mean and standard deviation values from a UK population (5–18 years), acquired using the same Tanita software[21]. Due to a lack of BIA reference values of 3–4-year-old children, we used sex and age-specific expected values of ASMM (kilogram), derived by a dual-energy X-ray absorptiometry prediction equation in Canadian children[22].

Structural and functional sarcopenia definition

Two definitions for sarcopenia were used. Structural sarcopenia encompassed low ASMM in combination with low muscle strength and/or low physical performance. Functional sarcopenia indicated low muscle strength combined

with low physical performance (Figure 1). Patients could meet the criteria for both structural and functional sarcopenia when they had low ASMM and low muscle strength and low physical performance, indicating that impairments were prevalent on a structural and functional level.

To define 'low', we selected the patients with values of the lowest 20% of the cohort, due to lack of pediatric reference values for sarcopenia, which is in line with previous studies using functional outcome measures of frailty.[23,24] Low muscle strength was defined as a (for sex and age) standardized score of handgrip strength, hip flexion strength or knee extension strength in the lowest 20% of all measured patients. If a child was physically incapable, i.e., movement against gravity or resistance was limited, this was also classified as low muscle strength.

Low physical performance was defined as a score in the highest 20% (higher score equals slower performance) of the 10-MWT, TRF or TUDS. One of the measurements had to be low for a child to be labeled as having low physical performance. If a child was incapable of rising or (stair)walking independently, this was also classified as low.

Low ASMM was defined as (for sex and age) standardized score in the lowest 20% of all measured patients.

Statistical analyses

All data were expressed as means and standard deviations (SDs) for normally distributed variables or median and interquartile ranges (IQRs) for skewed distributions and number (percent) for categorical variables.

We performed Spearman's rank correlation analyses to assess the correlations between the PED-SARC-F and the objectively measured components: handgrip strength, hip flexion strength, knee extension strength, 10-MWT, TRF, TUDS and ASMM. A Spearman coefficient (r_s) ranges from -1 to +1, where an r_s of 0 to 0.3 (0 to -0.3) means a negligible correlation, 0.3 to 0.5 (-0.3 to -0.5) means a low correlation, 0.5 to 0.7 (-0.5 to -0.7) means a moderate correlation, 0.7 to 0.9 (-0.7 to -0.9) means a high correlation, and 0.9 to 1.0 (-0.9 to -1.0) describes a perfect correlation.[25]

Multiple logistic regression analyses were used to assess the associations between the PED-SARC-F and the binary outcomes of functional and structural sarcopenia. Age was used in both models, while sex was incorporated only in the model for functional sarcopenia due to the small sample size for structural sarcopenia. The results are presented as odds ratio (OR) along with

95% confidence intervals (CI). We computed cluster robust standard errors for the estimated parameters to deal with multiple assessments. The area under the receiver operating characteristic curve (AUC) was estimated to assess discriminative accuracy of PED-SARC-F. The AUC values lie between 0.5-1; 0.5 suggests no discrimination and >0.9 = outstanding discrimination.[26]

Subsequently, we examined which PED-SARC-F cut-off point (0-10) had the highest diagnostic accuracy for detecting functional sarcopenia. For clinical purposes, we have determined the cut-off point assembling the highest AUC and the highest specificity as the most clinically relevant, yielding a low number of false positives. We therefore calculated the AUC, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)[27] for each PED-SARC-F score, to be able to distinguish between the number of false positives and false negatives cases per cut-off point.

All analyses were performed in Rstudio environment Version 1.4.1106 for Windows.[28]

Results

Patients

In total, 215 physiotherapy assessments in 167 patients were included in this study. Among the 167 patients, 126 had a single assessment, 34 children had two and 7 children had an assessment at three different time points. Sarcopenia may occur with different severity and during different phases of treatment. In the case of more than one assessment per patient it always took place at different treatment phases, as specified in Supplemental Table 1. The characteristics of the 167 individual patients at their first physiotherapy assessment are depicted in Supplemental Table 2. Due to the cross-sectional design of this study, we considered each physiotherapy assessment (during a different treatment phase) as an individual assessment in our analyses, rendering 215 assessments.

The majority of the 215 assessments was performed in boys (62.3%), the median age was 12.9 years (IQR: 8.5-15.8), the median height Z-scores were -0.27 (IQR: -0.8-1.2), the weight Z-scores were 0.13 (IQR: -0.8-1.2) and the BMI Z-scores were 0.33 (IQR: -0.8-1.6) (Table 1).

PED-SARC-F scores and physiotherapy assessment

The median PED-SARC-F score was 2 (range: 0-10). The results corresponding to the individual questions are depicted in Supplemental Figure 1. The mean Z-score of handgrip strength (n = 100) was -0.75, SD: 1.0.

Table 1. Patient characteristics at physiotherapy assessments (n = 215)

	No.	**%**
Sex		
Boy	134	62.3
Girl	81	37.7
Type of hematological disease		
Acute lymphoblastic leukemia	129	60
Acute myeloid leukemia	24	11.2
Chronic myeloid leukemia	6	2.8
Hodgkin lymphoma	8	3.7
Non-hodgkin lymphoma	16	7.4
Myelodysplastic syndrome	8	3.7
Fanconi anemia	14	6.5
Aplastic anemia	3	1.4
Other*	7	3.3
Treatment phase		
Intensive chemotherapy	54	25.1
Maintenance chemotherapy	57	26.5
1-12 months after chemotherapy cessation	19	8.9
Pre SCT conditioning phase	31	14.4
3-12 months post SCT	54	25.1
Assessment performed during		
Clinical admission	36	16.7
Daycare admission / Outpatient clinic visit	179	83.3
Body Mass Index, categories		
Underweight	18	8.4
Normal Weight	141	65.6
Overweight	41	19
Obesity	15	7
	Mean	**Median [IQR]**
Age, years	12.1	12.9 [8.5 to 15.8]
Height, SDS	-0.31	-0.27 [-0.8 to 1.2]
Weight, SDS	0.25	0.13 [-0.8 to 1.2]
Body Mass Index, SDS	0.33	0.33 [-0.8 to 1.6]

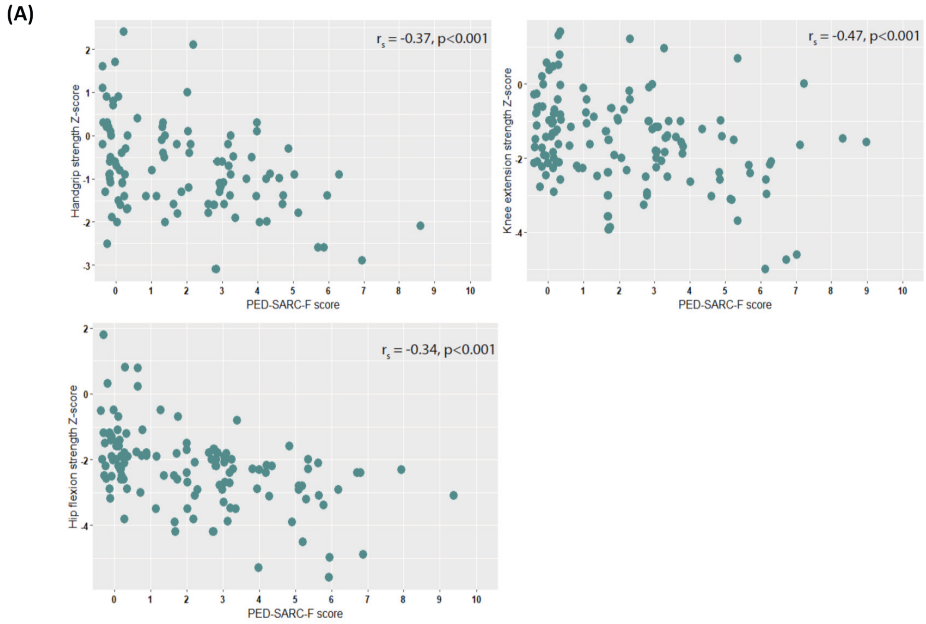
Abbreviations: SCT = stem cell transplantation, IQR = interquartile range, SDS = standard deviation score *Blastic plasma cytoid dendritic cell neoplasm (n = 2), common variable immunodeficiency (n = 1), de novo acute promyelocytic leukemia (n =1), Diamond-Blackfan anemia (n = 1), Langerhans cell histiocytosis (n = 1), Paroxysmal nocturnal hemoglobinuria (n = 1)

The mean Z-score of hip flexion strength (n = 123) was -2.3 SD: 1.2, and of knee-extension strength (n = 139) was Z-score: -1.5, SD: 1.2. The median walking pace in the 10-MWT (n = 144) was 1.23 m per second (IQR: 1-1.4). The median TRF

time (n = 141) was 2 s (IQR: 1.4–3). The mean ASMM Z-score (n = 150) was -0.6 (IQR: -1.2–0.0). The results of the total physiotherapy assessments, including the number of children that were not able to perform a test, are specified in more detail in Table 2. The results of the sub-cohort of the 167 individual patients on their first physiotherapy assessment were not different from the results of the complete cohort ($p > 0.05$).

Correlations of PED-SARC-F with muscle strength, physical performance and ASMM

The PED-SARC-F scores correlated with handgrip strength ($r_s = -0.37$, $p < 0.001$), knee extension strength ($r_s = -0.34$, $p < 0.001$), and hip flexion strength ($r_s = -0.47$, $p < 0.001$), i.e., higher PED-SARC-F scores correlated weakly to decreased Z-scores (Figure 1A). The PED-SARC-F scores correlated with 10-MWT (r_s=0.45, p<0.001), TRF (r_s=0.66, p<0.001) and TUDS (r_s=-0.64, p<0.001), i.e., a higher PED-SARC-F score correlated moderately to slower performance (Figure 1B). A lower PED-SARC-F correlated weakly with lower ASMM Z-scores ($r_s = -0.27$, $p < 0.001$) (Figure 1C).



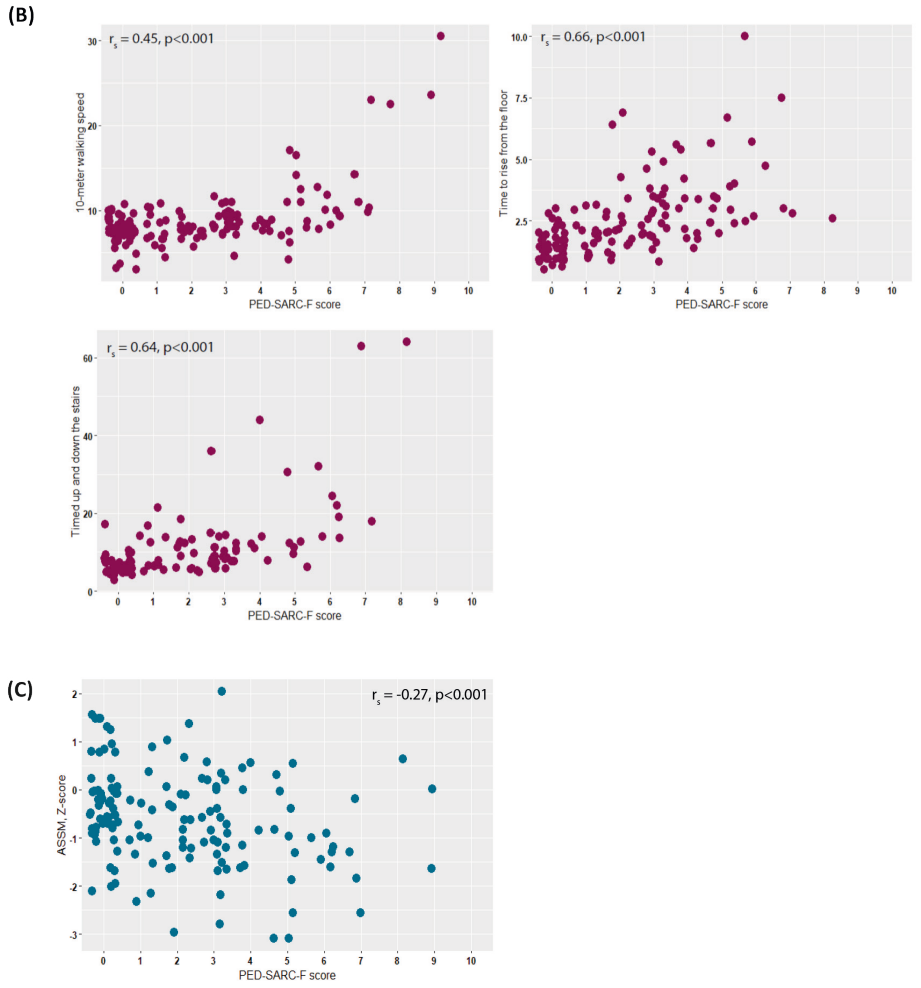


Figure 1. (**A**). Scattergraphs showing muscle strength measures by PED-SARC-F score; (**B**). Scattergraphs showing physical performance tests by PED-SARC-F score; (**C**). Scattergraph showing appendicular skeletal muscle mass (ASMM) by PED-SARC-F score. Abbreviations: r_s = Spearman's correlation coefficient.

Diagnostic accuracy of the PED-SARC-F for structural and functional sarcopenia

In total, 16 patients met the criteria for structural sarcopenia (7.4%) and 46 (21.4%) for functional sarcopenia (Figure 2). The classification of patients with structural, functional or no sarcopenia per the PED-SARC-F score is illustrated in Figure 3. Logistic regression analyses showed that the odds for functional sarcopenia were two times higher for every PED-SARC-F point increase

(OR = 2.07, 95% CI: 1.68-2.55), in models adjusted for sex and age. The model provided an AUC equal to 0.90 (95%CI: 0.84-0.95), indicating that 90% of the children with functional sarcopenia are classified correctly by the PED-SARC-F (Table 3). The odds of structural sarcopenia were 1.5 point higher for every PED-SARC-F score increase; the AUC was equal to 0.79 (95% CI: 0.69-0.90) (Table 3).

Table 2. Results of physiotherapy assessments (n = 215)

	N	Median	Interquartile range	Measurement not performed	
				Incapable	Other[I]
Muscle strength measurements					
Handgrip strength	100			14	101
Dominant hand, kilograms		17.4	8.7 to 27.5		
Dominant hand, Z-score[II]		-0.75	1.0		
Hip flexion, strength	123			23	69
Left hip, Newton		126	101 to 192		
Right hip, Newton		133	98 to 177		
Mean Left+Right hip, Z-score[II]		-2.3	1.2		
Knee extension strength	139			19	57
Left leg, Newton		184	131 to 259		
Right leg, Newton		186	128 to 269		
Mean Left+Right leg, Z-score[II]		-1.5	1.2		
Physical performance measurements					
10-meter Walk Test	144			11	60
Time, seconds		8.1	7.4 to 9.5		
Meters per second		1.23	1.0 to 1.4		
Time To Rise From the Floor	141			26	48
Time, seconds		2	1.4 to 2.9		
Timed Up and Down Stairs	115			27	103
Time, seconds		7.8	5.8 to 12.4		
Step per second		0.4	0.3 to 0.6		
Muscle mass measurement					
Bio-electrical impedance analysis	175			NR	70
ASMM, kg		14.5	8.4 to 19.8		
ASMM, %[II]		28.4	25.4 to 30.7		
ASMM, Z-score[II]		-0.60	-1.2 to 0.0		

Abbreviations: ASMM = Appendicular Skeletal Muscle Mass , NR = Not reported.
[I]Measurement was not performed because of various reasons i.e., hospital admission or connected to intravenous line, parent or child refusal, too much of a burden, child was fatigued/nauseous, had poor understanding or was too young. [II]Presented as mean and standard deviation.

In addition, the diagnostic accuracy of functional sarcopenia for different cut-off points of the PED-SARC-F was calculated. A score of ≥5 provides the best diagnostic accuracy (AUC: 0.82, 95% CI: 0.74-0.91), with a specificity of 91%, sensitivity of 74%, PPV of 68% and an NPV of 93%. Robust standard errors provided similar accuracy as the models estimated with traditional standard errors.

The results for each PED-SARC-F score are described in Supplemental table 3.

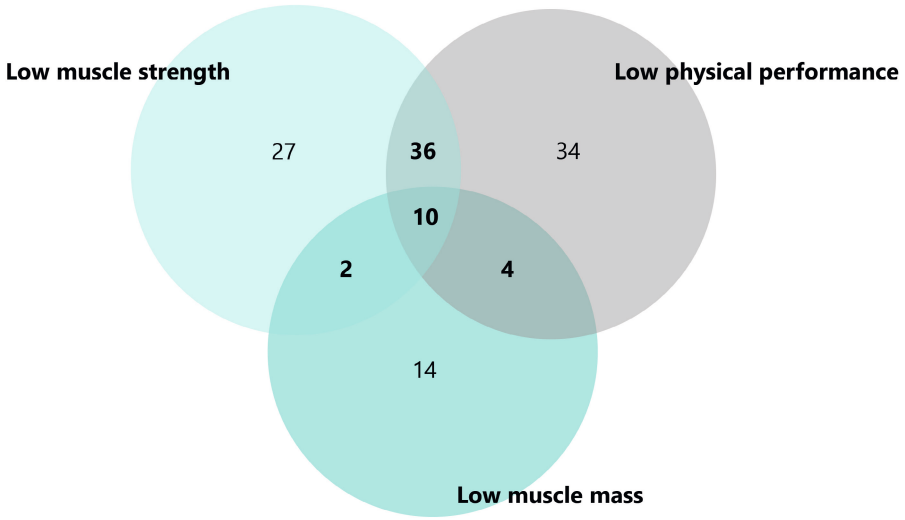


Figure 2. The occurrence of the sarcopenia components in the assessments. Co-occurrence of the components led to a number of 16 (2+10+4) for structural sarcopenia and 46 (36+10) assessments meeting the criteria for functional sarcopenia.

Table 3. The predictive accuracy of the PED-SARC-F for detecting functional and structural sarcopenia

	Odds Ratio	95% CI	AUC (95% CI)
Functional sarcopenia			0.90 (0.84 to 0.95)
PED-SARC-F, per point	2.07	1.68 to 2.55	
Sex, boy vs girl	0.71	0.28 to 1.78	
Age, years	0.98	0.89 to 1.08	
Structural sarcopenia			0.69 (0.57 to 0.80)
PED-SARC-F, per point	1.21	1.02 to 1.42	
Age, years	1.13	1.00 to 1.28	

Abbreviations: OR = odds ratio, CI = confidence interval, AUC = area under the curve

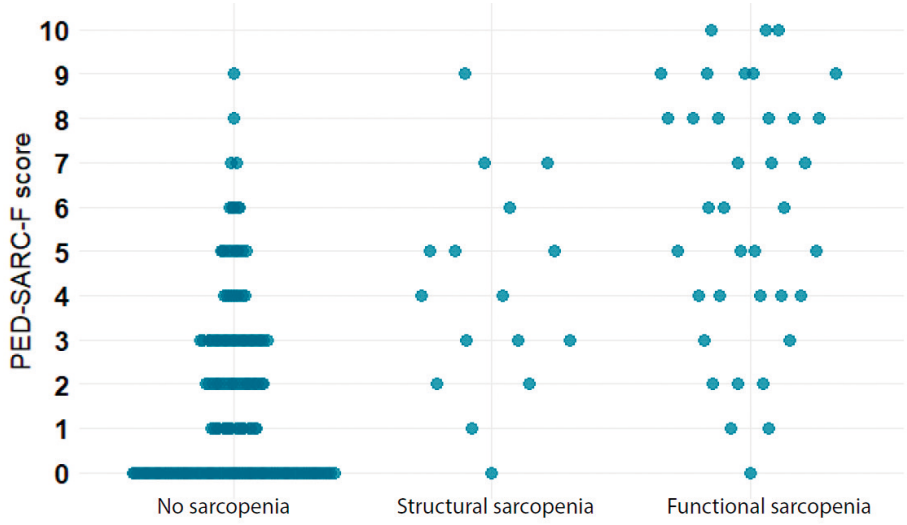


Figure 3. Scattergraph: No, structural and functional sarcopenia by PED-SARC-F score.

Discussion

Sarcopenia in children receiving intensive treatment for hemato-oncology diseases is undesirable because of the consequences it may have for treatment continuation, physical abilities, motor and neurodevelopment and participation in daily life. In the current study, we evaluated the diagnostic accuracy of our novel pediatric version of the SARC-F (PED-SARC-F), which has been used as part of our clinical physiotherapy care for pediatric hemato-oncology patients.

To the best of our knowledge, this is the first attempt to evaluate the use of the SARC-F in a pediatric population. For clinical purposes, we extended the definition of sarcopenia by separating structural and functional sarcopenia. So far, the sequence of events leading to sarcopenia in children with cancer has not yet been clearly discerned. In childhood cancer survivors, muscle mass can decrease prior to strength and function loss being observed, which is different from the elderly, who experience decreases in muscle strength preceding muscle mass loss[29]. The results of our study suggest that low muscle strength (28%) and impaired physical performance (32%) were more prevalent than low muscle mass (14%). This may indicate that muscle strength can deteriorate in the absence of or with only minimal muscle mass loss, which could be explained by the fact that muscle strength depends on many complex physiological mechanisms. Alternatively, loss of muscle strength and performance may be the early signs of sarcopenia in this population. Furthermore, some children

may partially recover their muscle mass, but muscle quality (and thus performance) may stay compromised. The precise understanding between the occurrence of muscle mass loss and strength or function loss in children treated for hemato-oncological diseases has yet to be elucidated.

The results of this study show that the PED-SARC-F is a suitable and accurate cross-sectional screening tool to identify pediatric hemato-oncology patients with functional sarcopenia (diagnostic accuracy: 90%, 95% CI: 0.84-0.95). Although the PED-SARC-F correlated only moderately with physical performance outcomes and even had a low correlation with muscle strength measurements, it is excellent at identifying patients who suffer from low muscle strength and impaired performance, after adjustment for sex and age. We found a weak correlation between the PED-SARC-F and ASMM. In contrast, we found a moderate-to-good accuracy for the detection of structural sarcopenia (discriminative ability: 79%, 95%CI: 0.68–0.9). This may be explained by the fact that a relatively large number of children with low ASMM also had impaired strength or performance (n = 10). The weak correlation may be diminished due to the fact that BIA could not be performed in bedridden patients, who probably had lower muscle mass but who did not have an ASMM measurement. Moreover, there is uncertainty about the reliability of BIA in children with high fat percentages[30], and also hydration status may affect the measurements, as it causes an increase in the body's electrical resistance[31]. Both overweight and disturbed fluid balance can occur in hemato-oncology patients, thus this may have influenced the results. Unfortunately, in our clinical cohort we had no availability of muscle mass measures other than BIA. Imaging techniques are frequently used in pediatric research but for clinical care these methods have several limitations. Computed tomography (CT) is undesirable due to radiation exposure and the calculation of muscle mass on CT scans is time-consuming. The current gold standard is magnetic resonance imaging (MRI) which is expensive, poorly accessible, time-consuming, needs mobilization of the patient to a radiology department and sedation in younger children. Another reliable technique is dual-energy X-ray absorptiometry (DXA), which has the same disadvantages as MRI, making these techniques unsuitable for routine evaluations. However, the finding that PED-SARC-F is less sensitive for detecting low muscle mass, resembles results of adult studies concerning community-dwelling elderly[32], patients with chronic kidney disease[33] and cancer patients[34], which also showed that the SARC-F is better in detecting alterations in muscle strength and function rather than muscle mass deterioration.

In previous studies in the elderly, a SARC-F cut-off of ≥4 points was proposed to identify patients with probable sarcopenia.[13,35] Our analyses show that a cut-off point of ≥5 for the PED-SARC-F had the highest AUC and specificity

for detecting functional sarcopenia in pediatric hemato-oncology patients. We aimed for the highest specificity because in clinical care, such a cut-off point reduces the number of false positives and therefore limits unnecessary assessments in patients that are not at risk.

Some methodological limitations should be addressed. First, patients in this study were selected for the availability of their physiotherapy assessments (selection bias). This may have led to stronger associations because the patients were more likely to have muscle weakness or physical impairments. Secondly, there is no uniform definition and there are no cut-off points with reference values for sarcopenia in children yet. We therefore decided for a margin of 20% in our definition, in line with previous studies using functional outcome measures of frailty.[23,24]

Based on the results of this study, we recommend the use of the quick and easily self-reported PED-SARC-F as a screening instrument by pediatric oncologists or nurse specialists, to identify hemato-oncology patients at risk of functional impairments due to loss of muscle strength. In patients with a PED-SARC-F score of ≥5 referral to a (pediatric) physiotherapist for specific function assessment and interventions should be considered.

Current evidence for interventions to improve muscle strength in children with cancer is not very comprehensive. It is known that treatment-induced denervation of muscle fibers and mitochondrial dysfunction may occur, but the direct molecular impact of cancer treatment is unknown. It has been suggested that exercise may potentially stimulate repair/replacement of damaged mitochondria[36]. A number of trials have been performed demonstrating that exercise is safe and feasible even during intensive treatment[37,38], but the effectiveness of interventions during cancer treatment on muscle mass and strength in pediatric patients has not been shown yet. For future research, it is important to determine the adequate moment for prevention and training during treatment, and to determine the most beneficial training for the individual patient, yielding the most resilient results. Further knowledge of the biological mechanism behind muscle dysfunctions in these patients is needed to develop successful interventions. The PED-SARC-F may play an important role in selecting patients who are at risk and may be a valuable tool in longitudinal evaluations.

To conclude, we adapted the SARC-F questionnaire to the PED-SARC-F, an easy-to-use self-reporting tool and showed its value for identifying functional sarcopenia in pediatric hemato-oncology patients. We recommend a PED-SARC-F cut-off score of ≥5 as clinically useful. This tool can identify children that

may need a physiotherapy assessment and further interventions to prevent physical deterioration during and shortly after treatment for a hemato-oncology disease.

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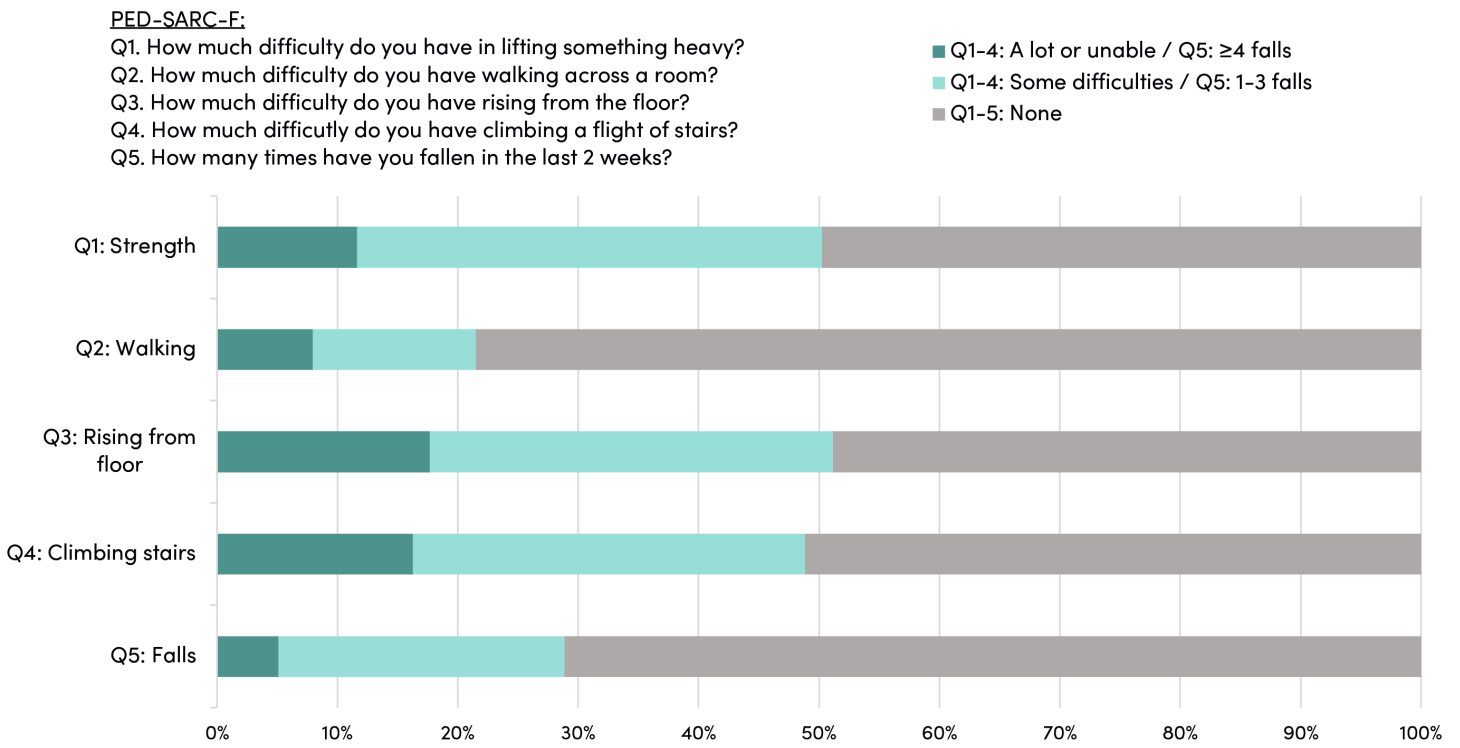


Supplemental Figure 1. The pediatric SARC-F (PED-SARC-F) and the results on the individual questions

Supplemental Table 1. Description of patients with ≥ 1 physiotherapy assessment(s)

			At time of physiotherapy assessment		
Patient	**Tumor type**	**Assessment no.**	**Age, years**	**Treatment phase**	**PED- SARC-F score**
1	AML	1	16.4	Pre SCT	4
		2	17.3	10 months post SCT	4
2	BPDCN	1	15.4	3 months post SCT	6
		2	15.9	9 months post SCT	3
3	SAA	1	16.4	7 months post SCT	2
		2	16.8	12 months post SCT	0
4	Pre B-ALL	1	3.3	First week of therapy	2
		2	3.6	End of induction phase	8
5	Pre B-ALL	1	3.8	Consolidation phase	9
		2	5.4	Pre SCT	3
		3	5.6	3 months post SCT	2
6	MDS	1	14.4	Pre SCT	2
		2	14.8	3 months post SCT	0
7	Pre B-ALL	1	3.8	Pre SCT	7
		2	4.3	5 months post SCT	4
8	Pre B-ALL	1	7.5	Induction phase	5
		2	8	Consolidation phase	3
9	T-ALL	1	16.7	Induction phase	3
		2	17.4	Maintenance phase	0

Supplemental Table 1. *(continued)*

			At time of physiotherapy assessment		
Patient	**Tumor type**	**Assessment no.**	**Age, years**	**Treatment phase**	**PED- SARC-F score**
10	BCR-ABL-like ALL	1	17.3	3 months post SCT	3
		2	17.5	5 months post SCT	3
11	Pre B-ALL	1	15.4	Pre SCT	0
		2	15.7	3 months post SCT	1
12	FA	1	12.5	3 months post SCT	2
		2	12.8	6 months post SCT	0
13	T-ALL	1	9.8	Pre SCT	5
		2	10.3	3 months post SCT	3
14	Pre B-ALL	1	15.5	Induction phase	5
		2	16.5	Consolidation phase	3
15	Pre B-ALL	1	16.6	Induction phase	5
		2	17.7	Maintenance phase	0
16	C-ALL	1	16.5	Induction phase	4
		2	17.4	Maintenance phase	2
		3	17.6	At therapy cessation	1
17	FA	1	7.5	Pre SCT	0
		2	7.8	3 months post SCT	0
18	C-ALL	1	12.7	3 months post SCT	6
		2	12.9	7 months post SCT	3

Supplemental Table 1. *(continued)*

			At time of physiotherapy assessment		
Patient	**Tumor type**	**Assessment no.**	**Age, years**	**Treatment phase**	**PED- SARC-F score**
19	AML	1	17.3	Pre SCT	0
		2	17.5	3 months post SCT	0
20	AML	1	14.5	3 months post SCT	2
		2	14.9	8 months post SCT	0
21	T-ALL	1	11.4	Pre SCT	1
		2	11.8	3 months post SCT	3
22	Pre B-ALL	1	18.2	Maintenance phase	3
		2	18.5	Maintenance phase	1
		3	19.5	6 weeks post therapy cessation	1
23	FA	1	8.5	Pre SCT	0
		2	8.9	3 months post SCT	0
24	Pre B-ALL	1	8.1	Maintenance phase	7
		2	9.9	3 months post therapy cessation	0
25	Pre B-ALL	1	12	Maintenance phase	4
		2	12.6	Pre SCT	0
		3	13	4 months post SCT	0
26	MDS	1	13.3	Pre SCT	0
		2	14.1	6 months post SCT	0

Supplemental Table 1. *(continued)*

			At time of physiotherapy assessment		
Patient	**Tumor type**	**Assessment no.**	**Age, years**	**Treatment phase**	**PED- SARC-F score**
27	Pre B-ALL	1	7.5	Induction phase	2
		2	8.8	Maintenance phase	0
28	AML	1	15.1	3 months post SCT	3
		2	15.3	6 months post SCT	0
29	FA	1	13.9	Pre SCT	0
		2	14.3	3 months post SCT	0
30	FA	1	10.4	Pre SCT	2
		2	10.8	3 months post SCT	1
		3	11.3	9 months post SCT	0
31	Pre B-ALL	1	17	Maintenance phase	6
		2	17.4	Maintenance phase	0
32	Pre B-ALL	1	11.2	Maintenance phase	3
		2	11.5	Maintenance phase	5
33	Pre B-ALL	1	17.9	Induction phase	5
		2	18.4	Maintenance phase	4
34	NHL	1	11.7	Pre SCT	0
		2	12.2	6 months post SCT	9
		3	12.5	9 months post SCT	5
35	AML	1	14.6	Pre SCT	3
		2	14.9	3 months post SCT	3

Supplemental Table 1. *(continued)*

			At time of physiotherapy assessment		
Patient	**Tumor type**	**Assessment no.**	**Age, years**	**Treatment phase**	**PED- SARC-F score**
36	Pre B-ALL	1	17	Induction phase	7
		2	18.8	Maintenance phase	3
		3	19.1	3 months post therapy cessation	0
37	AML	1	11.3	Intensive chemotherapy	3
		2	11.8	3 months post SCT	0
38	Pre B-ALL	1	8.3	Induction phase	6
		2	8.9	Maintenance phase	6
39	CML	1	11.8	Pre SCT	6
		2	12.1	3 months post SCT	2
40	ALCL	1	13.7	Pre SCT	2
		2	14.1	3 months post SCT	1
41	CML	1	15.6	Pre SCT	3
		2	16.1	3 months post SCT	2

Abbreviations:
AML = acute myeloid leukemia, BPDCN = blastic plasmacytoid dendritic cell neoplasm, SAA = severe aplastic anemia, ALL = acute lymphoblastic leukemia, MDS = myelodysplastic syndrome, FA = Fanconi anemia, NHL = Non-hodgkin lymphoma, ALCL = anaplastic large cell lymphoma

Supplemental Table 2. Characteristics of individual patients at their first physiotherapy assessment (n=167)

	No.	**%**
Sex		
Boy	105	62.9
Girl	62	37.1
Type of hematological disease		
Acute lymphoblastic leukemia	102	61
Acute myeloid leukemia	18	10.8
Chronic myeloid leukemia	4	2.4
Hodgkin lymphoma	8	4.8
Non-hodgkin lymphoma	13	7.8
Myelodysplastic syndrome	6	3.6
Fanconi anemia	8	4.8
Aplastic anemia	2	1.2
Other*	6	3.6
Treatment phase		
Intensive chemotherapy	51	30.5
Maintenance chemotherapy	46	27.5
1-12 months after chemotherapy cessation	16	9.6
Pre SCT conditioning phase	29	17.4
3-12 months post SCT	25	15
Assessment performed during		
Clinical admission	34	20.4
Daycare admission / Outpatient clinic visit	133	79.6
Body Mass Index, categories		
Underweight	11	6.6
Normal Weight	114	68.2
Overweight	31	18.6
Obesity	11	6.6
	Mean	**Median [IQR]**
Age, years	11.7	12.7 [7.5 to 15.6]
Height, SDS	-0.27	-0.22 [-1 to 0.47]
Weight, SDS	0.30	0.20 [-0.8 to 1.2]
Body Mass Index, SDS	0.36	0.32 [-0.8 to 1.5]

Abbreviations: SCT = stem cell transplantation, IQR = interquartile range, SDS = standard deviation score

*Blastic plasma cytoid dendritic cell neoplasm (n = 1), common variable immunodeficiency (n = 1), de novo acute promyelocytic leukemia (n =1), Diamond-Blackfan anemia (n = 1), Langerhans cell histiocytosis (n = 1), Paroxysmal nocturnal hemoglobinuria (n = 1)

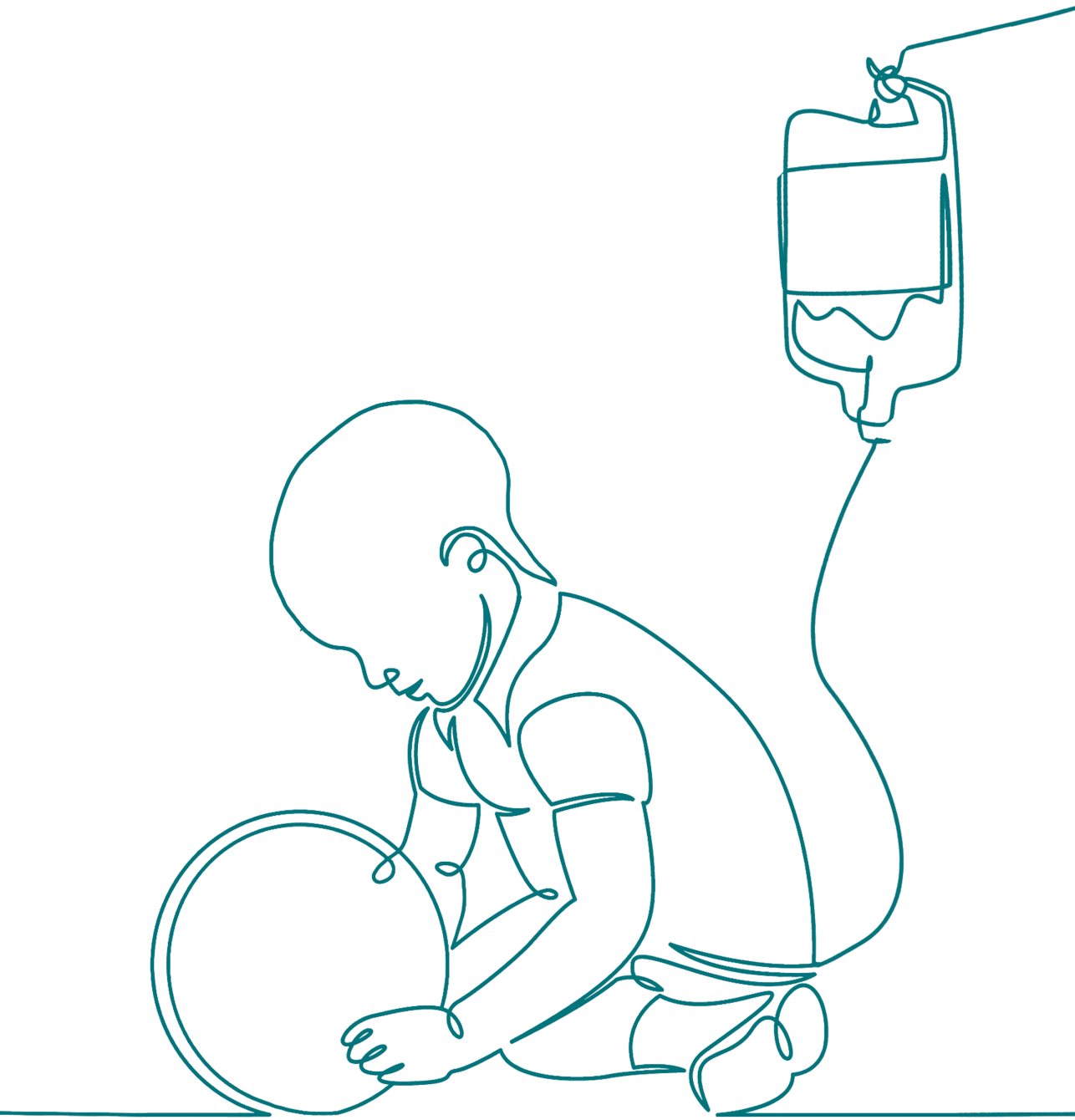
Supplemental Table 3. Diagnostic accuracy for the sarcopenia phenotype at different cut-off points of the PED-SARC-F

	Functional Sarcopenia		
	Yes	**No**	
PED-SARC-F score			
≥1	44	96	PPV: 0.31
<1	2	73	NPV: 0.97
	Sensitivity: 0.96	Specificity: 0.43	
Diagnostic accuracy: 0.69 (95% CI: 0.65 to 0.74)			
PED-SARC-F score			
≥2	43	77	PPV: 0.36
<2	3	92	NPV: 0.97
	Sensitivity: 0.93	Specificity: 0.54	
Diagnostic accuracy: 0.74 (95% CI: 0.69 to 0.79)			
PED-SARC-F score			
≥3	42	52	PPV: 0.45
<3	4	117	NPV: 0.97
	Sensitivity: 0.91	Specificity: 0.69	
Diagnostic accuracy: 0.80 (95% CI: 0.75 to 0.86)			
PED-SARC-F score			
≥4	36	29	PPV: 0.55
<4	10	140	NPV: 0.93
	Sensitivity: 0.78	Specificity: 0.83	
Diagnostic accuracy: 0.81 (95% CI: 0.74 to 0.87)			
PED-SARC-F score			
≥5	34	16	PPV: 0.68
<5	12	153	NPV: 0.93
	Sensitivity: 0.74	Specificity: 0.91	
Diagnostic accuracy: 0.82 (95% CI: 0.75 to 0.89)			
PED-SARC-F score			
≥6	27	6	PPV: 0.82
<6	19	163	NPV: 0.90
	Sensitivity: 0.59	Specificity: 0.96	
Diagnostic accuracy: 0.78 (95% CI: 0.7 to 0.85)			
PED-SARC-F score			
≥7	21	3	PPV: 0.88
<7	25	166	NPV: 0.87
	Sensitivity: 0.46	Specificity: 0.98	
Diagnostic accuracy: 0.72 (95% CI: 0.65 to 0.79)			

Supplemental Table 3. *(continued)*

	Functional Sarcopenia		
	Yes	**No**	
PED-SARC-F score			
≥8	16	1	PPV: 1
<8	30	168	NPV: 0.82
	Sensitivity: 0.22	Specificity: 1	
Diagnostic accuracy: 0.67 (95% CI: 0.6 to 0.74)			
PED-SARC-F score			
≥9	10	0	PPV: 0.7
<9	36	169	NPV: 0.82
	Sensitivity: 0.16	Specificity: 0.98	
Diagnostic accuracy: 0.61 (95% CI: 0.55 to 0.67)			
PED-SARC-F score			
≥10	3	0	PPV: 1
<10	43	169	NPV: 0.8
	Sensitivity: 0.07	Specificity: 1	
Diagnostic accuracy: 0.53 (95% CI: 0.5 to 0.57)			

Abbreviations: AUC = area under the curve PPV = positive predicted value, NPV = negative predicted value, CI = Confidence interval



The utility of a portable muscle ultrasound in the assessment of muscle alterations in children with acute lymphoblastic leukemia

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Abstract

Background

During treatment for acute lymphoblastic leukemia (ALL), children are prone to musculoskeletal alterations and impaired physical performance. However, non-invasive and reliable tools to measure muscle mass and intramuscular alterations are limited. In this study we explored the feasibility of using muscle ultrasound in children during ALL treatment, and analyzed whether automated ultrasound outcomes of muscle size and intramuscular fat infiltration (IMAT) were associated with total appendicular skeletal muscle mass (ASMM) and physical performance.

Methods

Children with ALL, aged 3-18 years were included during maintenance therapy. Bilateral images of the rectus femoris (RF) muscle were captured using a portable linear array transducer connected to a tablet. Subsequently, an automated image annotation software (MuscleSound) was used to estimate cross-sectional area, muscle thickness and IMAT. Feasibility was determined by capturing the refusal rate of children or parents and the number of patients with good-quality images. Assessments of ASMM by bioimpedance analysis, muscle strength using handheld dynamometry and timed physical performance tests, were administered at the same visit. Multivariable linear models were estimated to study the associations between muscle ultrasound outcomes and ASMM, strength and physical performance, adjusted for sex, age, body mass index and ALL treatment week.

Results

Muscle ultrasound was performed in 60/73 invited patients (76.9%), 37 were boys (61.7%), and median age was 6.1 years (range: 3, 18.8 years). Patients who refused the examination (n=13) were younger on average (median: 3.6, range: 3, 11.2 years) compared to the 60 examined children (p=0.0009). In multivariable models, cross-sectional area was associated with ASMM Z-scores (β=0.49, 95%-CI=0.3, 2.4), knee-extension strength (β=16.9, 95%-CI=4.8, 28.9), walking performance (β=-0.46, 95%-CI=-0.75, -0.18) and rising from the floor (β=-1.07, 95%-CI-1.71, -0.42). Muscle thickness was associated with ASMM (β=0.14, 95%-CI=0.04, 0.24), knee-extension strength (β=4.73, 95%-CI=0.99, 8.47), walking performance (β=-0.13, 95%-CI=-0.22, -0.04) and rising from the floor (β=-0.28, 95%-CI=-0.48, -0.08). Intramuscular fat infiltration (IMAT) was associated with knee-extension strength (β=-6.84, 95%-CI=-12.26, -1.41), walking performance (β=0.2, 95%-CI=0.08, 0.32) and rising from the floor (β=0.54, 95%-CI=0.27, 0.8). None of the muscle ultrasound outcomes was significantly associated with handgrip strength.

Conclusion

Bedside muscle ultrasound may be a useful tool to measure muscle and performance alterations particularly in immobilized patients with ALL. Validation studies using magnetic resonance imaging (gold standard) are necessary to further confirm accuracy in pediatric populations.

Introduction

For children with acute lymphoblastic leukemia (ALL) in high-income countries advances in treatment strategies have resulted in a 5-year survival rate of > 90%.[1] During ALL treatment, children are prone to musculoskeletal side-effects and impairments in physical performance.[2,3] Loss of muscle mass, strength and impaired physical performance can be caused by malnutrition, inflammation, pain, low physical activity and can be aggravated by different treatment components.[4,5] Especially dexamethasone, an essential component in the treatment of pediatric ALL, can induce catabolic effects and consequent muscle weakness.[6,7]

Loss of muscle mass, strength and function has been associated with the number and duration of hospital admissions[8], invasive fungal infections[9], impaired quality of life[2] and even with impaired survival.[10] Although it is unclear if these results indicate causality, they do give rise to further investigation of muscle deterioration in patients with ALL.

The current gold standard for muscle assessment is magnetic resonance imaging (MRI)[11], which is expensive, poor accessible and requires sedation for younger children. Computed tomography (CT) is unsuitable due to radiation exposure and also the calculation of muscle mass is time consuming. Another reliable technique for muscle mass measurement is dual-energy x-ray absorptiometry (DXA), which has similar disadvantages as MRI, making this technique also unsuitable for standard-of-care evaluations.

When pediatric cancer patients are critically-ill and/or immobilized, the ideal imaging technique requires bed-side accessibility, a low burden technique and it should not be time-consuming. Ultrasound has easy availability in the clinic, has been used for musculoskeletal tissue research in critically-ill children[12-14] and may therefore offer a promising role in the diagnosis of muscle deterioration in children with ALL. Moreover, muscle ultrasound has the ability to assess intramuscular alterations, such as fat infiltration.[15] This is relevant because intramuscular fat infiltration has been associated with deficits in strength and muscle function.[15-17]

In order to interpret the ultrasound images an automated annotation technology (MuscleSound®, Denver, CO, USA) has been used previously to identify muscle size and intramuscular alterations in ultrasound images in athletes[18,19] and in critically-ill adult patients[20]. This commercially available software provides a standardized method with built-in guidance for assessment of muscle size and intramuscular fat of the rectus femoris muscle.[21-23] Enabling such a standardized

non-invasive technique for children with cancer would be of great additional value in understanding and monitoring the process of muscle alterations and consequent deterioration of physical abilities. Moreover, in young and critically-ill children it is challenging to distinguish muscle weakness from poor cooperation or cognitive inability using functional measurements. Thus far the clinical usefulness of muscle ultrasound in combination with MuscleSound® software in children has not been reported.

The aims of this study were to explore the feasibility of muscle ultrasound in children during ALL treatment, and to investigate whether automated ultrasound outcomes of muscle size and intramuscular fat infiltration were associated with total appendicular skeletal muscle mass and physical performance.

Materials and methods

Study design and patients

This study was performed within the framework of the DexaDays-2 study: a national randomized controlled trial on neurobehavioral side effects of dexamethasone in pediatric ALL patients aged 3-18 years, conducted at the Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands, between 2019-2021. The design of this study, including in- and exclusion criteria, has been previously described[24,25]. In brief, Dutch ALL patients, aged 3-18 years and treated according to the Dutch Childhood Oncology Group ALL-11 protocol medium risk group protocol, were included during maintenance therapy. ALL11 MRG maintenance therapy contained 28 three week treatment cycles, with a 5-days dexamethasone administration course and vincristine push in every cycle.

All participating patients had a muscle function assessment in the outpatient clinic, on the first day of a 5-day dexamethasone course. The assessment consisted of a muscle ultrasound examination and measurements of muscle mass, muscle strength and physical performance[25], carried out by a pediatric physiotherapist (EV) or medical physician (AvH) at the Sports and Exercise center of the Princess Máxima Center.

The study was approved by the Medical Ethics Committee (reference number NL62388.078.174) and all patients and/or parents provided written informed consent to participate.

Muscle ultrasound imaging procedure and software

Two researchers (EV, AvH) involved in this study were trained to capture ultrasound images of the rectus femoris (RF) muscles using a portable linear array transducer (Lumify L12-4, Philips, Amsterdam, the Netherlands) connected to a portable tablet (Samsung Galaxy Tab 3, Samsung Electronics Benelux, Hoofddorp, the Netherlands). Bilateral ultrasound measurements were captured using the musculoskeletal preset, with the child in supine position on an examination table with the backrest elevated to approximately 70 degrees. To standardize the ultrasound location, the length of the thighs (from spina iliaca anterior superior to upper edge patella) was determined in standing position, thereafter a mark halfway the thigh was drawn. Ultrasound gel was applied to the marked location and the probe was placed horizontally (short axis). The muscles were relaxed during imaging and minimal pressure was applied to the probe. The total muscle ultrasound assessment was generally performed in less than 10 minutes. Images were obtained with the Lumify application (Philips Lumify, usa.philips.com). Subsequently, images were uploaded to the MuscleSound® platform (Denver, CO, USA).

The MuscleSound® algorithm automatically identifies, annotates and calculates cross-sectional area and thickness, as well as intramuscular adipose tissue (IMAT). The estimation of IMAT is based on echo intensity with which a sound wave is reflected from muscle tissue, i.e. more fat infiltration muscle produces a brighter image. Subsequently, the software calculates IMAT values for RF using the equations from Young et al, which were developed and validated through comparison of IMAT from T_1-weighted MRI images in adults[26]. For our analyses IMAT was adjusted for RF muscle cross-sectional area.

To our knowledge, muscle ultrasound had not been performed previously in children with cancer from the age of three years onwards. Therefore, we explored its feasibility by reporting situations in which performing the muscle ultrasound was not successful (refusal rate, or child was not able to lie still), and whether the software would be able to process and analyze RF images of young children.

Appendicular skeletal muscle mass, muscle strength and physical performance measurements

Skeletal muscle mass was estimated using a multi-frequency segmental bioimpedance analyzer (Tanita MC-780, Tanita Corporation, Tokyo, Japan). The sum of the skeletal muscle mass of the extremities (ASMM) was calculated and adjusted for body weight. The Tanita-device has shown excellent test-retest reliability.[27] High significant correlations (R≥0.85) were shown for body composition values in children and between BIA and DXA.[28] As reference data

for Dutch children were unavailable, to estimate Z-scores we used age and sex-specific mean and standard deviation values from a UK population (5-18 years), acquired using the same Tanita software[29]. Due to lack of bioimpedance reference values of 3-4 year old children, we used sex and age specific expected values of ASMM, derived by a dual-energy X-ray absorptiometry prediction equation in Canadian children[30].

Two different measures of muscle strength with the handheld dynamometry (HHD) were performed. Handgrip strength was assessed using a Jamar HHD (Sammons Preston, Bolingbrook, IL, USA). Handgrip dynamometry has shown good validity (intraclass correlation coefficients [ICCs] 0.73-0.91) with high reproducibility and has excellent test-retest reliability in children (ICCs 0.91-0.93).[31,32] The mean score of three repeats for the dominant hand was used and were compared to population-based age and sex-specific reference values[33].

Knee-extension strength was measured with the eccentric break-technique protocol using the MicroFET-2 HHD (Hoggan Health Industries, Salt Lake City, UT, USA). This method has shown good validity against Cybex (gold standard) (ICC 0.88, 95% CI: 0.72-0.95), intra-reliability (ICC 0.9, 95% CI 0.65-0.97) and inter-reliability (ICC 0.84, 95% CI 0.48-0.96).[34] Measures were carried out bilaterally and the mean of three repeats was calculated and was used for analyses, as reliable normative values are lacking.

Physical performance was assessed with the Timed Up and Go test (TUG). The children started seated on a chair and were asked to stand up, walk 3 meters, turn around, walk back and sit down again as quickly as possible. The average time in seconds of three trials was considered as the test result[35]. The TUG has shown excellent test-retest reliability (ICCs 0.80-0.98) and inter-observer reliability (ICCs 0.86-0.99) in the pediatric population[36], and the measurement was found to be feasible in children with leukemia.[37] We also used the 'Time to Rise from the Floor test' (TRF).[38] Children were asked to sit on the floor in cross-legged position and were asked to rise as fast as they can. The average time of two TRF trials in seconds was calculated.

Statistical analyses

Height, weight and body mass index (BMI) values were compared to Dutch national sex- and age-specific reference values[39,40], and Z-scores were calculated. All data were expressed as means along with standard deviations for normally distributed variables or median and interquartile ranges (IQRs) for skewed distributions and number (percent) for categorical variables. Feasibility was explored by determining the refusal rate and by determining whether it was possible to capture good-quality images in young (non-sedated) children.

Multivariable linear regression models were estimated to study the associations between muscle ultrasound outcomes of RF cross-sectional area and thickness, and outcome measures of ASMM, strength and physical performance. The means of the right and left RF together were used in analysis. Furthermore, to investigate the association between IMAT and muscle function, multivariable linear models were estimated to determine the associations between IMAT, and the outcomes of muscle strength and physical performance. In the models for which we had an outcome in Z-scores available (ASMM and handgrip strength), we adjusted for BMI and ALL treatment week as possible covariates. In the models for knee-extension strength (Newton) and physical performance (seconds), we also adjusted for sex and age (years). All analyses were performed in Rstudio environment Version 1.4.1106 for Windows.[41]

Results

Recruitment, patient characteristics and feasibility

Of the 105 patients who were included in the DexaDays-2 study, 78 were offered muscle ultrasound examination between March 2019 and March 2021, as the device only became available after the onset of the DexaDays-2 study. Twelve patients and one parent refused the examination (21.7%), during four examinations we had a device malfunction (broken cable) (6.7%) and one measurement could not be performed because of a logistic issue (1.7%). Muscle ultrasound was eventually performed in 60/78 patients (76.9%) (Figure 1). In total, 37/60 were boys (61.7%), with median age of 6.1 years (range: 3–18.8 years), mean height was -0.61 SDS (SD: 0.98), mean weight was 0.52 SDS (SD: 1.1) and mean BMI was 1.1 SDS (SD: 1.0) (Table 1).

The 12 patients who refused the muscle ultrasound assessment were similar for sex, but they were younger (median: 3.6, range: 3.0-11.2 years) compared to the 60 children who allowed the ultrasound examination (p=0.0009). Of the 78 invited patients, 17 were 3-year-olds, nine of them refused the ultrasound examination (52.9%). The parent who refused the examination thought it would be too burdensome and also did not want the child to participate in other physical measurements. We did not have any children unable to lay still during the examination. We managed to make good-quality images of the RF muscle in all children across all age groups.

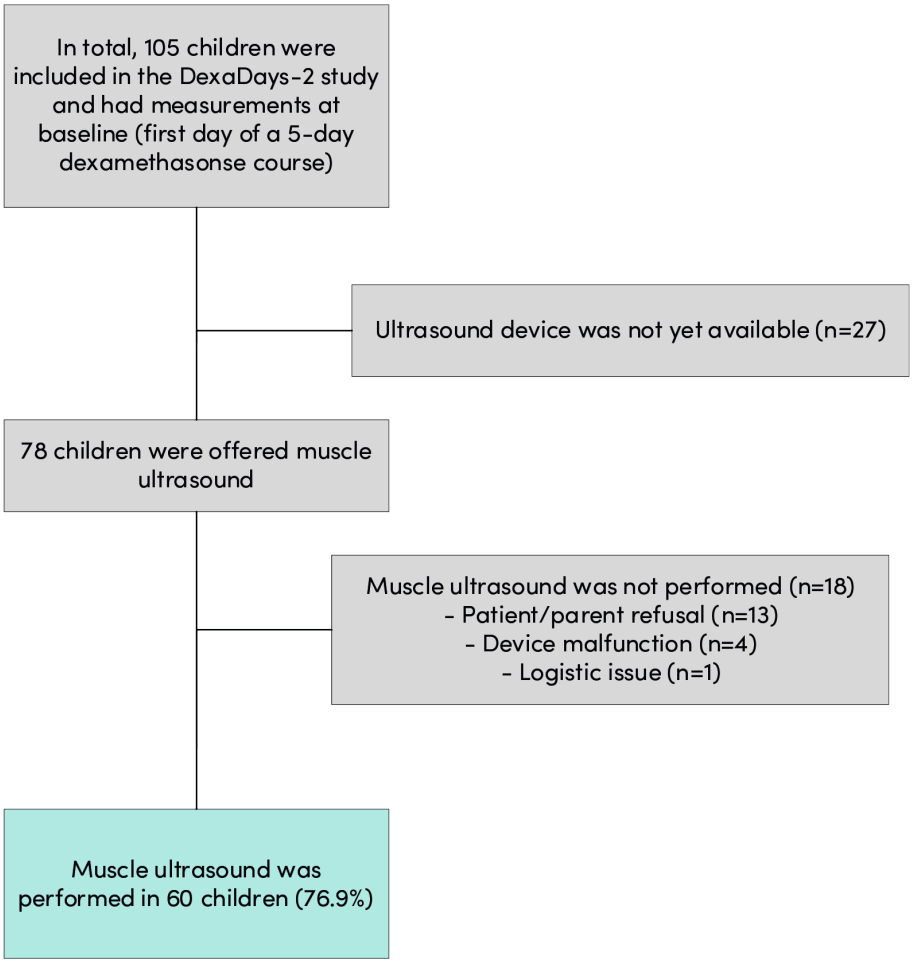

Figure 1. Flow diagram of patients in this study

Table 1. Patient characteristics

	Median	**IQR**	**Range**
Age, years	6.1	4.5 - 9.6	3 – 18.8
	Mean	**SD**	**Range**
Height, SDS	-0.61	0.98	-2.9 – 1.6
Weight, SDS	0.52	1.1	-1.8 – 4.4
Body mass index, SDS	1.1	1.0	-1.0 – 3.9
	No.	**%**	
Sex			
Boy	37	61.7	
Girl	23	38.3	
Type of ALL			
Precursor B-ALL	52	86.7	
T-ALL	7	11.7	
BPDCN	1	1.6	
	Median	**IQR**	**Range**
Maintenance treatment week	34	22 – 42	16 - 68

Abbreviations: IQR = Interquartile range, SD = standard deviation, SDS = standard deviation score, ALL = acute lymphoblastic leukemia, BPDCN = blastic plasmacytoid dendritic cell neoplasm

Muscle ultrasound, ASMM, muscle strength and physical performance outcome measures

The MuscleSound-derived estimates of cross-sectional area and IMAT, as well as ASMM, strength and physical performance outcomes are depicted in Table 2.

Median RF muscle thickness was 12.5 mm (range: 5.5, 26.0), cross-sectional area was 3.08 cm^2 (range: 1.2, 7.1) and IMAT was 4.6% adjusted for cross-sectional area (range: 1.5, 11.0).

Mean ASMM was 25.3% (IQR: 22.1, 27.8%). Compared to normative values, the mean standardized deviation score (SDS) was -0.41 (IQR: -1.36, 0.22). The mean SDS of the dominant hand was 0.01 (IQR: -0.58, 0.58). Median knee-extension strength of both legs was 105.7 Newton (range: 33.1, 400.8). The knee-extension strength measurement was assessed in fewer children (n=42) due to limited understanding and/or ability to perform the assignment. Median TUG time was 5.3 seconds (range: 3.7, 7.9 seconds) and median TRF time was 2.7 seconds (range: 1.3, 13.6 seconds).

Table 2. Results of the muscle ultrasound, muscle mass, muscle strength and physical performance assessments

	N	Median	IQR	Range
Ultrasound outcomes (MuscleSound)				
Thickness, mm	60			
Rectus femoris left		13	10.1 – 15	5 – 23
Rectus femoris right		12	11 – 14.5	6 – 29
Cross-sectional area, cm^2	60			
Rectus femoris left		3.1	2.5 – 3.8	1.1 – 6.3
Rectus femoris right		3.0	2.5 – 3.8	1.3 – 7.9
IMAT, percentage adjusted for area	60			
Rectus femoris left		4.6	3.7 – 6.3	1.6 – 12
Rectus femoris right		4.4	3.8 – 6	1.4 – 11.8
Appendicular skeletal muscle mass				
Bio-electrical impedance analysis	57			
Appendicular skeletal muscle mass				
Kilogram		6.5	4.7, 12.2	2.5 – 31.5
Percentage		25.5[I]	22.9, 29.3	14.6 – 68.6
Z-score		-0.6[I]	-1.24, 0.06	-2.5 – 2.7
Muscle strength				
Handgrip strength	54			
Left hand, kilograms		10	7.9 - 14.3	4 – 45.8
Right hand, kilograms		10.5	8.1 - 16.3	4.5 – 53.7
Dominant hand, Z-score[I]		0	0.9	-2 – 2.4
Knee extension strength	42			
Left leg, Newton		106.4	73.3 - 170.2	31.8 – 408.7
Right leg, Newton		104.9	81.5 - 181.2	34.4 – 393
Physical performance				
Timed Up and Go Test	59			
Time, seconds		5.3	4.6 - 6.1	3.7 – 7.9
Time To Rise From the Floor	60			
Time, seconds		2.7	2 - 4.2	1.3 – 13.6

Abbreviations: IMAT = intramuscular adipose tissue, IQR = Interquartile range
NOTE: Missing values are explained by impaired cooperativeness or limited understanding to perform the measurement.
[I]Presented as mean value

Associations between muscle ultrasound outcomes and ASMM, muscle strength and physical performance

The multivariable linear models are depicted in Table 3.

Mean estimated cross-sectional area of the RF muscles was significantly associated with total ASMM, knee-extension strength and physical performance. On average, one cm^2 increase was associated with 0.49 SDS (95%-CI 0.3-2.4) increase in ASMM, and with 16.9 Newton (95%-CI 4.8, 28.9) increase in knee-extension strength. One cm^2 increase in RF cross-sectional area was associated with -0.46 seconds (95%-CI -0.75, -0.18) faster TUG performance, as well as -1.07 seconds (95%-CI -1.71, -0.42) faster rising from the floor.

Mean estimated RF thickness was significantly associated with total ASMM, knee-extension strength and physical performance. On average, one millimeter increase in thickness was associated with 0.14 SDS (95%-CI 0.04, 0.24) increase in ASMM, and with 4.73 Newton (95%-CI 0.99, 8.47) increase in knee-extension strength. One millimeter increase in RF thickness was also associated with -0.13 seconds (95%-CI -0.22, -0.04) faster TUG performance, as well as -0.28 seconds (95%-CI -0.48, -0.08) faster rising from the floor.

Estimated IMAT adjusted for area, was significantly associated with functional muscle outcomes: knee-extension strength and physical performance. On average, one percentage increase in IMAT was associated with -6.84 Newton (95%-CI -12.26, -1.41) lower knee-extension strength, 0.2 seconds (95%-CI 0.08, 0.32) slower TUG performance, as well as 0.54 seconds (95%-CI 0.27, 0.8) slower rising from the floor (increased fat infiltration associated with poorer muscle function).

RF cross-sectional area, thickness and IMAT were not associated with handgrip strength.

Scatterplots are shown in Supplemental Figure 1.

Table 3. Multivariable linear models: the association of muscle ultrasound outcomes with appendicular skeletal muscle mass, knee extension strength and physical performance.

	Appendicular skeletal muscle mass (Z-score)		
	β	**SE**	**p-value**
Intercept	-1.47		
RF Cross-sectional area, cm^2	**0.49**	**0.16**	**0.003**
Body mass index, Z-score	-0.04	0.18	0.8
ALL Maintenance week	-0.01	0.01	0.62

Intercept	-1.73		
RF Thickness, mm	**0.14**	**0.05**	**0.007**
Body mass index, Z-score	-0.09	0.19	0.63
ALL Maintenance week	-0.01	0.01	0.72

	Knee extension strength (Newton)		
	β	**SE**	**p-value**
Intercept	-63		
RF Cross-sectional area, cm²	**16.9**	**5.93**	**0.007**
Sex (male versus female)	-4.48	11.2	0.69
Age, years	14.7	1.64	<0.0001
Body mass index, Z-score	7.55	5.38	0.17
ALL Maintenance week	-0.08	0.46	0.86
Intercept	-71.5		
Thickness, mm	**4.73**	**1.84**	**0.01**
Sex (male versus female)	-5.44	11.4	0.64
Age, years	14.9	1.67	<0.0001
Body mass index, Z-score	5.6	5.8	0.34
ALL Maintenance week	-0.01	0.46	0.98
Intercept	5.69		
RF IMAT index, %/cm²	**-6.84**	**2.67**	**0.015**
Sex (male versus female)	-0.97	11.7	0.93
Age, years	16.7	1.33	<0.0001
Body mass index, Z-score	12.96	5.24	0.019
ALL Maintenance week	-0.15	0.48	0.75

	Timed Up and Go Test (seconds)		
	β	**SE**	**p-value**
Intercept	6.72		
RF Cross-sectional area, cm²	**-0.46**	**0.14**	**0.002**
Sex (male versus female)	0.43	0.25	0.09
Age, years	-0.03	0.04	0.44
Body mass index, Z-score	0.27	0.12	0.029
ALL Maintenance week	-0.01	0.01	0.55

Intercept	7.02		
Thickness, mm	**-0.13**	**0.04**	**0.004**
Sex (male versus female)	0.48	0.25	0.06
Age, years	-0.04	0.04	0.29
Body mass index, Z-score	0.31	0.13	0.019
ALL Maintenance week	-0.01	0.01	0.44
Intercept	4.68		
RF IMAT index, %/cm²	**0.2**	**0.06**	**0.001**
Sex (male versus female)	0.37	0.25	0.14
Age, years	-0.08	0.03	0.005
Body mass index, Z-score	0.14	0.12	0.23
ALL Maintenance week	-0.002	0.01	0.82

	Time to Rise from the Floor (seconds)		
	β	SE	p-value
Intercept	4.06		
RF Cross-sectional area, cm²	**-1.07**	**0.32**	**0.002**
Sex (male versus female)	-0.06	0.56	0.91
Age, years	0.32	0.09	0.0005
Body mass index, Z-score	0.72	0.28	0.01
ALL Maintenance week	-0.02	0.02	0.43
Intercept	4.61		
Thickness, mm	**-0.28**	**0.1**	**0.007**
Sex (male versus female)	0.07	0.57	0.9
Age, years	0.28	0.09	0.002
Body mass index, Z-score	0.78	0.3	0.01
ALL Maintenance week	-0.02	0.02	0.32
Intercept	-1.16		
RF IMAT index, %/cm²	**0.54**	**0.13**	**0.0002**
Sex (male versus female)	-0.25	0.55	0.64
Age, years	0.2	0.06	0.002
Body mass index, Z-score	0.41	0.26	0.12
ALL Maintenance week	-0.006	0.02	0.78

B = Betacoefficient, SE = standard error, RF = rectus femoris muscle,
IMAT = intramuscular adipose tissue

Discussion

In this exploratory study, we showed that an automated annotation muscle ultrasound technique for RF muscle size may be a useful indicator for total skeletal mass, muscle strength and physical performance in children during ALL therapy. In addition, this is the first study in which we estimated IMAT using ultrasound in children with ALL, and found relevant associations with muscle strength and physical performance outcomes. Moreover, bedside muscle ultrasound of the upper leg was successfully performed in more than three quarters of patients with ALL, from the age of 3 years onwards. In 3-year-olds refusal was higher than in older children, but even in that age group, 50% of patients was cooperative. We had a negligible number of technical issues or children who were unable to lay still, which confirms that this usage of tool is feasible in children during therapy.

Our results showed that RF cross-sectional area and thickness were related to ASMM Z-scores. This finding cautiously supports the hypothesis that muscle ultrasound may be a valid method for estimating skeletal muscle mass in the extremities in children with ALL. This is of importance because serious reductions of ASMM with incomplete recovery have been observed in children with ALL, and the degree of loss has been associated with the burden of illness[8]. Moreover, ASMM is crucial for neurodevelopment and metabolic health[42] and a fundamental component of sarcopenia and frailty.[43] However, further validation against gold standard measures by DXA or MRI needs to reveal if muscle ultrasound can be used as a true indicator for ASMM.

Intramuscular adipose tissue adjusted for muscle area (IMAT) was associated with functional outcomes: knee-extension strength, TUG and TRF. This revealed that higher fat infiltration in the RF muscle was related to decreased force generation and functionally in slower performance in walking and turning, as well as rising from the floor. In previous studies, IMAT was inversely related to increased cardiometabolic risk and type 2 diabetes, as well as impaired muscle functionality (running/jumping) and increased disabilities in children and adolescents[15,44]. Moreover, recent results in adult cancer patients showed that IMAT accumulates during cancer treatment and is an important factor in the development of exercise intolerance[45]. Therefore, the availability of automatically estimated IMAT would be an advance in muscle deterioration assessment, to detect aggravation maybe even before it becomes clinically apparent, and will thus support our clinical decision making.

We hypothesized that decreased muscle size and quality of the RF in children with ALL may exemplify general muscle health, and we unraveled a part of this

theory with our findings. However, none of the muscle ultrasound outcomes was associated with handgrip strength. This was somewhat surprising, because in healthy children hand grip strength is an indicator for general muscle strength[46]. This may not apply to children with ALL, because high-dose corticosteroids (as well as other chemotherapeutic agents) induce proximal muscle weakness rather than distal muscle weakness.

Although our results are promising for future automated muscle assessments, caution with regard to interpretation is warranted because of limitations of the study. First, due to the cross-sectional nature of the study, our ability to establish causal relationships is limited. Second, we did not have ASMM data available measured by MRI, which limited us in validating the accurateness of MuscleSound® muscle size and IMAT calculations against gold standard measures. Third, because of lack of normative values for children, we are not able to interpret the MuscleSound® values in our cohort.

Nevertheless, bedside muscle ultrasound may be an important addition to the diagnostic assessment for muscle deterioration in children with cancer. Current methods, such as MRI, are expensive, poorly accessible, time consuming, and require sedation of younger children. Therefore, this convenient portable technique allowing rapid and non-invasive real-time monitoring is a sizeable reduction of burden in physically vulnerable children with cancer with a high risk of muscle wasting. Furthermore, this tool may help in distinguishing muscle impairments from poor cooperation or cognitive inability in immobilized patients.

In conclusion, bedside muscle ultrasound in combination with automated annotation seems a promising instrument, allowing quick and non-invasive diagnosis of muscle deterioration. However, validation studies using gold standard assessments are necessary to further determine the accuracy and validity in pediatric populations.

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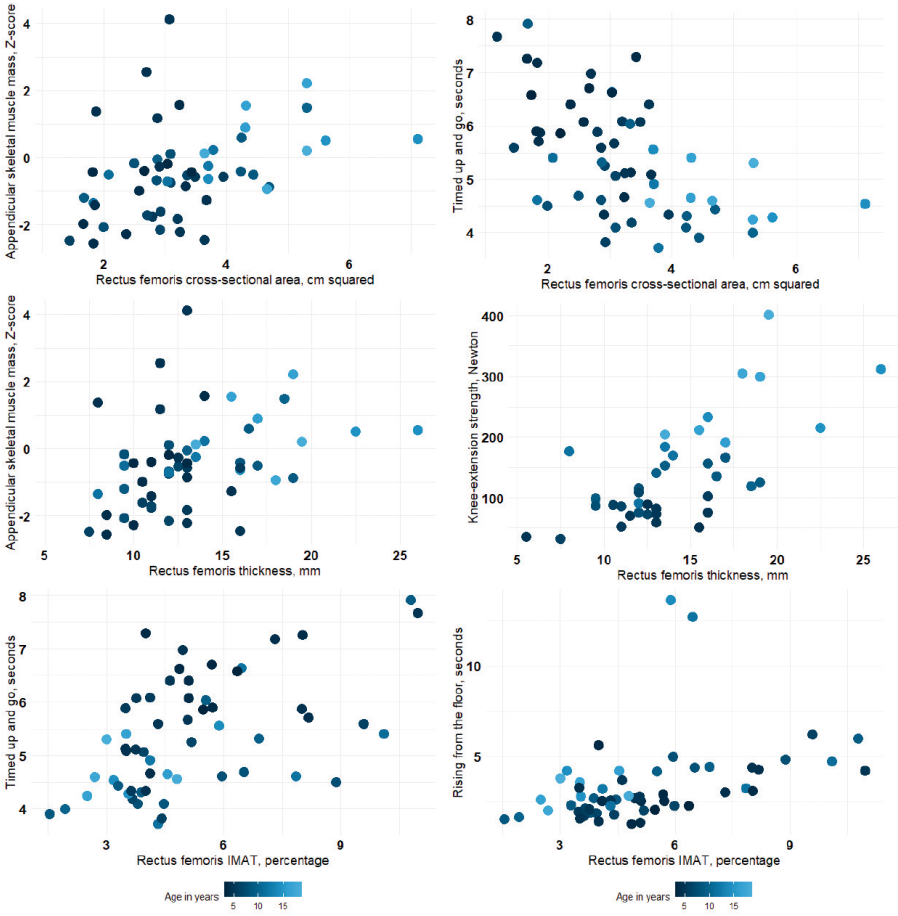
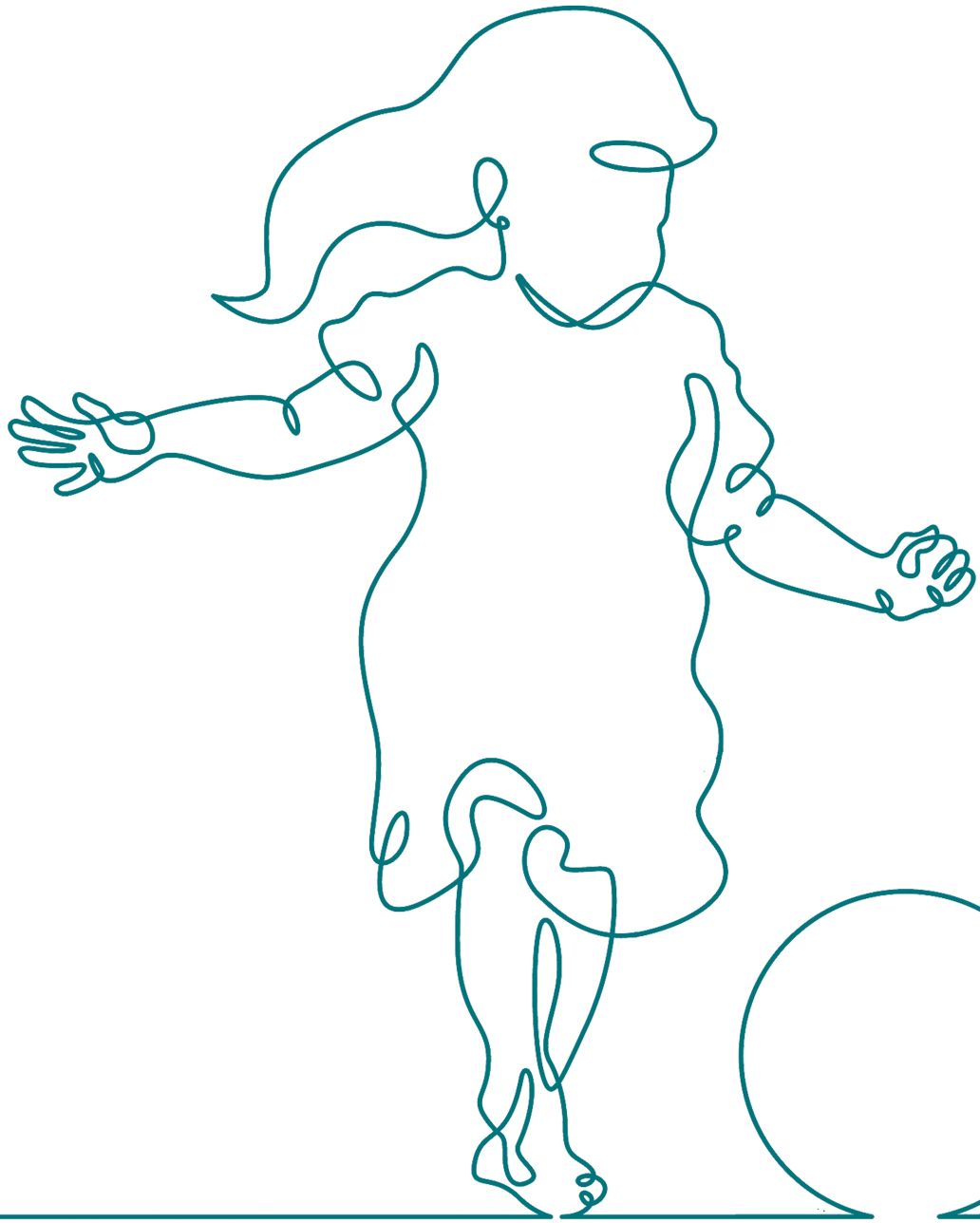


Supplemental Figure 1. Scatterplots displaying the relationship between muscle ultrasound outcomes of the rectus femoris muscles against outcomes of appendicular skeletal muscle, knee-extension strength, walking performance and time to rise from the floor. IMAT = intramuscular adipose tissue



Dexamethasone-induced sarcopenia and physical frailty in children with acute lymphoblastic leukemia: Protocol for a prospective cohort study

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Abstract

Background
During treatment for pediatric acute lymphoblastic leukemia (ALL), children receive high doses of dexamethasone for its apoptotic effect on leukemia cells; however, muscle atrophy is a well-known serious side effect. Muscle atrophy (loss of muscle mass) accompanied by a decreased muscle strength may lead to a generalized impaired skeletal muscle state called sarcopenia. Loss of muscle mass is also an indicator of physical frailty, which is defined as a state of increased vulnerability, that is characterized by co-occurrence of low muscle mass, muscle weakness, fatigue, slow walking speed and low physical activity. Both sarcopenia and physical frailty are related to an increased risk of infections, hospitalizations and decreased survival in children with chronic diseases.

Objective
This study aims to (1) estimate the occurrence of sarcopenia and physical frailty in children during ALL maintenance therapy, (2) evaluate the effect of administering dexamethasone, and (3) explore determinants associated with these outcomes.

Methods
This prospective study is being pursued within the framework of the DexaDays-2 study: a randomized controlled trial on neurobehavioral side effects in pediatric patients with ALL. A total of 105 children (3-18 years) undergoing ALL maintenance treatment at the Princess Máxima Center for Pediatric Oncology, are included in this study. Sarcopenia/frailty assessments are performed before and just after a 5-day dexamethasone course. A subset of 50 children participating in the DexaDays-2 trial because of severe dexamethasone-induced neurobehavioral problems, were assessed at 3 additional timepoints. The sarcopenia/frailty assessment consists of: bioimpedance analysis (skeletal muscle mass [SMM]), handheld dynamometry (handgrip strength), Pediatric Quality of Life Inventory Multidimensional Fatigue Scale (fatigue), Timed Up and Go test (TUG; walking speed), and physical activity questionnaires. To evaluate potential change in sarcopenia/frailty components after a 5-day dexamethasone administration, a paired Student t test or Mann-Whitney U test will be used. Because of the presence of repeated measurements generalized linear mixed models will be used to estimate the effect of dexamethasone on sarcopenia and frailty outcomes. Multivariable regression models will be estimated to investigate associations between the assessment scores and patient and treatment-related factors.

Results
Patient accrual started in 2018 and was finalized in spring 2021. From autumn 2021 onward final data analyses will be performed.

Conclusion
This first study combining parameters of sarcopenia and physical frailty, is of importance because these conditions can seriously complicate continuation of ALL therapy, independence in physical functioning, reaching motor milestones and participating in daily life activities. The results will provide knowledge about these complications, the association between dexamethasone-treatment and muscle loss and other components of frailty, and therefore insights into the severity of this side effect. By exploring potential determinants that may be associated with sarcopenia and physical frailty, we may be able to identify children at risk at an earlier stage and provide timely interventions.

Introduction

Acute lymphoblastic leukemia (ALL) is the most prevalent pediatric cancer worldwide. Advances in treatment strategies and supportive care have resulted in a 5-year survival rate of about 90% in high-income countries.[1-3] Consequently, there is growing attention for adverse health effects, including impairments in physical performance during and after therapy.[4-6] Impairments in physical performance, either transient or permanent, in children with ALL are usually explained by a neurological disorder, fractures, osteonecrosis, general malaise, pain or severe muscle atrophy.[7-11] Muscle atrophy, in turn, can be caused by malnutrition, inflammation, low physical activity and it can be aggravated by treatment with glucocorticoids.[12,13] Glucocorticoids -which are essential in the treatment of ALL-, are known to regulate protein metabolism in skeletal muscle, thereby inducing a catabolic effect and consequent muscle atrophy.[14,15]

Dexamethasone is the most potent glucocorticoid and a cornerstone for the treatment of pediatric ALL, because it reduces the frequency of central nervous system relapse.[15] As it is administered in high doses for considerable periods in various ALL protocols worldwide (6 mg/m^2 per day)[16-18], children with ALL carry an increased risk of glucocorticoid-induced muscle atrophy.[15]

Muscle atrophy (loss of muscle mass) when accompanied by decreased muscle strength may indicate a generalized skeletal muscle disorder called sarcopenia.[19] Sarcopenia, defined as the combination of low muscle mass and strength or function, is associated with increased adverse health outcomes in various adult populations.[20] The presence of sarcopenia has been investigated to a limited extent in 3 previous studies including children with ALL[4,21,22], which indicated that muscle mass loss in children during ALL therapy, was associated with the number and duration of hospital admissions[4], occurrence of invasive fungal infections, other adverse events of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥III[21], and even -when fat mass and body mass index were increased- with impaired survival.[22] However, due to small sample sizes and methodological limitations, which make it difficult to correct for relevant confounders, it is unclear if these results indicate a true causal relationship or coassociation.

Physical frailty is another undesired consequential state, and is characterized by 5 components: unintentional weight loss (due to muscle mass loss), muscle weakness, self-reported exhaustion, slow walking speed and low physical activity.[23] Physical frailty has been reported as a state of reduced physiologic reserve with increased vulnerability to stressors. It was first defined in the elderly by Fried et al[23], and was shown to be associated with disabilities and early

mortality in young adult survivors of childhood cancer.[24-27] The five components of physical frailty have all been individually described to occur in children with ALL. For example, higher levels of fatigue were reported in children with ALL compared with children from the general population, and more often during dexamethasone treatment.[28,29] Besides, several studies showed that children with ALL had muscle mass loss[22], muscle weakness[5,6,30], slow walking speed[5,31] and reduced physical activity levels.[32-34] It is therefore relevant to study whether co-occurrence of these 5 physical frailty components may be prevalent in children with ALL, putting them at risk for serious complications.

There is some known overlap between physical frailty and sarcopenia, in fact sarcopenia has been reported as a precursor of frailty in older adults.[23,35-37] The biological and clinical relationships between these 2 states in pediatric cancer populations are not clear yet.

The development of sarcopenia or physical frailty or both in children during ALL therapy is undesirable because of the consequences it may have for therapy (discontinuation or dose reduction due to clinical state), physical abilities, motor development, and child participation levels in daily life activities, as well as the potential negative effects on the longer term. To our knowledge, physical frailty in children has been assessed in only two previous studies, but not yet in pediatric patients with cancer. In both studies the frailty phenotype was associated with severe infections and increased hospitalizations.[38,39]

So far, frailty has not been examined in children during ALL treatment nor has the relationship between dexamethasone and, sarcopenia/frailty been investigated. Hence, the aims of this study are to estimate the occurrence of sarcopenia and physical frailty in children with ALL during maintenance therapy, to evaluate the effect of administering dexamethasone on sarcopenia and frailty (and their individual components) and to explore potential determinants associated with these outcomes. This paper describes the statistical design and methodology for this study.

Methods

Study design and patient recruitment

This prospective national observational cohort study is taking place at the Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands. The children included in this study are participating in the DexaDays-2 study: a randomized controlled trial on neurobehavioral side effects in pediatric patients with ALL.[40] In that study, Dutch ALL patients are eligible when they fulfill the following criteria: age 3-18, confirmed diagnosis of ALL, and inclusion in the

Dutch Childhood Oncology Group (DCOG) medium-risk group of the ALL-11 protocol. Only patients between 3 and 18 years can participate as this was an inclusion criterion for the DexaDays-2 study, because the questionnaires used in that study are validated only for those ages. Children who reach the age of 3 years during maintenance therapy and are still due to receive 5 dexamethasone courses after their birthday (at least 15 weeks before the end of therapy) are also eligible. Exclusion criteria of that study are anticipated compliance problems, underlying conditions that affect the absorption of oral medication, uncontrolled infections or any other complications that may interfere with administering dexamethasone treatment, insufficient command of the Dutch language, preexisting mental retardation, and hydrocortisone or risperidone use during the invitation to participate.

Our study on sarcopenia and frailty is being pursued within the framework of the aforementioned DexaDays-2 study. The latter consists of 2 parts: an identification study (including two timepoints: T1-T2) and a randomized controlled trial (T3-T11). The prospective observations of the current study are performed at a subset of these time points (Figure 1), during 15 weeks of the maintenance phase of ALL therapy.

A total of 105 patients will undergo a physical frailty assessment before (T1) and after 5 days (T2) of dexamethasone administration (6 mg/m^2 per day in 3 dosages). A subset of 50 children will be assessed at 3 additional timepoints (T3, T7 and T11), to observe the process of sarcopenia and physical frailty longitudinally. This subset comprised children participating in the DexaDays-2 randomized controlled trial based on the severity of their neurobehavioral problems. These 50 patients will receive physiological dosages of hydrocortisone or placebo during a 5-day dexamethasone treatment, and the cross-over will take place after 2 courses of dexamethasone treatment. The sample size is based on the DexaDays-2 study power calculation.[40]

Ethics Approval

The study was approved by the Medical Ethics Committees of the Erasmus Medical Center Rotterdam (reference number: NL62388.078.174).

Outcome definitions: Sarcopenia and Physical Frailty

Sarcopenia

We will use the most widely cited definition of sarcopenia as proposed by the European Working Group on Sarcopenia, that is the combination of low muscle strength or function, and impaired muscle mass.[20] For decades, the term sarcopenia had been used to describe muscle loss alone without

reference to function. However, recent updates and consensus definitions state the importance of including muscle function in the concept of sarcopenia.[19] Therefore, in this study sarcopenia is defined as a combination of impaired muscle mass and low muscle strength. These components are also separately included in the frailty definition (Table 1, Figure 2).

Physical frailty

In accordance with the original definition of Fried et al[23] and previous clinical frailty studies in childhood cancer survivors, we will define frailty using the following components: low muscle mass, muscle weakness, self-reported fatigue, slow walking speed and low physical activity.[24,25] Prefrailty and frailty will be defined, respectively, by the presence of 2, or 3 or more of the 5 components. Assessments are excluded if 3 or more components are missing.

The outcome measures to examine sarcopenia and physical frailty components are selected based on suitability for children with an age range of 3-18 years (*Table 2*).

Skeletal muscle mass

Total body SMM will be measured using multi-frequency segmental bioimpedance analysis (Tanita MC-780, Tanita Corporation, Tokyo, Japan).[41] The measurement procedure requires the child to stand in bare feet on the analyzer and to hold a pair of handgrips, one in each hand for approximately 15 seconds. Subsequently, the skeletal muscle index (SMI) will be calculated by dividing the individual SMM (kilogram [kg]) by height (m^2, SMI: SMM/height). The Tanita-device has shown excellent test-retest reliability.[42] High significant correlations (correlation coefficients ≥0.85) were shown for body composition values in children and adolescents, between bioimpedance analysis and dual-energy X-ray absorptiometry (which is the gold standard for the measurement of muscle mass).[43]

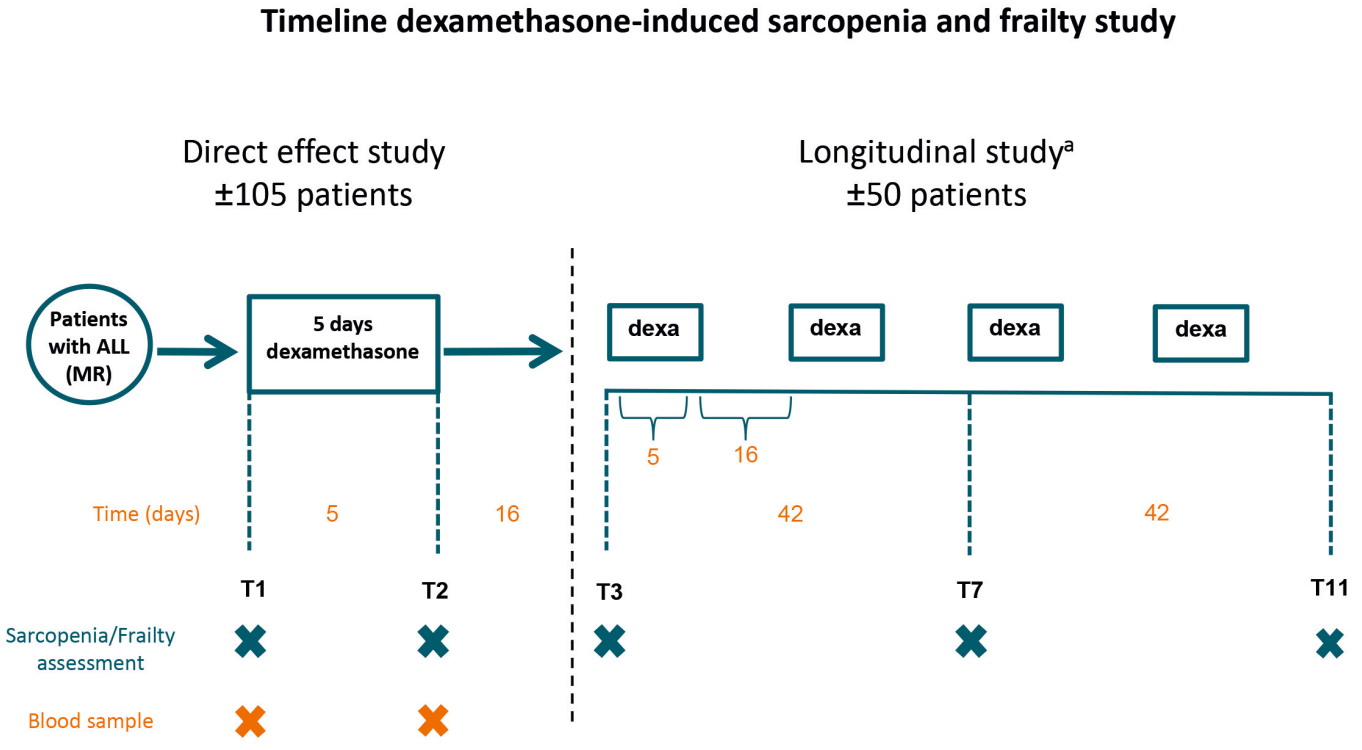

Figure 1. Timeline for sarcopenia and physical frailty assessment during the study. [a]Patients continue with this part of the study when they have significant dexamethasone-induced behavioral problems, based on the study design of the DexaDays-2 study. ALL: acute lymphoblastic leukemia; MR: medium risk; Dexa: dexamethasone.

Table 1. Short overview of definition and measurements used to assess sarcopenia in children with ALL

EWGSOP sarcopenia definition	Concept used in previous pediatric ALL studies	Method used in our study
Loss of muscle mass	Psoas muscle area loss using CT [20] Skeletal muscle mass or lean body mass using DXA [4,21]	Skeletal muscle mass by bioimpedance analysis
Muscle weakness	-	Handgrip strength using handheld dynamometry

Abbreviations: EWGSOP = the European Working Group on Sarcopenia in Older People, ALL = acute lymphoblastic leukemia, CT = Computed tomography, DXA = dual x-ray absorptiometry

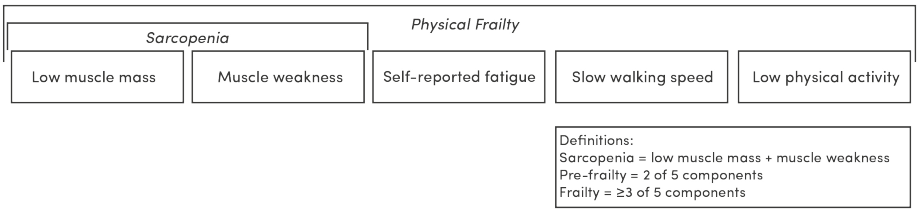

Figure 2. Physical frailty and sarcopenia definitions and the individual components.

Muscle strength

Handgrip strength (kilogram) will be measured in sitting position with the elbow flexed at 90° using a hydraulic Jamar handheld dynamometer (Sammons Preston). During the measurement the child will be verbally encouraged to achieve a maximum performance. For both the dominant and nondominant hand the mean score of 3 repeats will be calculated. Raw results will be compared with population-based age- and sex-specific reference values.[44] Handgrip dynamometry showed good validity (intraclass correlation coefficients [ICCs] 0.73-0.91) with high reproducibility in children from the age of 4 years old and has excellent test-retest reliability (ICC 0.91-0.93)[45,46], and the measurement was feasible in children with leukemia.[47]

Fatigue

Fatigue-related complaints will be assessed using the validated Dutch version of the Pediatric Quality of Life Inventory (PedsQL)–Multidimensional Fatigue Scale (MFS).[48,49] This questionnaire consists of 3 scales: General Fatigue,

Sleep/Rest Fatigue and Cognitive Fatigue, resulting in subscores and in a total fatigue score. We will use parent proxy-reports for children aged 2-4, 5-7, 8-12, and 13-18 years, as well as self-report versions for children: aged 8-12 and 13-18 years. The results of PedsQL-MFS will be compared with Dutch normative values from the general population.[48] The internal consistency of the Dutch version of the PedsQL–MFS has been reported as satisfactory (Cronbach coefficient α >.70), test-retest reliability was good (ICC 0.68-0.84) and the interobserver reliability varied from moderate to excellent (ICC 0.56-0.93).[48] The original version of PedsQL-MFS has been validated patients with pediatric cancer, 50% of whom had ALL[49], and the Dutch version has been used previously in studies in children with ALL.[28,50]

Walking speed

The TUG will be used to asses walking speed. A chair, without arm rests, allowing the child to sit with his feet flat on the floor and his hip and knees flexed at 90° will be used. The chair will be positioned at 3-m distance from a wall. The child will be asked to get up from the sitting position and walk 'as fast as he can, without running' to the wall and touch a self-chosen picture on the wall, turn around without using the wall for support, walk back to the chair and sit down. During the test verbal instructions will be repeated and encouragements are made. Time is recorded from the "go" cue to when the child is sitting down in the chair. The mean time of 3 trials will be considered as the test result.[51] The results of the test will be compared to age-specific reference values.[52] The TUG has shown excellent test-retest reliability (ICC 0.80 to 0.98) and inter-observer reliability (ICC 0.86 to 0.99) in the pediatric opulation[53], and the measurement was feasible in children with leukemia.[47]

Physical activity

Physical activity will be estimated using parent and self-reported questionnaires. We will use questionnaires generated in a Dutch population-based prospective cohort study investigating the development of a cohort of newborn children until young adulthood.[54] We will use parent proxy-reported versions for children aged 3-11 years, and child-reported versions for children aged 9-11 years.[55,56] These questionnaires comprise questions regarding frequency and duration of outdoor playing, sports participation and active transport to/from school, as well as sedentary behavior such as watching television and computer use. Children aged 12-18 years will be asked to fill in the modified Baecke questionnaire, which consists of 3 components: school activity, sports activity, and leisure activity.[57] The results of the physical activity questionnaires (type of activity, frequency, and duration) will be compared with the Youth Compendium of Physical Activities.[58] The age-specific metabolic

equivalent of the specific activity (either leisure or sports) will be used to estimate the energy expenditure in calories of an individual participant.

In addition, we hypothesized that generalized muscle weakness might be better expressed in a functional performance test, which is currently not a part of the frailty assessments. To explore the potential value of a functional muscle strength measurement in the concept of sarcopenia and frailty, we will use the 'Time to Rise from the Floor test' (TRF).[59] The child will be asked to sit in the cross-legged position on the floor and to get up as fast as possible. The TRF will be performed 2 times, and for both performances, the quantitative performance (time in seconds) and a quality grade will be scored. We will use the 'Gowers maneuver' as a quality performance by grading the amount of support needed to rise.[60] This is a standardized method to quantify on a 1-7 scale, where 1 means normal rising and 7 means unable to rise (Table 3).

All assessments will be performed by a pediatric physiotherapist (EV) or a trained medical doctor (AvH).

Table 2. Short overview of measurements used to assess frailty in childhood cancer survivors and in the current study

Frailty components	Concept used in CCS	Method used in the current study in children with ALL
Shrinking / Weight loss	Lean muscle mass using DXA[24,25]	Skeletal muscle mass by bioimpedance analysis
Weakness	Handgrip strength using handheld dynamometry[24,25]	Handgrip strength using handheld dynamometry
Exhaustion	Self-reported exhaustion assessed using the SF-36[25] or during a semi-structured interview[24]	Self-reported fatigue using PedsQL-MFS
Slowness	Slow walking speed based on cut-off points for 15 feet[25], or by using the six-minute walk test[24]	Slow walking speed using the Timed Get Up and Go test
Low physical activity	Energy expenditure during leisure time physical activity based on the NHANES Physical Activity[25] and based frequency and duration per week derived from a semi-structured interview[24].	Energy expenditure based on physical activity questionnaires

Abbreviations: CCS = Childhood Cancer Survivors, DXA = dual x-ray absorptiometry, PedsQL-MFS = Pediatric Quality of life - Multidimensional Fatigue Scale

Table 3. Gowers maneuver grade: to quantify the ability to rise from the floor

Performance	Grade
Normal rising	1
Butt-first maneuver, one hand on floor	2
Butt-first maneuver, two hands on floor	3
Unilateral hand support on thigh	4
Bilateral hand support on thighs	5
Arises only with aid of an object (table, chair)	6
Unable to arise	7

Standardized method to quantify the quality of rising by grading the amount of support needed to rise

Potential determinants

We will explore the following potential determinants for the components of sarcopenia and physical frailty: sex, age, weight Z-scores at diagnosis, time since the start of treatment, registered toxicity and serious adverse events in induction therapy, cumulative vincristine dosage, dexamethasone pharmacokinetics, and carrier of relevant genetic variants (candidate single-nucleotide polymorphisms). Information regarding these factors will be extracted from the electronic patient files or is collected in the DexaDays-2 study. Dexamethasone kinetics are measured through peak levels (2-3 hours after the first dexamethasone administration on day 1 of the dexamethasone course) and trough levels (measured on day 6, at least 12 hours after the last dexamethasone dose administered on the previous evening). A peripheral blood sample to extract germline DNA, for evaluation of carrier status of relevant candidate single-nucleotide polymorphisms related to sarcopenia and physical frailty, is taken on T1 as part of the DexaDays-2 study. As a complete array (Illumina GSA) will be run, we will be able to select the most relevant specific additional single-nucleotide polymorphisms of interest, based on evidence from the most recent literature (Figure 1).

Statistical analysis

The results of the physical frailty assessments, that is SMI, handgrip strength, self-reported fatigue, walking speed, and physical activity (component scores) will be reported as means and SDs, or as median and interquartile ranges if data are non-normally distributed. The frequency of sarcopenia and physical frailty, as well as the individual components at all timepoints will be reported in percentages and schematically visualized. A correlation matrix will be built to

explore coherence between the additional measure TRF and the other frailty components.

To evaluate the potential change in frailty components after 5 days of dexamethasone administration, a paired Student t test or Mann-Whitney U test will be used depending on the distribution of the data.

To evaluate whether the mean scores from the frailty components change between T1, T3, T7 and T11 1-way ANOVA will be employed.

To study the effect of dexamethasone administration at T1, T3, T7, and prior to T11 on sarcopenia, physical frailty and each individual components, generalized mixed models will be estimated. These models incorporate correlations between repeated responses on the same individual. Patient-specific random intercept, age, weight, time since the start of therapy and cumulative vincristine dosage will be included in the model.

Multivariable linear regression model will be estimated to investigate associations between the potential determinants (patient and treatment-related factors, pharmacokinetics, and genetics) and the assessment scores at T1 and T2 (SMI, handgrip strength, self-reported fatigue, walking speed, TRF, and physical activity). Results will be presented as regression coefficients along with 95% CI.

Multivariable logistic regression models will be estimated to explore associations between the aforementioned potential determinants and the occurrence of sarcopenia and physical frailty at T1 and T2. Odds ratios along with 95% CIs will be estimated.

Statistical analyses will be performed using software packages R Statistics (version 1.0.143; R Foundation) and SPSS (version 26.0.0.1) for Windows.

Results

Patient accrual started in 2018 and was finalized in spring 2021. A total of 105 children undergoing ALL therapy will participate in this study. From autumn 2021 statistical analyses will be performed.

Discussion

This paper describes the design of the first study on sarcopenia and physical frailty in children during maintenance therapy for ALL. The results of this study

will provide information and create awareness on the magnitude and severity of sarcopenia and physical frailty in this specific group of children, which may help us understand which factors are associated with the large variations in physical ability between children receiving similar treatments. With this knowledge we may be able to identify physically vulnerable children at an earlier stage. This is important because being vulnerable to sarcopenia or frailty, can complicate continuation of ALL therapy, independence in physical functioning, reaching motor milestones and participation in daily life activities.

In this study we will assess sarcopenia involving a combination of low muscle mass and low muscle strength for the first time in patients with ALL. The SMM will be estimated using the Tanita MC-780 multi-frequency segmental body composition analyzer, which is a validated, reliable, low-cost, fast and non-invasive method to estimate body composition in the pediatric population.[43]

None of the previous studies in children with ALL concerning muscle mass loss incorporated functional muscle strength assessments. We expect this to be of additional value because recent updates and consensus definitions state the importance of including muscle function in the concept of sarcopenia[61] as reduced muscle mass in combination with normal muscle strength may suggest malnutrition rather than sarcopenia.[62] Besides, in children impaired muscle function directly influences motor development and is therefore relevant.[63]

To explore this aspect further we added a functional strength measurement to the assessment: the TRF. Although the handgrip dynamometer is a reliable instrument to measure handgrip strength in children [46], this may not be the first sign of reduction of muscle strength. We suspect that a generalized reduction in muscle strength (such as in sarcopenia and physical frailty) might be better shown by a functional performance test. The time and degree of support needed to rise from the floor, are standardized measures to quantify deterioration and are associated with walking ability in children with muscular dystrophy.[64]
The results of this study will provide knowledge about the effect of treatment with high doses of dexamethasone on muscle loss and other components of physical frailty, and therefore insights into the severity and risks of these side-effects. Furthermore, through exploring potential determinants that could influence the occurrence of the sarcopenia or frailty, we might be able to identify children at risk for substantial problems at an earlier stage. As a result, we might be able to start targeted interventions and clinical studies on reducing the dexamethasone-induced components of physical frailty with for example nutrition and exercise.

This study has a number of strong points. First, because care for children with ALL in the Netherlands is centralized, a national cohort of Dutch children can be screened on eligibility for this study, rendering a large and hopefully unbiased population. Second, all children will have a physical frailty assessment by a skilled pediatric physiotherapist or a trained medical doctor, which benefits the validity and reliability of the performed physical assessment. Third, the burden of the study will be minimal because the assessments are performed during maintenance therapy of ALL, in which children experience less toxicities, fewer hospital admissions, and therapy is mainly administered at home and in the outpatient clinic. Fourth, we selected sarcopenia and frailty endpoints in accordance with previous research and the official definitions. Furthermore, we added 1 functional strength measurement, the TRF, based on expert opinion and on particular feasibility in children with ALL.

Some possible study limitations have to be taken into account as well. We will only include children participating in the DexaDays-2 study, which could potentially lead to selection bias, as patients who experience dexamethasone-induced neurobehavioral problems could be more motivated to participate because in that trial they will receive a drug to potentially reduce these problems. Furthermore, the subset of 50 children that will be measured longitudinally comprises children participating in the DexaDays-2 randomized controlled trial based on the severity of their neurobehavioral problems. These patients will receive physiological dosages of hydrocortisone or placebo during a 5-day dexamethasone treatment, and the cross-over will take place after 2 courses of dexamethasone treatment. We do not know if this affects the occurrence of sarcopenia and physical frailty in this cohort, for example, whether children with dexamethasone-induced clinically relevant neurobehavioral problems also show more physical side effects. Besiedes, within the DexaDays-2 study patients aged 3-18 years were selected, which complicated selecting outcome measures suitable for all participants. We succeeded in selecting measurements that have previously been used and validated in pediatric populations indicating their usefulness, however, with the exception of the PedsQL-MFS none of the measurements has been validated in pediatric oncology patients.

In conclusion, this study is designed to determine the occurrence and severity of sarcopenia and frailty components in children during the maintenance phase of ALL therapy, and to determine the effects of administration of high doses of dexamethasone on physical vulnerability. With this study we aim to create awareness about these potential risks in children with ALL, as well as expanding our knowledge for reducing further side effects.

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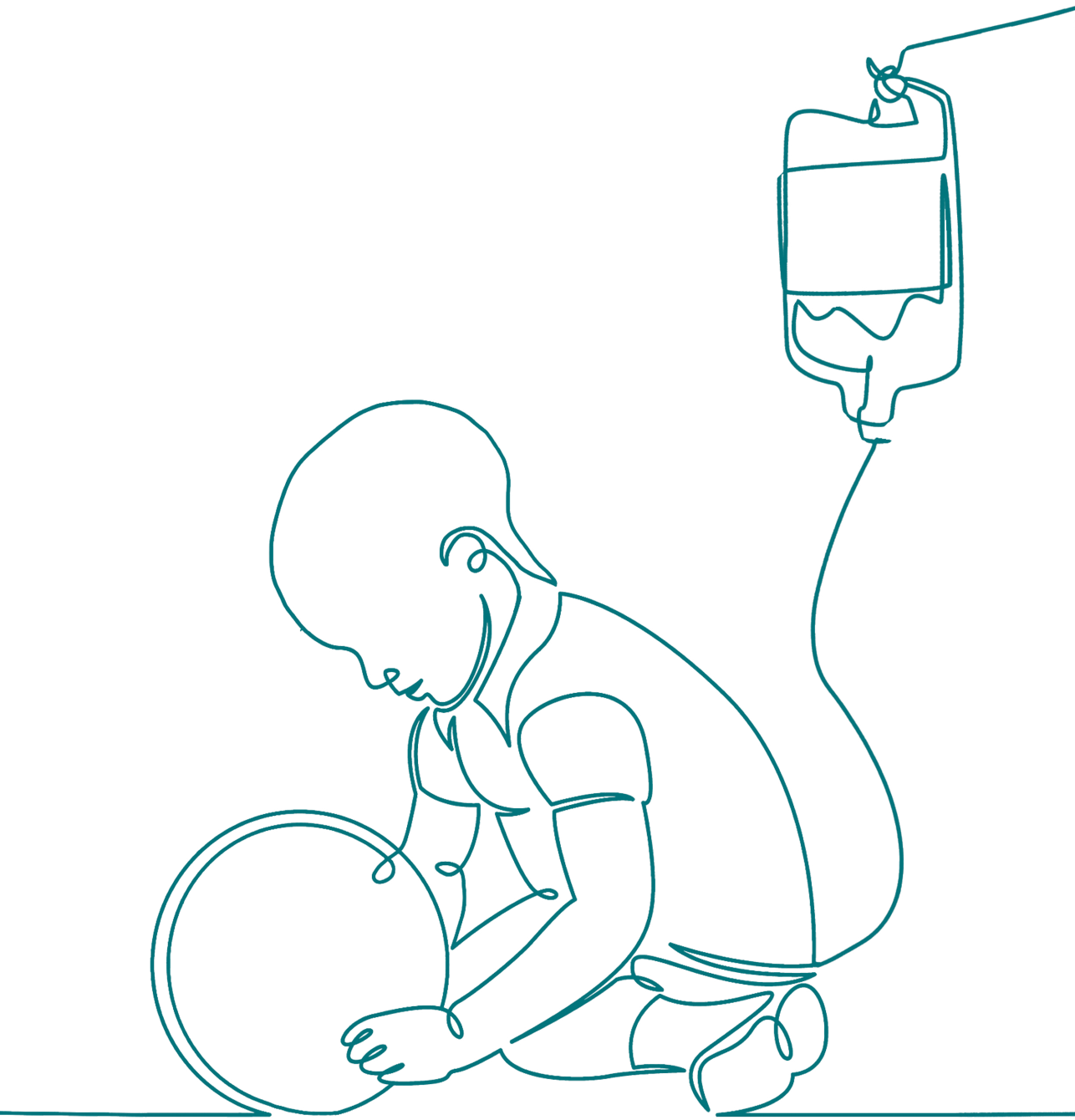

Physical frailty deteriorates after a 5-day dexamethasone course in children with acute lymphoblastic leukemia, results of a national prospective study

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Abstract

The aim of this study was to establish the effect of a dexamethasone course on sarcopenia and physical frailty in children with acute lymphoblastic leukemia (ALL), and to explore prognostic factors for frailty. Dutch ALL patients, aged 3-18 years were included during maintenance therapy. Patients had a sarcopenia/frailty assessment on the first day of (T1) and on the day after (T2) a 5-day dexamethasone course. Sarcopenia was defined as low muscle strength in combination with low muscle mass. Prefrailty and frailty were defined as having two or ≥three of the following components respectively: low muscle mass, low muscle strength, fatigue, slow walking speed and low physical activity. Paired tests were used to assess differences between T1 and T2. Logistic regression models were estimated to explore patient- and therapy-related prognostic factors for frailty. We included 105 patients. Median age was 5.3 years (range: 3-18.8). At T1, sarcopenia, prefrailty and frailty were observed in respectively 2.8%, 23.5% and 4.2% of patients. At T2, the number of patients with sarcopenia and prefrailty were similar, but frailty had increased to 17.7% (p=0.002). Weight (OR=0.54, 95% CI:0.33-0.89), maintenance treatment week (OR=0.94, 95% CI:0.9-0.98), muscle mass (OR=0.49, 95% CI:0.28-0.83), handgrip strength (OR=0.41, 95% CI:0.22-0.77), walking speed (OR=2, 95% CI:1.2-3.39) and physical activity (OR=0.98 95% CI:0.96-0.99) at T1, were associated with frailty at T2. Physical frailty increased strikingly after a 5-days dexamethasone course in children with ALL. Children with poor physical state at start of the dexamethasone course were more likely to be frail after the course.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer worldwide, with a prevalence up to 25% of all cancers. Advances in treatment strategies and supportive care have resulted in a 5-year survival rate of over 90% in high-income countries.[1,2] However, children experience treatment-related side effects which may interfere with physical abilities. These may include deterioration of muscle strength and muscle mass, which can be caused by malnutrition, infections, low physical activity and by treatment with glucocorticoids.

While sarcopenia -the combination of low muscle mass and low muscle strength- is mostly related to higher age in the general population[3], the phenotype is increasingly reported in chronically and critically-ill children[4], including pediatric ALL patients.[5,6] The same applies to the more extended vulnerability state: physical frailty. Frailty is characterized by three or more of these five components: low muscle mass, muscle weakness, self-reported fatigue, slow walking speed and low physical activity[7] (Figure 1). Each of these five components have individually been reported as side effects of treatment in children with ALL. Children with ALL develop muscle mass loss[8], muscle weakness[9,10], fatigue[11,12], slow walking speed[10] and reduced physical activity levels.[13,14]

There is a partly overlap between sarcopenia and physical frailty, with both involving comprised muscle health.[15] In the elderly, sarcopenia has been considered as a precursor of frailty[16,17], but the biological and clinical relations between these two states in pediatric cancer populations are not yet clear.[15] Nevertheless, as in older populations, sarcopenia and frailty have both been associated with acute adverse health outcomes, i.e. higher infection rates, increased hospitalizations, loss of ambulation, and even, impaired survival in children[6,8,18-20], and with the onset of chronic comorbidities, disabilities, and early death in childhood cancer survivors.[2] These vulnerable clinical state may also lead to adjustments or even discontinuation of therapy.

Dexamethasone is an important treatment component of ALL, but induces muscle atrophy of particularly type II muscle fibers (which are the force generating fibers supporting dynamic movements)[21] and consequently myopathy.[22] Among survivors of childhood cancer, higher cumulative doses of corticosteroids and prolonged exposure increased the risk for muscle wasting and weakness.[15]

To date, it is not clear whether sarcopenia and frailty directly increase after a dexamethasone course during ALL treatment, and if the child's physical state at start of a dexamethasone course is prognostic for developing these states. If we can identify treatable quantities, such as low muscle strength, we may be able to intervene to prevent deterioration to such a vulnerable state.

Hence, the primary aim of this study was to establish whether the frequency of sarcopenia, physical frailty and its individual components, increased after a 5-day dexamethasone course in children with ALL. Secondary, we aimed to explore whether patient- and/or treatment-related factors as well as the physical functioning state, were determinants for developing frailty following a 5-day dexamethasone course.

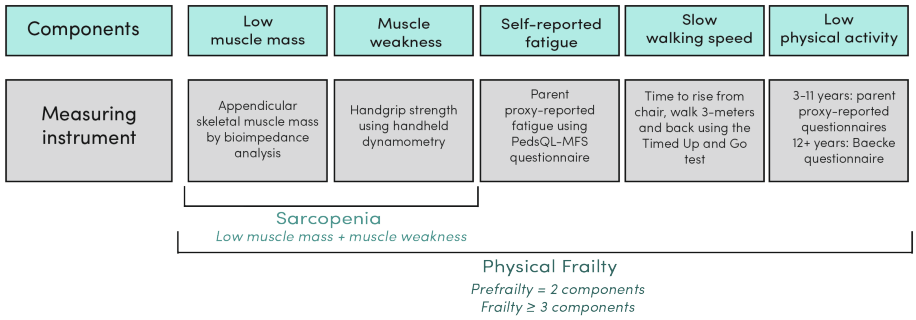

Figure 1. The definition of the sarcopenia and physical frailty constructs and the measuring instruments used to assess individual components

Methods

Study design and cohort

This study on sarcopenia and physical frailty was performed within the framework of the DexaDays-2 study: a national randomized controlled trial on neurobehavioral side effects of dexamethasone in pediatric ALL patients aged 3-18 years, conducted at the Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands, between 2019-2021. The design of this study including in- and exclusion criteria has been previously described.[23,24]

The maintenance therapy of ALL-11 MRG contained 28 three-week treatment cycles, with a 5-days dexamethasone administration course every cycle (6 mg/m^2 per day in three dosages). All participating patients had a sarcopenia/frailty assessment in the outpatient clinic, on the first day of a 5-day dexamethasone course (T1) and on the day after this same course (T2). The assessment consisted of measurements of fatigue, muscle mass, muscle strength and

physical performance[24], and was carried out by a pediatric physiotherapist (EV) or medical physician (AvH) at the Sports and Exercise center of the Princess Máxima Center.
The study was approved by the Medical Ethics Committee (reference number NL62388.078.174) and all patients and/or parents provided written informed consent to participate.

Outcome measures

Sarcopenia and physical frailty
Sarcopenia was defined as the combination of low muscle strength and low muscle mass[3] (quantification described in next paragraph) (Figure 1). Prefrailty and frailty were classified as the presence of respectively two, or more than two of the following five components: low muscle mass, low muscle strength, fatigue, slow walking speed and low physical activity.[7]

Appendicular skeletal muscle mass
Appendicular skeletal muscle mass (ASMM), the sum of muscle mass of the four limbs, was measured using a multi-frequency segmental bioimpedance analyzer (Tanita MC-780, Tanita Corporation, Tokyo, Japan). As reference data for Dutch children were unavailable, to estimate SDS we used age and sex-specific mean and standard deviation values from a UK population (5-18 years), acquired using the same Tanita software.[25] Due to lack of bioimpedance reference values of 3-4 year old children, we used sex and age specific expected values of ASMM (kilogram), derived by a dual-energy X-ray absorptiometry prediction equation in Canadian children[26] (Supplemental Table 1). Low ASMM was defined as SDS -1.5 or lower, in line with previous frailty studies.[2,27]

Muscle strength
Handgrip strength (kilogram) was measured in sitting position with the elbow flexed at 90^0 using a hydraulic Jamar handheld dynamometer (Sammons Preston, Bolingbrook, Illinois, United States of America). For both the dominant and non-dominant hand the mean score of three repeats was used. Mean values were compared to population-based age and sex-specific reference values and SDS[28] were calculated. Low muscle strength was defined as SDS -1.5 or lower.

Fatigue
The Dutch version of the Pediatric Quality of Life Inventory (PedsQL) – Multidimensional Fatigue Scale (MFS) was used to assess fatigue-related problems.[29] This questionnaire consists of three scales: general fatigue, sleep/

rest fatigue and cognitive fatigue. We used the parental versions for the specific age groups 3-4, 5-7, 8-12 and 13-18 years. Subsequently, we compared total scores of our population to Dutch reference values and calculated SDS.[29] Patients with a SDS of -1.5 or lower were classified as fatigued.

Walking speed

The Timed Up and Go test (TUG) was used to asses walking speed. The children started seated on a chair and were asked to stand up, walk 3 meters, turn around, walk back and sit down again. The mean time of three attempts was considered as the test result, and SDS were calculated using a Brazilian age and weight specific reference equation.[30] Patients with a SDS of 1.5 or higher were classified as slow (higher SDS indicates lengthier and thus slower performance).

Physical activity

Physical activity was assessed using questionnaires. For children 3-11 years of age we used parent proxy-reported questionnaires generated in a Dutch population-based prospective cohort study.[31] These questionnaires contained questions regarding frequency and duration of outdoor playing, sports participation and active commuting to/from school. Time per week spent on each activity was calculated by using the following equation: weekly time spent on the activity = (days per week) * (hours per day). Total physical activity was calculated by adding the hours of active commuting, outdoor play, and sport participation per week. For the definition of low physical activity, we used a cutoff of less than 60 active minutes per day, based on the World Health Organization guidelines for physical activity.[32]

Children 12-18 years were asked to fill in the modified Baecke questionnaire.[33] Physical activity during school, leisure time and organized sports were reported in frequency, intensity and duration. Total physical activity was calculated according to the Baecke formula.[34] As a reference cohort we used Baecke scores reported in 102 Dutch children, 10.5 ± 3.6 years of age.[35] We defined low physical activity in this study as a score 1.5 SDS below their reported mean score.

A complete overview of the measuring instruments including methods and psychometric properties have previously been described in our study protocol.[24] For the calculation of sarcopenia we could only include patients with both an ASMM and a handgrip strength measurement. Patients could only be classified for prefrailty if they had performed at least two measurements of the five, and for frailty if they had completed at least three of the measurements.

Potential prognostic factors for frailty

The following variables were assessed as prognostic factors for frailty after 5 days of dexamethasone administration: sex, age in years, weight SDS, body mass index (BMI) SDS, maintenance week, concomitant asparaginase (depending on ALL-11 randomization children received asparaginase until week 15 or week 27 of maintenance therapy). In addition, we assessed if the physical functioning state at T1 was associated with the occurrence frailty at T2. These outcomes were: ASMM SDS, handgrip strength SDS, PedsQL-MFS SDS (fatigue), TUG SDS (rising/walking speed) and physical activity minutes per day. The latter only applied to children aged 3-11 years.

Statistics

Patient characteristics and assessment results were presented as mean or median with interquartile range (IQR), according to the distribution of the variables. Paired t-test was used to assess differences in test results between at start (T1) and after 5-days (T2) of the dexamethasone course. In case of violation of the normality assumption, Wilcoxon ranked sum test was employed. Mean/median differences with 95% confidence interval in raw scores and SDS were reported. Chi-squared and Fisher's exact tests were used to compare the occurrence of sarcopenia and frailty and the individual components (low ASMM, low muscle strength, fatigue, slow walking speed and low physical activity) at T1 and T2. To investigate potential prognostic factors (patient-, disease- and therapy-related characteristics and T1 assessment results) for frailty at T2, univariable logistic regression models were estimated. Odds ratio (OR) was not estimated when the number of participants in a cell of the contingency table was ≤3.

All analyses were performed in R software environment Version 1.4.1106 for Windows.

Results

Patients

In total, 105 patients with ALL undergoing MRG maintenance therapy were included in this study (Figure 2) with a median age of 5.3 years (range: 3-18.8). The majority were boys (61%). Ninety-three patients (88.6%) had pre B-cell ALL, 11 patients (10.5%) had T-cell ALL and one patient had a blastic plasmacytoid dendritic cell neoplasm but was also treated according to the DCOG ALL-11 MRG protocol and therefore included (Table 1).

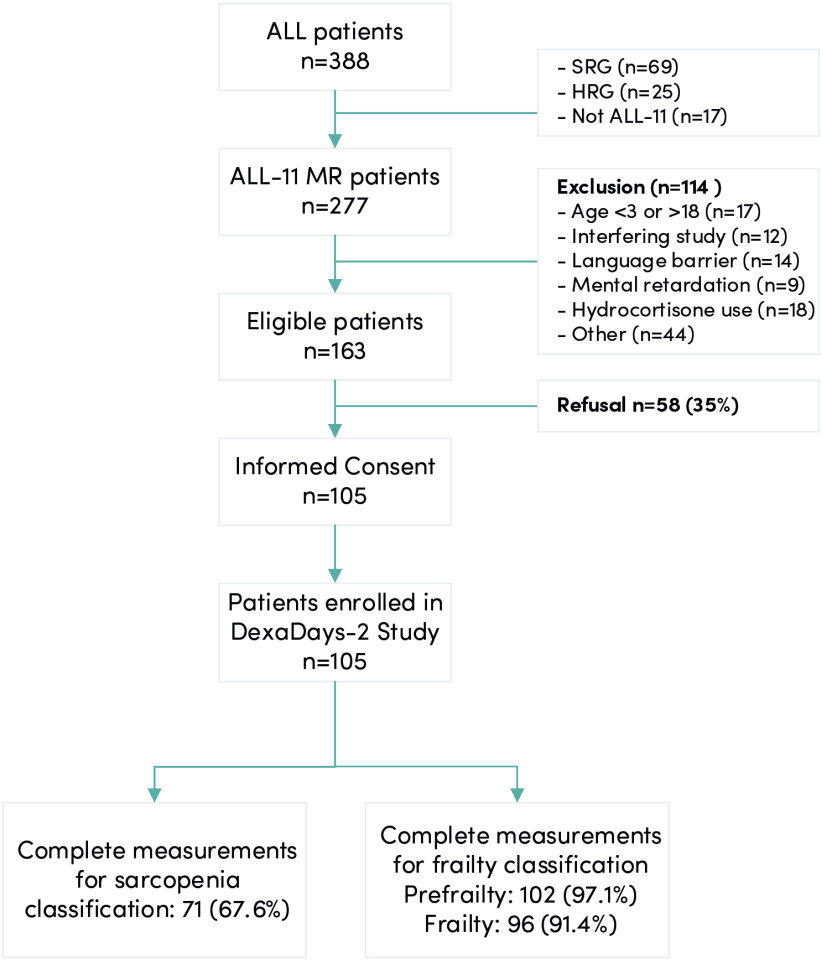

Figure 2. Flowchart of study patients and completed assessments

Due to variances in individual children's cooperativeness not all measurements were performed in every patient. For the calculation of sarcopenia we could only include patients with both an ASMM and a handgrip strength measurement. Patients could only be classified for prefrailty if they had performed at least two measurements of the five, and for frailty if they had completed at least three of the measurements.

Table 1. Patient characteristics (N=105)

	Median	IQR	Range
Age, years	5.33	4.17, 8.83	3.0, 18.83
Weight, SDS[I]	0.34	1.27	-3.62, 4.41
Height, SDS[I]	-0.83	1.05	-3.18, 1.56
Body Mass Index, SDSI	1.11	1.12	-3.28, 3.88
Maintenance week	34	22, 43	13, 68
	No.	**%**	
Sex			
Female	41	39	
Male	64	61	
Type of ALL			
Pre-B ALL	93	88.6	
T-ALL	11	10.5	
BPDCN[II]	1	0.9	

SDS = Standardized deviation score, ALL = acute lymphoblastic leukemia, BPDCN = blastic plasmacytoid dendritic cell neoplasm.
[I] SDS values are mean with standard deviation
[II]One patient had BPDCN and was also treated according to the ALL-11 protocol

Sarcopenia and physical frailty (components) at the start of the 5-day dexamethasone course (T1)

At T1 sarcopenia (low ASMM and low strength) was present in 2 (2.8%) patients. Prefrailty and frailty occurred in 24 (23.5%) and 4 (4.2%) patients, respectively.

Muscle mass

Mean ASMM was 25% (IQR: 21.7, 27.2), which was lower compared to normative values (SDS: -0.65, IQR: -0.37, -0.08). Twenty (24.1%) patients were classified with low ASMM.

Muscle strength:

Handgrip strength results were within normal ranges (SDS: -0.02, IQR: -0.7, 0.8). Ten (12.2%) patients had low strength.

Fatigue:

Median total PedsQL-MFS score was 76.4 (IQR: 58.3, 87.9). Compared to normative values, mean SDS was -0.55 (IQR: -2.2, 0.5) and 35 (38%) children were classified as fatigued.

Walking speed
Mean TUG time was 5.6 seconds (IQR: 4.6, 6.4), which was lower compared to normative values (SDS: -0.5, IQR: -1.3, 0.1). Four (4.4%) children had a low score.

Physical activity
Children 3-11 years were on average 83.6 minutes active per day (IQR: 44.5, 120.2). Older children and adolescents (12-18 years) had a Baecke physical activity SDS of -1.7 (IQR: -2.9, -0.3). In total, 31 patients (39.7%) met the criteria for low physical activity.

Results of paired analyses: sarcopenia and physical frailty (components) after 5-day dexamethasone course (T1-T2)
The number of patients with sarcopenia and prefrailty at T2 did not change compared to T1. The number of patients with frailty had increased from 4.2% to 17.7% (p=0.002). Complete assessment results of T1 and T2 are depicted in Table 2.

Muscle mass:
Compared to T1, the mean ASMM on the sixth day (T2) had decreased with -0.54 SDS (95%CI: -0.65, -0.44), while body weight remained the same (mean Δ = -0.05, 95%CI: -0.2, 0.1). There was a 14.5% increase of patients with low ASMM (p<0.01).

Muscle strength
Handgrip strength had improved with 0.2 SDS (95%CI: 0.1, 0.4), but the number of children with low strength remained the same (p=0.68).

Fatigue
The PedsQL-MFS total score had decreased with -2.13 SDS (95%CI: -2.54, -1.72), which led to an increase of 44.6% of patients with the fatigue classification (p<0.01).

Walking speed
The number of patients with slow walking speed did not differ between T1 and T2 (p=0.68).

Physical activity
In 3-11 year olds (n=72) physical activity decreased with -26.8 minutes per day (95%CI: -39.6, -15). The Baecke SDS (only available for 6 children) showed a decrease of -0.54 (95%CI: -1.41, 0.14) in patients 12-18 years. The number of patients with low physical activity had increased with 18% (p<0.01).

The differences in mean scores are visualized in Figure 3.

Table 2. Assessment results and paired analyses of the frailty components on day 1 (T1) and one day after (T2) a 5-day dexamethasone course

		Day 1		Day 6		Paired difference day 1 - day 6	
	N	**Mean**	**IQR**	**Mean**	**IQR**	**Mean Δ**	**95% CI**
Weight, kilogram	86	21.6[I]	28.7, 37.5	22.1[I]	18.5, 37.9	-0.05	-0.2 to 0.1
Appendicular skeletal muscle mass	83						
Kilogram		5.4[I]	4, 10.5	5[I]	3.8, 10	**-0.55**[II]	**-0.7 to -0.45**
Percentage		25.03	21.71, 27.24	23.06	20.25, 25.82	**-1.97**	**-2.3 to -1.65**
SDS		-0.65	-1.37, -0.08	-1.19	-1.88, -0.59	**-0.54**	**-0.65 to -0.44**
Muscle strength							
Handgrip strength, dominant hand	82						
Kilogram		9.15[I]	6.35, 14.7	10.1[I]	7, 16	**0.65**[II]	**0.25 to 1.05**
SDS		-0.02	-0.7, 0.8	0.22	-0.7, 0.98	**0.24**	**0.13 to 0.35**
Fatigue							
PedsQL - MFS	92						
Total score		76.39[I]	58.33, 87.85	41.67	31.6, 57.29	**-24.31**[II]	**-29.17 to -19.44**
SDS		-0.55	-2.18, 0.53	-3.17	-4.6, -2.04	**-2.13**	**-2.54 to -1.72**
Slow walking speed							
Timed Up and Go test	91						
Seconds		5.62	4.58, 6.44	5.63	4.55, 6.33	0.02	-0.19 to 0.23
SDS		-0.47	-1.25, 0.13	-0.42	-1.33, 0.07	0.05	-0.14 to 0.24
Physical activity							
3-11 years – questionnaire	72						
Active minutes per day		83.57[I]	44.46, 120.18	49.29[I]	15, 103.57	**-26.79**[II]	**-39.64 to -15**
12-18 years - Baecke questionnaire	6						
Total score		7.24[I]	6.32, 9.01	6.27[I]	5.17, 8.38	-0.56[II]	-1.45 to 0.14
SDS		-1.71[I]	-2.88, -0.27	-2.93[I]	-4, -0.88	-0.54[II]	-1.41 to 0.14

Table 2. *Continued.*

		Day 1		Day 6		Paired difference day 1 - day 6
		No.	%	No.	%	p-value
Frailty components						
Low skeletal muscle mass	83	20	24.1	32	38.6	**.003**
Low handgrip strength	82	10	12.2	8	9.76	.683
Fatigue	92	35	38.04	76	82.61	**< .00001**
Slow walking speed	91	4	4.4	6	6.59	.683
Low physical activity	78	31	39.74	45	57.69	**0.004**
Sarcopenia	71	2	2.8	2	2.8	0.999
Prefrailty	102	24	23.5	29	28.4	0.458
Frailty	96	4	4.2	17	17.7	**0.002**

SDS = standardized deviation score. [I]Median, [II]Median value based on Wilcoxon signed rank test. Bold indicates statistical significance.

Table 3. Univariable association between determinants at day 1 (T1) and having frailty at day 5 (T2)

Determinants at T1	Frail at T2	Non-Frail at T2	Odds Ratio	95% CI
Sex			1.0	0.35 to 2.92
Female	7 (41.2)	32 (41)		
Male	10 (58.8)	46 (59)		
Age, years	6.4 (4, 9)	5.3 (4.25, 8.85)	1.0	0.9 to 1.14
Weight, SDS	-0.34 (-0.83, 0.32)	0.43 (-0.31, 1.24)	**0.54**	**0.33 to 0.89**

Table 3. *Continued.*

Determinants at T1	Frail at T2	Non-Frail at T2	Odds Ratio	95% CI
Body mass index, SDS	1.05 (0.22, 1.7)	1.01 (0.36, 1.9)	0.72	0.45 to 1.15
Maintenance week, number	25 (16, 31)	37 (25.5, 46)	**0.94**	**0.9 to 0.98**
Concomitant asparaginase Yes No	4 (23.5) 13 (76.5)	7 (9) 71 (91)	3.12	0.8 to 12.2
Current or previous physiotherapy Yes No	 5 (29.4) 12 (70.6)	 24 (30.8) 54 (69.2)	0.94	0.3 to 2.96
Appendicular skeletal muscle mass, SDS	-1.39 (-1.84, -0.87)	-0.54 (-1.28, -0.02)	**0.49**	**0.28 to 0.83**
Dominant handgrip strength, SDS	-0.73 (-1.65, 0.2)	0 (-0.6, 0.88)	**0.41**	**0.22 to 0.77**
Fatigue (PedsQL-MFS), SDS	-0.46 (-1.31, 0.38)	-0.49 (-2.1, 0.56)	1.0	0.98 to 1.03
Timed Up and Go test, SDS	0.26 (-0.52, 0.68)	-0.54 (-1.28, -0.02)	**2.02[III]**	**1.2 to 3.39**
Physical activity, minutes per day[II]	44 (23, 62)	90 (45, 147)	**0.98**	**0.96 to 0.99**

Values are depicted as median (interquartile range) or number (%), Bold indicates statistical significance.
BPDCN = blastic plasmacytoid dendritic cell neoplasm, n.a. = not applicable
[II]Analyzed in subcohort of children 3-11 years of whom physical activity minutes per day were available (n=72)
[III]Higher SDS = slower performance increases the risk of frailty

Determinants for frailty after a 5-day dexamethasone course (T2)
Seventeen patients were classified as frail at T2. Univariable logistic regression models showed that lower weight SDS at T1 was negatively associated with frailty at T2 (OR: 0.54, 95%CI: 0.33-0.89) (Table 3). Patients who were further into maintenance therapy were less prone to become frail (OR: 0.94, 95%CI: 0.9-0.98). Concomitant administration of asparaginase seemed to have a negative effect on developing frailty but the number of children still receiving asparaginase (n=11) was too small to reach statistical significance (OR: 3.12, 95%CI: 0.8-12.2).

Poor physical status and performance at T1 were associated with a higher frailty occurrence at T2 (Table 3). Higher ASMM (OR: 0.49, 95%CI: 0.28-0.83), stronger handgrip strength (OR: 0.41, 95%CI: 0.22-0.77) and more physical activity minutes per day (OR: 0.98 95%CI: 0.96-0.99) decreased the risk of frailty at T2 significantly. Slower performance on the TUG (OR: 2, 95%CI: 1.2-3.39) increased the risk. Fatigue levels at T1 were not associated with frailty at T2.

Discussion

Our study showed that the occurrence of physical frailty increased with 13.5% directly after a 5-day dexamethasone course in children with ALL. This is a concerning finding since dexamethasone pulses are recurrently administered in many ALL maintenance chemotherapy schedules, and a physical frail state has been associated with an increased risk of adverse events in pediatric populations.[19,20]

There was a notably smaller number of patients with sarcopenia (low muscle mass *and* muscle strength) (2.8%) and this occurrence was not increased after a dexamethasone course. This may indicate that the combination of low ASMM and low handgrip strength is not very relevant, or handgrip strength may not resemble total muscle strength in these young patients.

We did found a marked decrease of -0.5 SDS in ASMM after 5 days of dexamethasone administration, which may be related to the catabolic effect of dexamethasone.[36] However, the acute effect of dexamethasone administration and the role of pharmacokinetics in muscle deterioration needs to be studied in further depth. The decrease in ASMM could also potentially explained by the striking observed decline in physical activity (on average 27 minutes less physically active per day). Studies in healthy young, and older adults indicated that short-term sedentary behavior already led to significant loss of skeletal muscle mass.[37,38] It is not known whether this effect of muscle breakdown in children is also this profound. Although ASMM decreased during the dexamethasone course, total body weight remained the same which may be explained by fluid imbalances or fat increase (cushingoid features). Our analyses also showed that lower body weight SDS and

lower ASMM SDS at T1 were associated with frailty at T2, unlike BMI SDS, which was unexpectedly not associated.

Parents reported a dramatic increase in their children's fatigue after 5 days of dexamethasone administration. At day one, 38% already had a high fatigue score but this increased to 83% of the children on day six. This increase is consistent with a previous study in children with ALL.[11,39] The precise mechanism behind dexamethasone-induced fatigue has not been elucidated yet.[40] Although fatigue was the component that showed the largest increase after five days of dexamethasone, this was the only component at T1 that was not prognostic for frailty at T2. Nonetheless, fatigue is a striking problem for which there are no standardized effective interventions available yet, although previous studies indicated that exercise interventions may be promising. In a small controlled trial (n=22), a 6-week homebased aerobic exercise intervention during ALL maintenance therapy showed reductions in fatigue.[41] In a longitudinal observation of 68 children with various types of cancer increased physical activity levels were associated with less fatigue.[42] Another pilot study (n=17) showed that children with the highest step counts in the week before the corticosteroid course, reported less fatigue during the corticosteroid course.[43] However, it is unclear if these results indicates a causal relationship or co-association. Moreover, in adolescents without cancer, cognitive behavior therapy has been shown to be a successful intervention in reducing severe fatigue.[44] In children with cancer there has been only one non-controlled pilot study so far, which does show promising results.[45]

Somewhat surprisingly, patients did not reveal a decline in handgrip strength and movement speed. We even reported an increase in handgrip strength SDS. However, we suspect this improvement may have been based on a learning effect (repetition of the measurement within five days may have had a beneficial effect on performance). We are also hesitant about whether the instruction (squeezing as hard as possible) can be performed properly by three- and four-year-olds. We expected to observe a decline in both handgrip strength and walking speed, partly because of the co-administration of vincristine at T1. Vincristine is known to induce peripheral neuropathy with consequent strength loss in distal muscles and clumsiness[46], which we expected to negatively affect muscle strength, walking ability and physical activity.

Since dexamethasone courses are repeated 28 times (every 3 weeks for 1.5 years) during ALL maintenance therapy, it is conceivable that the repetitive impact of dexamethasone treatment may change over time. We observed that children who were further into maintenance therapy (rather than newly started), were less often frail.

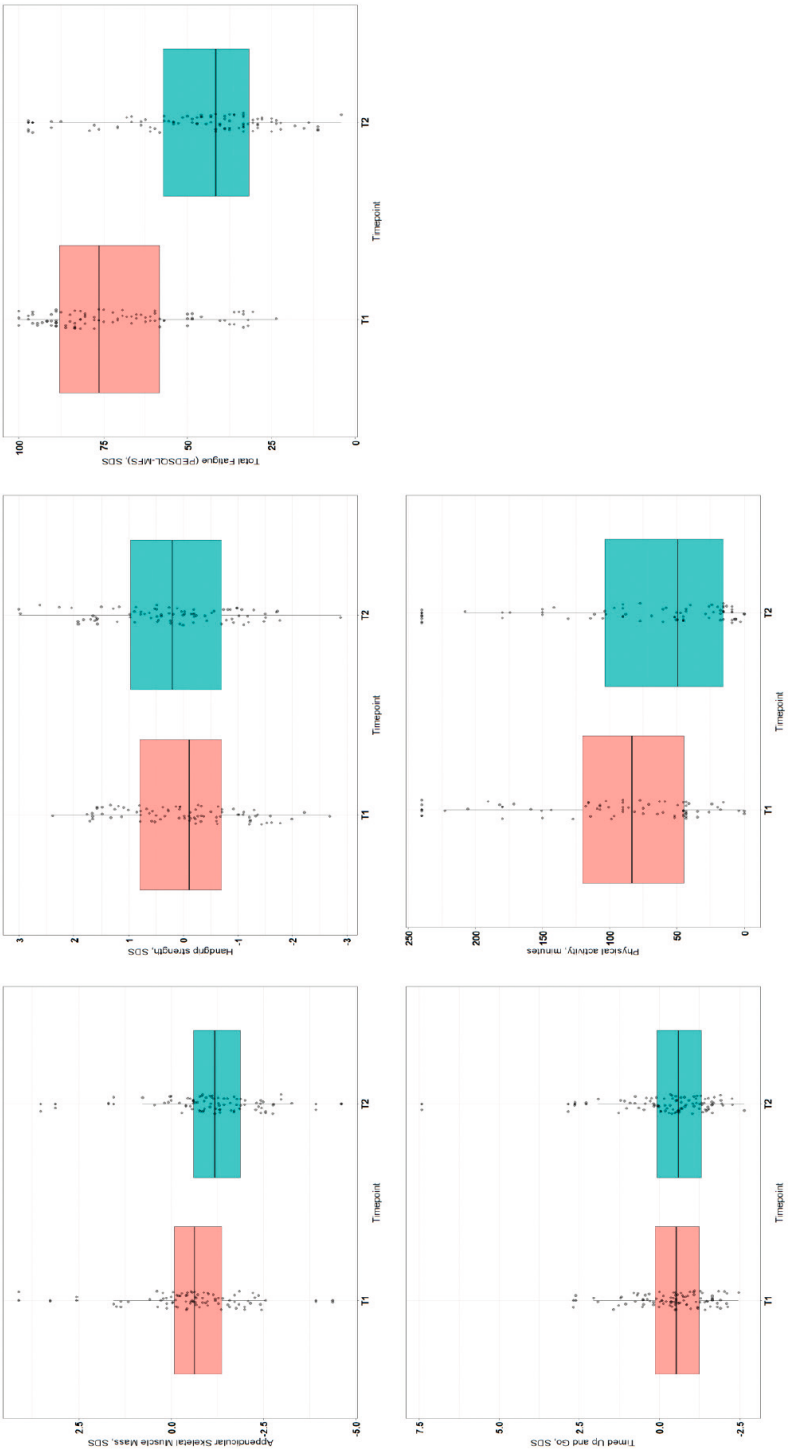

Figure 3. Boxplots visualizing the score differences between the first day (T1) and sixth day (T2) of dexamethasone administration

Patients early in maintenance phase, may not have entirely recovered from the intensive induction phase (high doses of chemotherapy, immobilization, infections) or there may be a nuisance effect of asparaginase administration. Asparaginase has also been implicated as a potential contributor to reduced muscle health[15], but the exact mechanism is currently unknown. Asparaginase has an inhibitory effect on protein synthesis in cancer cells, it is hypothesized that muscle protein synthesis in muscle cells may also be compromised.[15] As our study had only 11 children who still received asparaginase, we were not able to analyze this thoroughly.

This is the first prospective study to assess the acute effect of dexamethasone administration on the individual components of sarcopenia and physical frailty in a national cohort of children with ALL. We showed that a patient's muscle mass, muscle strength and physical performance, before the start of a dexamethasone course, is prognostic for developing frailty after the course. This finding may endorse the 'better in and better out principle', and gives us reason to explore specific interventions for dexamethasone resilience, to prepare our patients for dexamethasone courses. Current evidence for interventions to improve muscle mass and function in children with cancer is not very comprehensive. From a biological perspective it is hypothesized that exercise interventions potentially increase repair of -by chemotherapy-damaged mitochondria.[47] However, only a number of exercise trials have been performed and showed mixed success in effectiveness, but did show that exercise is safe and feasible even during intensive treatment.[48-50] For future research, we aim to determine the most beneficial training and right timing for the individual patient, i.e. whether structured aerobic exercise, resistance training or only a higher level of physical activity (increased step count) will yield positive results on muscle health. Moreover, further knowledge and deep understanding of frailty in pediatric cancer patients is needed to develop successful interventions.

This study has some limitations to be addressed. Firstly, we used bioimpedance analysis to assess ASMM, which is a safe, cost-efficient, and quick method. The downside is uncertainty about the reliability of bioimpedance analyses in children with high fat percentages[51], and also hydration status may affect the measurements, as it causes an increase in the body's electrical resistance.[52] Both overweight and disturbed fluid balance can occur in ALL patients, thus this may have influenced our results. However, current reliable imaging techniques such as computed tomography (unsuitable due to radiation exposure), magnetic resonance imaging and dual-energy x-ray absorptiometry are expensive, poor accessible and time consuming. Secondly, we had no availability of Dutch normative values for the used measurement instruments (besides PedsQL-

MFS). Therefore, we used pediatric reference values from cohorts with other origins, which may have influenced our results.

In conclusion, 5 days of dexamethasone increased physical frailty in children with ALL. A poorer physical state at start of a dexamethasone course (lower muscle mass, muscle strength and slower movement ability) was prognostic for developing frailty after a dexamethasone course.

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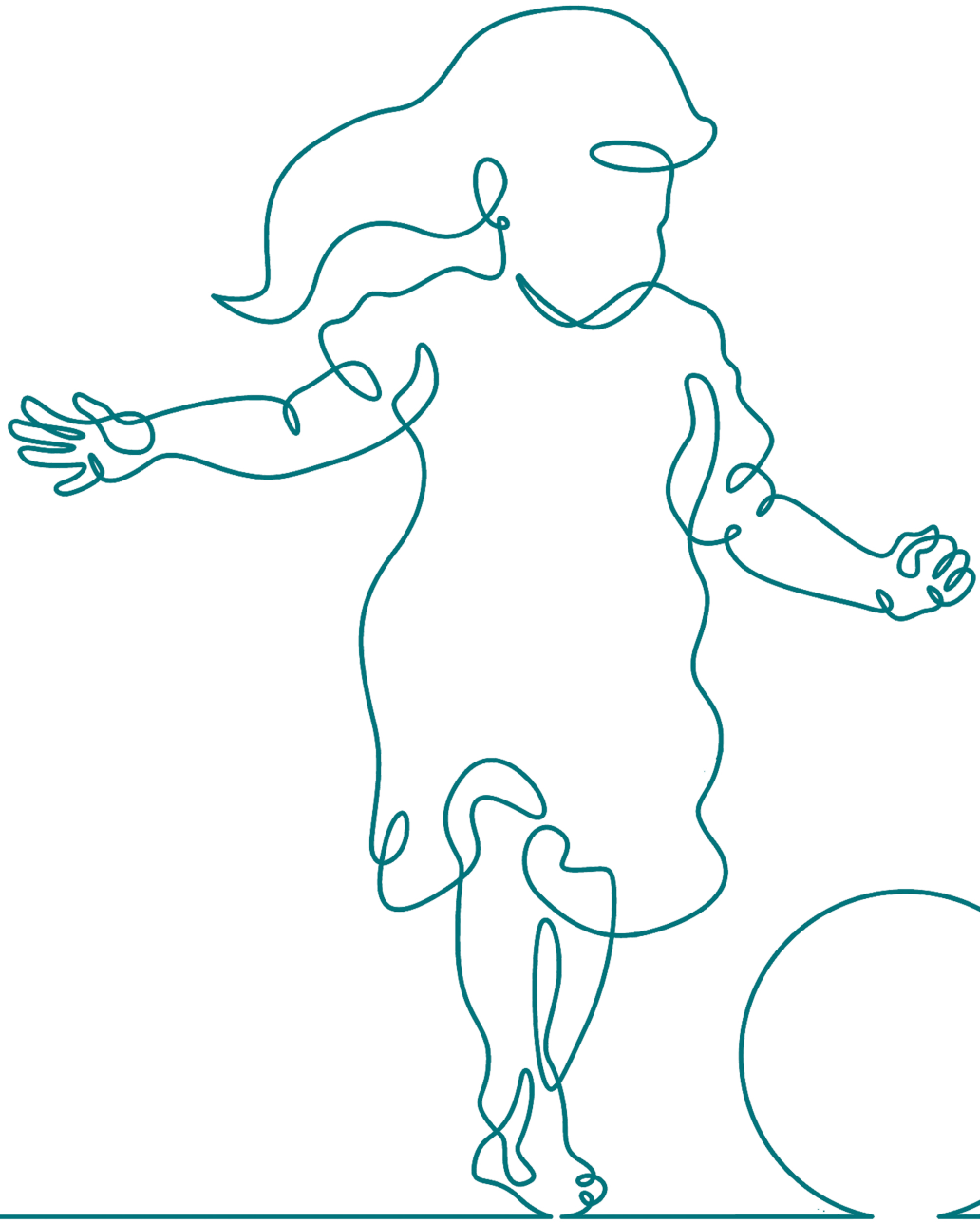
Supplemental Table 1. Appendicular skeletal muscle mass values in the DexaDays-2 cohort, and UK and Canadian reference values

	Dutch ALL cohort (Tanita bio-impedance analysis at T1)					UK reference values (Tanita bio-impedance analysis)				Predicted ASMM based on Canadian DXA reference equation	
Boys											
Age	**N**	**BMI, kg/m²**	**ASMM, kg**	**95% CI**	**ASMM, %**	**N**	**BMI, kg/m²**	**ASMM, kg**	**ASMM, %**	**ASMM, kg**	**95% CI**
3-4 years	22	17.1 (1.3)	3.5	2.4 – 6.3	20.1 (3.3)					4.3	2.5 - 6.8
5–7 years	15	16.4 (1.4)	5.2	3.2 – 8.4	23.7 (3.6)	329	15.4 (2.3)	6.3 (1.8)	27.2 (2.9)	7.6	4.1 – 11.6
8–10 years	7	18.8 (2.6)	10.2	6.2 – 13.6	28.5 (4.4)	296	17.5 (3.3)	10 (2.9)	29.6 (5.1)	11.3	6.1 – 17.5
11–13 years	5	17.3 (0.9)	11.6	10.2 - 14	29.8 (1.6)	204	19 (3.2)	14.8 (3.8)	32.6 (3.4)	15.4	7.7 – 23.1
14–16 years	6	23.2 (6.2)	21.9	17.1 – 30.6	31.8 (4.1)	149	20.4 (2.7)	21.7 (4.7)	35.3 (4.8)	26.2	10.1 – 38.4
17-18 years	3	24.5 (6.4)	27.4	22.2 – 30.5	32.9 (3.7)	138	22.4 (2.8)	24.8 (4.3)	34.9 (4.8)	31.6	11.8 – 43.4
Girls											
3-4 years	16	16.8 (1.8)	4	2.6 – 5.7	23.3 (2.7)					4.1	2.6 – 5.6
5–7 years	14	16.8 (2)	5.3	4.1 – 7.5	24.1 (2.2)	217	15.4 (2.3)	6.1 (1.4)	27.1 (2.4)	5.8	3.7 - 8
8–10 years	5	19.5 (1.4)	9.3	5.9 – 10.5	25.6 (3)	157	18 (3.6)	9.1 (2.5)	27.1 (4.2)	8.3	5.1 – 11.3
11–13 years	2	16.8 (0.4)	9.8	8.2 – 11.2	26.5 (2.5)	199	19.2 (3.1)	12.8 (3)	28.3 (4.3)	14.2	10.2 – 18.2
14–16 years	1	24.3	20.4		26.6 (0.8)	123	20.7 (2.4)	16.2 (2.6)	29.6 (3.8)	18.4	13.8 – 23.1
17-18 years	2	26.5 (0.06)	19.3	18.7 – 19.8	24.9 (1.1)	116	21.5 (2.7)	17.5 (3.4)	29.9 (5.3)	19.9	14 – 25.7

Values are depicted as mean (standard deviation) or median along with 95% confidence interval
ASMM = appendicular skeletal muscle mass, CI = confidence interval



Frailty in long-term Dutch adult survivors of childhood Acute Myeloid Leukaemia, Neuroblastoma and Wilms Tumour

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Abstract

Background
Several simultaneous impairments in physical ability may be an indication of frailty in adult survivors of childhood cancer (CCS). The aim of our study was to assess the occurrence of frailty and to explore potential determinants in a selected Dutch cohort of long-term adult CCS.

Methods
In this cross-sectional study, we used data of 70 very long-term CCS (median age 28.8 years [interquartile range: 23.9-34.6]) of acute myeloid leukemia (AML) (n = 17), neuroblastoma (NBL) (n = 25) and Wilms tumour (WT) (n = 28). Prefrailty and frailty were defined as having, respectively, 2 and ≥3 of the five following components: low relative lean body mass (by dual energy X-ray absorptiometry < -1.5 standard deviation, SD), self-reported exhaustion (fatigue, exhaustion or exertion related complaints), low energy expenditure (men <383 kcal/wk and women <270 kcal/wk), slow walking speed (<-2.0 SD on the six-minute walk test) and weakness (hand grip strength <-2.0 SD). Potential determinants of prefrailty and frailty (≥2 components) including, treatment components, sociodemographic and lifestyle factors, were evaluated using logistic regression analysis.

Results
Respectively, 6.3% and 28.1% women, and 5.3% and 26.3% men were classified as frail and prefrail. Six percent of the AML, 8% of the NBL and 3.6% of the WT CCS were frail. Forty-one per cent of the AML, 28% of the NBL and 17.9% of the WT CCS were prefrail. No significant associations were found between any of the investigated determinants and frailty or prefrailty.

Conclusion
Our results confirm previous reports that CCS, in particular intensively treated, have a potential risk of (pre)frailty.

Introduction

The 5-year survival rate of childhood cancer has currently reached about 80%.[1] As the number of adults who survived childhood cancer is increasing, more attention is being paid to the various long-term health-related side-effects. Fatigue, musculoskeletal impairments, such as osteopenia and sarcopenia (low muscle mass or strength), and limited endurance capacity are experienced more frequently in adults who have survived childhood cancer and may lead to reduced participation in physical activities and activities of daily living even at a relatively young age.[2-6] Simultaneous occurrence of several of these impairments may be an indication of frailty[2], a clinical state of reduced physiological reserve associated with a subsequent increased susceptibility to chronic diseases, disabilities and early death. Frailty has been mainly described in the elderly.[2,7-9] In childhood cancer survivors (CCS) the risk of early frailty is a concern because it increases their already enhanced risk of chronic impaired health conditions and early mortality.[5,10-12]

Fried et al[8] described frailty as a highly prevalent undesired clinical state in elderly adults. They defined frail people as those showing at least three of the five following indicators: unintentional weight loss in the previous year, muscle weakness, fatigue or poor endurance capacity, slow walking speed and low activity level. Three previous studies examined the prevalence of frailty in survivors of childhood, adolescent and young adult cancer (AYA).[2,12,13] Ness et al[2] used a modified frailty definition, i.e. the presence of three or more of the following indicators; low muscle mass, muscle weakness, slow walking speed, low energy expenditure and exhaustion. They reported an overall frailty prevalence of 7.9% in a United States (US) single-center cohort of 1922 CCS of all types childhood cancer with a mean age of 33.6 years (standard deviation [SD], 8.1), which was comparable to the frequency in adults at the age of 65 years and older.[9] Recently, Hayek et al[12] enumerated these findings in a large multi-institutional cohort of 10 899 CCS with a mean age of 37.6 years (SD 9.4), using modified frailty criteria. Physical measures of lean body mass, walking speed and grip strength were replaced with information derived from questionnaires regarding, unexpected weight loss, walking limitations and weakness. They reported a frailty prevalence of 6.4% among survivors and 2.2% among siblings. Smitherman et al[13] studied frailty in a group of 184 AYA cancer survivors, aged 15-29 years at diagnosis and 30-39 years at time of the study, at least one year following treatment. However, they only assessed frailty by using the FRAIL Questionnaire[14], including self-reported fatigue, weight loss, physical morbidities, difficulty with ambulation, and difficulty walking up the stairs. In the latter study the prevalence of frailty was even higher (10%).[13]

The aforementioned studies on frailty in CCS, were performed in the USA and some by questionnaires. So far, no studies in Europe have been carried out. Therefore, in this study we explored the frequency and the risk factors of frailty in a Dutch single centre cohort, including a subset of CCS who had been intensively treated in the past.

Methods

Study population

In the current study, we used data of a subset of a single center cohort of Dutch CCS that was previously recruited for a study on metabolic syndrome[15,16] and health-related physical fitness.[17] Briefly, long-term CCS (≥5 years since therapy cessation) of acute myeloid leukaemia (AML), neuroblastoma (NBL) or Wilms' tumour (WT), who were eighteen years or older were recruited.

Information regarding medical history and treatment was retrieved from the medical records. As previously reported, these participants had an assessment of physical performance components[17], body composition[15,16], and provided additional information through a semi-structured interview about current physical limitations, lifestyle habits, education and work.[17]

The Medical Ethical Committee of the Erasmus Medical Center, Rotterdam approved of the study and written informed consent was obtained from all participants (MEC2009-030).[17]

Outcome measures

The primary aim of the current study was to determine the occurrence of prefrailty and frailty. We used the same components as previous clinical studies[2,8], but the definition of the components had to be slightly amended, for usage in this particular cohort (Supporting information Table 1). In accordance with the aforementioned studies, participants were classified as prefrail if they had 2, and frail if they had ≥3 of the following five components.[2,8,13]

Low relative lean body mass

Total lean body mass (LBM) in kilograms (kg) was retrieved from dual energy X-ray absorptiometry ([DXA], GE Lunar Prodigy, Madison, WI, USA). Relative LBM (kg/m^2) was determined by dividing total LBM, by height in metres squared and was compared with Danish age and sex specific reference values[18], as normative values for relative LBM in Dutch adults are currently lacking in literature. Low relative LBM was defined as less than -1.5 SD. We selected Danish reference values after comparing the mean absolute LBM values of

adults aged 20-29 years of a Danish[18], as well as Canadian[19] and Australian[20] cohort to the LBM of Dutch 18-year-olds[21,22] (Supporting information Table 2).

Self-reported exhaustion

Survivors who reported fatigue, exhaustion, or exertion related complaints (dyspnoea, pain on the chest, and reduced endurance) in reply to the open question in the semi-structured interview of whether they experienced limitations in daily life, were classified as positive for self-reported exhaustion.

Low energy expenditure

Exercise activities were identified during the semi-structured interview and type, frequency, and duration per week were reported, and converted to kilocalories (kcal) per week using the metabolic equivalent of the specific sport type.[23] Similar to previous studies[2,8], men with less than 383 kcal/week and women with less than 270 kcal/week were classified as survivors with low energy expenditure.[8]

Slow walking speed

Walking speed was assessed using the 6-min walk test (6-MWT).[17] The distance covered in 6 min was measured in metres and compared to population normative values of healthy adults 20–50 years of age.[24] Previous studies used sex and height specific cut-off points for a 15 feet pace[2,8], but we used age specific reference values for the 6-MWT.[24] CCS with a Z-score of -2.0 or lower were classified as being slow.

Weakness

Grip strength (Newton) was measured in sitting position with the elbow flexed at 90^{0} using a Citec 3001 hand held dynamometer (HHD) (CIT Technics: Groningen, The Netherlands).[25] A mean value of three repeats of the dominant hand below or equal to –2.0 SD compared with age and sex specific Australian reference values[26] was considered as muscle weakness.

Determinants

Sex, age at diagnosis, age at study time, time since diagnosis, BMI, current smoking (yes/no), alcohol consumption (do you drink alcohol and if so, how many units per week), performing physically heavy work (yes/no) and self-reported highest level of education were included as potential determinants of the occurrence of frailty.[2,8] Highest level of education was classified into two categories (low/moderate: elementary school, secondary school, and moderate professional education; and high: higher professional education and university). Also, treatment components were taken into account. Chemotherapeutics which might potentially influence the occurrence of neuropathy, bone and

muscle wasting, and cardiomyopathy were included (vincristine, prednisone and doxorubicin). In addition, the role of administered radiotherapy (including cranial [CRT], chest, total body [TBI] and abdominal irradiation) and relevant surgery were included (yes/no). Lastly, myeloablative chemotherapy followed by stem cell transplantation (SCT) (autologous/allogenic/none), was explored as a contributing variable.

Statistical analysis

Descriptive statistics were used to characterize the study population. Chi-squared tests (χ^2) or Fisher's exact tests (if the number of participants in a cell of the contingency table was ≤5) were used to compare percentages of prefrailty, frailty and the frailty components stratified by sex and cancer type. Univariable logistic regression analyses were applied to examine the associations between relevant determinants and the combined outcome of prefrailty and frailty (≥2 components). Associations between potential determinants and frailty were presented as odds ratios (ORs) and 95% confidence intervals (CIs). OR was not calculated when the number of participants in a cell of the contingency table was <5. The determinants which appeared to be important for frailty in a certain cancer type subgroup, were explored using χ^2 or Fisher's exact tests. Analyses were performed by using software package R Statistics™ Version 1.0.143 for Windows.

Results

Participants

In the current study 70 CCS of AML (n = 17), NBL (n = 25) and WT (n = 28) were included. Their median age at time of the study was 28.8 years (interquartile range (IQR), 23.5 – 34.5 years), median age at diagnosis was 2.6 (IQR, 0.7 – 6.3) and median time since diagnosis was 24.4 years (IQR, 20.2 - 31.1). All survivors of NBL and WT underwent relevant surgery (n = 53), 59 CCS had received chemotherapy (AML [n = 16], NBL [n = 19], WT [n = 24]), 26 had received radiotherapy (AML [n = 7], NBL [n = 5] , WT [n = 14]), and 5 AML CCS underwent myeloablative chemotherapy and stem cell transplantation (SCT) (three autologous, two allogenic). Extensive characteristics of the participants are shown in Table 1.

Table 1. Characteristics of study participants (n = 70)

Characteristic	**Median**	**IQR**
Age at study time, years	28.8	23.5 - 34.5
Age at diagnosis, years	2.6	0.7 - 6.3
Time since diagnosis, years	24.4	20.2 - 31.1
	Mean	**SDS**
Height, SDS	-0.49	1.2
	No. of patients	**%**
Sex		
Female	32	45.7
Male	38	54.3
Body mass index, kg/m^2		
< 18.5	1	1.4
18.5 – 24.9	39	55.7
25 – 29.9	22	31.5
≥ 30	8	11.4
Childhood cancer diagnosis		
Acute myeloid leukaemia	17	24.3
Neuroblastoma	25	35.7
Wilms tumour	28	40
Radiotherapy		
Any±	26	37.1
Abdominal/Pelvic	17	21.4
Chest	4	5.7
Cranial	3	4.3
Total body	4	5.7
Chemotherapy		
Any	59	84.3
Doxorubicine	21	30
Predniso(lo)ne	8	11.4
Vincristine	47	67.1
Surgery		
No	17	24.3
Yes	53	75.7
Stem cell transplantation		
Autologous	3	4.3
Allogenic	2	2.9
None	65	92.9
Level of education		
Low	41	58.6
High	29	41.4

Table 1. *Continued.*

	No. of patients	%
Smoking status		
Never smoked	47	64.3
Former smoker	6	8.6
Current smoker	16	25.7
Not reported	1	1.4
Alcohol use		
No	18	25.7
Yes	52	74.3
Heavy physical work		
No	44	62.9
Yes	21	30
Not reported	5	7.1

IQR = interquartile range; SDS = standard deviation score± 2 survivors had both abdominal and chest irradiation

Frailty

Four (5.7%) survivors met the criteria (≥3 components) of frailty, and 19 (27.1%) survivors were classified as being prefrail (two components). The occurrence was similar among women and men, for frailty (6.3% vs 5.3%, P = 0.99), and prefrailty (28.1% and 26.3%, P = 0.99). Six per cent of AML, 8% of NBL and 3.6% of WT survivors met the frailty criteria (P = 0.66). Forty-one per cent of AML, 28% of NBL and 17.9% of WT were classified as prefrail (P = 0.09) (Figure 1).

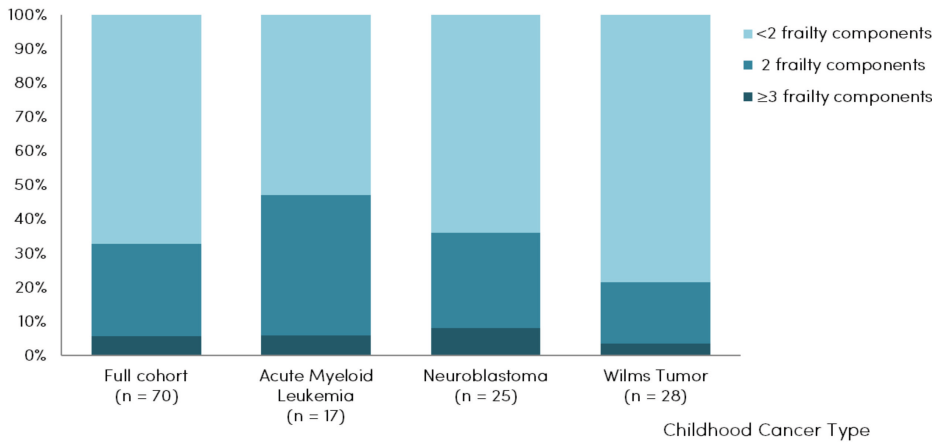

Figure 1. Percentage of frailty (≥3 components) and prefrailty (2 components) by childhood cancer type

Low relative LBM was present in 11.4% of the included CCS (women: 15.6%, men: 7.9%, P = 0.46). Six percent of AML, 16% of NBL and 10.7% of WT survivors had low relative LBM (P = 0.77). Exhaustion was reported by 10% of survivors (12.5% women, 7.9% men), and in 17.6%, 4% and 10.7% of survivors of AML, NBL and WT, respectively (P = 0.65). Low energy expenditure, which was the most common frailty component, was found in 52.9% of survivors (women: 56.3%, men: 50%) (AML: 58.8%, NBL: 60%, WT: 42.9%). Slow walking speed was a relatively uncommon component with an occurrence of 7.1% (women: 3.1% and men: 10.5%). It occurred in 17.6% of AML, 4% of NBL and 3.6% of WT survivors (p = 0.12). Handgrip strength was weak in 27.1% of the included CCS (women: 31.3%, men: 34.2%) (AML: 23.5%, NBL: 44% and WT: 28.6%) (Figure 2).

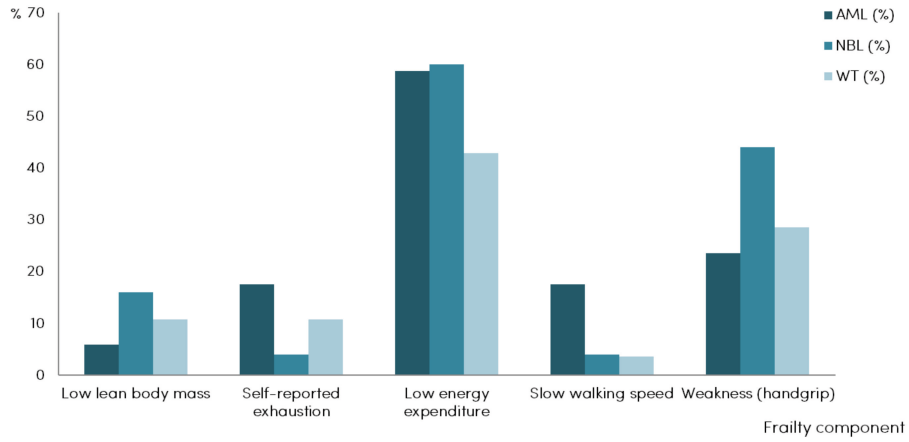

Figure 2. The occurrence of frailty components by childhood cancer type

Determinants associated with frailty

No determinants were found that showed significant associations with ≥2 components of frailty (Table 2). However, higher OR suggested potential higher odds of ≥2 frailty components for survivors who were treated with radiotherapy (OR 1.9, 95% CI 0.7-5.3) and those who were smokers at time of recruitment (OR 1.9, 95% CI 0.6-5.9).

Explorative analyses in a sub-cohort of only AML survivors showed that those classified with ≥2 frailty components had more often been treated with radiotherapy (TBI/CRT [n = 6] versus not radiated [n = 2]) (Figure 3). Also, four out of the five who had a stem cell transplantation (two allogenic, two autologous) were classified with ≥2 components of frailty.

Table 2. Determinants associated ≥2 components in survivors of childhood cancer

	Prefrailty + Frailty (n = 23)		Not Frail (n = 47)			
	No.	**Row (%)***	**No.**	**Row (%)****	**OR**	**95% CI**
Childhood cancer diagnosis						
Wilms' tumour	6	21.4	22	78.6		
Neuroblastoma	9	36	16	64		
Acute myeloid leukaemia	8	47.1	9	52.9		
Factor						
Sex						
Female	11	34.4	21	65.6	1.0	
Male	12	31.6	26	68.4	1.1	0.4 to 3.1
Age at study time, years						
18-29	12	31.6	26	68.4	1.0	
30-39	6	33.3	12	66.7	1.1	0.3 to 3.5
40-62	5	35.7	9	64.3	1.2	0.3 to 4.3
Age at diagnosis, years						
0-3	12	31.6	26	68.4	1.0	
4-9	5	29.4	12	70.6	0.9	0.2 to 3.1
10-18	5	41.7	7	58.3	1.5	0.4 to 5.9
Time since diagnosis, years						
6.5-19	7	43.8	9	56.3	1.0	
20-29	7	31.8	15	68.2	0.6	0.2 to 2.3
30-43.6	8	27.6	21	72.4	0.5	0.1 to 1.8
Radiotherapy‡						
No	12	27.9	31	72.1	1.0	
Yes	11	42.3	15	57.7	1.9	0.7 to 5.3
Abdominal/Pelvic radiation						
No	19	35.8	34	64.2		
Yes	4	23.5	13	76.5		
Cranial/Total body radiation						
No	17	27	46	73		
Yes	6	85.7	1	14.3		
Surgery						
No	8	47.1	9	52.9	1.0	
Yes	15	28.3	38	71.7	0.4	0.1 to 1.4
Chemotherapy, any						
No	2	18.2	9	81.8		
Yes	21	35.6	38	64.4		
Chemotherapy, Vincristine						
No	7	30.4	16	69.6	1.0	
Yes	16	34.0	31	66.0	1.2	0.4 to 3.6

Table 2. *Continued.*

	Prefrailty + Frailty (n = 23)		Not Frail (n = 47)			
	No.	**Row (%)***	**No.**	**Row (%)****	**OR**	**95% CI**
Chemotherapy, Prednisone						
No	20	32.3	42	67.7		
Yes	3	37.5	5	62.5		
Chemotherapy, Doxorubicin						
No	15	30.6	34	69.4	1.0	
Yes	8	38.1	13	61.9	1.4	0.5 to 4.1
Overweight/Obese (BMI ≥25)						
No	16	40	24	60	1.0	
Yes	7	23.3	23	76.7	0.5	0.2 to 1.3
Smoking						
No	15	29.4	36	70.6	1.0	
Yes±	8	44.4	10	55.6	1.9	0.6 to 5.9
Alcohol use						
No	5	27.8	13	72.2	1.0	
Yes	18	34.6	34	65.4	1.4	0.4 to 4.8
Heavy physical work						
No	13	9.5	31	70.5	1.0	
Yes	6	28.6	15	71.4	0.9	0.3 to 2.9
Level of education						
Low	12	29.3	29	70.7	1.0	
High	11	37.9	18	62.1	1.5	0.5 to 4.1

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; BMI, Body Mass Index
* Percentage of persons in each category with ≥2 components of frailty
** Percentage of persons in each category with ≤1 components of frailty
‡ Includes abdominal, chest, total body and cranial radiation
± 2 survivors stopped smoking <6 months ago and were classified as smokers

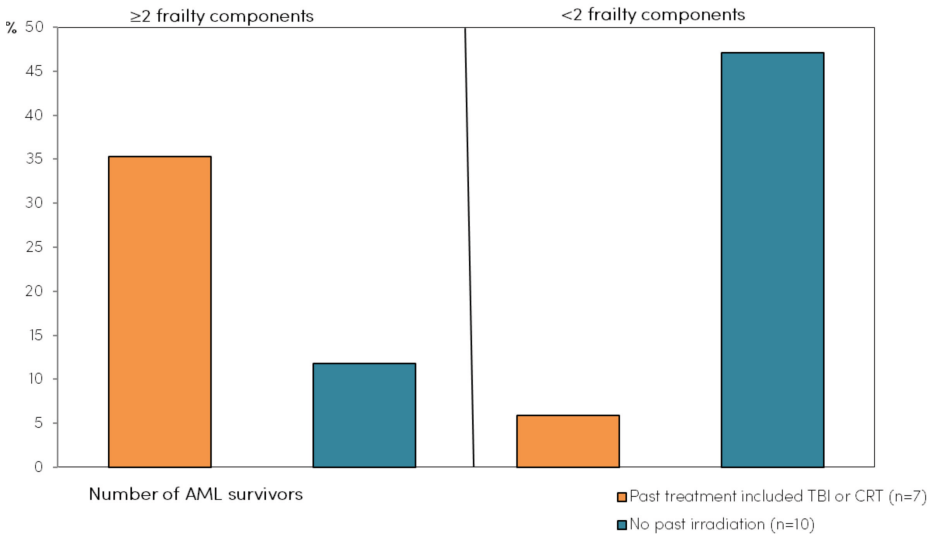

Figure 3. The occurrence of ≥2 Frailty components and <2 components in AML survivors, with and without past treatment with Total Body Irradiation (TBI) or Cranial Radiation (CRT).

Discussion

Frailty in childhood cancer survivors is an undesired clinical state because it has shown to be associated with chronic conditions and adverse health outcomes[2,8,12,27]. In the current study, we examined the occurrence of prefrailty and frailty in a small Dutch single centre cohort consisting of exclusively of long-term adult survivors of childhood AML, NBL and WT. To our knowledge, this is the first study to evaluate frailty in Dutch CCS and to explore sociodemographic and cancer specific determinants possibly associated with frailty.

This study showed that frailty (≥3 components) occurred in almost 6% of long-term survivors of childhood AML, NBL and WT at a median age of only 29 years old. This was consistent with the prevalence of 6.4% in the large representative US CCS cohort (mean age: 37.6) reported by Hayek.[12] A slightly higher occurrence was reported by Ness et al (7.9%)[2] in relatively older CCS (mean age: 33.6) and by Smitherman et al[13] within AYA survivors (10%) (age range: 30-39). Prefrailty (two components) was found in 27% of our survivors vs, respectively 18%, 22% and 12%, in the aforementioned studies.[2,12,13] It is conceivable that because of our selected cohort of intensively treated CCS, more are classified as prefrail already. Also, Hayek et al[12] and Smitherman et al[13] determined frailty and prefrailty based on questionnaires.

In our cohort frailty and prefrailty occurred at an equal frequency among men (5% and 26%) and women (6% and 28%). In contrast to the previous clinical study in CSS, where the prevalence in men was markedly lower (3% and 13%) compared with women (13% and 32%).[2] This contrast is probably due to our low CCS number.

In our cohort, almost half of the AML survivors (47%) met the criteria of either frailty or prefrailty, which was higher compared with 30% in leukaemia survivors reported by Ness et al.[2] This is conceivably due the fact that they also included survivors of acute lymphoblastic leukaemia who received less intensive treatment than AML survivors. The frequency of frailty and prefrailty among WT was 21% in our cohort, which was comparable with the 25% reported by Ness et al. Lastly, we observed an occurrence of (pre)frailty of 36% within our NBL survivors, which was markedly higher than the 25% reported by Ness et al[2]. Adequate and reliable comparisons can however, not be made between these two cohorts, because of our small selected population and our mainly descriptive results.

Clear associations between sociodemographic, lifestyle or cancer and treatment related factors were not detected in this cohort of survivors of AML, NBL and WT. However, in a small subset analysis, we did show that survivors of AML who received TBI or CRT were more likely to be prefrail or frail. This is consistent with earlier studies[2,12], which reported that cranial radiation was associated with frailty components in both men and women. They also showed abdominal/pelvic radiation associated with frailty in men, but we did not find such an association in our cohort.

A limitation of this study was that this cohort was not primarily designed to measure frailty but to study metabolic syndrome[15,16] and health-related physical fitness.[17] We have attempted to align the frailty criteria to the methodology of previous clinical studies of Ness et al[2] and Fried et al.[8] Hence, some differences need to be taken into account when interpreting the results and comparing these to other studies. First, self-reported exhaustion was classified by answers to an open question about experienced limitations in daily life, and not with a standardized questionnaire for measuring fatigue. This may have led to either over, as well as underestimation, of the occurrence of this component. Second, low energy expenditure was calculated using the self-reported sports activities of the participant, as data on activities of daily life were not available. This could have led to an overestimation of low energy expenditure in these survivors. However, a major strength of this study is that all survivors had a physical performance assessment including DXA examination, measurement

of walking speed and grip strength and that these data were expressed in relation to normative values.

In clinical practice, health-care professionals should be aware of frailty in CCS. Especially for those who have had more intensive treatment or were radiated, further health examinations are recommended. Future prospective studies, such as the ongoing DCOG-LATER study, are necessary to determine the prevalence of frailty, to identify risk factors to target vulnerable CCS and to explore potential interventions to delay this process.

In conclusion, our results confirm previous reports that (pre)frailty is a potential risk for intensively treated and especially irradiated CCS.

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Addendum Table 1. Criteria used to define frailty components in previous studies and the current study

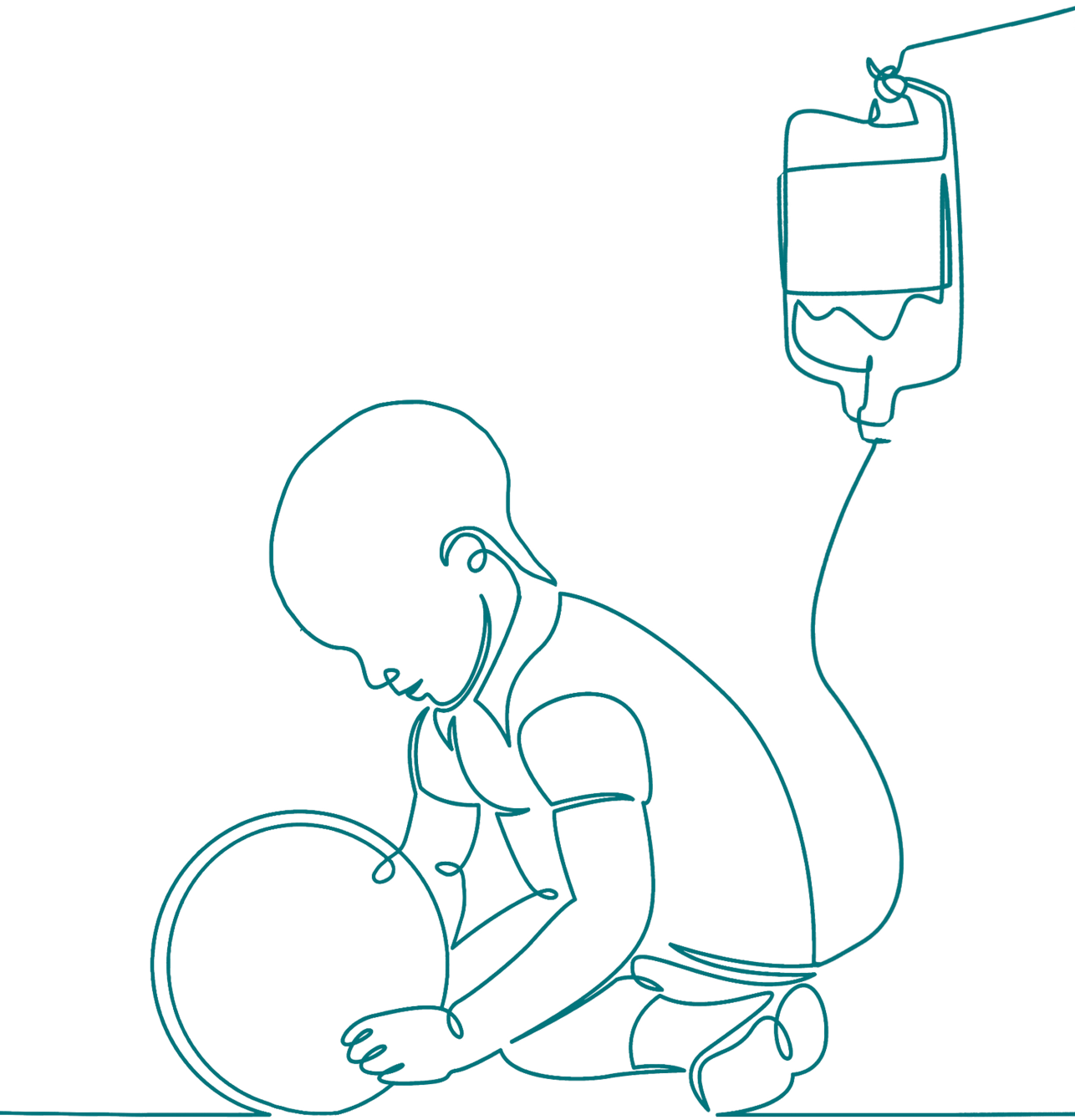
Frailty component	Fried et al[8] Cardiovascular Health Study	Ness et al[2] St Jude Lifetime Cohort	Current study
Weight loss / Low lean mass	Unintentional weight loss of ≥10 pounds in the previous year.	Lean muscle mass by DXA ≤ -1.5 age and sex-specific SDS (NHANES).[28]	Relative lean muscle mass by DXA ≤ -1.5 compared to age and sex-specific SDS.[18]
Self-reported exhaustion	Answered either a moderate amount of time or all of the time on either of the CES-D questions: I felt that everything I did was effort; and I could not get going.[29]	Score of ≤40 on the vitality subscale of the SF-36.[30]	Fatigue, exhaustion or exertion related complaints in answer to open question in a semi-structured interview of whether there were limitations in daily life.
Low energy expenditure	Expended <383 Kcal/week (men) or <270 Kcal/week (women) during leisure time physical activity (based on the short version of the Minnesota Leisure time Activity Questionnaire)	Expended <383 Kcal/week (men) or <270 Kcal/week (women) during leisure time physical activity based on the NHANES Physical Activity Questionnaire.[23]	Expended <383 Kcal/week (men) or <270 Kcal/week (women) during leisure time sport activities[23], based on sport type, frequency and duration per week derived from a semi-structured interview.
Slow walking speed	Women <159 tall and men <173 cm tall were classified as slow if they took ≥ 7 sec to walk 15 feet at their usual pace; and women ≥159 cm tall and men ≥173 cm tall were classified as slow if they took ≥ 6 sec to walk 15 feet at their usual pace, based on the lowest 20% of the Cardiovascular Health study.		Walking speed measured with the Six-Minute Walk test, was classified as slow when ≤ -2.0 compared to age and sex-specific SDS.[24]
Weakness	Hand grip strength measured with Jamar Dynamometer, lowest 20% stratified by body mass index and sex, based on the lowest 20% of the Cardiovascular Health study.		Hand grip strength measured with Citec Dynamometer, was classified weak when ≤ -2.0 compared to SDS.[26]

Abbreviations: DXA, Dual X-ray Absorptiometry; SDS, Standard deviation score; CES-D, Centers for Epidemiology Depression Scale; NHANES, National Health and Nutrition Examination Survey; SF-36, Medical Outcome Survey Short Form 36; MET, The Metabolic Equivalent of Task

Addendum Table 2. Comparison of the total lean body mass between different reference cohorts

	Age, years±	**Peak LBM, kg**	
Dutch young adults[21]			
Female (n = 360)	17.7 (0.54)	42.77 (4.45)	
Male (n = 141)	18.1 (0.88)	61.21 (6.51)	
	Age group, years	**Mean LBM, kg**	***P*‡**
Danish adults[18]	20-29		
Female (n = 98)		41.74 (5.32)	0.06*
Male (n = 59)		61.33 (7.26)	0.91
Australian adults[20]	20-29		
Female (n = 176)		41.22 (5.04)	<0.01
Male (n = 180)		59.54 (6.86)	0.03
United States adults[19]	20-29		
Female (n = 562)		43.0 (6.1)	0.54
Male (n = 384)		65.0 (11.0)	<0.01

Abbreviations: LBM, lean body mass; kg, kilograms
All values are means with standard deviations
± Mean age (standard deviation) at the attainment of peak total lean body mass
‡Compared to Dutch peak LBM values using two-sample independent t test
*Difference in height between the Danish and Dutch female adults (p=<0.01)



Determinants of impairments in functioning, fatigue and participation ability in pediatric brain tumor survivors

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ABSTRACT

Background
Pediatric brain tumor survivors (PBTS) experience disease- and treatment-related sequelae. We aimed to investigate the occurrence of participation limitations, impairments in functioning, fatigue, and the association between patient, tumor- and treatment-related factors and these outcomes.

Methods
Children (4-18 years) after treatment for a brain tumor between 2005 and 2014 at the Erasmus Medical Center, Rotterdam, the Netherlands, were eligible. The parent-reported Child and Family Follow-up Survey developed to measure participation and impairments in functioning in youth with acquired brain injury, was used. Fatigue was assessed using the Pediatric Quality of Life Inventory Multidimensional Fatigue Scale. Associations with patient, tumor- and treatment-related factors were explored using univariable analyses.

Results
Ninety-one PBTS (median age: 11.3 years [range: 9.5-14.1], time since treatment: 3.9 years [range: 4-6.2]) were included (response rate: 55%). Participation limitations were reported in 53% and were associated with impairments in functioning (15-67%) ($P \leq .01$) and fatigue ($P \leq .03$). Parent- and child-reported fatigue was increased compared to normative values ($P \leq .02$). History of hydrocephalus was associated with increased fatigue ($P \leq .04$). Younger age at diagnosis and longer time since diagnosis were associated with impairments in functioning and cognitive fatigue ($P < .05$). Participation limitations, impairments in functioning and fatigue were similar in PBTS who were <3 or ≥3 years since completion of treatment.

Conclusion
More than half of PBTS reported limited participation ability, which is associated with impairments in functioning and fatigue. The complication hydrocephalus seems to lead to more fatigue. Participation limitations, impairments in functioning and fatigue appear not to diminish in the longer term.

Background

Brain tumors are the most common pediatric solid tumors and represent the second most frequently diagnosed malignancies in childhood.[1] Currently, an overall 5-year survival rate of approximately 75% is reached.[2] Improvements in neuro-imaging, treatment modalities and risk stratification as well as supportive care, have resulted in a growing population of pediatric brain tumor survivors (PBTS). However, this improvement is accompanied with various disease and treatment related sequelae[3-6], which can have serious implications on participation in daily life activities and meaningful life situations in various settings.[7]

The effect of a pediatric brain tumor and its treatment on different aspects of functioning has been investigated, but either in small sample sizes, in cohorts of adult survivors or focusing predominantly on neuro-behavioral disorders.[7-13] Results therefore vary and are sometimes contradictory. For example, more neurocognitive problems have been reported in children with an infratentorial located tumor compared to those with a supratentorial tumor.[14] In contrast, a different study associated a supratentorial location with more severe disabilities in children treated for a low-grade astrocystoma.[15] This was supported by another study, in which a supratentorial tumor location, recurrent neurosurgery, shunt revisions, and chemotherapy were associated with major disabilities.[3]

Fatigue is another regularly reported short- and long-term side effect. An increase in fatigue was reported in PBTS one year after completion of treatment.[16] Further into survivorship, fatigue remains a problem with 13-15% of adolescent and adult PBTS having severe fatigue complaints.[17, 18]

The extent of daily life participation in PBTS in the subsequent years of childhood has not been investigated nor have influencing factors been systematically recognized. It also remains unclear, if the severity of participation limitations, impairments in functioning and fatigue, increase, decrease, or stabilize after therapy cessation. Early identification of PBTS who are at risk of participation limitations and fatigue may aid early and appropriate rehabilitation care.

Hence, the aims of this study were to investigate: the occurrence of self-reported participation limitations, impairments in functioning and fatigue in childhood PBTS in the short and long term. In addition, to identify potential patient, tumor- and treatment-related determinants for participation limitations, impairments in functioning and fatigue, and to investigate the associations between impairments in functioning and fatigue, and participation.

Methods

Study design and participants

In this cross-sectional study, all PBTS (aged 4-18 years) who were diagnosed between January 2005 and June 2014 at the Erasmus Medical Center Rotterdam (EMC) – Sophia Children's Hospital, Rotterdam, the Netherlands, were eligible and actively recruited. Medical treatment had to be completed prior to enrollment in the study, or children had to be under active surveillance with stable neurology, no tumor growth or recurrence, at time of the study. An overview of the study design is schematized in Figure 1.

Ethical approval of the study was obtained from The Medical Ethics Committee of the EMC Rotterdam (MEC-2014-197). Written informed consent according to the Helsinki agreement was obtained from all participating parents, and from children aged ≥12 years.[19] This study was conducted between June 2014 and March 2015.

Data collection and general information

Information regarding demographics and brain tumor-related characteristics were obtained from the medical records and the pediatric oncology database of the EMC. The following information was collected: sex, age at study time, age at diagnosis, type of brain tumor, presence of neurofibromatosis type 1 (NF-1) as underlying predisposing condition, date of last treatment, tumor grade (according to the World Health Organization, grade I/II = low-grade, grade III/IV = high-grade), tumor location (infratentorial or supratentorial), type of treatment (neurosurgery, radiotherapy, chemotherapy or active surveillance). Neurosurgical treatment was categorized as radical or partial resection of the tumor. Details on surgical procedures for treatment of hydrocephalus were collected, ie endoscopic third *ventriculostomy or ventriculoperitoneal shunt placement.* Time since end of treatment was defined as the time since the last day of chemo/radiotherapy administration, last surgical procedure or since the decision for a surveillance approach, until the day the questionnaires were filled out. We dichotomized time since end of treatment at <3 and ≥3 years, respectively short- and long-term.

Data were collected using questionnaires that were sent by regular mail. Paper forms were filled out by parents and children at home. If a child version of a questionnaire was not returned, only the parental version was included.

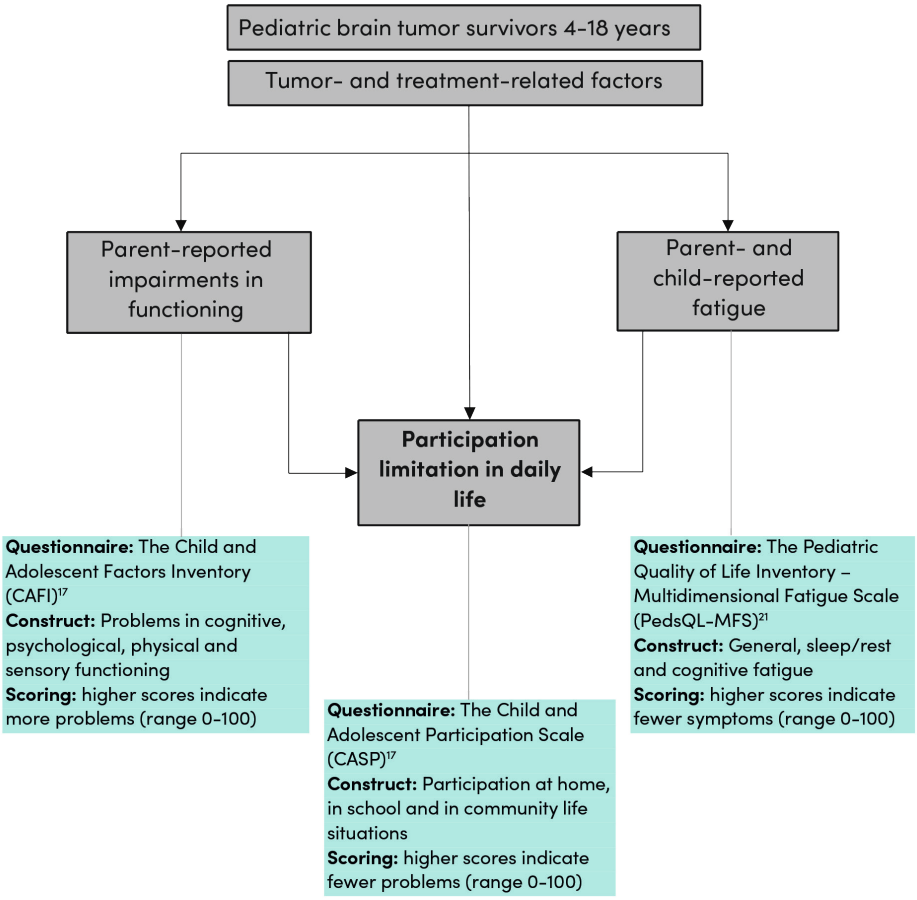

Figure 1. Overview of study design

Outcome Measures

Participation

The Dutch parental version of the Child and Adolescent Scale of Participation (CASP) was used to measure participation, which is part of the Child and Family Follow-up Survey (CFFS).[20] This questionnaire has been specifically developed to assess outcomes in children and adolescents (4-21 years) with acquired brain injury.[21] The CASP is a 20-item questionnaire and measures the extent of participation and limitations in home, in school and community life situations and activities, on a 4-point scale (unable, very limited, somewhat limited or age-expected). Scores for each item are summed and divided by the maximum possible score, the results multiplied by 100, give a final score between 0-100, with a higher score indicating a better participation level (Figure 1). The Dutch version of the CFFS (including CASP) has been validated in youth with acquired brain injury, and was found to have good to excellent internal consistency.[20] In accordance with previous studies, we defined that a CASP score of ≥97.5 indicates 'age-expected participation', subsequently a CASP score below 97.5 refers to "limited participation", and a score ≤81 indicates "very limited participation" (Supplementary Table 1).[22, 23]

Impairments in functioning

The Child and Adolescent Factors Inventory (CAFI), which is also part of the CFFS, was used to assess parent-reported impairments in functioning.[20] The CAFI consists of 17 items and focuses briefly on health-related impairments in cognitive, psychological, physical, and sensory functions. Each impairment is rated on a 3-point scale, (major, minor or no problem) summed up to a total score. A lower score indicates a better level of functioning (0-100) (Figure 1). One previous study divided CAFI scores based on the median CAFI score in their cohort of children with acquired brain injury (≤40 indicated a low score).[23] No studies using a cutoff point for CAFI are available.

Fatigue

The Dutch version of the Pediatric Quality of Life Inventory (PedsQL) – Multidimensional Fatigue Scale (MFS) was used to assess fatigue-related problems.[24, 25] This questionnaire consists of three scales: general fatigue, sleep/rest fatigue and cognitive fatigue (Figure 1). Higher scores indicate less fatigue. We used the parental versions for children aged 2-4, 5-7, 8-12, 13-18 years, and self-report versions for children aged 8-12 and 13-18 years, of which Dutch norm-references are available.[24] Previous studies showed that the internal consistency of the Dutch version of the PedsQL–MFS was satisfactory, test-retest reliability was good and the inter-observer reliability varied from moderate to excellent.[24]

Statistics
The frequency of participation limitations (CASP) and major/minor impairments in functioning (CAFI) were calculated in percentages.

Fatigue levels (PedsQL–MFS scores) were compared to normative values[24] using Two-sample t-tests. In small groups (n ≤ 25), the Mann-Whitney U test was performed. Possible confounding by age and sex distributions between the normative values and our cohort was assessed.

To quantify the difference in PedsQL-MFS between our cohort and the normative values we used Cohen's d effect sizes, calculated by dividing the difference in mean scores of our cohort and the normative cohort by the standard deviation of the normative cohort. Effect sizes between 0.2 and 0.5 were considered small, effect sizes between 0.5 and 0.8 moderate, and effect sizes ≥0.8 large.[26]

The CASP, CAFI and PedsQL-MFS scale scores were compared in PBTS who were <3 and ≥3 years since end of therapy, using Mann-Whitney U tests or two-sample t-tests, based on the (non-)normally distribution of the data.

To identify potential patient, tumor- and treatment-related determinants, chi-squared or Fishers exact tests were used to assess associations between the following independent variables: sex, tumor grade, tumor location, cranial radiotherapy, chemotherapy, active surveillance, partial or radical resection, procedure for hydrocephalus treatment, NF-1, and the dependent variables: "limited participation" and "very limited participation" (CASP). Two-sample t-tests were used to explore these associations with age at study time, age at diagnosis and time since diagnosis.

Furthermore, to explore associations between the aforementioned independent variables and impairments in functioning (CAFI) and fatigue (Parent- and self-reported PedsQL-MFS scores), we used the Mann-Whitney U tests and Two-sample t-tests, respectively.

To investigate whether impairments in functioning and fatigue were associated with participation, we tested whether the occurrence of impairments (CAFI) and fatigue (PedsQL-MFS), in children with limited participation differed from those with age-expected participation, using Fishers exact tests and two-sample t-tests respectively. In addition, we compared the PedsQL-MFS scores of children with limited and age-expected participation to the Dutch normative values, separately as well.

Level of significance for all analyses was set at P-value below .05. All analyses were performed using software package R Statistics™ Version 1.1.456 for Windows.

Results

Cohort

One hundred and fifty-one children who were diagnosed with a brain tumor between January 2005 and June 2014 at the EMC were eligible to participate in this study. After exclusion of children who were lost to follow-up or nonresponders, ninety-one PBTS participated (55%). (Figure 2: Flow diagram).

The included survivors had a median age of 11.3 years (interquartile range [IQR]: 9.5-14.1) at study time, and a median of 3.9 years (IQR: 2-6.2) since end of treatment or decision for active surveillance (8.8%). Forty-nine (53.8%) were boys, the majority had a low-grade tumor (80.2%) and astrocytoma was the most frequent type of tumor (37.4%). Complete characteristics are described in Table 1.

Responders (n = 91) did not differ significantly from the nonresponders (n = 74) with regard to sex, age at study inclusion, age at diagnosis, time since diagnosis, tumor grade, and location (P ≥ .05).

Table 1. Characteristics of pediatric brain tumor survivors (PBTS) (n = 91)

	Median	**Interquartile range**
Age at study time, years	11.3	9.5 – 14.1
Age at diagnosis, years	5.9	3.8 – 9.2
Time since diagnosis, years	4.4	2.4 – 6.7
Time since end of treatment [i], years	3.9	2.0 - 6.2
	No.	**%**
Sex		
Boy	49	53.8
Girl	42	46.2

Table 1. *Continued.*

	No.	%
Type of brain tumor		
Astrocytoma	34	37.4
Ependymoma and choroid plexus tumors	10	11
Medulloblastoma	9	10
Tractus opticus/chiasma	8	8.8
Other gliomas	7	7.7
Craniopharyngioma	6	6.6
Other tumors	11	12.1
Unidentified	6	6.6
Tumor grade [II]		
High-grade	18	19.8
Low-grade	73	80.2
Tumor location		
Infratentorial	46	50.5
Supratentorial	45	49.5
Treatment modalities		
Neurosurgery		
Radical or partial resection	65	71.4
Procedure for treatment of hydrocephalus [III]	13	14.3
Chemotherapy	28	31.9
Cranial radiotherapy	37	33
Active surveillance	8	8.8
Combination of radio/chemotherapy and neurosurgery	37	40.6
Neurofibromatosis type 1		
Yes	13	14.3
No	78	85.7
Type of education		
Regular education	61	67
Special education	28	30.8
Not attending school	2	2.2

[I]End of treatment was defined as last the day of chemo/radiotherapy administration, time since surgical procedure or time since decision for active surveillance
[II]grade I/II equals low-grade, grade III/IV equals high-grade
[III]endoscopic third ventriculostomy or ventriculoperitoneal shunt placement

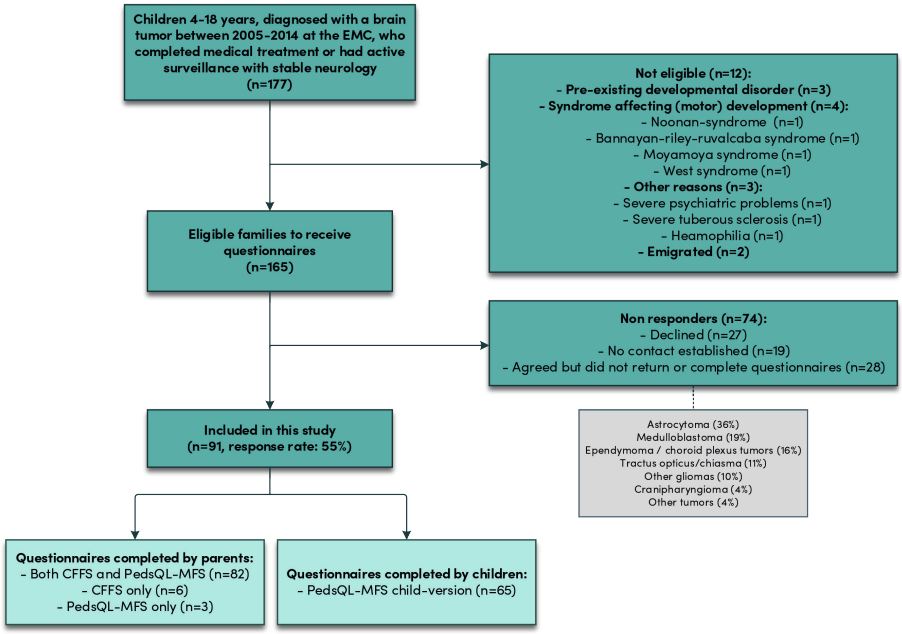

Figure 2. Flow diagram of participant inclusion and response.
Abbreviations: CFFS: Child and Family Follow-up Survey; PedsQL-MFS: Pediatric Quality of Life Inventory – Multidimensional Fatigue Scale

Participation (CASP)

The median total score reported on the CASP was 95.3 (IQR: 82.5-100), with median scores of 95.8 (IQR: 87.5-100) for participation at home, 93.6 (IQR: 79.7-100) for participation in the community, 100 (IQR: 90-100) at school and, 95 (IQR: 80-100) for home and community living activities (Table 2).

Participation was limited (CASP <97.5) in 47/88 (53.4%) children; 51.1% was experiencing limitations in participation at home and in the community, 46.7% at school and 52.8% in home and community living activities (ie, household activities, managing a daily schedule) (Results on item level are shown in Supplementary Figure 1). Very limited participation (CASP ≤ 81) was reported in 19/88 (21.6%) of the cohort. The remaining 41 children (46.6%) had age-expected participation.

In children with limited participation the frequency of special education needs was higher compared to children with age-expected participation (46.8% versus 13.5%, P <.01).

The extent of participation was no different in children who were <3 or ≥3 years since their last treatment (P ≥ .19) (Table 2).

Impairments in cognitive, psychological, physical, and sensory functioning (CAFI)

The median total score reported on the CAFI was 47.1 (IQR: 39-57). Frequencies of the self-reported impairments in cognitive, psychological, physical and sensory functioning are shown in detail in Supplementary Figure 2. Of the 17 items measured by the CAFI the following three were a minor or major problem in >50% of the children: attention/concentration (67%), movement (balance, coordination, muscle tone) (57%) and strength/energy level (51%). CAFI scores were no different in children who were <3 or ≥3 years after cessation of treatment (P = .16) (Table 2).

General, sleep/rest and cognitive fatigue (PedsQL-MFS)

General and cognitive fatigue in the total cohort were increased in both the parent- and child-reports compared to normative values of Dutch children (P ≤ .02), sleep/rest fatigue was also increased but only in parent-reports (P = .01).

Differences in subscales between the three age-specific versions (respectively 5-7 years; 8-12 years; 13-18 years) were observed. In 5-7 year old children, parents reported only more general fatigue (P = .03), but in 8-12 year old children, parents reported increased fatigue on all three subscales (general, sleep/rest and cognitive) compared to normative values (P ≤ .02). Self-reported child scores in this age group also indicated more general and cognitive fatigue (P ≤ .01). In 13-18 year old children, parents reported more cognitive fatigue (P ≤ .02). However, there were no significant differences on the self-reported scales of children in this age group (n = 31), a moderate effect size of -0.52 was found for cognitive fatigue (P = .09). Complete results on the PedsQL-MFS scales and comparison to normative values are presented in Table 3, with the exception of the age group 2-4 years, as there was only one child aged <5 years old.

PedsQL-MFS scores were no different in children who were <3 or ≥3 years after last treatment (P = .45) (Table 2).

Table 2. CASP, CAFI, CASE and PedsQL-MFS scores in total PBTS cohort and in subgroups (<3 or ≥3 years follow-up)

	Total cohort			<3 years since last treatment[I]			≥3 years since last treatment[I]			
	N	**Mean**	**Median (IQR)**	**N**	**Mean**	**Median (IQR)**	**N**	**Mean**	**Median (IQR)**	**p II**
CASP total score (range 0-100)[III]	85	90.4	95.3 (82.5-100)	31	91.2	95.3 (83-100)	46	89.4	93.9 (81-100)	.62
Home participation	88	91.7	95.8 (87.5-100)	32	93.7	97.9 (87.5-100)	48	90	95.4 (83.3-100)	.25
Community participation	88	88.1	93.6 (79.7-100)	32	88.5	96.9 (79.7-100)	48	87.1	93.8 (75-100)	.63
School participation	87	93.6	100 (90-100)	32	94.9	100 (93.8-100)	47	92.3	95 (85-100)	.19
Home and community living activities	86	87.3	95 (80-100)	31	88.4	95 (80-100)	47	86.1	93.8 (77.5-100)	.43
CAFI total score (range 0-100)[IV]	88	48.9	47.1 (39.2-56.9)	32	46.9	44.1 (37.3-55.4)	48	51	48 (40.7-59.3)	.16
PedsQL-MFS parent-form (range 0-100)[III]										
Total Fatigue	85	67.9	66.7 (54.2-84.7)	32	68.2	70.8 (51-87.5)	45	65.6	65.3 (54.2-80.6)	.59
General fatigue	85	65.3	66.7 (50-87.5)	32	65.8	64.6 (49-87.5)	45	63.2	62.5 (50-75)	.65
Sleep/rest fatigue	86	78.5	83.3 (66.7-91.7)	32	79.3	83.3 (65.6-95.8)	46	77.2	79.2 (66.7-91.7)	.82
Cognitive fatigue	86	59.5	60.4 (34.4-82.3)	32	60.6	62.5 (36.5-80.2)	46	55.7	52.1 (33-78.1)	.45

Table 2. *Continued.*

	Total cohort			<3 years since last treatment[I]			≥3 years since last treatment[I]			
	N	Mean	Median (IQR)	N	Mean	Median (IQR)	N	Mean	Median (IQR)	p II
PedsQL-MFS child-form (range 0-100)[III]										
Total Fatigue	62	70.1	68.8 (57.3-84.4)	24	67.5	70.1 (51-76.7)	36	71.3	68.1 (59.4-85.1)	.46
General fatigue	62	73.1	75 (60.4-91.7)	24	67.4	70.8 (50-87.5)	36	75.4	75 (66.7-91.7)	.19
Sleep/rest fatigue	64	73.6	75 (62.5-87.5)	24	72.6	75 (60.4-89.6)	38	74.1	72.9 (63.5-87.5)	.77
Cognitive fatigue	65	64.2	62.5 (41.7-87.5)	24	62.7	58.3 (41.7-87.5)	38	63.6	64.6 (43.8-83.3)	.89

Abbreviations: CASP = Child and Adolescent Participation Scale, CAFI = Child and Adolescent Factors Inventory, PedsQL-MFS = Pediatric Quality of Life Inventory – Multidimensional Fatigue Scale, PBTS = Pediatric brain tumor survivors, IQR = Interquartile range

[I]Last treatment is defined as last day of chemo/radiotherapy administration, or day of surgery. Children under active surveillance (no treatment) are excluded from this analysis (n=8)

[II]Mann-Whitney U tests based P-value for difference in subgroup scores CASP, CAFI and CASE (<3 or ≥3 years since last treatment); Two-sample T-tests were used for PedsQL-MFS scores

[III] Higher scores indicate less problems

[IV] Lower scores indicate less problems

Table 3. PedsQL Multidimensional Fatigue Scale scores in PBTS and comparison to children from the general Dutch population

	Young child (5-7 years)					Child (8-12 years)					Adolescent (13-18 years)					Total sample				
	N	**Mean**	**SD**	**P**	**da**	**N**	**Mean**	**SD**	**P**	**da**	**N**	**Mean**	**SD**	**P**	**da**	**N**	**Mean**	**SD**	**P**	**da**
Child report																				
Total Fatigue	-					31	67.3	17.7	**.00****	-0.91	31	72.9	18.4	.50	-0.20	62	70.1	18.1	**.00***	-0.55
General fatigue	-					32	71.4	21.8	**.00***	-0.88	31	74.9	20	.63	-0.13	63	73.1	20.8	**.02**	-0.46
Sleep/rest fatigue	-					33	72.7	17.2	.11	-0.32	31	74.6	20	.48	0.19	64	73.6	18.5	.70	-0.07
Cognitive fatigue	-					34	59.7	25.4	**.00***	-0.84	31	69.2	24.1	.09	-0.52	65	64.2	25.1	**.00****	-0.71
Parent report																				
Total Fatigue	13	73.5	20.8	.13	-0.84	41	64.8	20	**.00****	-1.29	31	69.7	21	**.02**	-0.68	85	67.9	20.5	**.00****	-0.99
General fatigue	13	69.2	21.6	**.03**	-1.23	41	61.3	25.3	**.00****	-1.50	31	69.1	23.3	.06	-0.54	85	65.3	24.1	**.00****	-1.05
Sleep/rest fatigue	13	83.0	17.4	.36	-0.39	42	78.8	16.9	**.02**	-0.51	31	76.2	22.1	.27	-0.31	86	78.5	18.9	**.01**	-0.40
Cognitive fatigue	13	68.3	26.4	.13	-0.49	42	53.6	29.3	**.00****	-1.14	31	63.7	26.4	**.00***	-0.85	86	59.4	28.2	**.00****	-0.97

Abbreviations: PedsQL = Pediatric Quality of Life Inventory, PBTS = Pediatric brain tumor survivors
Note: Higher scores indicate less fatigue
P-values at Mann-Whitney U or two-sample t-test; level of significance at P≤ 0.05, *P ≤ 0.01, **P ≤0.001; d = effect size; [a]Pediatric brain tumor survivors versus normative group

Potential patient-, tumor- and treatment-related determinants of participation, impairments in functioning, and of fatigue

Participation
Active surveillance was the only factor associated with participation and had a positive effect on age-expected participation (2.1% vs 18.4%, P = .02). Sex, age at study time, age at diagnosis, time since diagnosis, time since end of treatment, tumor location, tumor grade, type of received treatment (chemotherapy, cranial radiotherapy, or neurosurgery) and underlying predisposition (NF-1) were not associated with limited or very limited participation (Supplementary Table 2 & 3).

Impairments in cognitive, psychological, physical and sensory functioning
In children who were aged <6 years at diagnosis more impairments in cognitive, psychological, physical, and sensory functioning were reported (median CAFI score: 51 vs 43, P ≤ .01), compared to PBTS who were ≥6 years of age at diagnosis.

Also in children who had been diagnosed ≥5 years ago, more impairments in functioning were reported (median CAFI score: 51 vs 43, P = .04) compared to those who had been diagnosed <5 years ago. The remaining factors were not associated with self-reported impairments in functioning (Supplementary Table 4).

General, sleep/rest and cognitive fatigue
A history of hydrocephalus was associated with increased general fatigue, as reported by parents (mean: 50 vs 67.1, P = .02) and also by children themselves (mean: 59.7 vs 75.3, P = .04), compared to children who did not undergo such a procedure. Parents of children who had a history of hydrocephalus also reported increased sleep/rest fatigue (mean: 66.3 vs 80.5, P = .02).

Children who had NF-1 reported more general fatigue compared to those without NF-1 (mean: 54.2 versus 75.1, P = .02).

Increased cognitive fatigue was reported by parents of children that had a radical or partial resection, compared to children who did not have resections (mean: 55.1 vs 70.7, P = .02) (this is most likely explained by the location of tumor which would not need or allow a resection rather than the resection per se; 30% of these children had optic pathway gliomas).

Parents of children who were ≥5 years since diagnosis, reported more cognitive fatigue compared to those who were <5 years since that time (mean: 51. vs

65.7, P = .02). Children (self-reported) who were aged <6 years at diagnosis reported more cognitive fatigue in comparison with children who were ≥6 years of age at diagnosis (mean: 56 vs 69.4, P = .04). Also, those who were treated with chemotherapy reported more cognitive fatigue, as opposed to children who had not received chemotherapy (53.9 vs 67.9. P = .04). There were no associations between the remaining factors and the three fatigue categories (parent-report nor children-report) in this cohort of PBTS (Table 4).

Associations between impairments in functioning and fatigue, with participation

In PBTS with limited participation the majority of impairments in cognitive, psychological, physical and sensory functioning (median CAFI score: 54.9 vs 39.2; P ≤ .01) were significantly more frequently reported compared to PBTS with age-expected participation. Only speech, vision, and hearing problems as well as physical symptoms (ie headaches, dizziness, and nausea) were not associated with limited participation (P ≥ .13). (Supplementary Table 5).

In PBTS with limited participation, parents reported more fatigue on all scales: general fatigue, sleep/rest fatigue and cognitive fatigue, compared to children with age-expected participation (P ≤ .03). In addition children with limited participation themselves reported more general fatigue and cognitive fatigue (P ≤ .01) than children with age-expected participation (Supplementary Table 5).

Furthermore, PBTS with age-expected participation (n = 38) had similar levels of general, sleep/rest and cognitive fatigue compared to normative values of Dutch children (P ≥ .32).

Table 4. Associations between patient, tumor- and treatment-related factors and parent- and self-reported fatigue in PBTS

	PedsQL-MFS Parent-form								PedsQL-MFS Child-form							
Determinant	**Total fatigue**	**P**	**General fatigue**	**P**	**Sleep/ rest fatigue**	**P**	**Cognitive fatigue**	**P**	**Total fatigue**	**P**	**General fatigue**	**P**	**Sleep/ rest fatigue**	**P**	**Cognitive fatigue**	**P**
Age at study time		.73		.36		.99		.91		.30		.41		.69		.22
<11 years (n=44)	67.1 (20)		62.9 (24)		78.5 (17)		59.1 (28)		77.8 (17)		70 (20)		72.4 (17)		58.9 (24)	
≥11 years (n=47)	68.7 (21)		67.7 (24)		78.5 (21)		59.8 (28)		71.6 (19)		74.6 (21)		74.3 (19)		67 (26)	
Age at diagnosis		.18		.14		.83		.09		.24		.7		.5		**.04**
<6 years (n=46)	65 (20)		61.7 (23)		78.1 (18)		54.6 (30)		66.6 (17)		71.7 (18)		71.7 (17)		56 (25)	
≥6 years (n=45)	71 (21)		69.3 (25)		79 (20)		64.7 (25)		72.2 (19)		73.9 (22)		74.9 (19)		69.4 (24)	
Time since diagnosis		.07		.14		.51		**.02**		.34		.74		.62		.07
<5 years (n=53)	71.3 (20)		68.6 (24)		79.9 (19)		65.7 (25)		72.2 (19)		73.9 (22)		74.8 (21)		69.6 (23)	
≥5 years (n=38)	63.2 (20)		60.9 (24)		76.9 (18)		51.1 (30)		67.8 (17)		72.1 (19)		72.5 (16)		58.3 (26)	
Sex		.38		.49		.27		.67		.85		.61		.99		.78
Boy (n=49)	66.1 (22)		63.7 (25)		76.4 (20)		58.2 (31)		70.5 (20)		74.4 (24)		73.6 (20)		65.1 (26)	
Girl (n=42)	70 (18)		67.3 (23)		80.9 (17)		60.8 (26)		69.7 (16)		71.7 (17)		73.7 (17)		63.3 (25)	
Tumor grade[!]		.69		.57		.84		.64		.99		.99		.39		.46
High-grade (n=18)	65.8 (18)		61.9 (25)		79.5 (22)		56.1 (24)		70.1 (19)		73.1 (24)		78 (21)		59.1 (20)	
Low-grade (n=73)	68.3 (21)		66 (24)		78.3 (19)		60.1 (29)		70.1 (18)		73.1 (20)		72.7 (18)		65.3 (26)	
Tumor location		.39		.58		.45		.31		.83		.54		.90		.57
Infratentorial (n=45)	65.9 (19)		63.8 (23)		76.9 (17)		56.3 (28)		70.6 (18)		74.9 (17)		73.9 (17)		62.4 (27)	
Supratentorial (n=46)	69.8 (22)		66.7 (26)		80 (21)		62.5 (29)		69.7 (19)		71.6 (23)		73.4 (20)		65.9 (24)	

Table 4. *Continued.*

	PedsQL-MFS Parent-form								PedsQL-MFS Child-form							
Determinant	**Total fatigue**	**P**	**General fatigue**	**P**	**Sleep/ rest fatigue**	**P**	**Cognitive fatigue**	**P**	**Total fatigue**	**P**	**General fatigue**	**P**	**Sleep/ rest fatigue**	**P**	**Cognitive fatigue**	**P**
Neurosurgery Radical or partial resection		.09		.73		.19		**.02**		.56		.77		.56		.09
												.04				
Yes (n=65)	65.6 (21)		64.8 (24)		76.8 (20)		55.1 (29)		69.4 (18)		73.5 (20)		72.9 (19)		61.3 (25)	
No (n=26)	74.2 (17)		66.9 (24)		82.8 (15)		70.7 (24)		72.6 (18)		71.7 (24)		76.2 (17)		73.9 (24)	
Procedure for treatment of hydrocephalus[II]		**.03**		**.02**		**.02**		.33		**.04**				.12		.09
Yes (n=13)	56.1 (23)		50 (22)		66.3 (26)		52.1 (30)		58.5 (20)		59.7 (25)		64.8 (24)		50.9 (18)	
No (n=78)	69.8 (20)		67.9 (24)		80.5 (17)		60.6 (28)		72.1 (17)		75.3 (19)		75.1 (17)		66.4 (26)	
Chemotherapy		.43		.25		.82		.43		.13		.09		.88		**.04**
Yes (n=28)	64.9 (18)		60.2 (23)		77.7 (22)		55.4 (25)		64.2 (19)		65.6 (27)		73 (21)		53.9 (20)	
No (n=63)	68.9 (21)		67.1 (24)		78.8 (18)		60.9 (29)		72.2 (18)		75.6 (18)		73.9 (18)		67.9 (26)	
Cranial radiotherapy		.38		.44		.55		.33		.30		.33		.37		.66
Yes (n=37)	70.4 (20)		68 (24)		80.1 (20)		63.3 (26)		72.9 (17)		76.1 (19)		76.1 (19)		65.9 (23)	
No (n=54)	66.4 (21)		63.8 (24)		77.6 (18)		57.2 (29)		68.1 (19)		71 (22)		71.9 (18)		63.1 (27)	
Active surveillance		.08		.19		.18		.07		.41		.11		.79		.15
Yes (n=8)	79.9 (18)		76 (23)		87 (13)		76.7 (23)		80.6 (18)		91.7 (11)		77.1 (9)		84.7 (26)	
No (n=83)	66.7 (20)		64.2 (24)		77.6 (19)		57.7 (28)		69.8 (18)		72.1 (21)		73.5 (19)		63.2 (25)	

Table 4. *Continued.*

	PedsQL-MFS Parent-form								PedsQL-MFS Child-form							
Determinant	**Total fatigue**	**P**	**General fatigue**	**P**	**Sleep/ rest fatigue**	**P**	**Cognitive fatigue**	**P**	**Total fatigue**	**P**	**General fatigue**	**P**	**Sleep/ rest fatigue**	**P**	**Cognitive fatigue**	**P**
Neurofibromatosis-1		.65		.14		.80		.91		.12		**.02**		.56		.31
Yes (n=13)	65.4 (18)		55.9 (23)		77.2 (20)		60.3 (24)		59.3 (21)		54.2 (29)		69.4 (19)		54.2 (26)	
No (n=78)	68.3 (21)		66.9 (24)		78.7 (19)		59.3 (29)		71.3 (18)		75.1 (19)		74.1 (19)		65.3 (25)	

Abbreviations: PBTS = Pediatric brain tumor survivors, PedsQL-MFS = Pediatric Quality of Life Inventory – Multidimensional Fatigue Scale
Results are reported as mean with standard deviation, higher scores indicate less fatigue; P-values are based on two sample T-tests ; P-values marked in bold indicate numbers that are significant on the 95% confidence limit
[I]grade I/II indicates low-grade, grade III/IV indicates high-grade
[II]endoscopic third ventriculostomy or ventriculoperitoneal shunt placement

Discussion

Curation from a pediatric brain tumor requires very intensive treatment. After treatment, survivors can be left with a brain injury that predisposes them to several limitations, challenging their ability to participate in daily life.

In this cross-sectional study of 91 PBTS, which is the first with a substantial percentage of younger children (ie 57% aged 4-12 years), we found that in more than half of these children limitations in participation at home, in school and in community life situations were reported. This frequency was lower compared to the 72% in a previous study in 345 Dutch children and young adults (5-24 years) with acquired brain injury using the same cutoff point (CASP <97.5).[22] However, as their cohort consisted exclusively of patients who received treatment at a rehabilitation center this would indicate that they all had impairments. Also, the majority (74%) were patients with traumatic acquired brain injury, making an adequate comparison with our cohort difficult. In contrast, the results from another study in 112 Dutch children and young adults (6-22 years)[27] showed limited participation – measured with CASP - in 42% of participants with acquired brain injury 2 years after onset, which is less than in our study. Again, comparison is difficult as 77% of their cohort patients had a traumatic brain injury and not all of the remaining 23% were PBTS.

Our results show that impairments in functioning (ie cognitive, physical, psychological, and sensory) are frequently experienced as problems – minor or major - in PBTS. We found that younger age at diagnosis (<6 years) was associated with more impairments in functioning, which is in accordance with previous studies in PBTS where younger age at treatment has been related to more disability.[3, 28]

Active surveillance was the only factor that was positively associated with participation limitations, which is not very surprising because these children did not need treatment in view of their tumor type, location, or lack of tumor progression. They would have had adequate functioning and stable neurology. We did not find any other patient, tumor- or treatment-related factors influencing participation. Previous studies among PBTS with a comparable follow-up time (1-15 years) did report that recurrent neurosurgery, shunt revisions, and chemotherapy were associated with major disabilities and poorer motor skills.[3, 15, 28] We found these factors to be associated with fatigue in our cohort but not with participation or impairments in functioning. A potential explanation is the heterogeneity of our cohort with various types of brain tumors and/or overlap between treatment modalities, which challenges detecting relationships.

We did find that general and cognitive fatigue were important factors associated with participation ability. Especially striking was that PBTS with age-expected participation not only had less fatigue than the children with limited participation, but also that their fatigue levels were no different from the normative values of Dutch children. This may indicate that fatigue is an important factor in the ability for PBTS to participate.

Fatigue was assessed using a validated instrument with normative values of children from the general Dutch population. It is one of the first studies where this instrument was used in PBTS <12 years of age.

Parents and children both reported increased fatigue when a procedure for treatment of hydrocephalus (such as an endoscopic third *ventriculostomy or ventriculoperitoneal shunt placement*) had taken place compared to children who did not have hydrocephalus, which may be due the severity of this often acute complication rather than the procedure itself. However, it was uncertain whether it was the presence of preoperative hydrocephalus, the attendant difficulties at surgery or the actual need for a post-operative shunt following tumor resection, that posed the risk.[6]

In our cohort PBTS with NF-1 reported increased general fatigue compared to those without NF-1, which was expected because children with NF-1 reported more perceived fatigue.[29]

We expected to find an association between children who received radiotherapy and fatigue since radiotherapy is a known risk factor for decreased processing speed and cognitive decline[6], which has been associated with more cognitive fatigue in PBTS.[30] The reasons we did not find such an association could be that, first, the number of children in this cohort who had radiation was too small (n = 37, 33%). Second, the large heterogeneity in our cohort makes it difficult to detect such a possible effect in univariable analyses, and we had insufficient power to explore this in multivariable analyses. Third, we did not have exact data on the amount of radiation exposure but could only analyze radiotherapy dichotomously, which lowers the chance of finding specific associations.

We expected that longer time since end of treatment would result in better participation and less fatigue. However, we found that the extent of participation limitations, impairments in functioning and fatigue was similar in children <3 and ≥3 years since cessation of treatment. Moreover, when we analyzed time since diagnosis (which differs from time since last treatment because of variations in therapy duration), we found an increase in impairments in functioning and cognitive fatigue in children ≥5 years compared to those

<5 years since diagnosis of the brain tumor (P ≤ .04). This raises concerns about whether impairments actually lessen over time. Specific limitations (ie cognitive fatigue) may become more noticeable as the child ages, that is that the phenomenon 'growing into deficit' emerges.[15] This phenomenon is based on the assumption that while growing older a child's impairments become more pronounced compared to his peers as the demands of the environment increase.[31, 32]

To our knowledge, this is the first study examining participation limitations and fatigue in a relatively large group of children of four years and older after treatment for a brain tumor. Given the acceptable response rate (55%) and that responders did not differ from nonresponders with regard to the majority of characteristics, the results may be considered representative. However, the cohort included a relatively large number of survivors of low grade tumors. It is conceivable that these children are more likely to be survivors. Nevertheless, children with high grade tumors known to have good survival rates (eg medulloblastoma) were underrepresented. The reported limitations in this study may therefore be an underestimation, because children with high grade tumors are expected to experience physical impairments more often due to the location of their tumor (most commonly in the cerebellum).

Furthermore, the following limitations should be taken into account when interpreting the results. First, although the CFFS questionnaire is presented as a promising instrument for children with acquired brain injury[33, 34], so far only one study evaluated psychometric qualities in a relatively small Dutch cohort.[20] Second, although in accordance with previous Dutch studies in children with acquired brain injury[22, 23], the cutoff point of limited participation (CASP <97.5) we used remains arbitrary. A study using the German CASP version showed a ceiling effect in a disability-free sample (n = 215, 3-11 years) where >50% had a CASP score of 100 (mean: 98)[33], which would support our choice. Third, we were not able to perform multivariable analyses because of high heterogeneity in the cohort and lack of power due to limited sample size, leading to wide confidence intervals. Fourth, due to the design of the study information regarding specific learning difficulties, epilepsy, physical disabilities (eg hemiplegia, cerebellar syndrome), somatosensory, endocrine disorders and socioeconomic status were not available, but are likely contributory factors of participation ability. Future studies addressing these factors would increase our risk understanding for limited participation.

The results of this study show that participation in PBTS is often reduced and that impairments in cognitive and physical functioning as well as increased fatigue, were negatively associated with participation ability. Participation

limitations, impairments in functioning and fatigue appeared did not differ between the short and the longer term. These results underline the importance of follow-up of children after brain tumor treatment, and their reintegration in daily life.

Fatigue appears a commonly observed issue and yet few recognized interventions seem to be offered or available, despite research showing that in the longer term the levels of fatigue in PBTS remain unsatisfactory. We hypothesize that by recognizing and addressing the problems of fatigue in an earlier phase combined with offering structured interventions, may mitigate these problems.

In adult cancer survivors, interventions targeting physical training and psychosocial interventions (such as cognitive behavior therapy) have shown to be effective in the management of cancer-related fatigue.[35-41] Unfortunately, studies on effectiveness of such interventions in pediatric cancer patients are sparse. It has been shown that physical exercise training in childhood cancer patients is feasible, safe and effective in improving outcomes such as mobility and muscle strength[42, 43], and also that more physically active patients report less fatigue.[44] However, there are no trials that evaluate the effect of physical exercise training on fatigue. To our knowledge, there has been only one noncontrolled pilot study in childhood cancer survivors (n = 25, 3 of whom were PBTS), in which a clinically reduction in fatigue following cognitive behavior therapy was found.[45]

Possible underlying phenomena in PBTS will need to be further investigated and should receive special attention in health care and in multidisciplinary follow up.

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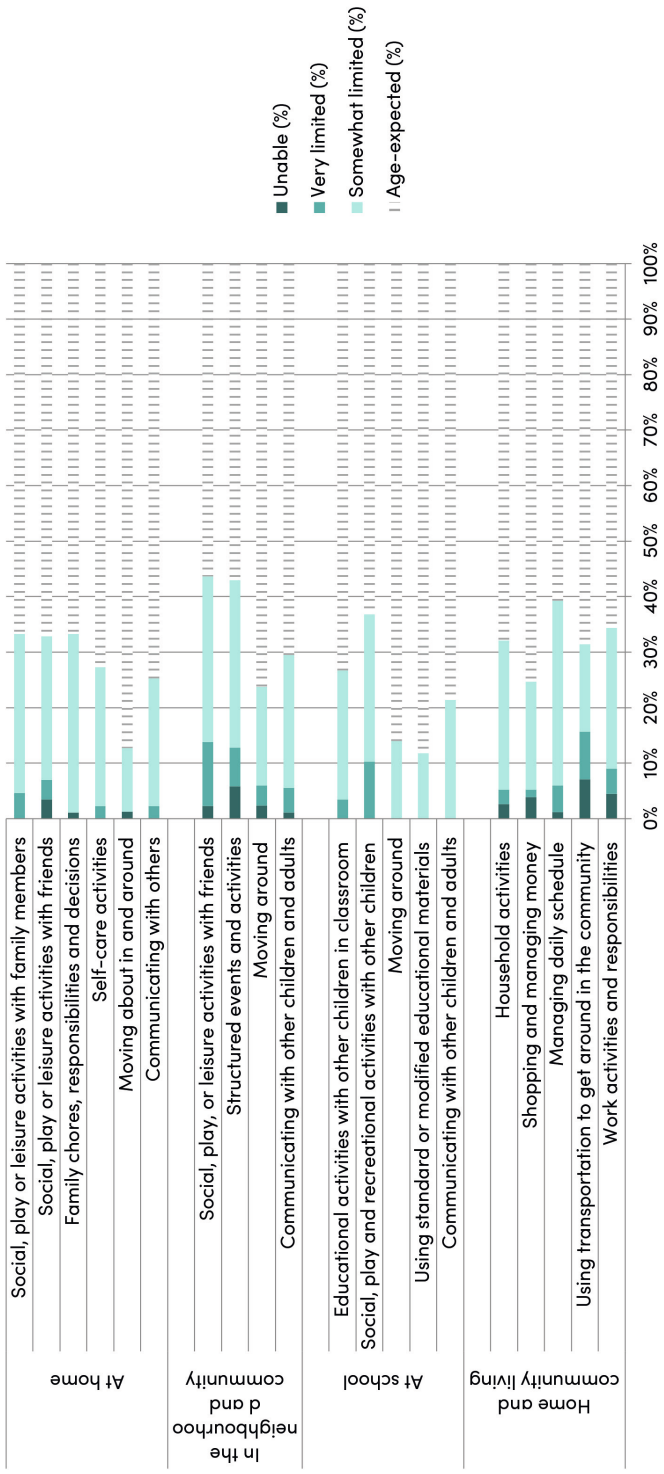
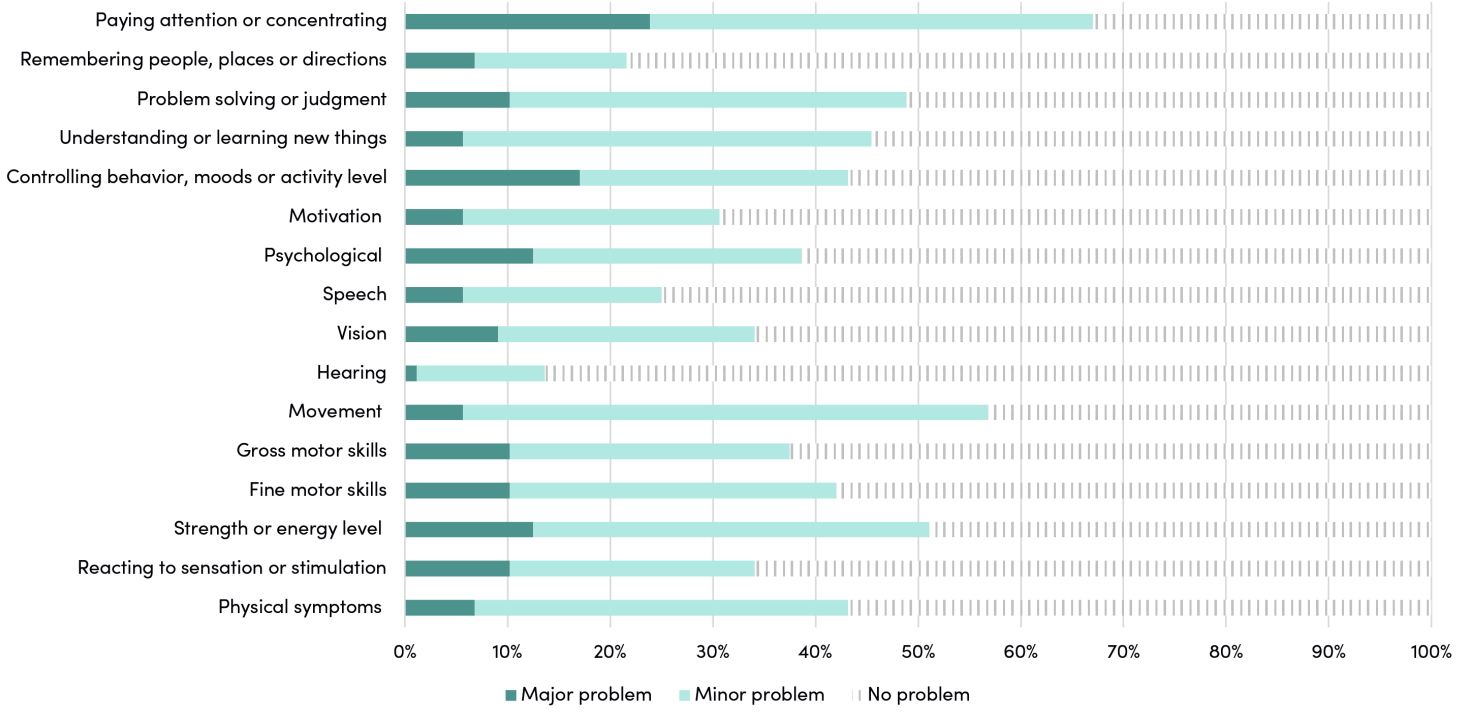


Supplemental Figure 1. Participation limitations in PBTS reported by parents on the Child and Adolescent Participation Scale (CASP)



Supplemental Figure 2. Results of the CAFI questionnaire; reported impairments in functioning in PBTS

Supplemental Table 1. Cut-off points for the CASP questionnaire used in previous studies and the current study

	Cohort	CASP scores	Cut-off point normal participation
De Kloet et al 2015	108 Dutch children and young adults (5-22 years) with acquired brain injury (~2 years after onset)	Mean (SD): 92.5 (11.3)	≤97 = low participation >97 = high participation (based on median score)
Lambregts et al 2018	112 Dutch children and young adults (6-22 years) with acquired brain injury (2 years post)	Mean (SD): 92.4 (11.4)	100 = age-expected participation ≤99 = restricted participation (based on median score)
De Bock et al 2019	215 German population-based disability-free cohort of children (3-11 years)	Mean (SD): 98.2 (5.8)	<95 = mildly impaired participation <92 = severely impaired participation (based on 10th and 5th percentile)
Allonsius et al 2021	245 Dutch children and young adults (5-24 years) with acquired brain injury and referred to an outpatient rehabilitation center (4; 1-18 years since onset)	Median (IQR): 91.3 (80-97.5)	100-97.5 = full participation 97.5-81 = somewhat limited participation 81-68.5 = limited participation 68.5 or less = very limited participation (based on experts opinion and data analysis)
Current study	91 Dutch pediatric brain tumor survivors (4-18 years), 4 (0.3-10) years since end of therapy	Median (IQR): 95 (82.5-100) Mean (SD): 90.4 (11.8)	≥97.5 = age-expected participation [I] 97.5-81 = limited participation [I] ≤81 = very limited participation [II]

[I]In accordance with Allonsius et al
[II]Cut-off point based on the lowest tertile of the group that were not meeting the maximum CASP score (CASP <100)

Supplemental Table 2. Associations between patient, tumor- and treatment-related factors and participation limitations (CASP) in PBTS

	Limited participation (n = 47)		**Age-expected participation (n = 38)**		
	Median	**IQR**	**Median**	**IQR**	***P*** [IV]
Age at study time, years	11.3	9.6 – 14.3	11.8	9.6 – 14.3	.51
Age at diagnosis, years	5.3	3.7 – 7.8	7.3	4.4 – 10.4	.06
Time since diagnosis, years	5.3	2.9 – 7.8	3.8	2.3 – 5.8	.07
Time since end of treatment [I], years	4	2.1 – 7.0	3.8	1.9 – 4.8	.25
	No.	**%**	**No.**	**%**	
Sex					.82
Boy	27	57.4	20	52.6	
Girl	20	42.6	18	47.4	
Tumor grade [II]					.96
High-grade	10	21.3	7	18.4	
Low-grade	37	78.7	31	81.6	
Tumor location					.45
Infratentorial	26	55.3	17	44.7	
Supratentorial	21	44.7	21	55.3	
Neurosurgery Radical or partial resection					.11
Yes	38	80.9	24	63.2	
No	9	19.1	14	36.8	
Procedure for treatment of hydrocephalus [III]					.5 [V]
Yes	7	14.9	3	7.9	
No	40	85.1	35	92.1	
Chemotherapy					.75
Yes	15	31.9	10	26.3	
No	32	68.1	28	73.7	
Cranial radiotherapy					.43
Yes	16	34	17	44.7	
No	31	66	21	55.3	
Active surveillance					**.02** [V]
Yes	1	2.1	7	18.4	
No	46	97.9	31	81.6	

Supplemental Table 2. *Continued.*

	Limited participation (n = 47)		Age-expected participation (n = 38)		
	No.	**%**	**No.**	**%**	***P*** [IV]
Neurofibromatosis-1					.18
Yes	4	8.5	8	21.1	
No	43	91.5	30	78.9	

Abbreviations: Limited participation = CASP score <97.5, Age-expected participation = CASP score ≥97.5, IQR = Interquartile range
[I]End of treatment was defined as last the day of chemo/radiotherapy administration, time since surgical procedure or time since decision for active surveillance
[II]grade I/II indicates low-grade, grade III/IV indicates high-grade
[III] endoscopic third ventriculostomy or ventriculoperitoneal shunt placement
[IV]P-value based on Mann-Whitney U test or Chi-squared test
[V]P-value based on Fishers exact test

Supplemental Table 3. Associations between patient, tumor- and treatment-related factors and very limited participation (CASP) in PBTS

	Very limited participation (N=19)		Limited participation (N=28)		
	Median	**IQR**	**Median**	**IQR**	***P*** [IV]
Age at study time, years	10.6	9.5 – 13.1	11.5	9.6 – 14.6	.39
Age at diagnosis, years	5.3	3.5 – 7.8	5.8	3.8 – 7.6	.58
Time since diagnosis, years	4.8	3.4 – 7.2	5.3	2.7 - 8.3	.77
Time since end of treatment [I], years	3.9	2.2 – 6.7	4.4	2.1 – 7.5	.79
	No.	**%**	**No.**	**%**	
Sex					.99
Boy	11	57.9	16	57.1	
Girl	8	42.1	12	42.9	
Tumor Grade [II]					.99
High-grade	4	21.1	6	21.4	
Low-grade	15	78.9	22	78.6	
Tumor location					.55
Infratentorial	12	63.2	14	50	
Supratentorial	7	36.8	14	50	

Supplemental Table 3. *Continued*

	Very limited participation (N=19)		Limited participation (N=28)		
	No.	**%**	**No.**	**%**	***P*** [IV]
Neurosurgery					
Radical or partial resection					.72
Yes	16	84.2	22	78.6	
No	3	15.8	6	21.4	
Procedure for treatment of hydrocephalus [III]					.68
Yes	2	10.5	5	17.9	
No	17	89.5	23	82.1	
Chemotherapy					.54
Yes	5	26.3	13	34.2	
No	14	73.7	25	65.8	
Cranial radiotherapy					.21
Yes	4	21.1	18	47.4	
No	15	78.9	20	52.6	
Active surveillance					-
Yes	1	5.3	0	0	
No	18	94.7	28	100	
Neurofibromatosis-1					.29
Yes	3	15.8	1	3.6	
No	16	84.2	27	96.4	

Abbreviations: CASP = Child and Adolescent Participation Scale, Very limited participation = CASP score ≤81, Limited participation = CASP score 81-97.5, IQR = Interquartile range

[I]End of treatment was defined as last the day of chemo/radiotherapy administration, time since surgical procedure or time since decision for active surveillance

[II]Grade I/II indicates low-grade, grade III/IV indicates high-grade

[III] Endoscopic third ventriculostomy or ventriculoperitoneal shunt placement

[IV] P-value based on Mann-Whitney U test or Chi-squared test, or on Fishers exact test if N = <5

Supplemental Table 4. Associations between patient, tumor- and treatment-related factors and impairments in functioning (CAFI) in PBTS

	Total CAFI score		
Determinant	**Median**	**IQR**	**P-value** [IV]
Age at study time			.12
<11 years (n=44)	50	39.7 – 56.9	
≥11 years (n=47)	44	37.8 – 54.4	
Age at diagnosis			**.00***
<6 years (n=46)	51	41.2 - 60.8	
≥6 years (n=45)	43	37.3 - 51	
Time since diagnosis			**.04**
<5 years (n=53)	43	37.3 – 53	
≥5 years (n=38)	51	41.2 – 60.8	
Sex			.59
Boy (n=49)	47	39.2 - 56.9	
Girl (n=42)	47	39.2 – 53.9	
Tumor grade[I]			.87
High-grade (n=18)	46	40.2 – 53.9	
Low-grade (n=73)	47	39.2 – 56.9	
Tumor location			.70
Infratentorial (n=45)	47	39.2 – 55.4	
Supratentorial (n=46)	47	38.7 – 56.9	
Neurosurgery			
Radical or partial resection			.78
Yes (n=65)	47	39.2 – 56.9	
No (n=26)	47	39.2 – 51.5	
Procedure for treatment of hydrocephalus[II]			.12
Yes (n=13)	55	43.1 – 64.7	
No (n=78)	47	39.2 - 54.9	
Chemotherapy			.23
Yes (n=28)	49	42.2 – 54.9	
No (n=63)	45	37.3 – 56.9	
Cranial radiotherapy			.34
Yes (n=37)	45	39.2 – 50	
No (n=54)	51	39.2 – 58.8	
Active surveillance			.15
Yes (n=8)	40	33 – 49.5	
No (n=83)	47	39.2 – 56.9	

Supplemental Table 4. *Continued*

	Total CAFI score		
Determinant	**Median**	**IQR**	**P-value** [IV]
Neurofibromatosis-1			.22
Yes	51	41.2 – 58.8	
No	45	29.2 -54.9	

Abbreviations: CAFI = Child and Adolescent Factors Inventory; Lower scores indicate less problems, IQR = Interquartile range
[I]End of treatment was defined as last the day of chemo/radiotherapy administration, time since surgical procedure or time since decision for active surveillance
[II]grade I/II indicates low-grade, grade III/IV indicates high-grade
[III] endoscopic third ventriculostomy or ventriculoperitoneal shunt placement
[IV]P-value based on Mann-Whitney U test; level of significance at P≤ 0.05, *P ≤ 0.01, **P ≤0.001

Supplemental Table 5. Results CAFI and PedsQL-MFS questionnaire in PBTS with limited and age-expected participation

	Limited participation (n=47)		**Age-expected participation (n=38)**		
	Median	**IQR**	**Median**	**IQR**	***P*** [I]
CAFI total score	54.9	46.1 – 60.8	39.2	37.3 – 45.1	**.00****
	No.	**%**	**No.**	**%**	***P*** [II]
CAFI item scores					
Paying attention or concentrating					**.00****
Major problem	18	38.3	1	2.6	
Minor problem	21	44.7	16	42.1	
No problem	8	17	21	55.3	
Remembering people, places or directions					**.00***
Major problem	5	10.6	0	0	
Minor problem	11	23.5	2	5.3	
No problem	31	66	36	94.7	
Problem solving or judgment					**.00****
Major problem	9	19.1	0	0	
Minor problem	25	53.2	7	18.4	
No problem	13	27.7	31	81.6	

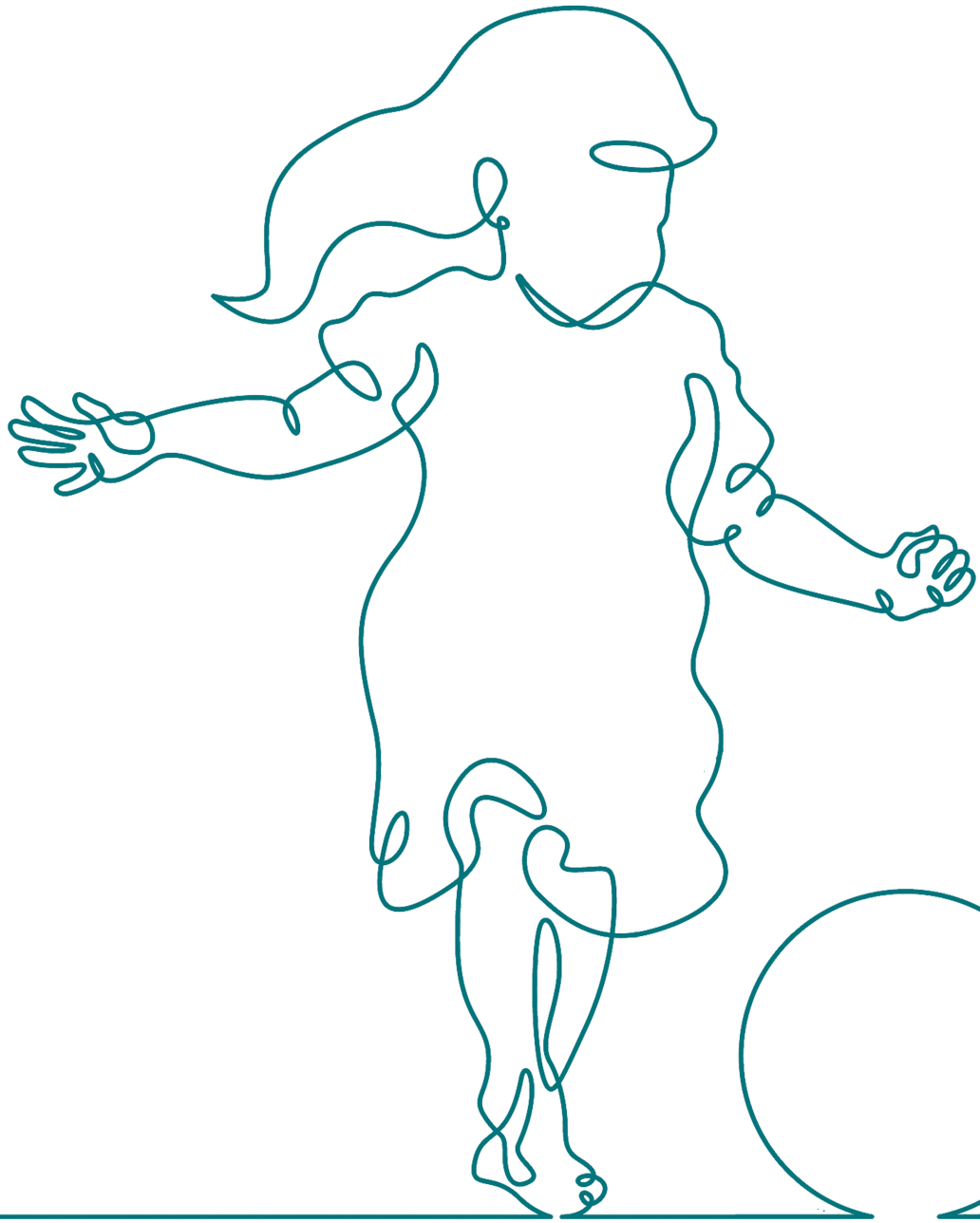
Supplemental Table 5. *Continued*

	Limited participation (n=47)		Age-expected participation (n=38)		
	No.	**%**	**No.**	**%**	***P*** [‖]
Understanding or learning new things					**.00****
Major problem	4	8.5	0	0	
Minor problem	27	57.5	7	18.4	
No problem	16	34	31	81.6	
Controlling behavior, moods or activity level					**.00****
Major problem	14	29.8	0	0	
Minor problem	15	31.9	8	21.1	
No problem	18	38.3	30	78.9	
Motivation (lacks interest or initiative)					**.00****
Major problem	5	10.6	0	0	
Minor problem	18	38.3	3	7.9	
No problem	24	51.1	35	92.1	
Psychological (depression or anxiety)					**.00***
Major problem	10	21.3	1	2.6	
Minor problem	15	31.9	8	21.1	
No problem	22	46.8	29	76.3	
Speech					0.13
Major problem	5	10.6	0	0	
Minor problem	8	17	8	21.1	
No problem	34	72.4	30	78.9	
Vision					0.24
Major problem	6	12.8	1	2.6	
Minor problem	11	23.4	11	29	
No problem	39	63.8	26	68.4	
Hearing					0.86
Major problem	1	2.1	0	0	
Minor problem	5	10.7	5	13.2	
No problem	41	87.2	33	86.8	
Movement (balance, coordination, muscle tone)					**.00***
Major problem	4	8.5	0	0	
Minor problem	30	63.8	14	36.8	
No problem	13	27.7	24	63.2	
Gross motor skills					**.00***
Major problem	7	14.9	0	0	
Minor problem	16	34	8	21.1	
No problem	24	51.1	30	78.9	

Supplemental Table 5. *Continued*

	Limited participation (n=47)		**Age-expected participation (n=38)**		
	No.	**%**	**No.**	**%**	***P*** [II]
Fine motor skills					**.00***
Major problem	7	14.9	0	0	
Minor problem	19	40.4	8	21.1	
No problem	21	44.7	30	78.9	
Strength or energy level					**.03**
Major problem	8	17	1	2.6	
Minor problem	21	44.7	13	34.2	
No problem	18	38.3	24	63.2	
Reacting to sensation or stimulation					**.01**
Major problem	9	19.1	0	0	
Minor problem	10	21.3	10	26.3	
No problem	28	59.6	28	73.7	
Physical symptoms (headaches, dizziness, pain)					0.64
Major problem	4	8.5	1	2.6	
Minor problem	17	36.2	15	39.5	
No problem	26	55.3	22	57.9	
	Mean	**SD**	**Mean**	**SD**	***P*** [III]
PedsQL-MFS parent-form					
Total Fatigue	58.7	19.2	78.9	16	**.00****
General fatigue	55.7	23	77.5	19.3	**.00****
Sleep/rest fatigue	73.9	20.1	83	16.7	**.03**
Cognitive fatigue	46.6	26.3	74.7	22.1	**.00****
PedsQL-MFS child-form					
Total Fatigue	63.8	17.5	77.9	16.6	**.00***
General fatigue	66.4	20.6	81.3	19.1	**.00***
Sleep/rest fatigue	70.9	19	77.4	18.5	.17
Cognitive fatigue	54	20.4	75.4	20.4	**.00****

Abbreviations: CAFI = Child and Adolescent Factors Inventory; Lower scores indicate less problems, PedsQL-MFS = Pediatric Quality of Life Inventory – Multidimensional Fatigue Scale, SD = Standard deviation, IQR = Interquartile range
Limited participation = CASP score <97.5, Age-expected participation = CASP score ≥97.5
P-values are based on Mann-Whitney U tests[I], on Fisher's exact test for group comparisons[II] or on two sample T-tests[III]; level of significance at P≤ 0.05, *P ≤ 0.01, **P ≤0.001



Discussion and future perspectives

The aims of this thesis were to develop and validate simplified tools to identify musculoskeletal impairments in children with cancer, as well as to increase knowledge on the occurrence of, and determinants of sarcopenia, physical frailty and related problems, during and after treatment. The findings in this thesis may have positive implications with regard to timely risk detection and screening, prevention of physical deterioration, and development of tailored exercise interventions, as well as for future research, as discussed below.

Risk identification, screening and assessment of musculoskeletal impairments

Risk prediction for bone fragility and (preventive) interventions

It has been well-established that children with acute lymphoblastic leukemia (ALL) are at increased risk of fractures[1-3], and that low lumbar spine bone mineral density (LSBMD), especially at diagnosis, plays an important role in this fracture risk.[4,5] Numerous risk factors for low LSBMD have been identified in previous studies[4-7], but these factors had not yet been combined in a clinical prediction model. In this thesis, we developed prediction models for LSBMD at time of diagnosis and at cessation of treatment in a Dutch multicenter cohort of newly diagnosed ALL patients, and externally validated these models in a Canadian multicenter cohort (*Chapter 2*).[8] Our prediction model shows that patients with low LSBMD can be simply but adequately predicted by using weight Z-scores and age already at diagnosis. Clinically useful models such as these, are not only important for targeted identification of patients with increased fracture risk, but also supportive in deciding whether a child should undergo a dual-energy X-ray absorptiometry (DXA) examination for LSBMD assessment, as well as determining the need of referral to a pediatric physiotherapist for exercise recommendations.

The discriminative accuracy of the prediction model for low LSBMD at diagnosis may be further improved by including other clinical factors such as muscle parameters, genetic susceptibility and/or pharmacokinetics. The fact that we found that lower weight Z-scores (indicating lean children) are important in identifying low LSBMD, and that changes in BMD are associated with changes in muscle mass and strength[9], suggests that these muscle parameters may improve prediction of low LSBMD. In addition, previous studies have identified genetic factors as determinants of impaired BMD in childhood ALL patients and incorporating such factors in polygenic risk scores may improve prediction.[10-12] Glucocorticoids are a known factor for BMD decline[12], but the absorption, distribution and excretion influence blood concentration (pharmacokinetics) and may vary among individual patients. Other chemotherapeutic agents may also contribute, for example concurrent administration of asparaginase

is known to increase glucocorticoid plasma levels and may enhance the detrimental effect on BMD.[13] Taking into account pharmacokinetics in individual patients might therefore improve risk stratification for bone fragility. Including these aspects may improve the prediction model, but will also complicate its use and hamper clinical implementation.

Potential preventive strategies and interventions to decrease the risk of bone fragility lie in the scope of nutrition and exercise. Adequate dietary vitamin D and calcium intake are important for bone mineralization, and routinely supplementation is often used as an attempt to prevent BMD decline in children with cancer. However, a recent systematic review found very low evidence for the effect of vitamin D and calcium supplementation on BMD and fractures in children with cancer, and therefore recommended supplementation only in patients with low levels.[14]

Physical activity during childhood is positively associated with BMD, neuromuscular function and muscle strength, which all decrease fracture risk in the general pediatric population.[15-17] However, randomized exercise intervention studies showed contrary effects on BMD during ALL treatment.[18-20] Lack of effect in these studies is possibly explained by the fact that intensive training is not often feasible in early treatment phase[20], and by compliance problems.[18] Nevertheless, exercise interventions may offer a promising role for improvement in BMD during therapy.[19] Specific muscle strengthening is associated with improved BMD in adult survivors of childhood ALL[21], but this principle has yet to be studied in pediatric patients.

An opportunity for decreasing fracture risk may also exist in enhancing balance and motor skills [22], because children with ALL are prone to clumsiness, impaired balance and subsequent increased risk of falls[23] (for example due to vincristine-induced neuropathy). The challenge however, remains to identify the ideal timing (both physiologically as well as psychologically) to offer interventions and create parent and patient commitment.

Screening for structural and functional sarcopenia and assessment of muscle impairment

Childhood cancer patients are at risk of muscle impairments due to the disease itself and to side-effects of treatment. Co-occurrence of such impairments (low muscle mass, muscle weakness and impaired physical performance), indicates the vulnerable state known as sarcopenia. Because of the serious consequences of sarcopenia-related impairments[24-28], early identification of patients at risk is important and would support clinicians in offering interventions timely. In this thesis, we determined the diagnostic accuracy of the pediatric version of

the SARC-F (PED-SARC-F) questionnaire to identify patients with structural sarcopenia and functional sarcopenia in a pediatric hemato-oncology cohort (*Chapter 3*).[29] We found that the PED-SARC-F is excellent at selecting patients with muscle weakness and impaired physical performance (functional sarcopenia). We proposed a PED-SARC-F score of ≥5 as clinically useful for clinicians in identifying patients that need a physiotherapy consultation. In contrast, the PED-SARC-F proved to be less accurate in identifying patients with primary low muscle mass (structural sarcopenia).

Loss of muscle mass in children with cancer has adverse consequences for infection rates, frequency and duration of hospital admissions and overall survival.[24-26] Therefore, optimizing our screening strategy is warranted. A comprehensible explanation for the finding that PED-SARC-F is less accurate in identifying patients with low muscle mass, is that the questions address muscle function components and are not specifically related to muscle mass. Expanding the PED-SARC-F with an anthropometric measure (such as limb circumference) may improve accuracy, rather than monitoring weight changes because gain of fat tissue may mask the loss of muscle mass.[25,30] In adult cancer patients, the accuracy of the SARC-F has been successfully enhanced by incorporating calf circumference.[31]

For clinical implementation in pediatric hemato-oncology care, involvement of pediatric oncologists and nurse specialists is essential and the proposed procedure should be clinical relevant and feasible. Providing education and training, as well as automated reminders and decision support in the electronic medical records, may aid in optimal clinical implementation.[32] After successful implementation, the PED-SARC-F can conceivably lead to early identification of muscle weakness and subsequent timely referral to physiotherapists. Moreover, to realize broad usability of the PED-SARC-F among various pediatric cancer patients with large variation in treatment modalities, side effects and treatment burden including physical inabilities, validation in other cohorts is needed.

At this point, the PED-SARC-F is excellent in identifying patients with existing muscle weakness and may have great potential for predicting deterioration over time or treatment. In older adults, the SARC-F has shown to be a prognostic indicator for disability and mortality.[33-35] Therefore, we recently started two research projects in children with renal tumors and in pediatric stem cell transplantation recipients, in which we aim to unravel the predictive value of PED-SARC-F for adverse events, physical disability and treatment outcomes. In case of prognostic capability for such outcomes over time, this will further benefit adequate screening and establish timely referral of patients that may benefit from (preventive) exercise interventions.

Imaging technique to assess muscle mass and intramuscular alterations
The assessment of (skeletal) muscle mass and intramuscular alterations in children is challenging, because non-invasive yet valid methods are very limited. Intramuscular alterations may already be present long before muscle atrophy and functional impairments appear[36], and thus supportive in early identification. The current gold standard for muscle mass and muscle quality quantification is magnetic resonance imaging (MRI) or computed tomography (CT)[37], but these techniques are time-consuming and invasive as sedation is required for younger children. Muscle ultrasonography is a non-invasive and low cost tool that can be performed at the bedside, but correct interpretation requires significant expertise of different structures and echogenicity, which limits usability in clinical practice.[38] In this thesis, the utility of bedside muscle ultrasound in combination with automated annotation technology, as an indicator for skeletal muscle mass, muscle strength and physical performance in children with ALL was shown (*Chapter 4*). This non-invasive technique may be a sizeable reduction of burden in physically vulnerable children with cancer, especially in critically-ill and non-ambulating children. In addition, the potential for assessing intramuscular alterations is a major upgrade in muscular assessments, possibly detecting deterioration even before it becomes clinically apparent.

Subsequent steps towards realization of this technique in pediatric cancer care are needed. The outcomes generated by the automated annotation software, i.e. muscle size and intramuscular fat tissue, need to be compared to simultaneously made MRI images, to determine criterion validity. Moreover, inter-rater (consistency between different assessors) and intra-rater (consistency of images and interpretation by same assessor) reliability is crucial before use in clinical care can be pursued. For increased understanding of intramuscular changes in children with cancer, reference values from the general population need to be developed, to recognize by disease or treatment-induced alterations as such.

Physical vulnerability and fatigue in childhood cancer patients and survivors

Frailty and sarcopenia in children with acute lymphoblastic leukemia
Over the past decades, muscular impairments have been increasingly reported in children with cancer[28], which led to the hypothesis that co-occurrence of such impairment may indicate a state of vulnerability, such as frailty. Muscle wasting is one of the major side effects of high-dose or sustained glucocorticoid treatment[39,40], but the acute impact on muscle mass, strength and physical performance in pediatric cancer patients had never been studied. In this

thesis, we showed that the occurrence of physical frailty increased with 13.5% directly after a 5-day dexamethasone course in children with ALL (*Chapter 5*). Sarcopenia occurred in only 2.8% and did not increase during treatment with dexamethasone, whereas appendicular skeletal muscle mass decreased noticeably. Especially patients that had received maintenance therapy for a shorter time had an elevated risk of physical frailty, which may be because they had not entirely recovered from the intensive induction phase or there may be a nuisance effect of asparaginase. Our results indicated that a poorer physical state (lower muscle mass, lower muscle strength and slower movement) at the start of a dexamethasone course seems prognostic for developing frailty after a dexamethasone course.

Whether the aggravation of frailty in ALL patients can be attributed specifically to dexamethasone remains unknown, as vincristine was also administered on the first day of this course. In addition, asparaginase has been implicated as a potential risk factor for muscle depletion[41] and was administered concurrently in some of the patients. Also, the aberrant nutritional habits[42] and physical inactivity during dexamethasone treatment, as well as genetic susceptibility and pharmacokinetics, should be considered in this matter. In subsequent projects, we will study the course of frailty longitudinally during maintenance therapy, as well as the role of dexamethasone pharmacokinetics and potential single nucleotide polymorphisms in multivariable models.

Despite the widespread use of handgrip strength as surrogate for total muscle strength in research[43], we advocate that this should be reconsidered in pediatric cancer patients. Handgrip strength is a distal measurement of strength in the upper extremity, while in pediatric cancer patients lower limb muscle weakness occurs more often[44], and dexamethasone induces primary proximal muscle weakness.[45] In general, standardization of a physical assessment for sarcopenia and frailty in pediatric cancer patients is needed, as well as the determination of clinically-useful cut-off points.

As for low bone mineral density, potential interventions to decrease the risk of frailty- and sarcopenia-related impairments are in the area of physical activity and exercise. It has been well-recognized that physical activity, including exercise, are safe and potentially beneficial for children affected by cancer, regardless of treatment phase.[46] Recent studies have shown positive effects of various exercise interventions on independence in daily life activities and gross motor performance during cancer treatment.[47,48] In particular, muscle strengthening interventions seem beneficial for improving muscle strength[48-51] and tend to increase daily physical activity level.[48] Beneficial effects of exercise on muscle mass have been scarcely studied during treatment for childhood

cancer.[52] Besides exercise, optimal nutritional state and adequate sleep are often also compromised in children with cancer[53,54], but are mandatory for improving muscle mass, strength and physical performance.[55,56] Future studies focusing on the effectiveness of such three-component (nutrition, sleep and physical activity) interventions are needed.

Accelerated aging in childhood cancer survivors

While in childhood cancer patients the occurrence of frailty is attributed to the disease itself along with acute side-effects of treatment and physical inactivity, frailty has also been recognized as a burdensome long-term side effect.[57] During cancer treatment these patients were exposed to damaging agents (e.g. radiotherapy and chemotherapy) affecting cellular repair mechanisms, which may have accelerated physiologic aging.[58] The frailty phenotype is considered a sign of accelerated aging.[59] In this thesis, we confirmed that frailty is a potential risk for intensively treated Dutch long-term survivors of childhood acute myeloid leukemia, neuroblastoma and Wilms tumor.[60] We found that survivors of acute myeloid leukemia, especially irradiated survivors, seem to have a higher risk of frailty.

Recently, the Dutch Childhood Cancer Survivor Late Effect Study showed that frailty occurs in 7.4% of Dutch childhood cancer survivors and more than three decades earlier in life.[61] Frailty in childhood cancer survivors is of clinically concern. Two previous studies showed that frailty in childhood cancer survivors was associated with onset of several grade 3 to 4 chronic medical conditions and predictive of early disability and mortality.[59,62] Development of prediction models for frailty will facilitate identifying childhood cancer survivors at risk, and supports targeted surveillance and interventions. Moreover, an easy screening method to identify early signs of frailty may aid in timely identifying survivors at risk.

Reversing or slowing the progression features of frailty is of key importance since the exposure from cancer treatment in survivors is irreversible. Clinical trials preventing or remediating frailty in childhood cancer survivors have not yet been pursued or published. Future studies need to unravel if combined exercise and nutritional interventions[63] may aid in preventive, delaying or even reversing the aging process, for example by offering intensive rehabilitation shortly after cessation of therapy.

Cancer-related fatigue

In addition to its share in the frailty phenotype, cancer-related fatigue in itself is one of the most frequently reported side effects during and after treatment for childhood cancer.[64] Cancer-related fatigue is multifactorial and the result

of a complex interaction between biological, psychological and social factors. Acute forms of cancer-related fatigue can occur during treatment and are often related to treatment components (e.g. dexamethasone, radiotherapy). Chronic fatigue is also common and can persist even years after treatment cessation. In this thesis, we observed both increased general and cognitive fatigue in pediatric brain tumor survivors who were on average four years after treatment cessation (*Chapter 8*).[65] Our results also suggested that cognitive fatigue increases in the years after therapy cessation, rather than improving.

The Dutch Childhood Cancer Survivor Late Effect Study reported a prevalence of severe chronic fatigue among adult survivors (median 22.4 years since diagnosis) of 26.1% compared to 14.1% in sibling controls.[66] Survivors of central nervous tumors had an elevated risk of reporting chronic fatigue compared to survivors of other tumors. Cancer-related fatigue limits survivors in attending school or to work, and has a negative effect on quality of life.[66]

Currently, there are no standardized effective interventions available for children with cancer or childhood cancer survivors (under 18 years of age), but given the results from adults with cancer, exercise interventions and cognitive behavior therapy may be promising. In adults with cancer, cancer-related fatigue can be successfully treated with physical exercise programs and/or cognitive behavior therapy.[67,68] Physical exercise programs aim to increase physical activity levels, physical capacity and muscle strength, as well as reducing stress and anxiety. Cognitive behavior therapy addresses triggering and perpetuating factors of chronic fatigue, such as dysfunctional thoughts regarding fatigue, disturbed sleep-wake rhythm and dysfunctional social interactions. Comparable to these results in adults with cancer, increased physical activity levels have shown to be associated with less cancer-related fatigue in children during treatment and/or one year after treatment cessation.[69,70] Moreover, in adolescents with chronic fatigue syndrome (not related to cancer), cognitive behavior therapy has been shown to be a successful intervention in reducing severe fatigue[71], and one previous non-controlled pilot study, showed promising results of cognitive behavior therapy in childhood cancer survivors (mean follow-up 13 years).[72] For effective individual management of fatigue, it is important to unravel the dimension of perceived fatigue, whether its physically (due to limited capacity), cognitive-based fatigue (e.g. caused by brain injury) or induced by disturbed sleep patterns. Future intervention studies with a multidimensional focus incorporating both physically and psychologically aspects of fatigue are essential.

Impact on participation in daily life

Treatment of childhood cancer is burdened with several short and long-term side effects with consequences for physical abilities, cognitive function and subsequent participation in daily life. In particular, pediatric brain tumor survivors may have been exposed to damaging treatment, such a cranial radiation and brain surgery. In this thesis, we showed that age-expected participation was limited in over 50% of brain tumor survivors (on average 11 years of age and 4 years since treatment).[65] These participation restrictions did not seem to diminish over time and were associated with impairment in physical ability and experienced fatigue.

Rehabilitation strategies addressing adaptive techniques to attain independent task performance and provision of environmental adaptations are essential to facilitate optimal participation conditions for a physically and/or cognitive disabled individual. In addition, exercise interventions to optimize and prevent further loss of physical function (i.e. muscle function, cardiorespiratory fitness) and to limit fatigue complaints will likely support participation. The fact that we found that survivors who had similar fatigue levels compared to the general population, also did not report restricted participation, suggests that addressing fatigue (as discussed in the previous paragraph) may be a key treatable factor to reduce participation restrictions.

It is important to acknowledge that generating optimal (physical) circumstances may not be sufficient. Previous studies in children with cerebral palsy for example, showed that participation-focused therapy enabled children to participate in leisure-time physical activities by targeting individual modifiable barriers and facilitators to participation[73], rather than solely improvements of muscle strength and motor function.[74] Two previous studies also urged the importance of potential facilitators and barriers for participation in physical activities for childhood cancer patients and survivors.[75,76] Such standardized participation-focused guidance may be helpful to improve participation in daily life in limited patients and survivors, however this has not yet been studied.

Gaps of knowledge and (pediatric) physiotherapy perspectives

The research described in this thesis is an important step towards improving musculoskeletal health, preventing fractures, muscle weakness, impaired physical functioning, fatigue and increased participation ability for children during and after treatment for cancer. In addition, we identified several gaps of knowledge that need to be addressed in future research (Table 1).

The amount of potential interventions discussed in this thesis underscribe the importance of exercise and the role of physiotherapists in pediatric cancer care. Exercise interventions are important for reducing side effects and treatment burden, preventing physical deterioration and disabilities, enhancing quality of life, and in some cases even improve survival. Risk identification using screening tools and non-invasive diagnostics, as well as timely involvement of professionals is of key importance. The ultimate goal is to eliminate side effects that can be prevented with physiotherapeutic and exercise interventions for all children with cancer. Following the research described in this thesis, expanding knowledge on bone and muscle toxicities, developing and validating non-invasive muscle assessments, as well as developing tailored interventions for specific musculoskeletal vulnerabilities will support children with cancer in maintaining (or retaining) their functional abilities and improving quality of life.

Domain	Directions for future research
Bone fragility	• Further improvement of prediction models by incorporating muscle parameters, treatment and genetic factors • Development of a prediction model for fragility fractures
Muscle impairment assessments	• Validation of the PED-SARC-F in various pediatric oncology patients, such as solid and brain tumors • Prognostic value of the PED-SARC-F for adverse events and disability over treatment • Improving the PED-SARC-F identification of impaired muscle mass • Validation PED-SARC-F, muscle ultrasound and bio-impedance analysis against gold standard measure MRI • Reliability of bio-impedance analysis in different pediatric cancer patients with variation in body size and fluid retention • Normative reference values for bio-impedance analysis and muscle ultrasound • Causality of intramuscular alterations and impaired muscle mass and physical deterioration
Frailty and sarcopenia	• Occurrence of sarcopenia and frailty in different treatment phases and after cessation of treatment • Risk factors for frailty, including dexamethasone pharmacokinetics, vincristine, asparaginase, genetic factors and lifestyle habits • Development of core-set of measurements for frailty assessment

Domain	Directions for future research
Physiotherapeutic and exercise interventions	• Muscle strengthening exercises on preventing or reducing low bone mineral density, fractures, low muscle mass, muscle weakness and impaired functioning. • Multidimensional interventions for severe fatigue and participation limitations • Effect of physical activity on adverse health events and treatment outcome • Prehabilitation for preventing physical deterioration over treatment or after surgery

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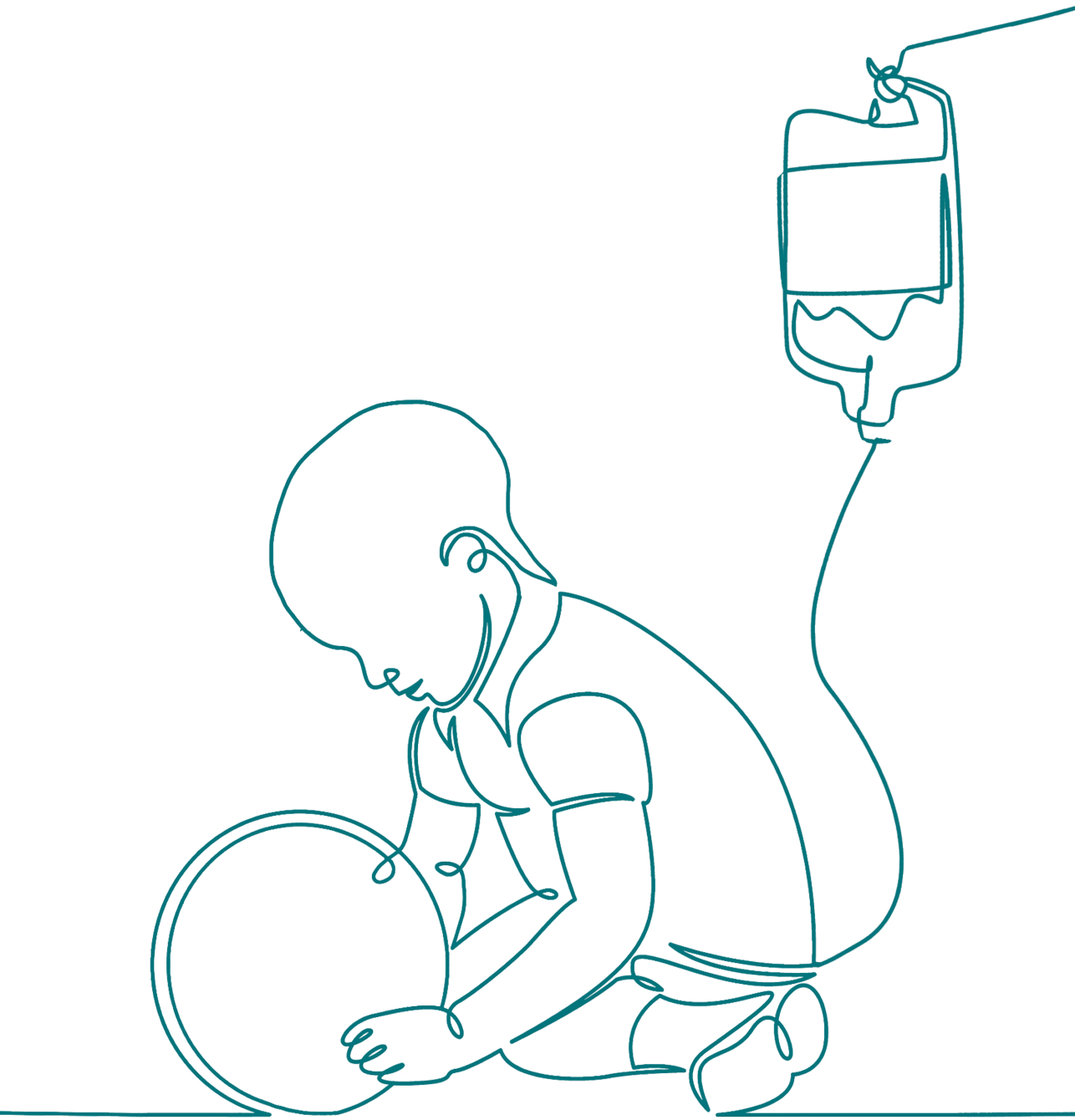

Appendices

English Summary

Every year in the Netherlands, between 550 and 600 children under the age of 19 are diagnosed with a type of cancer. Childhood cancers can be classified into three primary subtypes: hematological, solid, and neurological tumors. Significant advancements in treatment strategies and supportive care over the past decades have resulted in a current 5-year overall survival rate of approximately 83% for the period of 2010-2020. This improved prognosis of childhood cancer treatment has been accompanied by the emergence of acute and late treatment-related complications, resulting from either the cancer itself or its treatment.

During treatment, patients are susceptible to side effects such as general malaise, gastrointestinal problems (leading to malnutrition), pain, increased infection risk, and prolonged hospital stays, which often include periods of compromised mobility. In addition, certain chemotherapeutic agents can have detrimental effects on the musculoskeletal system. These side effects can lead to musculoskeletal impairments, with negative effects on motor development, functional independence, and physical fitness in both the short and long term. On average, 17 years after completing treatment, 75% of childhood cancer survivors experience one or more severe side effect, with 40% suffering from a physical disability.

This thesis focuses on the development and validation of simplified tools for early identification of musculoskeletal impairments in children with cancer. It also explores the risk factors associated with physical vulnerability, specifically sarcopenia (characterized by low muscle strength/function and low muscle mass) and frailty. Frailty is defined as the presence of three or more of the following components: low muscle mass, low muscle strength, fatigue, slow walking speed, and low physical activity. Additionally, in this thesis we examined the prevalence of frailty-related impairments and fatigue, and also the ability to participate in everyday activities in survivors of childhood cancer.

Prior to the work presented in this thesis, it was already known that children with acute lymphoblastic leukemia (ALL) have an increased risk of sustaining fractures. This risk is closely linked to low lumbar spine bone mineral density (LSBMD), particularly at diagnosis. While numerous risk factors for low LSBMD have been identified in past research, these factors had not yet been incorporated into a clinical prediction model. In chapter 2, we developed prediction models for LSBMD at the time of diagnosis and at the end of treatment using a multicenter cohort of newly diagnosed ALL patients from the Netherlands. These models were externally validated in a multicenter

cohort from Canada. Our prediction model demonstrated that patients with low LSBMD can be accurately and simply predicted by using weight Z-scores (a measure that describes its comparison to normative values) and age, right at diagnosis. Clinically useful models like these are not just important for the targeted identification of patients with an increased risk of fractures, but they also assist in making decisions such as whether it is necessary that a child needs a dual-energy X-ray absorptiometry examination for LSBMD assessment.

Besides the risk of bone deterioration, children with cancer are at risk of muscle impairments, such as sarcopenia. Given the serious consequences of sarcopenia leading to increased infections and disability, it is important to identify at-risk patients early. In chapter 3, we examined the diagnostic accuracy of the pediatric version of the SARC-F questionnaire (PED-SARC-F) in identifying structural and functional sarcopenia in children with a hematological malignancy (e.g. leukemia, lymphoma). Our findings demonstrated that the PED-SARC-F is an excellent tool for identifying patients with functional sarcopenia (muscle weakness in combination with impaired physical performance). We proposed a PED-SARC-F score of ≥ 5 as a clinically relevant threshold to identify patients who may benefit from physiotherapist consultation.

Assessing skeletal muscle mass and intramuscular changes in children poses a challenge due to the limited availability of non-invasive, yet valid methods. Intramuscular alterations may already be present long before muscle atrophy and functional impairments become apparent, and thus of importance for early identification. The gold standard for evaluating muscle changes is Magnetic Resonance Imaging (MRI), which enables both quantitative (muscle size) and qualitative (internal muscle aspects) assessments. However, MRI has drawbacks such as being time-consuming, relatively invasive (especially for younger children who may require sedation), and requiring a radiologist for interpretation of the results. Considering the risks and consequences of muscle deterioration in pediatric cancer patients, there is a need for an easy-to-use, non-invasive tool for assessment of muscle alterations. Muscle ultrasonography, a low-cost tool readily available in clinical settings, can assess both muscle size and internal muscle changes and is non-invasive. However, the accurate interpretation of the images requires extensive knowledge of different structures and echogenicity, which limits its usability in clinical practice. In chapter 4, we demonstrated that portable muscle ultrasound was feasible in over three-quarters of patients undergoing treatment for ALL. Additionally, we explored an automated annotation software, that automatically calculates cross-sectional area, thickness, and intramuscular fat tissue based on muscle ultrasound images. The results revealed significant correlations between

muscle cross-sectional area and thickness with overall skeletal muscle mass, as well as a relationship between higher intramuscular fat infiltration and reduced force generation and slower walking performance. These findings support the hypothesis that this method may be a valid approach for estimating skeletal muscle mass and detecting early muscle deterioration in children with ALL.

Prior to this thesis, it was well-known that dexamethasone treatment could lead to muscle wasting, but the relationship between dexamethasone administration and sarcopenia and frailty had not been studied. In Chapter 6, we found a 13.5% increase in the occurrence of physical frailty directly following a 5-day course of dexamethasone. Sarcopenia was present in only 2.8% of cases and did not increase during dexamethasone treatment, whereas there was a noticeable decrease in appendicular skeletal muscle mass. Importantly, our results suggest that a poorer physical state (indicated by lower muscle mass, reduced muscle strength, and slower movement speed) at the onset of a dexamethasone course, seems predictive of developing frailty following the course of the treatment.

Although the occurrence of frailty in pediatric cancer patients can be attributed to the disease itself and/or as acute side-effects of treatment, frailty has also been recognized as a significant long-term side effect. In chapter 7, we showed that frailty poses a potential risk for Dutch long-term survivors of childhood acute myeloid leukemia, neuroblastoma, and Wilms' tumor. Notably, we discovered that survivors of acute myeloid leukemia, particularly those who underwent radiation therapy, appear to be at a higher risk of frailty.

All the previous mentioned short-term and long-term side effects can have a significant impact on everyday life participation. Specifically, survivors of pediatric brain tumors who have been exposed to damaging treatments such as cranial radiation and brain surgery. In chapter 8, we revealed that over 50% of brain tumor survivors (averaging 11 years of age and 4 years post-treatment) experienced limited everyday life participation compared to their age-expected level. Remarkably, these participation limitations did not appear to diminish over time and were associated with physical impairment and reported fatigue. Interestingly, our study revealed that survivors, who reported fatigue levels similar to the general population, did not indicate restricted participation.

In conclusion, the studies presented in this thesis have contributed to the improved identification of bone fragility and functional sarcopenia in pediatric ALL patients. Additionally, we have made the initial steps towards a non-invasive tool for muscle assessment. We have demonstrated the existence of a vulnerability phenotype in both children undergoing treatment and in survivors.

This finding paves the way for potential interventions, and even prehabilitation, to create the physical conditions necessary for participation in daily life. Moreover, we identified several knowledge gaps that future research needs to address, with the ultimate goal of improving musculoskeletal health and enhancing participation ability for children during and after cancer treatment.

Nederlandse samenvatting

Elk jaar worden in Nederland tussen de 550 en 600 kinderen onder de 19 jaar gediagnosticeerd met kanker. Kanker bij kinderen kan worden onderverdeeld in drie primaire subtypes: hematologische, solide en neurologische maligniteiten. Significante verbeteringen in behandelingsstrategieën in de afgelopen decennia hebben geresulteerd in een 5-jaars overleving van ongeveer 83% in de periode van 2010-2020. Echter, deze verbeterde prognose gaat gepaard met korte en lange termijn complicaties die een gevolg kunnen zijn van zowel de kanker zelf als de (intensieve) behandeling ervan.

Tijdens de behandeling krijgen patiënten vaak bijwerkingen zoals algehele malaise, gastro-intestinale problemen (die kunnen leiden tot ondervoeding), pijn, verhoogd infectierisico met langdurige ziekenhuisopnames, en periodes van verminderde fysieke activiteit. Daarnaast hebben specifieke (chemo) therapeutische middelen een negatieve invloed op het musculoskeletaal systeem. Dit kan leiden tot schade van het bewegingsapparaat, met negatieve gevolgen voor de motorische ontwikkeling, functionele vaardigheden en fysieke fitheid op zowel de korte als de lange termijn. Gemiddeld 17 jaar na het voltooien van de behandeling ervaart 75% van 'survivors' (overlevenden) van kinderkanker een of meer ernstige bijwerkingen, waarbij 40% lijdt aan een fysieke beperking.

Dit proefschrift richt zich op de ontwikkeling en validatie van eenvoudige meetinstrumenten voor vroege detectie van musculoskeletale beperkingen bij kinderen met kanker. Daarnaast onderzoekt het de risicofactoren die verband houden met fysieke kwetsbaarheid, specifiek sarcopenie (gekenmerkt door een lage spierkracht/functie en een lage spiermassa) en 'frailty'. Frailty wordt gedefinieerd als de aanwezigheid van drie of meer van de volgende componenten: verminderde spiermassa, lage spierkracht, vermoeidheid, langzame loopsnelheid en lage fysieke activiteit. Ten slotte beschrijft het de prevalentie van fysieke kwetsbaarheid, vermoeidheid en participatie in dagelijkse activiteiten bij survivors van kinderkanker.

Voorafgaand aan het werk in dit proefschrift was al bekend dat kinderen met acute lymfatische leukemie (ALL) een verhoogd risico hebben op het oplopen van botfracturen. Dit risico is geassocieerd met een, vooral bij diagnose, lage botmineraaldichtheid van de lumbale wervelkolom (LSBMD). Hoewel er in eerder onderzoek risicofactoren voor een lage LSBMD zijn geïdentificeerd, waren deze factoren nog niet opgenomen in een klinisch voorspelmodel. In hoofdstuk 2 hebben we voorspelmodellen ontwikkeld voor LSBMD zowel op het moment van diagnose als aan het einde van de behandeling met behulp

van een multicenter cohort van kinderen met ALL uit Nederland. Deze modellen werden vervolgens extern gevalideerd in een multicenter cohort uit Canada. De modellen toonden aan dat patiënten met een lage LSBMD nauwkeurig en eenvoudig kunnen worden voorspeld door het gebruik van gewicht Z-scores (een maat die de vergelijking met normatieve waarden beschrijft) en leeftijd bij diagnose. Klinische voorspelmodellen zoals deze zijn niet alleen belangrijk voor de gerichte identificatie van patiënten met een verhoogd risico op fracturen, maar helpen ook bij het nemen van beslissingen zoals bijvoorbeeld of een kind een botdichtheidsmeting (DXA scan) moet ondergaan.

Naast het risico op fracturen, lopen kinderen met kanker ook het risico op spierschade, zoals sarcopenie. Gezien de ernstige gevolgen van sarcopenie, zoals een verhoogd risico op infecties en beperkingen in functioneren, is het belangrijk om patiënten vroegtijdig te identificeren. In hoofdstuk 3 hebben we de diagnostische nauwkeurigheid van de pediatrische versie van de SARC-F vragenlijst (PED-SARC-F) onderzocht voor het identificeren van sarcopenie bij kinderen met een hematologische vorm van kanker (bijvoorbeeld leukemie of een lymfoom), waarbij wij onderscheid hebben gemaakt in structurele en functionele sarcopenie. Onze bevindingen toonden aan dat de PED-SARC-F een uitstekend instrument is voor het identificeren van patiënten met functionele sarcopenie (spierzwakte in combinatie met verminderde fysieke functie). Voor het identificeren van patiënten met structurele sarcopenia bleek de PED-SARC-F minder geschikt, omdat het instrument minder gevoelig is voor het herkennen van een verminderde spiermassa. We stelden een PED-SARC-F score van ≥ 5 voor als een klinisch relevante drempelwaarde om patiënten met functionele sarcopenie te identificeren die in aanmerking komen voor een (kinder)fysiotherapeutisch consult.

Het meten van de spiermassa en intramusculaire veranderingen bij kinderen is een uitdaging vanwege de beperkte beschikbaarheid van niet-invasieve valide methoden. Intramusculaire veranderingen kunnen al aanwezig zijn lang voordat verlies van spiermassa en functionele beperkingen optreden, en vroege herkenning kan daarmee ondersteunend zijn bij identificatie van fysieke achteruitgang. De gouden standaard voor het meten van spierveranderingen is middels magnetische resonantie beeldvorming (MRI), die beoordeling van zowel kwantitatieve (spiergrootte) als kwalitatieve (interne spieraspecten) factoren mogelijk maakt. Echter, MRI heeft nadelen zoals de tijdsinvestering, relatieve invasiviteit (vooral voor jongere kinderen die mogelijk sedatie nodig hebben), en een vereiste radioloog voor interpretatie van de beelden. Gezien de risico's en gevolgen van sarcopenie bij kinderen met kanker, is er behoefte aan een eenvoudig te gebruiken, niet-invasief meetinstrument. Spierechografie, een goedkoop meetinstrument dat direct beschikbaar is in

de kliniek, kan zowel de spiergrootte als intramusculaire veranderingen meten. Echter, de juiste interpretatie ervan vereist uitgebreide kennis van verschillende structuren van spierweefsel en echogeniciteit, wat de inzetbaarheid in de zorg tot heden beperkt. In hoofdstuk 4 hebben we aangetoond dat spierechografie uitvoerbaar was bij meer dan driekwart van de patiënten tijdens behandeling voor ALL. Daarnaast hebben we een annotatie software onderzocht, die automatisch de dwarsdoorsnede, dikte, en hoeveelheid intramusculair vetweefsel berekent op basis van spierechografiebeelden. De resultaten lieten significante correlaties zien tussen de dwarsdoorsnede en dikte van de spier, en de totale spiermassa. Ook was er een relatie tussen een hogere vetinfiltratie in de spier en een verminderde spierkracht en tragere loopsnelheid bij de patiënt. Deze bevindingen ondersteunen de hypothese dat spierechografie een valide techniek kan zijn voor het inschatten van de spiermassa en het vroegtijdig detecteren van spierverlies bij kinderen met ALL.

Voorafgaand aan dit proefschrift was het al bekend dat behandeling met dexamethason (een veelgebruikt glucocorticoïd) kan leiden tot afbraak van spieren, maar de directe impact van een dexamethasonkuur op sarcopenie en frailty was nog niet onderzocht. In hoofdstuk 6 beschrijven we een 13,5% toename in frailty direct na een 5-daagse kuur met dexamethason bij kinderen met ALL. Sarcopenie daarentegen was aanwezig in slechts 2,8% en nam niet toe tijdens de behandeling met dexamethason, terwijl er wel een opmerkelijke afname was in spiermassa. Dit is te verklaren uit het feit dat de handknijpkracht (de andere component van sarcopenie) niet afnam tijdens de kuur. Belangrijk is dat onze resultaten suggereren dat een verminderde fysieke fitheid (gekenmerkt door lagere spiermassa, verminderde spierkracht en langzamere bewegingssnelheid) bij aanvang van een dexamethason kuur voorspellend lijkt te zijn voor het ontwikkelen van frailty direct na de kuur.

Hoewel frailty bij kinderen met kanker kan worden toegeschreven aan de ziekte zelf en/of acute bijwerkingen van de behandeling, is het ook erkend als een lange termijn effect. In hoofdstuk 7 bevestigen we dat frailty een potentieel risico vormt voor survivors van acute myeloïde leukemie (AML), neuroblastoom en Wilms tumor. Specifiek survivors van AML die bestraling hebben ondergaan, lijken een hoger risico te lopen op frailty.

Alle eerder genoemde korte en lange termijn bijwerkingen kunnen een aanzienlijke invloed hebben op deelname (participatie) aan het dagelijks leven. In dit proefschrift werden specifiek survivors van pediatrische hersentumoren onderzocht, die zijn blootgesteld aan schadelijke behandelingen zoals craniale bestraling en hersenchirurgie. In hoofdstuk 8 zagen we dat meer dan 50% van de hersentumor survivors (gemiddeld 11 jaar oud en 4 jaar na behandeling)

beperkte deelname aan het dagelijks leven ervaarde in vergelijking met wat op basis van hun leeftijd verwacht zou worden. Opmerkelijk is dat deze participatiebeperkingen niet leken af te nemen na verloop van tijd en waren geassocieerd met fysieke beperkingen en mate van vermoeidheid. Hersentumor survivors die vermoeidheid rapporteerden vergelijkbaar met die van de algemene bevolking, hadden echter geen participatie beperkingen.

Samengevat hebben de studies in dit proefschrift bijgedragen aan de verbeterde identificatie van een risico op botfragiliteit en functionele sarcopenie bij kinderen met ALL. Daarnaast hebben we de eerste stappen gezet naar de introductie van een niet-invasief instrument voor het meten van spieraspecten. We hebben laten zien dat frailty zowel bij kinderen tijdens de behandeling als bij survivors voorkomt. Deze bevindingen banen de weg naar mogelijke interventies en wellicht zelfs prehabilitatie, om de fysieke voorwaarden te creëren die noodzakelijk zijn voor deelname aan het dagelijks leven. Bovendien hebben we verschillende kennishiaten geïdentificeerd voor toekomstig onderzoek, met als uiteindelijk doel het verbeteren van de musculoskeletale gezondheid en het verbeteren van het vermogen tot deelname aan het dagelijks leven van kinderen tijdens en na behandeling voor kanker.

Curriculum Vitae

Emma Jacobine Verwaaijen was born in Amsterdam, The Netherlands, on December 13th 1988. She graduated from Vechtstede College in Weesp in 2007. In the same year, she began her studies in physiotherapy at the Amsterdam University of Applied Sciences, where she obtained her bachelor's degree in 2011. Following that, she pursued a master's degree in pediatric physiotherapy at Avans University of Applied Sciences, which she completed in 2015.

Motivated by the scientific aspects of her profession, she obtained her master's degree in Evidence Based Practice in Health Care from the University of Amsterdam in 2017. Alongside her master's studies, she worked as a (pediatric) physiotherapist in a primary care setting in Amsterdam from 2011 to 2016. Subsequently, she gained experience as a clinical pediatric physiotherapist in various academic medical centers in the Netherlands, ultimately specializing in pediatric oncology.

In April 2018, she started her PhD trajectory at Princess Máxima Center for Pediatric Oncology under the supervision of prof. dr. Marry M. van den Heuvel-Eibrink, prof. dr. Rob Pieters and dr. Annelies Hartman. She combined her work as a PhD-student with her clinical responsibilities as a pediatric physiotherapist at the Sports and Exercise center of the Princess Máxima Center. Additionally, she has been supervising several master students and since October 2021, a PhD student.

During her PhD trajectory she participated in the Training Upcoming Leaders in Pediatric Science (TULIPS) PhD curriculum from 2019 to 2021. Since September 2021, she has also been actively involved in the 'Child 2040' committee of the Dutch Association for Pediatric Physiotherapists (NVFK), and starting from March 2022, she has been chairing the NVFK research network for pediatric physiotherapists. Internationally, she has been appointed as the Research Lead within the steering group of the Rehabilitation and Physical Medicine Special Interest Group of the International Society of Paediatric Oncology, which was officially launched in March 2023.

Currently, Emma holds the position of postdoctoral researcher at the Princess Máxima Center. Starting from September 2023, she will also assume the role of postdoctoral researcher at the University of Applied Sciences Utrecht and start as a lecturer in the master's program of Clinical Health Sciences at the University Utrecht. Alongside her research commitments, she continues her work as a pediatric physiotherapist in the pediatric hemato-oncology department and the cancer in pregnancy outpatient clinic at the Princess Máxima Center.

List of publications

This thesis

- **Verwaaijen EJ**, van Hulst AM, Hartman A, Pieters R, Fiocco M, Pluijm SMF, van Litsenburg RRL, Grootenhuis MA, van den Akker ELT, van den Heuvel-Eibrink MM. Physical frailty deteriorates after a 5-day dexamethasone course in children with acute lymphoblastic leukemia, results of a national prospective study. *Submitted*

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- **Verwaaijen EJ**, van Hulst AM, Molinger J, Hartman A, Pieters R, Grootenhuis MA, van den Akker ELT, van den Heuvel-Eibrink MM. The utility of muscle ultrasound in the assessment of muscle alterations in children with acute lymphoblastic leukemia. *J Cachexia Sarcopenia Muscle. 2023.*

- **Verwaaijen EJ**, van der Torre P, Vormoor J, Pieters R, Fiocco M, Hartman A, van den Heuvel-Eibrink MM. Novel Adaption of the SARC-F Score to Classify Pediatric Hemato-Oncology Patients with Functional Sarcopenia. *Cancers (Basel). 2023 Jan 3;15(1):320.*

- **Verwaaijen EJ**, van Hulst A, Fiocco M, Hartman A, Grootenhuis MA, Pluijm S, Pieters R, van den Akker ELT, van den Heuvel-Eibrink MM. Dexamethasone-Induced Sarcopenia and Physical Frailty in Children With Acute Lymphoblastic Leukemia: Protocol for a Prospective Cohort Study. *JMIR Res Protoc. 2022 Apr 11;11(4):e33517.*

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Other

- van Hulst A, **Verwaaijen EJ**, van den Berg SAA, van Litsenburg RRL, Grootenhuis MA, Fiocco M, Neggers SJCMM, van den Heuvel-Eibrink MM, van den Akker ELT. Leptin increase during dexamethasone and its association with hunger and fat, in pediatric acute lymphoblastic leukemia. *Submitted.*

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PhD Portfolio

Name:	Emma Jacobine Verwaaijen
PhD period:	April 2018 – April 2023
Research School:	Clinical and Translation Oncology (Utrecht University)
Department:	Pediatric Oncology (Princess Máxima Center for Pediatric Oncology)
Promotors:	Prof. dr. Marry M. van den Heuvel-Eibrink Prof. dr. Rob Pieters
Co-promotor:	dr. Annelies Hartman

1. PhD training	**Year**
Courses	
SNP Course XVIII: SNPs and Human diseases – MolMed, Erasmus MC (online)	2021
Basic Human Genetics Course: Genetics for Dummies – MolMed, Erasmus MC (online)	2021
Repeated Measurements - NIHES, Erasmus MC (online)	2021
Adobe Illustrator – GSLS, UU (online)	2020
Writing a Scientific Paper – GSLS, UU (online)	2020
Giving Effective Presentations – GSLS, UU	2019
Musculoskeletale Echografie Histologie/Fysiologie – Sonoskills, Rotterdam	2018
Basic course on Regulation and Organization for Clinical Investigators (BROK)	2018
Seminars and Workshops	
Research Retreat Princess Máxima Center	2021
Clinical and Translation Oncology PhD Retreat	2020
PhD Retreat Van den Heuvel-Eibrink Group	2019 2020 2023
Weekly PhD Meetings Van den Heuvel-Eibrink Group	2018 - 2023
Conferences	
Invited speaker	
Dutch Society of Pediatrics (NVK) congress, Arnhem, Nederland.	2022
Oral presentations	
4th Childhood Leukemia Early Adverse Reactions conference	2023

4th Annual meeting of the European Society for Paediatric Oncology (SIOPE), Valencia, Spain	2023
2nd European Congress of Pediatric Physical Therapy, Florence, Italy.	2022
15th International conference on sarcopenia, cachexia and wasting disorders (SCWD), Lisbon, Portugal.	2022
3rd Annual Meeting of SIOPE, online.	2022
Dutch Society of Pediatric Physiotherapy (NVFK) Conference, Zeist, Nederland.	2021
Children's Bone Health (ICCBH) Virtual Forum, online.	2020

Poster presentations

54nd International Society of Pediatric Oncology (SIOP), Barcelona, Spain.	2022
10th International ICCBH conference, Dublin, Ireland.	2022
53nd Congress of SIOP, online.	2021
63nd American Society of Hematology (ASH) Annual Meeting, online.	2021
52nd Congress of SIOP, online.	2020

Attended

The 12th Childhood Leukemia and Lymphoma Symposium, online.	2021
Childhood Leukemia Early Adverse Reactions Symposium, online.	2021
62nd ASH Annual Meeting, online.	2020
11th International Conference SCWD, Maastricht, Nederland.	2018

2. Teaching activities

Supervising a fellow PhD student	2021 – present
Assessing presentations of graduation theses (HU, pediatric physiotherapy)	2022
Supervising master students (HU, pediatric physiotherapy)	2021 - 2023
Supervising a master student (UM, Human Movement Sciences)	2020
Supervising master students (Avans+, pediatric physiotherapy)	2019 - 2020

3. Other activities

Research Lead of the SIOP Physical Medicine and Rehabilitation Special Interest Group	2022 - present

Chair of the Dutch research network of pediatric physiotherapists of the NVFK	2022 – present
Member of the 'Child 2040' Committee of the NVFK: the future of pediatric physiotherapy	2021 - present
Member of the Diversity, Equity & Inclusion working group in the Princess Máxima Center	2020 - 2022
Training Upcoming Leaders in Pediatric Science (TULIPS) PhD Curriculum	2019 - 2021

4. Granted Grant Proposals	
In Beweging: Kinderfysiotherapeut 2040 - Regieorgaan SIA, in collaboration with HU	2023
Travel grant by the Dutch Scientific College of Physiotherapy	2023

5. Awards	
Award for best scientific poster ICCBH Conference, Dublin, Ireland.	2022

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