Physical fitness throughout chemotherapy in children with acute lymphoblastic leukaemia and lymphoma

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RESEARCH

Physical fitness throughout chemotherapy in children with acute lymphoblastic leukaemia and lymphoma

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Abstract

Acute lymphoblastic leukaemia/lymphoma (ALL/LBL) and its treatment interfere with normal physical functioning. However, it remains unclear how physical fitness (PF) is affected throughout treatment for ALL/LBL. Sixty-two patients (2.1 to 18.3 years) treated for ALL/LBL underwent four physical tests at nine timepoints from baseline up to 6 months post-treatment. We assessed muscle strength of the quadriceps and tibialis anterior, standing broad jump test (SBJ) for functional mobility and six-minute walk test (6MWT) for endurance. One-sample *t*-tests were used to compare our results to the norm at each timepoint. Norm-referenced *Z*-scores were predicted based on time, risk group and age at diagnosis, using linear mixed models. Quadriceps strength, SBJ and 6MWT scores were significantly lower than norm values at all timepoints from diagnosis up to 6 months after maintenance therapy. Significant decreases over time were encountered for quadriceps strength and SBJ, mainly occurring after induction therapy ($F=3.568$, $p<0.001$ and $F=2.699$, $p=0.008$, respectively). Age at diagnosis was a significant predictor for tibialis anterior strength ($F=5.266$, $p=0.025$), SBJ ($F=70.422$, $p<0.001$) and 6MWT ($F=15.890$, $p<0.001$) performances, with lower results in adolescents at all timepoints. Six months after treatment, quadriceps strength, 6MWT and SBJ scores remained below expected levels.

Conclusion: The decreased quadriceps strength, functional mobility and endurance at all timepoints, with a large deterioration following induction therapy, suggest the need for early interventions, specifically in the adolescent population. The continued low results 6 months after therapy emphasise the importance of long-term rehabilitation.

What is Known:

- *Acute lymphoblastic leukaemia is the most common type of cancer among children, with increasing survival rates due to therapeutic improvements.*
- *Acute lymphoblastic leukaemia/lymphoma and its treatment can cause muscle weakness, neuromuscular toxicity and a decreased cardiopulmonary fitness. Together with physical inactivity, this can result in a decreased physical fitness.*

What is New:

- *Quadriceps strength, functional mobility and endurance are decreased during treatment for acute lymphoblastic leukaemia/lymphoma. The lowest measurements are observed after induction therapy, suggesting the need for early interventions.*
- *We observed continued lower results for quadriceps strength, functional mobility and endurance at the end of treatment, up to 6 months after therapy, supporting the need for long-term rehabilitation.*

Keywords Acute lymphoblastic leukaemia · Lymphoblastic lymphoma · Physical fitness · Muscle strength · Endurance · Functional mobility

Abbreviations

6MWT	Six-minute walk test
6MP	6-Mercaptopurine
AIC	Akaike's Information Criteria
ALL	Acute lymphoblastic leukaemia
AR	Average risk
ARA-C	Cytarabine
CR	Complete remission
D	Day
Df	Degrees of freedom

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EORTC-CLG	European Organisation for Research and Treatment of Cancer, Children's Leukaemia Group
H	Hour
IT	Intrathecally
IV	Intravenously
LBL	Lymphoblastic lymphoma
MTX	Methotrexate
N	Number of observations
PF	Physical fitness
PO	Orally
POEM	Paediatric Oncology Exercise Manual
SBJ	Standing broad jump
SD	Standard deviation
Sig	Significance
T	Timepoint
VHR	Very high risk
VLR	Very low risk

Introduction

Acute lymphoblastic leukaemia (ALL) is the most common type of cancer among children [1]. Lymphoblastic lymphoma (LBL) is a highly aggressive non-Hodgkin lymphoma variant virtually indistinguishable from ALL and treated according to the same protocol [2]. Over the last few decades, more effective multimodal chemotherapy regimens have greatly improved the outcome of children with ALL/LBL [1, 3]. This has resulted in an overall survival rate of almost 90% in Europe [1, 4]. Consequently, current studies increasingly focus on the potential long-term sequelae of treatments in these survivors [1]. Such sequelae can include a range of physiological changes that interfere with normal physical functioning [5].

First, ALL patients suffer from muscle weakness, as a result of corticosteroid-induced myopathy and disuse atrophy [6, 7]. Second, vincristine, dexamethasone and intrathecal methotrexate can cause significant neuromuscular toxicity [5]. Third, several studies showed lower peak oxygen uptake and anaerobic thresholds in patients with ALL associated with decreased cardiopulmonary fitness [5, 8, 9].

It is well established that children with ALL already have muscle weakness and poor endurance at time of diagnosis [10, 11]. During treatment for ALL, muscle strength in the lower limbs especially has been shown to be significantly decreased [12]. Furthermore, survivors of childhood ALL may experience functional impairments as a result of low levels of muscle strength and poor cardiorespiratory fitness [9, 12–14].

Besides these physiological changes, cancer sequelae and treatment limit participation in physical activity [15, 16]. More specifically, 67% of ALL survivors did not meet the physical activity guidelines in a recent study of Lemay et al. [17].

The abovementioned physiological comorbidities, which are enhanced by physical inactivity, could potentially lead to long-term impaired physical outcomes in ALL patients and survivors.

Some previous studies have investigated functional mobility, endurance and muscle strength in childhood ALL patients and survivors. In one pilot study, hand-held dynamometry and timed up and go were tested, showing children with ALL to have decreased strength and functional mobility early in their treatment compared to healthy peers [18]. Another study reported weaker isokinetic strength during maintenance treatment, comparing ten ALL patients to a matched control group [19]. To estimate functional mobility and endurance, tests such as standing broad jump (SBJ) and six-minute walk test (6MWT) could be used [20, 21]. Hung et al. conducted a cross-sectional, observational study 3 to 36 months post-treatment. Out of 13 participants, 11 underperformed for endurance (estimated with the 6MWT) [22]. Even at ≥ 5 years after completion of ALL therapy, survivors still showed such impaired functional capacity [23].

Although these earlier studies suggested altered physical functioning in ALL patients and survivors, assessments have not been implemented in a longitudinal design yet. To investigate the impact of specific treatment phases, we prospectively investigated objective physical measures in ALL/LBL patients throughout and after their treatment. The first aim of this study was to compare physical fitness (PF) (including muscle strength, functional mobility and endurance) in patients treated for ALL/LBL to the levels of healthy peers before, during and after treatment. The second aim of this study was to investigate the changes of PF over time during treatment. We aimed to address which treatment phase induces the largest decrease in PF, in order to better tailor individualised physiotherapy in the future. Finally, we investigated the influence of age and risk group on the change in PF.

Methods

Participants

In this prospective cohort study, patients aged 3 to 19 years who were diagnosed with ALL/LBL at the Paediatric Oncology department of the University Hospital of Leuven between January 2013 and December 2018 were recruited. Exclusion criteria were mental retardation (e.g. syndrome of Down), patients who relapsed or needed transplantation. All patients were treated according to the treatment guidelines of the European Organisation for Research and Treatment of Cancer, Children's Leukaemia Group (EORTC-CLG) 58,081 study, based on EORTC-protocol 58,951, with a

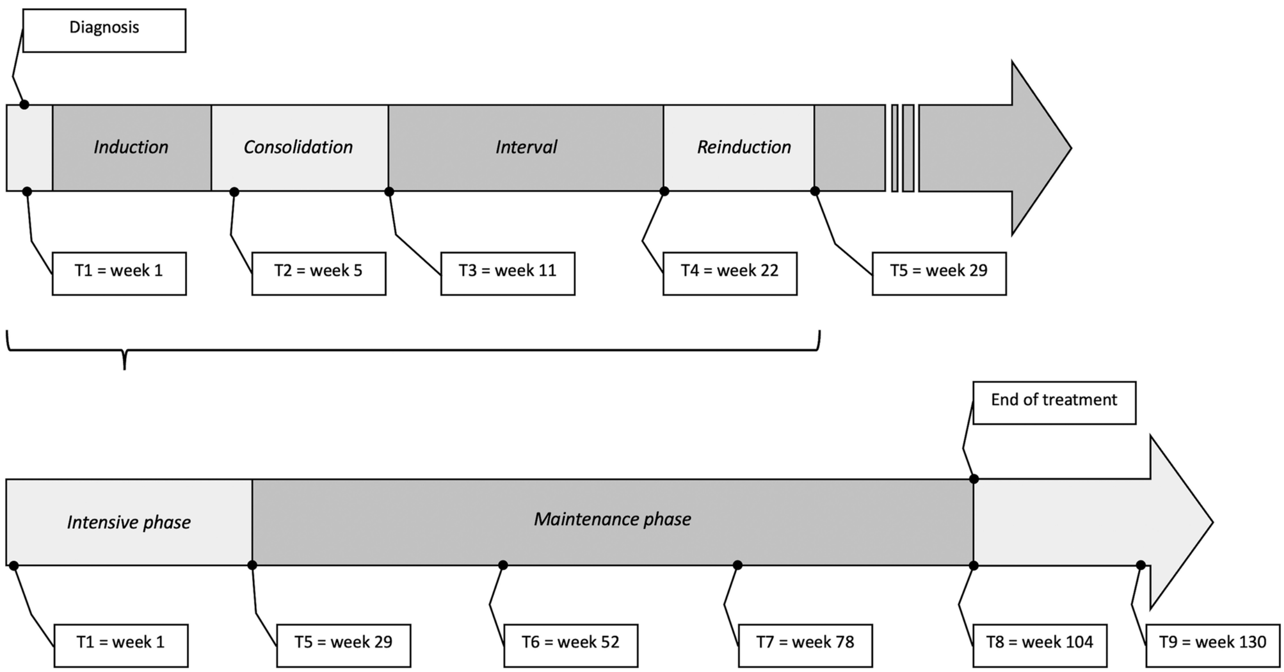

Fig. 1 Overview of treatment and timepoints of physical assessments (T1–T9). T1: pre-phase timepoint, T2: post-induction timepoint, T3: post-consolidation timepoint, T4: pre-reinduction timepoint, T5: post-reinduction timepoint, T6: 6 months after the start of maintenance therapy, T7: 12 months after the start of maintenance therapy, T8: at the end of maintenance therapy and T9: 6 months post-treatment

standard duration of 2 years, including an intensive phase (6 months: induction, consolidation, interval, reinduction phase) and a maintenance phase (1.5 years) (Fig. 1) [4, 24, 25]. Patients were stratified into four risk groups, based on age at diagnosis, white blood cell count at diagnosis, genetic pattern of leukemic blasts, immunophenotype (B-cell or T-cell lineage), corticosteroid responsiveness at day 8, response to induction therapy and minimal residual disease at day 35 and day 90 of treatment. Risk groups were defined as very low risk (VLR), average risk (AR1 and AR2) and very high risk (VHR). A standard treatment protocol can be found in Appendix 1. In addition to chemotherapy and supportive medication, physiotherapy was provided in the hospital during the intensive treatment 2 to 5 times a week, depending on the physical status of the patient. We obtained the most recent data of relevant anthropometrics, including height (cm) and weight (kg) from the patients' medical records at each test session.

Test instruments

We conducted four physical tests evaluating muscle strength, functional mobility and endurance. For muscle strength, quadriceps and tibialis anterior muscle strength were assessed using a hand-held dynamometer type MicroFET 2 (Hoggan Health Industries, USA) [26]. Standing broad jump test (SBJ) and six-minute walk test (6MWT) were assessed to estimate functional mobility and endurance, respectively [27, 28]. These assessments were performed at nine standardised timepoints (T1–T9) throughout and after treatment (Fig. 1).

To test quadriceps muscle strength, the patient sat on a table with hips and knees 90° flexed and feet unsupported. The dynamometer was positioned on the anterior and distal side of the tibia. This position needed to be maintained against traction on the dynamometer. To test tibialis anterior muscle strength, the patient sat on the table in long-sitting position with extended knees and 90 degrees dorsiflexion of the ankle. The dynamometer was placed on the dorsal side of the foot proximal to the metatarsophalangeal joints II to IV. The patient needed to maintain this position while the assessor gave resistance towards plantar flexion. Each strength test was performed three times both on the dominant and the non-dominant side of the patient. The highest value of muscle strength of the dominant side was used as outcome measurement. We focused on the dominant side, as the dominant leg is stronger and thus represents maximal performance, which is in accordance with earlier studies [19].

For the SBJ, we used a nonslip mat and measured how far the patient could jump with both legs together. The longest distance that was reached after three attempts was used as outcome measurement. During the 6MWT, the child was instructed to walk as far as possible within a time frame of 6 min, using a chronometer to measure elapsed time. The test was taken along a 25-m course, indicated by orange cones. Children were not allowed to run during the test. The SBJ was always performed before the 6MWT. All children were verbally encouraged during the test session to reach maximal performance.

Statistical analyses

In order to investigate PF in this population, raw test scores were converted to *Z*-scores using gender- and aged-matched test-specific normative values (i.e. for the hand-held dynamometer [29], SBJ [30–32] and 6MWT [33]). Tests performed at an age exceeding the ranges of available test norms were excluded from analyses (i.e. exceeding the range of 4–16 years for tibialis anterior strength, 6–16 years for quadriceps strength, 3–17 years for SBJ and 3–18 years for 6MWT). Patients treated according to the VHR protocol ($n = 7$) were excluded at timepoint 4 and 5 since the intensive phase in their treatment takes 1 year instead of 6 months in the other groups.

For our first aim, one-sample *t*-tests were used to check if mean *Z*-scores in our patients differ from healthy peers at each timepoint. For our second aim, *Z*-scores (at 9 timepoints) were predicted based on a linear mixed model for each of the four outcomes. Each linear mixed model included the following predictors: ‘time of assessment’ (repeated measure), ‘risk group’ (fixed factor) and ‘age at diagnosis’ (fixed covariate). We added an interaction factor to test whether change over time is subject to age. We checked the Akaike’s Information Criteria (AIC) to select the best fitting covariance structure for each of the four models. All covariance structures and results are provided in Appendix 4. Based on these results, the first-order autoregression structure with homogenous variances was selected for quadriceps strength and SBJ, whereas compound symmetry was chosen for tibialis anterior strength and 6MWT.

To account for missing data, multiple imputations were applied in a secondary analysis [34], assuming data were missing at random. Multiple imputation is a method that allows for uncertainty in the imputed data by creating several plausible imputed datasets (incl. 10 datasets), analysing them and consolidating the results. The minimum and maximum test scores of our original dataset were used as constraint for imputed values. The four statistical models were repeated for each imputed dataset in order to check for robustness of findings. Results are reported as significance in *x*/10 imputations.

A *p*-value ≤ 0.05 was considered to be statistically significant. A Bonferroni correction was applied to account for multiple testing (36 tests for our first aim and 4 tests for our second aim). IBM SPSS Statistics version 28.0.0.0 was used for all statistical tests.

Table 1 Baseline characteristics

	Total ($n = 62$)
Gender	
Male (%)	37 (60)
Female (%)	25 (40)
Risk group	
VLR (%)	4 (6.5)
AR1 (%)	26 (42)
AR2 (%)	25 (40)
VHR (%)	7 (11)
Age group	
Preschool (%)	21 (34)
School age (%)	32 (52)
Adolescent (%)	9 (15)

Age groups are defined as preschool: < 5 years old, school-age: 5–13 years old; adolescent: > 13 years old

AR average risk, *VHR* very high risk, *VLR* very low risk

Results

Study population

In total, 62 patients were included (participation degree of 65%), of which 51 children were diagnosed with ALL and 11 with LBL. The mean age at diagnosis was 7.6 ± 4.3 years, ranging from 2.1 to 18.3 years. This means our youngest patients were only eligible for study later on in treatment. For quadriceps strength, this means we only have data from the preschool group after T7. After this timepoint, 12 patients aged < 5 years at diagnosis had reached the age of 6, for whom normative values are available. Descriptive data can be found in Table 1. Appendix Table 2 shows the mean *Z*-scores for our outcomes at all timepoints and the number of data per timepoint.

Quadriceps strength

At all tested timepoints, quadriceps strength was significantly lower compared to healthy peers (see Fig. 2 and Appendix Table 2). A significant change in quadriceps strength is observed throughout treatment ($F(8, 136.773) = 3.568$, $p < 0.001$), confirmed in all ten imputations (see Table 2 and Appendix Tables 3 and 4). The strongest decrease in strength can be observed between T1 and T2 (i.e. thus after the induction phase) (mean $Z = -1.36$ at T1 to mean $Z = -2.62$ at T2). We observed a slight improvement of strength during the remaining intensive therapy (T2 to T5) and after treatment (T8 to T9), but still no full recuperation to the mean normative values at T9 (mean $Z = -0.80$,

Table 2 Outcomes of linear mixed model analyses

		F	Numerator *df*	Denominator *df*	*p*
Tibialis anterior	Intercept	0.543	1	58.049	0.464
	Timepoint	1.100	8	247.424	0.364
	Risk group	0.337	3	55.069	0.798
	Age at diagnosis	5.266	1	60.141	0.025
	Timepoint × age at diagnosis	0.554	8	246.269	0.815
Quadriceps	Intercept	22.521	1	63.344	< 0.001*
	Timepoint	3.568	8	136.773	< 0.001*
	Risk group	0.230	3	65.097	0.875
	Age at diagnosis	0.799	1	57.353	0.375
	Timepoint × age at diagnosis	1.339	8	134.559	0.229
SBJ	Intercept	5.694	1	66.693	0.020
	Timepoint	2.699	8	196.235	0.008*
	Risk group	2.428	3	63.154	0.074
	Age at diagnosis	70.422	1	69.522	< 0.001*
	Timepoint × age at diagnosis	1.743	8	197.942	0.091
6MWT	Intercept	16.716	1	62.328	< 0.001*
	Timepoint	0.240	8	250.028	0.983
	Risk group	0.684	3	56.719	0.565
	Age at diagnosis	15.890	1	67.808	< 0.001*
	Timepoint × age at diagnosis	2.201	8	251.389	0.028

6MWT six-minute walk test, *df* degrees of freedom, *SBJ* standing broad jump

**P*-values indicated with an asterisk were significant after Bonferroni correction ($\alpha \leq 0.0125$)

$p < 0.001$). Age was not a significant predictor for *Z*-scores of quadriceps strength ($F(1, 57.353) = 0.799$, $p = 0.375$) and the change over time was not significantly different between age groups ($F(8, 134.559) = 1.339$, $p = 0.229$).

Tibialis anterior strength

Our population scored significantly lower on tibialis anterior strength compared to healthy peers at T2 and T7 with the lowest score at T2 (mean $Z = -1.52$, $p < 0.001$) (see Fig. 3 and Appendix Table 2). A recovery of tibialis anterior strength can be observed between T2 and T4 (i.e. during consolidation and interval phase). At T8 and T9, representing the end of treatment and 6 months post-treatment, mean *Z*-scores were slightly positive (mean $Z = 0.33$, $p = 0.370$ and mean $Z = 1.46$, $p = 0.086$, respectively). Despite these differences, the overall change over time was not significant ($F(8, 247.424) = 1.100$, $p = 0.364$) (see Table 2). Furthermore, age at diagnosis was not a significant predictor ($F(1, 60.141) = 5.266$, $p = 0.025$). Comparing age groups, adolescents obtained lower *Z*-scores from diagnosis onwards. The change over time was similar for all ages, as no significant interaction effect was found ($F(8, 246.269) = 0.554$, $p = 0.815$).

Functional mobility

SBJ scores were significantly lower compared to healthy peers at all measured timepoints, except at T9 (see Fig. 4 and Appendix Table 2). Figure 4 shows the changes in SBJ scores over time ($F(8, 196.235) = 2.699$, $p = 0.008$) (see Table 2). The strongest decrease can be observed between T1 and T2 after induction. A smaller decrease can be seen between T4 and T5, representing reinduction. Age at diagnosis was a strong predictor for SBJ ($F(1, 69.522) = 70.422$, $p < 0.001$), consistently across all imputations (see Appendix Table 5). The change over time was not significantly different between age groups ($F(8, 197.942) = 1.743$, $p = 0.091$). However, a trend towards lower SBJ *Z*-scores can be observed for school-aged children and adolescents. Moreover, 6 months after treatment SBJ scores seem to recover for preschool children ($Z = 0.22$), whereas they remain below expected levels (i.e. $Z = 0$) for school-aged children ($Z = -1.19$) and adolescents ($Z = -2.58$).

Endurance

6MWT scores were significantly lower at all timepoints compared to healthy peers (see Fig. 5 and Appendix Table 2). A similar decrease after induction is seen.

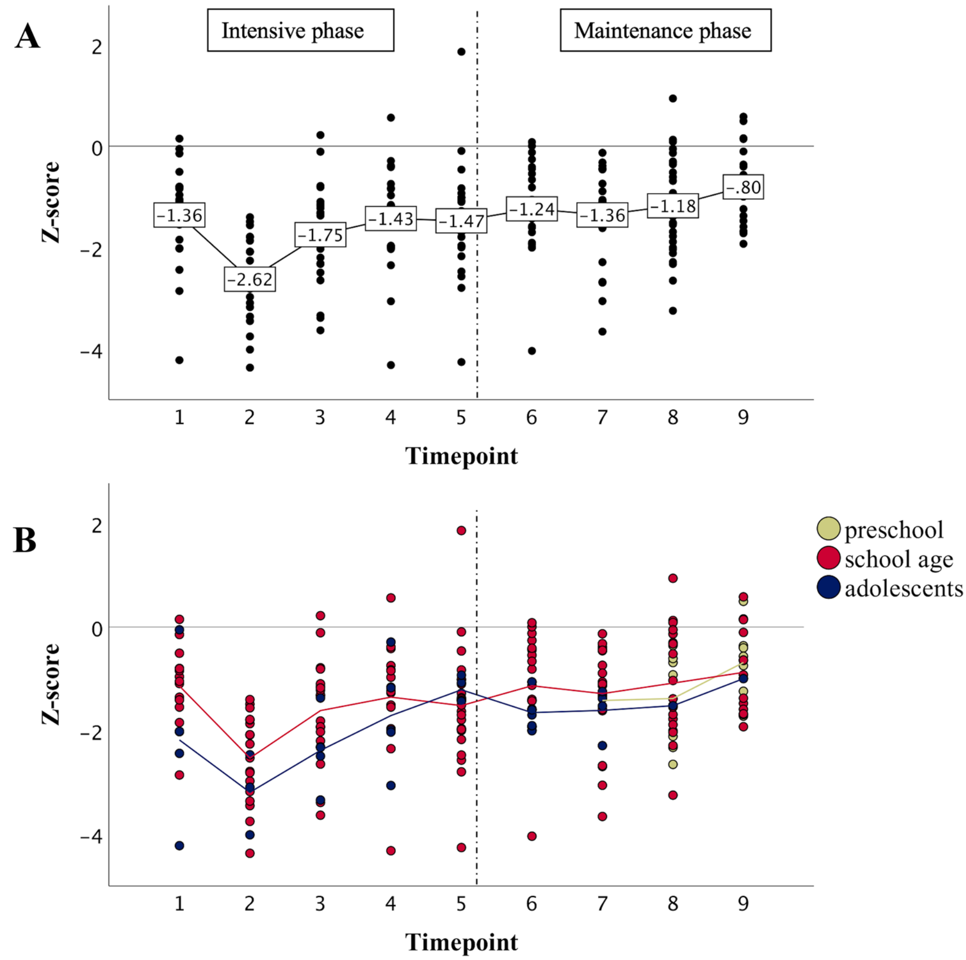

Fig. 2 *Z*-scores for quadriceps muscle strength over time. **A** Mean *Z*-scores of the quadriceps strength at timepoints T1 to T9, compared to norm values. **B** *Z*-scores of the quadriceps strength per age group at timepoints T1 to T9

Although change over time was not significant ($F(8, 250.028) = 0.240$, $p = 0.983$), 9 out of 10 imputations did show significant alterations over time (see Table 2). Age at diagnosis was a strong predictor for 6MWT results ($F(1, 67.808) = 15.890$, $p < 0.001$), confirmed in all imputations (see Appendix Table 6). Clearly, lower scores are again observed in the adolescent group. There is no significant difference in change over time between age groups ($F(8, 251.389) = 2.201$, $p = 0.028$). A partial recovery is seen during maintenance treatment (T5 to T8) even though results remain below predicted values 6 months after treatment for all age groups ($Z = -0.96$ for preschool children, $Z = -1.11$ for school-aged children and $Z = -1.63$ for adolescents).

For all performed tests, no significant differences in outcome were observed between risk groups (see Table 2).

Discussion

In this study, we assessed the changes of muscle strength, functional mobility and endurance throughout treatment for ALL/LBL. Quadriceps strength and 6MWT scores were significantly lower in patients with ALL/LBL compared to the test-specific norm values at all timepoints from diagnosis up to 6 months after maintenance therapy. For SBJ scores, significantly lower results were observed at all timepoints except T9, and for tibialis anterior strength, significantly lower results were only observed at T2 and T7.

The most important decreases in relative test scores were found for quadriceps strength and SBJ with the most remarkable decreases shortly after induction therapy for both tests and a second decrease after reinduction for SBJ only. There was no significant change over time for tibialis anterior strength, nor for 6MWT. Age at diagnosis was a significant predictor for SBJ and 6MWT, with adolescents showing the lowest *Z*-scores at almost all timepoints. For all of our four tests, the changes over time were similar for all ages, and risk group was not a significant predictor.

At the end of treatment, tibialis anterior strength seemed to recover, while quadriceps strength, functional mobility and endurance remained significantly lower than the expected levels. More specifically, SBJ normalised at the end of treatment for the preschool group, but remained below the expected levels for school-aged children

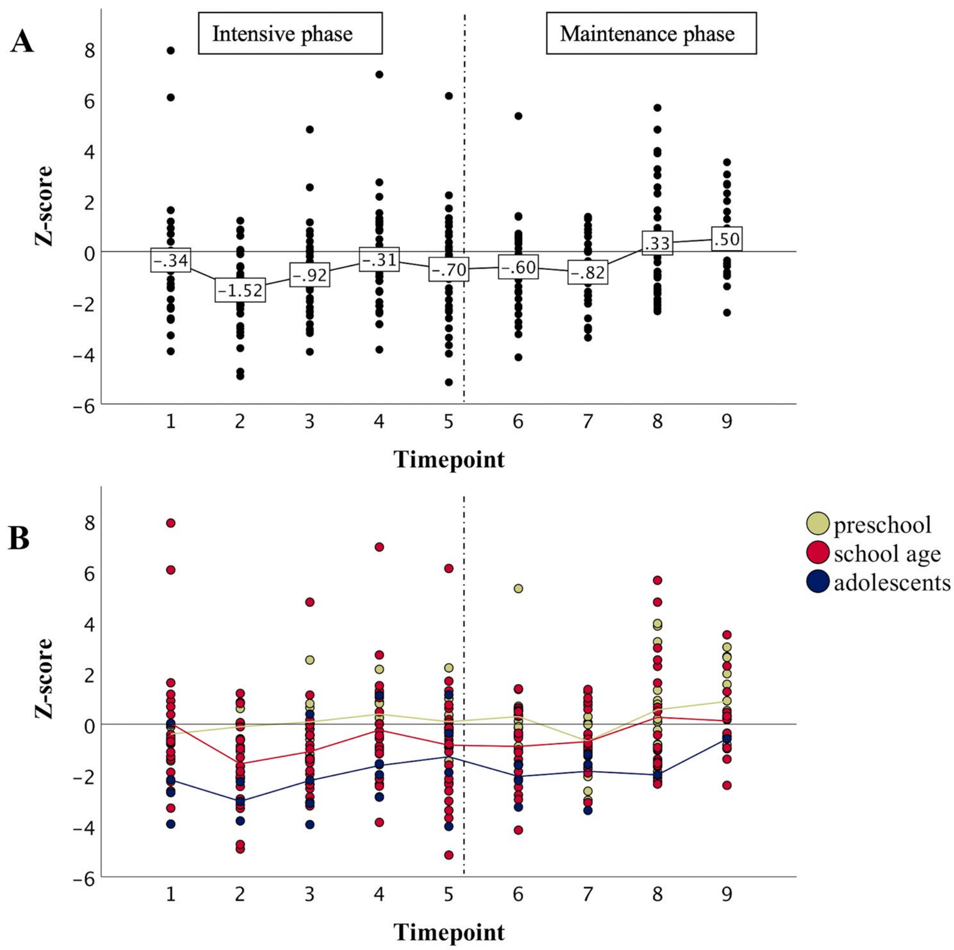

Fig. 3 *Z*-scores for tibialis anterior muscle strength over time. **A** Mean *Z*-scores of the tibialis anterior strength at timepoints T1 to T9, compared to norm values. **B** *Z*-scores of the tibialis anterior strength per age group at timepoints T1 to T9

and adolescents at T9. Quadriceps and 6MWT results remained below the expected levels for all age groups, even 6 months after treatment (T9).

Baseline characteristics

Already at diagnosis (T1), we observed lower test results on all performed tests compared to the norm, except for tibialis anterior strength. This could be explained by an important influence on PF of the disease itself and by the overwhelming psychological impact of the cancer diagnosis. One previous study by Ness et al. revealed similar results 7–10 days after diagnosis with significantly lower quadriceps strength and 6MWT scores, while tibialis anterior strength was not significantly reduced [10]. These findings suggest that children with newly diagnosed ALL already present with deconditioning either related to disease progress and illness or to markedly reduced levels of physical activity. They imply the need for early start of rehabilitation interventions including strengthening and aerobic conditioning.

Changes in physical fitness throughout treatment

Quadriceps strength was significantly lower than norm values at all timepoints. Moreover, the most important decrease in strength was present after induction therapy and a slight improvement in strength was observed during the remaining intensive therapy (T2 to T5) and after maintenance treatment (T8 to T9). Still no full recuperation to the norm was present 6 months after treatment. Such weakness in the quadriceps can partly be explained by the previously reported pattern of change in skeletal muscle mass in ALL patients, observed in a study by Rayar et al. [11]. They showed a drop in lean tissue mass *Z*-score from −0.18 at diagnosis to −1.08 after 6 months of intensive therapy, while partial recovery was seen 12 to 24 months after diagnosis [11]. Moreover, a systematic review on muscle strength in childhood cancer patients and survivors reported impaired strength in 10 to 80% of patients during treatment for haematological malignancies and 11 to 30% in survivors of ALL [12]. These deficits were related to muscles of lower extremities and trunk in general, but quadriceps strength was especially impaired [12].

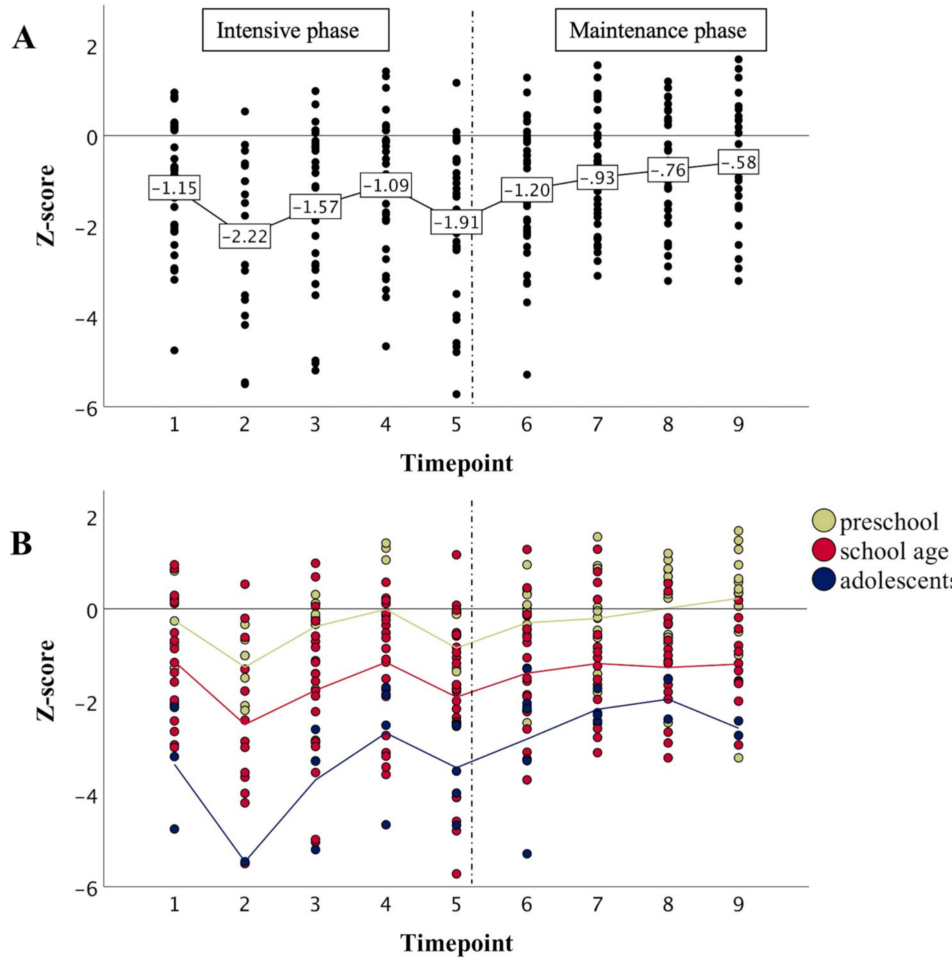

Fig. 4 *Z*-scores for SBJ over time. SBJ, standing broad jump. **A** Mean *Z*-scores of the SBJ at timepoints T1 to T9, compared to norm values. **B** *Z*-scores of the SBJ per age group at timepoints T1 to T9

Regarding functional outcomes, *Z*-scores for SBJ and 6MWT were lower at all timepoints compared to the norm. Moreover, SBJ results showed a large decrease between T1 and T2 (thus after induction) and a smaller decrease between T4 and T5 (thus after reinduction). The 6MWT results showed a similar pattern, although the overall time effect was not significant. Existing literature on 6MWT and SBJ during treatment for ALL/LBL remains very scarce. One observational case–control study assessed a fitness test battery 10 to 24 months after remission, including the SBJ [20]. They showed smaller jumps in the ALL survivor group compared to controls. Hung et al. conducted a cross-sectional, observational study using the 6MWT at 3 to 36 months post-treatment. Out of 13 participants, 11 performed below the norm [22]. Although our patients were tested at 6 months after cessation of treatment, the persistent low SBJ and 6MWT results are concordant with these findings.

Despite our longitudinal design, we are currently not able to distinguish between agent-specific effects for the observed changes in physical fitness, nor to infer causality. The greatest decrease in PF was observed after induction therapy. Besides the neurotoxic effect of vincristine and intrathecal methotrexate, the proximal myopathy secondary to corticosteroids could also contribute to these observations [35]. During the pre-phase and induction, patients receive prednisolone, or a combination with dexamethasone, and during reinduction phase, all patients receive dexamethasone (see Appendix 1). Dexamethasone has been reported to have a greater risk compared to prednisolone to induce myopathy [36–38]. Therefore, a greater decrease in PF would be expected during reinduction phase. Nevertheless, this study shows a larger decrease in PF during the induction phase, suggesting the timing of glucocorticoid therapy and possibly the physical inactivity at the time have a greater influence on PF decrease than the type of steroid itself. Social and behavioural aspects can differ between induction and reinduction phase, with a larger patient and parental motivation for physiotherapy and enhanced coping with the disease and treatment during reinduction phase [39].

During maintenance treatment, our patients continued to show lower PF, despite less intensive treatment at the time. This is in accordance with a previous study demonstrating motor impairments, including balance, flexibility, strength, posture, gait, functional mobility, pain and fatigue during maintenance treatment [40].

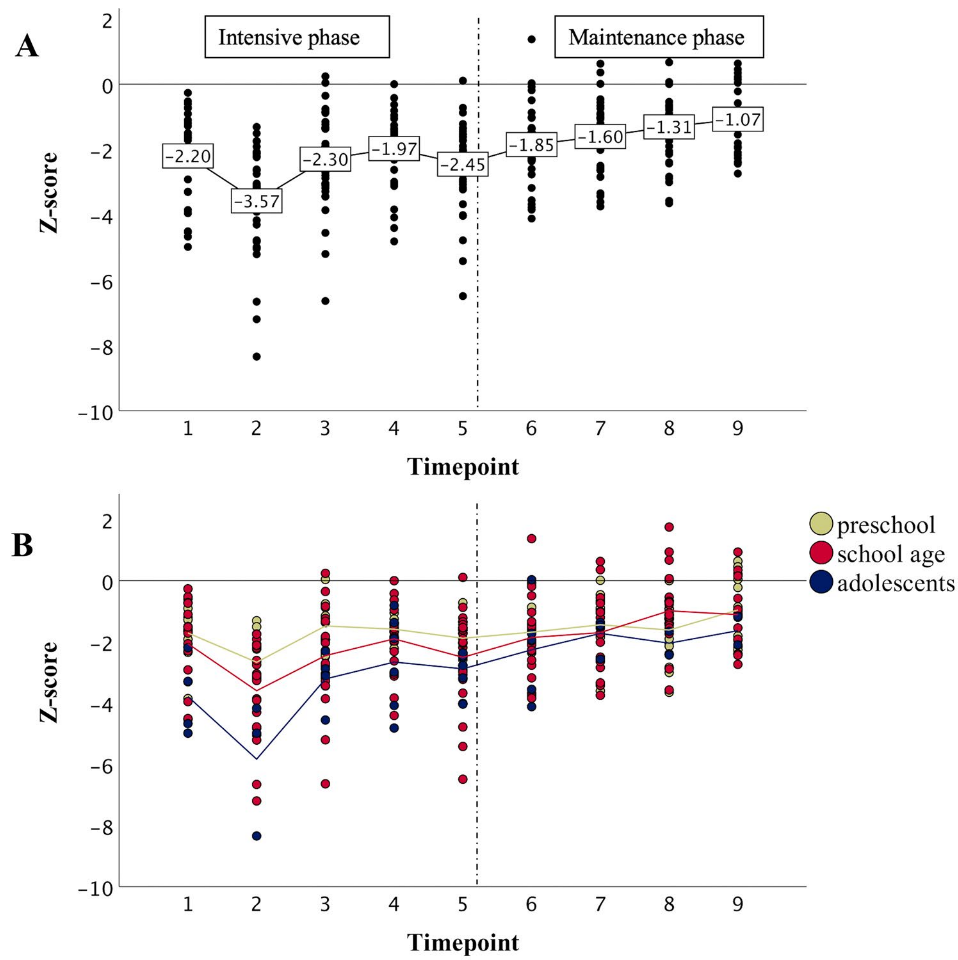

Fig. 5 *Z*-scores for 6MWT over time. 6MWT, six-minute walk test. **A** Mean *Z*-scores of the 6MWT at timepoints T1 to T9, compared to norm values. **B** *Z*-scores of the 6MWT per age group at timepoints T1 to T9

The observation of persistent impairment of functional mobility and endurance 6 months after treatment could be related to late effects of chemotherapy, including cardiotoxic effects, metabolic abnormalities and obesity [40]. Besides these medical risk factors, inactivity and sedentary behaviour of ALL patients play an important role [12, 15, 41]. One study investigated barriers for physical activity during maintenance therapy, showing more than 50% of patients had no exercise habit across all age groups [42]. This trend continues after treatment, with 67% of ALL survivors not meeting physical activity guidelines [17].

Age at diagnosis

Age at diagnosis was a significant predictor for SBJ and 6MWT scores, with lower *Z*-scores in adolescents. In a recent review by Brito-Suárez et al., a higher prevalence of gross motor disorders was found in older children as well, during and after treatment for ALL [43]. Increased age has been associated with a higher risk of vincristine-induced peripheral neuropathy [44]. This could have contributed to the lower observed *Z*-scores in adolescents. Future research could focus on other factors making adolescent more susceptible to a decline in PF. Although we believe adolescents tend to be more inactive than preschool and school-aged children, this could not yet be confirmed by literature [41, 42].

Due to exclusion of tests performed at an age outside the ranges of available norm values, age effects only apply to the normed age ranges as defined in our methods.

Potential interventions

In addition to chemotherapy and supportive medication, all patients in our sample received physiotherapy during the intensive treatment in the hospital 2 to 5 times a week, depending on their physical status. The sessions focused on reconditioning, stretching and tonification of the lower limbs and trunk, according to the Paediatric Oncology Exercise Manual (POEM) [45]. Despite these efforts, patients continue to show lower PF results compared to healthy peers at all timepoints, except for the tibialis anterior strength. After the intensive phase, patients often return to school and pick up their normal daily life, so physiotherapy is not routinely offered anymore. A Cochrane meta-analysis studied the effects of physical exercise training interventions during and after treatment for childhood ALL [46]. Exercise interventions can have a positive effect on bone mineral density, muscle strength, flexibility and cardiorespiratory fitness, facilitating the resumption of activities of daily living [13, 16, 40, 46]. A more recent systematic review evaluated the effect of exercise interventions on motor outcomes within specific phases of treatment [40]. They concluded that *during intensive treatment*, evidence on the efficacy of individualised, supervised exercise intervention is still preliminary [40, 47]. To be able to improve individualised programmes, future research should focus on the type, dose and intensity of early exercise programmes, targeting the prevention of treatment side effects, especially after induction therapy [40, 47]. Exercise interventions *during maintenance treatment* result in positive effects on PF and physical activity [40]. Our results suggest that such interventions need to be individualised, but that most patients would consistently need a combination of strengthening and aerobic exercises. Such exercise programmes should be complete, varied, age-appropriate and embedded in interdisciplinary family-centred care, in order to support children and their families with adherence to exercise recommendations [13, 40]. In the *post-treatment phase*, positive effects of physical activity and exercise interventions are well established, yet inactivity tends to continue after treatment [17, 40]. Altogether, this emphasises the need for incorporation of physical activity and exercise into treatment and post-treatment rehabilitation recommendations [15].

Limitations and future perspectives

The present study had a number of limitations. First, the study sample was relatively limited, similar to previous studies [12, 19, 42]. Second, as a result of the longitudinal design, a substantial number of data were missing, often due to sickness or isolation of the patients at the time of the test. Some patients were not included yet as the timepoint had passed, or some patients were too young to include as there were no age-matched reference data available. Hence, we cannot exclude the possibility of bias in our population. We applied multiple imputation to maximally counter this issue. For each finding, the results were reported for the original dataset, as well as the 10 imputed datasets, to critically interpret the significant results from the dataset and across the imputations.

In this study, Bonferroni correction was selected to correct for multiple comparisons, in order to minimise the risk of type 1 errors, and thus false-positive findings. We mainly focused on the results surviving this correction, to state conclusions based on the encountered significant findings. Still, we cannot exclude the possibility that by applying this relatively stringent correction, non-significant results could currently be underestimated [48].

Another limitation is the lack of a control group. Test scores were currently only norm-referenced based on reference values from literature.

Still, this is the first longitudinal study showing objectively assessed PF tests during and after treatment for childhood ALL/LBL. Hence, future studies including longitudinal designs are needed to validate our findings and identify factors that could influence responsiveness to exercise in patients with ALL/LBL, in order to better tailor individualised physiotherapy. Other studies might focus on ways to overcome the barriers of physical inactivity during and after treatment.

Conclusion

We conclude that continuous attention to low PF in children with ALL/LBL is required throughout treatment and post-treatment. Children with ALL/LBL appear to be most susceptible to decline in physical capacity during induction phase, but continue to show significantly lower PF results compared to healthy peers throughout and after the treatment. Additional research will need to determine whether early exercise or rehabilitation could prevent this decline in functioning. Besides, future interventions might need to target prevention of the low functional mobility and endurance post-treatment, specifically in the adolescent subgroup. These observations can be used to implement better standardised follow-up of PF and tailor individualised physiotherapy throughout treatment.

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Authors' contributions All authors contributed to the study conception and design. Material preparation and data collection were performed by MG, VD and EV. Data analysis was performed by CS and AV. The first draft of the manuscript was written by AV and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethics approval The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University Hospitals of KU Leuven (Date: February 22, 2013, No: B322201317067).

Consent to participate Written informed consent was obtained from the parents. No additional consent was requested for data sharing, so data are only available in case of additional requests and approval by the ethical committee.

Conflict of interest The authors declare no competing interests.

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