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Effects of a structured exercise therapy on health-related quality of life in pediatric stem cell transplantation

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Abstract

Introduction. This randomized controlled trial investigated the effects of exercise therapy on cancer-related fatigue (CRF) and its association with health-related quality of life. The effect of exercise therapy on the quality of life of children after stem cell transplantation has not been extensively studied to date.

Methods. Seventy-two children and adolescents after stem cell transplantation were randomly assigned to either an exercise therapy intervention group (IG) or a control group (CG). The children in IG received sports therapy, while the children in the CG engaged in concentration tasks, memory games, and quizzes.

Results. Significant improvements in CRF were found in IG only after discharge from the hospital. The improved CRF correlated significantly with increased health-related quality of life. However, during the inpatient phase, there was a rapid increase in CRF initially, which was accompanied by a significant reduction in health-related quality of life.

Conclusions. Exercise therapy can help reduce CRF and, therefore, increase health-related quality of life after the inpatient phase.

Key words: pediatric oncology, childhood cancer, stem cell transplantation, physical therapy, quality of life, fatigue

Introduction

Pediatric hematopoietic stem cell transplantation (HSCT) is a renowned therapy for curing various pediatric hematological and oncological diseases [1]. An improvement in the overall survival rate can be seen, but it is also associated with physical and mental side effects that children suffer from, such as neutropenia, mucositis, and cancer-related fatigue (CRF) [2–5]. These side effects can last for several years, which affects participation in daily life activities, social interactions, and family relationships, resulting in reduced health-related quality of life (HRQoL) in patients [6–10]. Tremolada et al. [7] show in their review that HRQoL decreases during HSCT before improving after four to 12 months, but it can take up to three years to return to pre-treatment levels. The lowest scores of HRQoL can be observed between one and three months after HSCT.

One approach to minimizing these side effects of HSCT is exercise therapy. Research on adult patients after cancer treatment has shown promising results regarding the improvement of mental well-being and lower levels of fatigue due to exercise therapy [11]. The same positive effect of physical exercise on quality of life was found in several studies [11–13]. Kisch et al. [14] are promoting a feasible exercise program for adult patients undergoing HSCT. Two meta-analyses [15, 16] recommend incorporating an exercise program into HSCT care in adults, suggesting it helps reduce negative side effects in adult patients after stem cell transplantation.

Further research shows that exercise therapy can also have positive effects on children after HSCT. A recently published systematic review and meta-analysis [17] suggest an exercise program including aerobic, flexibility, and strength training 3–5 times a week, starting immediately after admission and continuing after discharge. The program helped patients improve their physical well-being and might affect HRQoL similarly. This is supported by another systematic review and meta-analysis [18]. While most studies included in these reviews showed a positive response regarding HRQoL, none provided statistically significant results.

Rosenhagen et al. [19] evaluated exercise therapy during pediatric HSCT in their implementation study. Thirteen children were assigned to an intervention group (IG) and received a special exercise program shown to be feasible, safe, and promising toward improving HRQoL and CRF results. The BISON-study group provided evidence of the effectiveness of exercise therapy on CRF in pediatric HSCT [20]. This kind of therapy can, therefore, be recommended to reduce CRF.

Despite significant research on exercise therapy after HSCT in the last 15 years, there are still insufficient statistically significant results proving its effect on HRQoL in pediatric oncology. Because there is evidence of a positive effect on CRF in children after HSCT [20], and because CRF is a reason for reduced HRQoL, it is worth investigating whether there is a correlation between the two.

The aim of the following study is to evaluate the impact of exercise therapy on HRQoL in children and adolescents undergoing HSCT. This leads to the following research questions:

– The main research question is: Does exercise therapy improve HRQoL in pediatric patients after HSCT?

– A second research question is: Does exercise therapy significantly improve HRQoL more than the control condition?

– The third research question is: Is there a correlation between HRQoL and CRF?

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Subjects and methods

The short- and medium-term effects of structured exercise therapy during and after HSCT in children and adolescents were investigated in this randomized controlled trial. Throughout the study, the effects of exercise therapy on HRQoL and CRF were measured. Data collection was conducted between January 2011 and December 2014 at the Stem Cell Transplantation Centre of the Department of Pediatric and Adolescent Medicine at Goethe University Hospital, Frankfurt, Germany.

It was ethically difficult to justify using an untreated control group (CG) because comparable trial results suggest the success of the intervention. To address concerns that social contact would affect the results of the experiment, CG also received social contact and human empathy. Therefore, it was possible to ensure that the only difference between the two groups was the therapy for IG.

The so-called BISON study was a monocentric prospective, randomized-controlled intervention study for evaluating supportive exercise therapy, where two phases were distinguished after HSCT: an inpatient (phase 1) and an outpatient (phase 2) phase. Participants were randomly allocated to IG or CG at the beginning of phase 1. Computer-assisted randomization was performed by an internal study director and was subsequently discussed in detail with patients and parents.

In phase 1, patients were observed during the acute phase of transplantation from inpatient admission (t_{pre}) to discharge (t_{post}). During inpatient treatment, IG and CG received 45–60 min of therapy five times a week.

IG received age-appropriate, individualized treatment that incorporated strength, endurance, and flexibility training. Patients ≥ 136 cm tall used a bicycle ergometer for the endurance training with a target exercise time of 10–30 min and self-adjustment of the resistance during training. When a continuous 10-min load time was not possible, it was achieved using an interval method on a cumulative basis. Children below this height did alternative endurance-oriented exercises such as step aerobics, ball games, movement stories, or endurance games with the Nintendo Wii console. Continuous heart rate monitoring ensured safety, with a limit of (180 – age) bpm based on an implementation study [21].

Strength training aimed to improve ADL-related mobility and muscle strength with exercises for lower extremities and trunk muscles (5 times/week, 3–6 exercises, 1–3 sets, 8–15 repetitions, rests 60–120 s). The intensity of each exercise was adjusted using incremental resistance and exercise modifications. Exercises were conducted off-bed, but a bed-adapted program was used when health restrictions applied. Flexibility training included active and passive stretching with mainly low-intensity static exercises to prevent injury and hemorrhage.

CG received age-specific concentration training (memory training/mental training, e.g., puzzles), perception, and relaxation exercises daily for 45–60 min to ensure that these children also benefited socially from the treatment. A low-movement intervention (e.g., attention and concentration training, relaxation elements) was provided daily. Given the increasing prevalence of long-term effects, especially after CNS-specific therapy, the 45–60 min control intervention included predominantly cognitive enhancement:

– riddles, knowledge quizzes, social games with cognitive targets, perceptual exercises, etc.

– passive relaxation methods such as hedgehog ball massages, autogenic training, or free activities based on patient preferences.

To prevent serious movement restrictions, the control intervention for CG occurred off-bed at a table whenever possible. This approach enabled physiotherapists to detect early contractures or muscle atrophies and initiate necessary measures with the ward physicians.

Both treating female therapists had equal training, experience, and qualifications. The two therapists studied together at the same university, graduated in the same year, and started working in the children's clinic at the same time. Only these two therapists were used across all groups and were not blinded.

In phase 2 of the study, participants were examined on day +100 (t_{100} = 3-month follow-up) and day +200 (t_{200} = 6-month follow-up). A new stratification of the subjects (shown in Figure 1) was necessary to meet the special requirements of outpatient follow-up care. Participants originally randomized into one of the two study conditions were divided into four new groups in phase 2. Children and adolescents receiving medical care in Frankfurt participated in outpatient exercise ther-

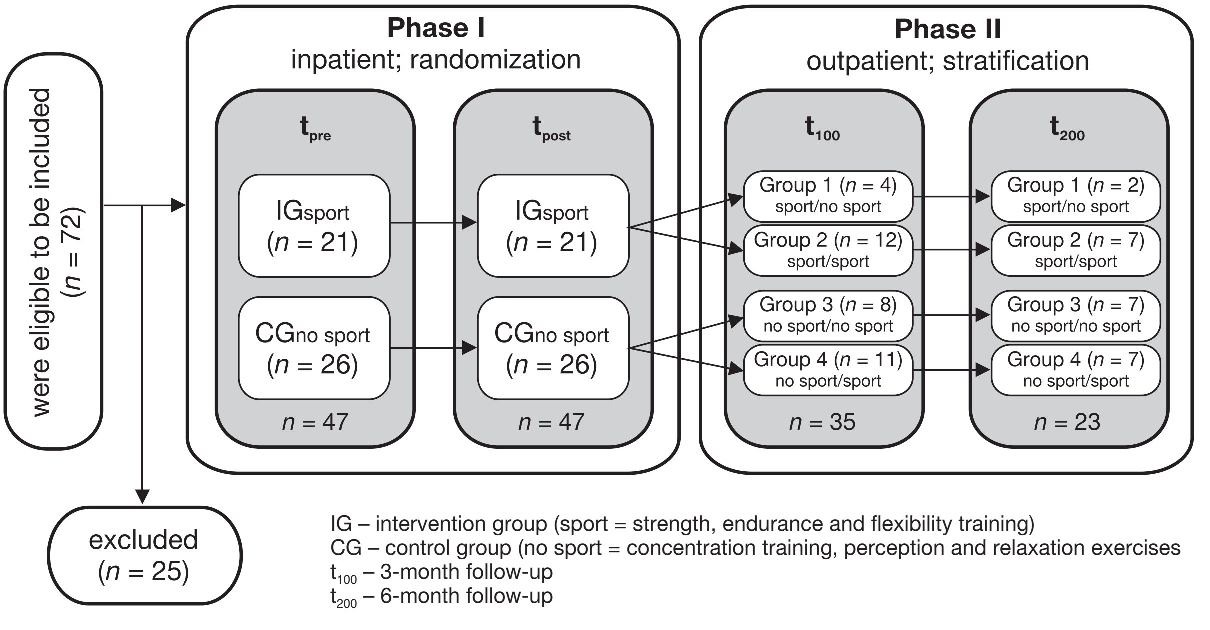


Figure 1. Flow diagram – participants after randomization and stratification

apy, while foreign minors were assigned to a waiting CG. Outpatient treatment was completed six months after the HSCT.

The content of the interventions and exercises remained consistent for both inpatient and outpatient children. Only the inpatient CG received a kind of "sham" treatment from the therapists, while outside the hospital, the "no-sport groups" chose not to engage in sports at their own risk.

The entire study protocol can be accessed at the Department of Stem Cell Transplantation and Immunology at the Goethe University Children's Hospital in Frankfurt. After obtaining written informed consent, the children completed a series of subjective and objective tests to assess physiological and psychometric criteria at least seven days before hospitalization. After the tests, the sealed, opaque, and consecutively numbered envelopes were opened by the study coordinators.

The PedsQL 4.0 (Pediatric Quality of Life Inventory Version 4.0) was used to examine the effect of exercise therapy on HRQoL [22]. The questionnaire has four dimensions, with 23 questions in total (8, 5, 5, 5) that add up to a total scale score (TSS). Items are reverse-scored and transformed to a 0–100 scale. A higher score indicates better health-related quality of life; lower values indicate reduced HRQoL. This questionnaire was designed to measure the core dimensions of health (physical, emotional, and social activities) as well as school activities. The TSS and the scores of the four dimensions were used as primary outcomes. Both the PedsQL child self-report and the PedsQL parent proxy-report were used to determine participants' HRQoL at four measuring points (t_{pre}, t_{post}, t_{100}, t_{200}). A blind reviewer scored all PedsQL questionnaires at the end of the study.

All child and adolescent responses came directly from the children themselves, who completed these questionnaires while their parents filled out corresponding parent questionnaires. This simultaneous completion helped minimize parental influence.

A total of 72 children and adolescents (24 girls, 48 boys) aged 5 to 18 years (mean 11.1 years) who underwent allogeneic or autologous stem cell transplantation were included in the study. We calculated a posteriori power analysis according to Kumle et al. [23] with the following properties: We set the sample sizes for the simulations equal to the actual sample sizes and conducted 200 simulations each. The critical value was set to 2. Effect sizes were computed using Brysbaert and Stevens' method [24]: *d* = estimated difference / sqrt(sum of all variances in random effects). Recruitment was based on inclusion and exclusion criteria as part of the medical preparation for transplantation by the physicians.

The inclusion criteria were as follows: Children aged five years and older could be included with written parental consent if there was an indication for allogeneic or autologous stem cell transplantation. Basic knowledge of German or English was essential for children and parents.

The exclusion criteria were as follows: Children aged < 5 or > 18 years; families with language barriers; children with contraindications to physical activity; children requiring special physiotherapy treatment during transplantation or suffering from severe orthopedic, neurological, or cardiopulmonary comorbidities.

Participants and their parents received detailed verbal and written information from a physician about the aims of the study and subsequently provided written consent to participate voluntarily. Participants could discontinue their participation at any stage without justification and without negative effects on their medical therapy. IG included 21 subjects, and CG included 26 subjects after excluding 25 subjects (e.g., due to missing values or medical problems) (see Figure 1). The sample consisted of 18 girls and 29 boys diagnosed with various tumors, as shown in Table 1.

In phase 2, the two groups were stratified based on the proximity of their home to our center: Children living far away received follow-ups at their home clinics (which could not perform HSCT), whereas those living nearby were offered an outpatient sports program with the same content as IG. Phase 2 began immediately after hospital discharge (t_{post}) and was initiated with a stratified sample of four groups. Participants in these groups received an average of about 1.5 exercise sessions per week lasting 30–50 min (mean 40 min). Children living further away only underwent testing at t_{100} and t_{200} and did not receive exercise therapy at their home clinics. Survey responses did not indicate whether they engaged in private sporting activities.

This resulted in the following new grouping:
Group 1 = inpatient sports and outpatient no sports (s/ns; *n = 4*)
Group 2 = inpatient sports and outpatient sports (s/s; *n = 12*)
Group 3 = inpatient no sports and outpatient no sports (ns/ns; *n = 8*)
Group 4 = inpatient no sports and outpatient sports (ns/s; *n = 11*)

All outcome subscores and the total score are the mean values of the questionnaire items. Because the questionnaire items were coded between 0 (lowest value) and 100 (highest value), the scores can be interpreted on a common scale. To test for group differences between the scores within phases 1 and 2, linear mixed-effects models (i.e., mixed-model ANOVAs) with time and group (both as fixed factors), time × group as an interaction effect, and subjects as a random factor were conducted. This procedure is appropriate to account for the high dropout rate (e.g., regarding the total fatigue score (TFS), from $n = 61$ in pre to $n = 53$ in post to $n = 40$ in t_{100} to $n = 28$ in t_{200}) without excluding data case-wise. All fixed effects – i.e., two main effects and one interaction effect – were analyzed with type II Wald χ^2-tests, yielding a 2 × 2 design in phase 1 with a dichotomous group variable (IG, CG) and the time points t_{pre} and t_{post}. In phase 2, a 3 × 4 design was used due to the new stratification (groups 1–4) and the time points t_{post}, t_{100}, and t_{200}. We differentiated between sub-hypotheses regarding each subscore of the questionnaires. The significance level was set at $\alpha = 0.05$ (trend significance defined as $\alpha = 0.1$). Concerning the assumptions of the models, normality was assessed using Shapiro–Wilk tests, and histograms were visually inspected. Homoscedasticity was tested using Levene tests. In cases of significant results due to the model outcomes, post-hoc tests were not calculated. Descriptive results include estimated marginal means and standard deviations, presented as simple error bar charts. In addition, Pearson correlations between children's and parents' subscores and total score were calculated. We also computed correlations between self-reported fatigue score and HRQoL.

Results

In terms of HRQoL, the analysis of phase 1 showed the following:

Based on self-report, a significant reduction ($\chi^2_1 = 28.4$, $p < 0.001$) in physical activities (PA) is found as a main effect from t_{pre} to t_{post} (IG: 73.01 to 51.33; CG: 66.16 to 52.39). No interaction effect is detected ($\chi^2_1 = 1.45$, $p = 0.23$).

The parent proxy-report for phase 1 shows a significant reduction over time ($\chi^2_1 = 23.4$, $p < 0.001$) in children's HRQoL

Table 1. Biometrical data of the samples considering the different phases (numbers in brackets represent the smaller sample size in t_{200})

Inpatient phase		Overall		IG		CG					
Sex	girls	18		7		11					
	boys	29		14		15					
		mean	*SD*	mean	*SD*	mean	*SD*				
Height (cm)		150,0	20,7	150,4	21,0	149,7	20,9				
Body weight (kg)		41,1	16,9	44,0	17,0	38,7	16,8				
Age (years)		11,3	3,6	11,3	3,6	11,3	3,7				
Leukemia		11		12							
Myelodysplastic syndromes		3		4							
Neuroblastoma		2		1							
Hematologic disease		2		2							
Soft tissue sarcoma		1		3							
Lymphoma		2		3							
Malignant tumor		0		1							
Outpatient phase		Overall		Group 1		Group 2		Group 3		Group 4	
Sex	girls	12 (7)		2 (1)		2 (1)		1 (1)		7 (4)	
	boys	23 (16)		2 (1)		10 (6)		7 (6)		4 (3)	
		mean	*SD*	mean	*SD*	mean	*SD*	mean	*SD*	mean	*SD*
Height (cm)		150,4 (152,3)	20,8 (19,2)	155,3 (176,5)	31,6 (26,2)	147,1 (141,4)	18,3 (7,6)	155,4 (154,1)	23,5 (25,1)	148,7 (154,6)	19,4 (14,6)
Body weight (kg)		41,3 (42)	17,1 (16,7)	43,7 (57,8)	20,6 (18)	41,7 (36,9)	15,9 (11,2)	42,8 (43)	21,4 (23,1)	38,9 (41,4)	15,9 (14,1)
Age (years)		11,4 (11,4)	3,7 (3,2)	12,5 (15,5)	5,1 (0,7)	10,6 (9,9)	3,1 (1,2)	11,5 (11,1)	4 (4,2)	11,8 (12,1)	3,8 (3)
Leukemia				1 (1)		8 (6)		4 (3)		5 (3)	
Myelodysplastic syndromes				1 (0)		1 (1)		3 (3)		1 (1)	
Neuroblastoma				0 (0)		1 (0)		0 (0)		0 (0)	
Hematologic disease				2 (1)		0 (0)		1 (1)		1 (0)	
Soft tissue sarcoma				0 (0)		0 (0)		0 (0)		1 (0)	
Lymphoma				0 (0)		2 (0)		0 (0)		3 (3)	
Malignant tumor				0 (0)		0 (0)		0 (0)		0 (0)	

IG – intervention group, CG – control group, t_{200} – 6-month follow-up

related to PA in both groups (IG: 59.6 to 35.2, CG: 56.2 to 38.9; no interaction effect: $\chi^2_1 = 0.7$, $p = 0.4$).

Parents perceive their children's HRQoL in PA to be more affected (generally lower values) than the children's self-report indicates. However, there is general agreement regarding the reduction in quality of life in phase 1.

In IG, from t_{pre} to t_{post}, emotional activities (EA) values decrease from 78.55 to 71.35, while in CG, values increase from 70.56 to 77.69, resulting in no significant time effect ($\chi^2_1 = 0.02$, $p = 0.9$), but there is an interaction effect ($\chi^2_1 = 8.3$, $p = 0.004$).

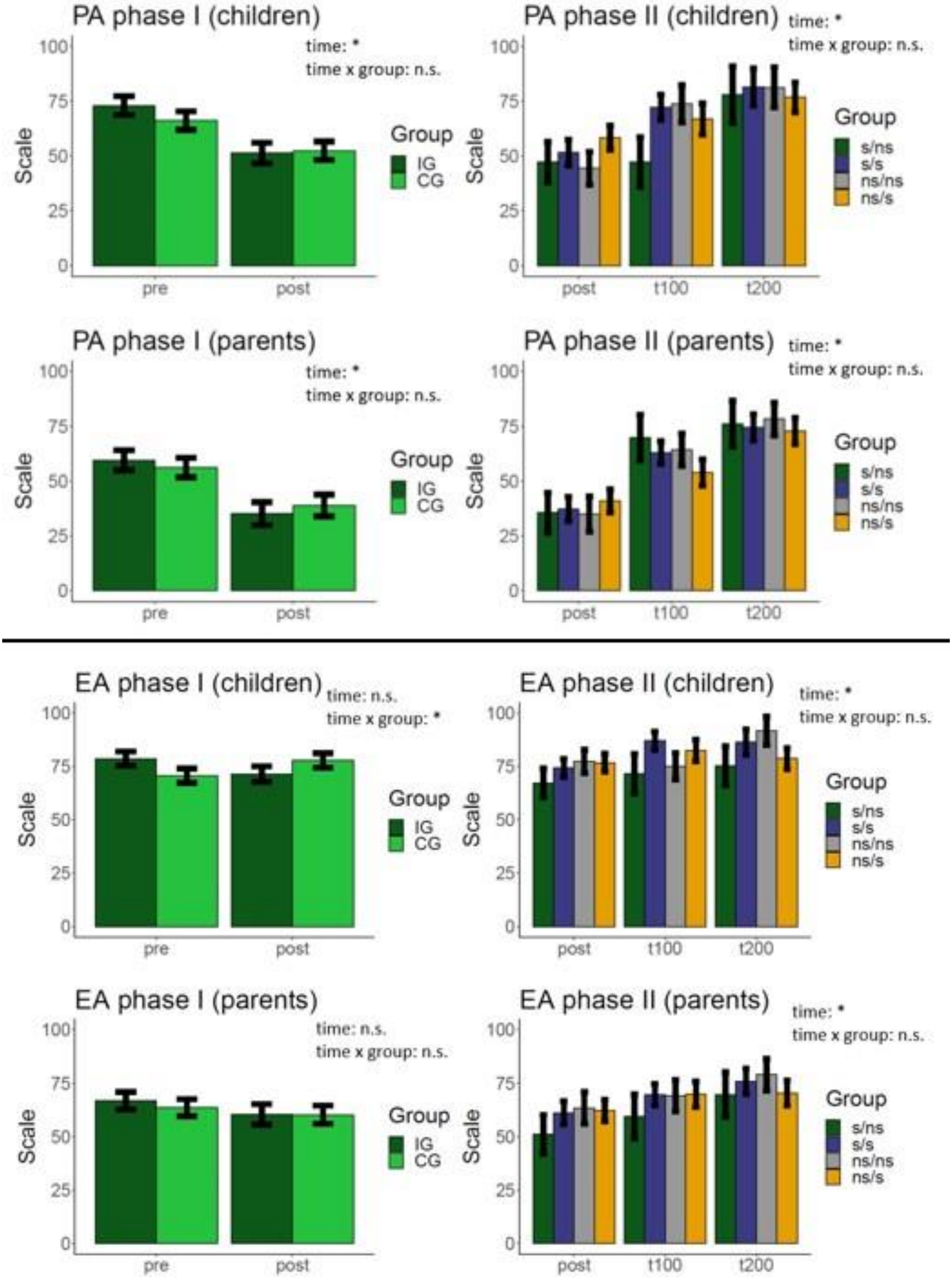
Parents perceive their children's HRQoL in EA to be more affected than indicated by the children's self-report, reflected in lower parent evaluations (IG: 66.8 to 60.4, CG: 63.6 to 60.3). The time effect is non-significant ($\chi^2_1 = 1.22$, $p = 0.27$), as is the interaction effect ($\chi^2_1 = 0.13$, $p = 0.72$). Thus, there are differing evaluations of quality of life from t_{pre} to t_{post}.

The results of phase 2 after hospital discharge with new stratification are We do not report descriptive values as for phase 1; respective values can be found in the figures 2–5. Self-reports from all four groups show a significant increase ($\chi^2_2 = 31.5$, $p < 0.001$) over time for PA. All groups show a similar increase ($\chi^2_6 = 5.68$, $p = 0.46$) and reach the initial values before hospitalization by t_{200}.

External assessments from the parents' perspective in phase 2 also show a significant increase ($\chi^2_2 = 77$, $p < 0.001$) in HRQoL related to PA across all groups over time. Parents' evaluations reach pre-hospitalization values by t_{100} and exceed them by t_{200}. No interaction effect is detected ($\chi^2_6 = 3.64$, $p = 0.73$).

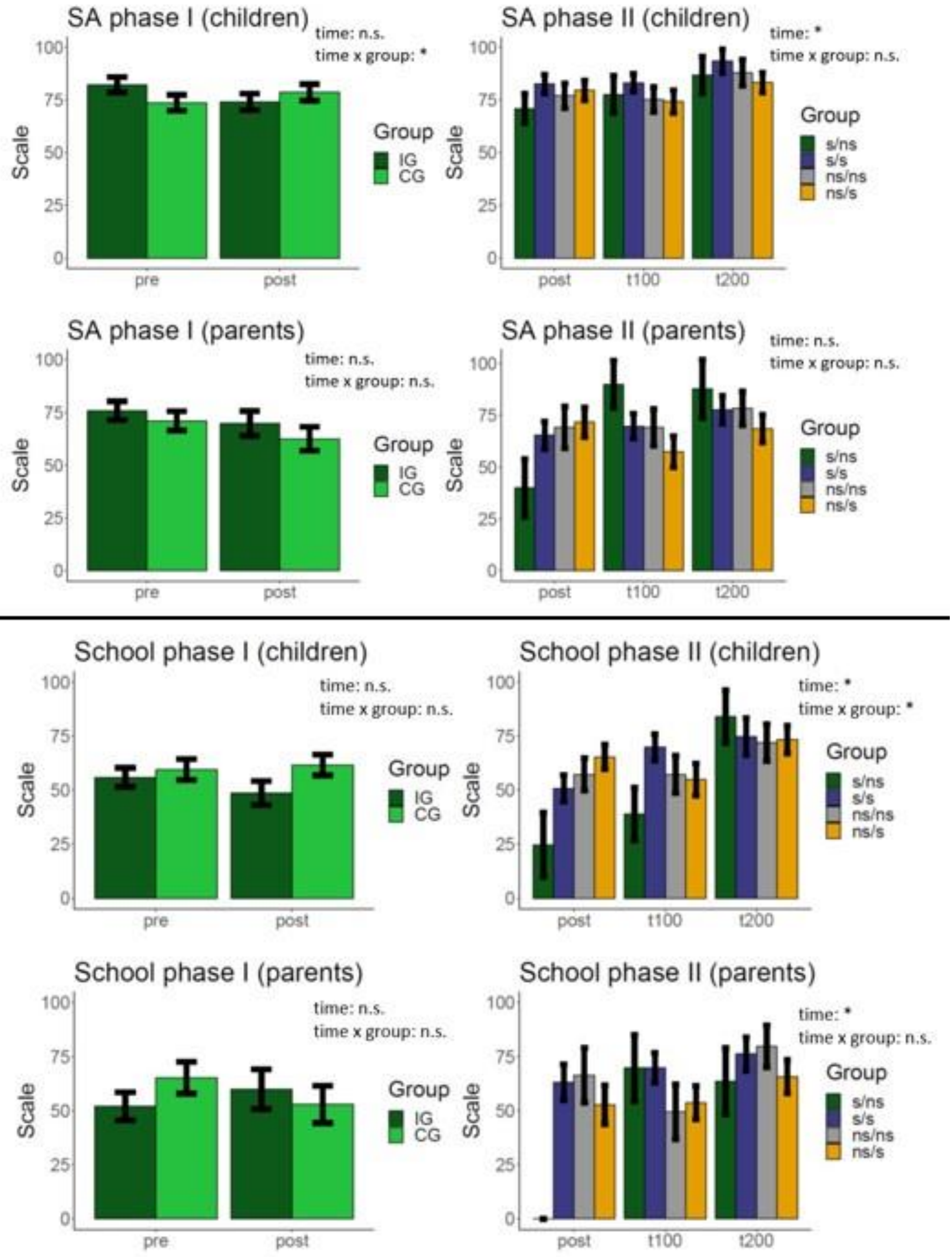
Self-reports from patients in phase 2 show a significant increase across all groups ($\chi^2_2 = 7.6$, $p = 0.02$) in EA, with no group dependency ($\chi^2_6 = 7.2$, $p = 0.3$).

External assessments from the parents' perspective show a significant increase over time ($\chi^2_2 = 11.1$, $p = 0.004$) across



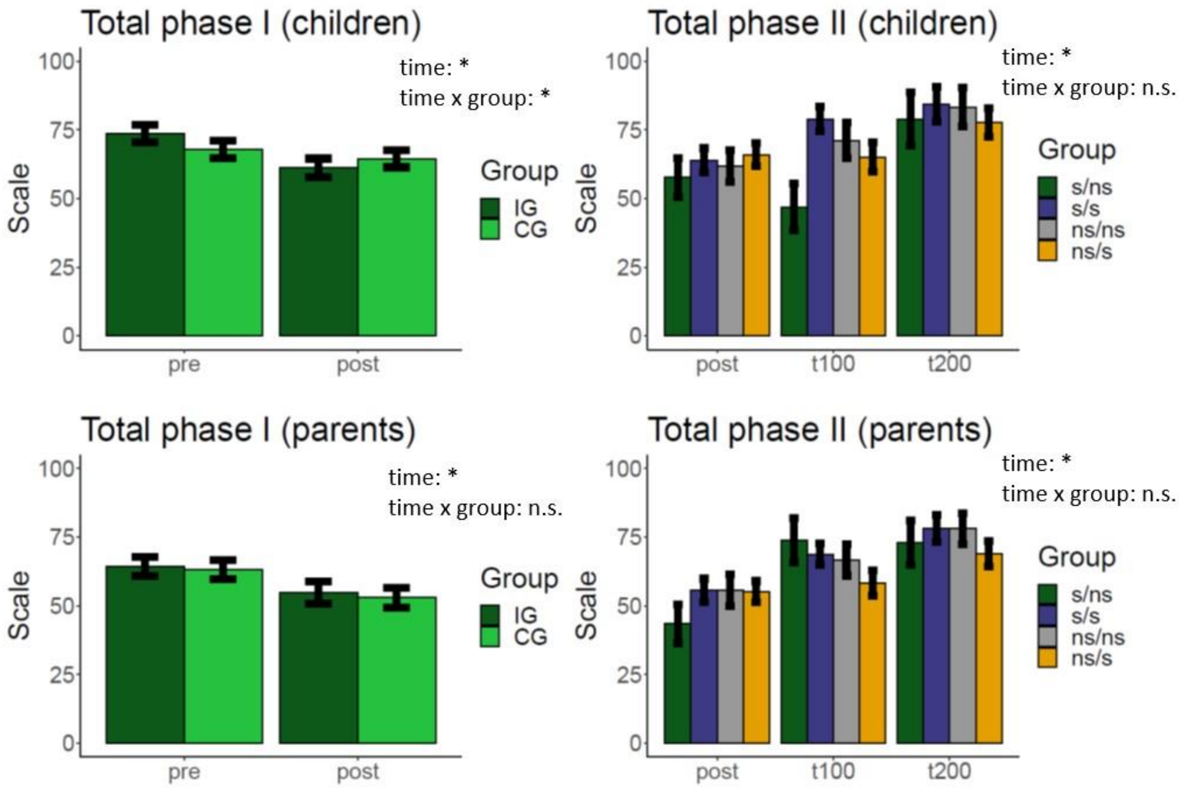
IG – intervention group
CG – control group
t_{100} – 3-month follow-up
t_{200} – 6-month follow-up
s – sports
ns – no-sports

Figure 2. Error bar charts of subscores physical activities and emotional activities of estimated marginal means from ANOVA models (mean and standard error). Upper row: children's perspective, lower row: parents' perspective (* $p < 0.05$, n.s. – non-significant)



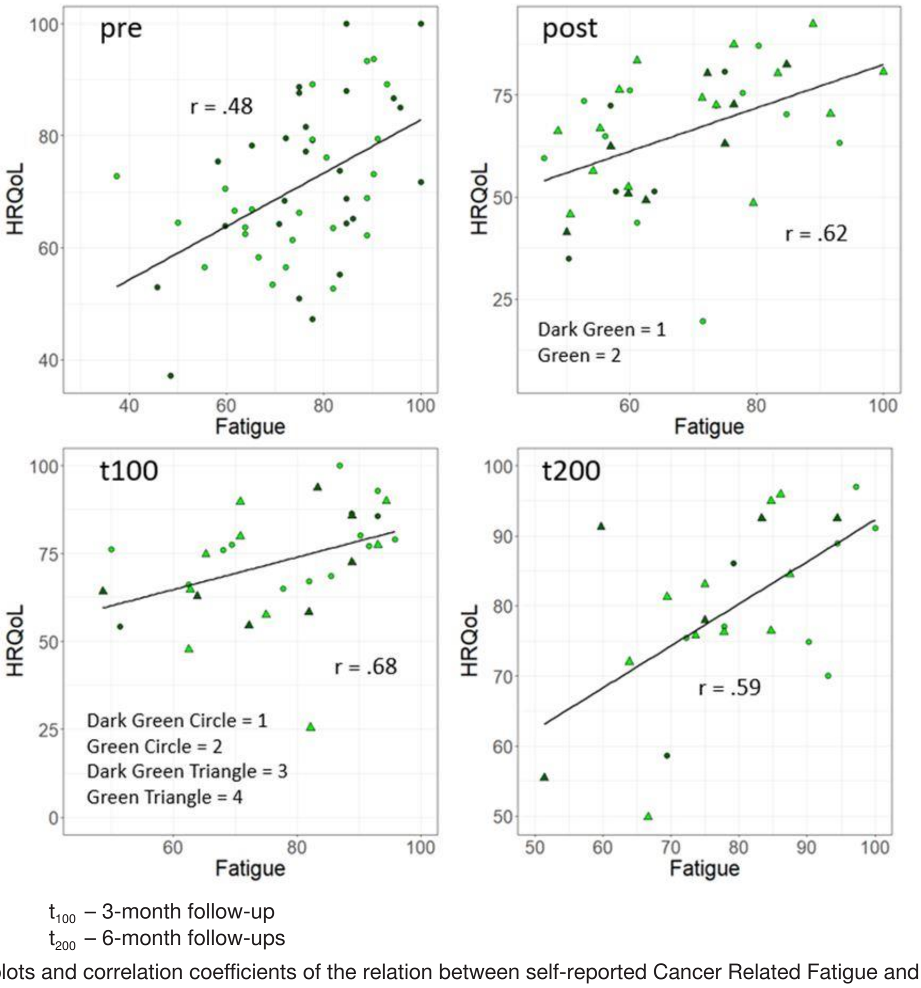
IG – intervention group
CG – control group
t_{100} – 3-month follow-up
t_{200} – 6-month follow-up
s – sports
ns – no-sports

Figure 3. Error bar charts of subscores social activities and school activities of estimated marginal means from ANOVA models (mean and standard error). Upper row: children's perspective, lower row: parents' perspective (* $p < 0.05$; n.s. – non-significant)



IG – intervention group t_{100} – 3-month follow-up s – sports
CG – control group t_{200} – 6-month follow-up ns – no-sports

Figure 4. Error bar charts of total scale score of estimated marginal means from ANOVA models (mean and standard error). Upper row: children's perspective, lower row: parents' perspective (* $p < 0.05$; n.s. – non-significant)



t_{100} – 3-month follow-up
t_{200} – 6-month follow-ups

Figure 5. Scatterplots and correlation coefficients of the relation between self-reported Cancer Related Fatigue and Health-Related Quality of Life (HRQoL) concerning the different times (phase 1: pre, post; color codes: dark green = group 1, green = group 2; phase 2: t_{post}, t_{100}, t_{200}; color codes: dark green circle = group 1; green circle = group 2, dark green triangle = group 3, green triangle = group 4)

all groups in EA in phase 2, with no interaction effect ($\chi^2_6 = 1.19$, $p = 0.98$). Thus, there is agreement that quality of life in EA increases irrespective of the group after hospital discharge.

In IG, from t_{pre} to t_{post}, social activities (SA) values decrease from 82.19 to 74.11, while in CG, values increase from 73.63 to 78.61, resulting in a non-significant time effect ($\chi^2_1 = 0.81$, $p = 0.37$) and a significant interaction effect ($\chi^2_1 = 11.58$, $p < 0.001$).

There is disagreement between children's and parents' perceptions of SA: The parents' perspective suggests a potentially significant time effect (IG: 75.9 to 69.9; CG: 71 to 62.6; $\chi^2_1 = 2.88$, $p = 0.09$), whereas no interaction effect is detected ($\chi^2_1 = 0.08$, $p = 0.78$).

Self-reports show a reduction in school activities (school) in IG (55.9 to 48.67), but an increase in CG (59.5 to 61.67). Both effects (time: $\chi^2_1 = 0.3$, $p = 0.59$; time × group: $\chi^2_1 = 1.22$, $p = 0.27$) are not significant.

Parents report an increase in HRQoL related to school activities in phase 1 for IG (52.1 to 60), whereas CG shows a reduction (65.3 to 53). Neither time ($\chi^2_1 = 0.08$, $p = 0.78$) nor interaction ($\chi^2_1 = 1.7$, $p = 0.19$) effects are significant. From a descriptive point of view, parents' values are diametrically opposed to the patients' self-report for phase 1.

From the patients' perspective, HRQoL in SA significantly increases over time after hospital discharge (phase 2) ($\chi^2_2 = 10.28$, $p = 0.006$) across all groups, independent of the group ($\chi^2_6 = 2.2$, $p = 0.9$).

Parents across all groups report a non-significant increase in HRQoL related to SA after hospital discharge at measurement points t_{post}, t_{100}, and t_{200} ($\chi^2_2 = 3.15$, $p = 0.21$).

Agreement with the children's perspective shows no interaction effect ($\chi^2_6 = 10.6$, $p = 0.1$).

In phase 2, patient self-reports show a significant increase over time ($\chi^2_2 = 15.89$, $p < 0.001$) and with respect to groups ($\chi^2_6 = 15.5$, $p = 0.02$) in school activities.

The external assessment of phase 2 from the parents' perspective shows a significant increase over time ($\chi^2_2 = 6.45$, $p = 0.04$) across all groups in school activities. However, no group dependency is detected in parents' evaluations ($\chi^2_6 = 8.7$, $p = 0.19$).

In IG, from t_{pre} to t_{post}, TSS decreases from 73.63 to 61.15, and in CG, it decreases from 67.82 to 64.47, resulting in significant effects for both the time effect ($\chi^2_1 = 11.81$, $p < 0.001$) and the interaction effect ($\chi^2_1 = 4.17$, $p = 0.04$).

The external assessment of phase 1 from the parents' perspective regarding TSS shows a significant reduction in HRQoL over time (IG: 64.3 to 54.7, CG: 63.2 to 53, $\chi^2_1 = 8.6$, $p = 0.003$), but no significant interaction effect ($\chi^2_1 = 0.01$, $p = 0.92$).

So, regarding time, both evaluations agree, although disagreement occurs in CG, where children tend to report a weaker decrease compared to the parents.

Calculation of TSS for patient information in phase 2 shows a significant increase ($p < 0.001$) in HRQoL over time in both the patients' evaluation ($\chi^2_2 = 23.56$, $p < 0.001$) and parents' evaluation ($\chi^2_2 = 36.67$, $p < 0.001$). No interaction effect is observed (patients: $\chi^2_6 = 8.97$, $p = 0.18$; parents: $\chi^2_6 = 6.69$, $p = 0.35$) in TSS.

Over time, a significant decrease ($\chi^2_1 = 28.4$, $p < 0.001$) in body mass index (BMI) is observed in phase 1 (IG: 18.2 to 17.7, CG: 16.6 to 15.8), with no interaction effect ($\chi^2_1 = 0.84$, $p = 0.36$). In phase 2, a general increase in BMI is observed, except for group 2, which shows rather constant values. There is no significant time effect ($\chi^2_2 = 2.48$, $p = 0.29$) and no group dependence ($\chi^2_6 = 4.3$, $p = 0.64$).

Correlations between CRF and HRQoL

The question of whether a low level of CRF (high CRF scores) in children indicates increased HRQoL (high HRQoL scores) can be answered as follows based on this study:

The correlations in total scores (TSS HRQoL and TFS) are as follows:

t_{pre}: $r = 0.48$ ($n = 51$)
t_{post}: $r = 0.62$ ($n = 44$)
t_{100}: $r = 0.68$ ($n = 32$)
t_{200}: $r = 0.59$ ($n = 24$)

All correlations are significant ($p < 0.01$). These positive correlations indicate that higher fatigue scores (indicating low fatigue) correspond to greater health-related quality of life.

From the patients' and parents' perspectives, two trends emerge: During hospital stay, there is a significant reduction in HRQoL and an increase in CRF. After hospital discharge and at follow-up examinations, there is a reduction in CRF and a corresponding increase in HRQoL.

Discussion

Despite the high level of physical activity and associated risks, no injuries or adverse events were documented in this study. The results of this study correspond with the meta-analysis by Oberoi et al., who described exercise therapy as safe and effective for improving CRF [16].

Since these patients are extremely vulnerable, the sample size is small (especially in phase 2 after stratification), which may have influenced the results. Due to multifactorial reasons, including non-responders and a high risk of morbidity and mortality, only a few HSCT patients completed the study.

Cumulative toxicity increases the extent to which transplantation can be negatively affected and increases the risk of morbidity and mortality. During and after primary treatment, children are observed to have muscle atrophy, neuromuscular deficits, and cardiopulmonary impairments, which should be treated with physiotherapy.

Similarly, the daily hospital routine alone may be a significant stress factor that could have influenced the outcome of the study. Another frequently underestimated factor is the decrease in physical health and fitness of patientsin the context of HSCT pre-treatment. The conditioning regime is an important determinant of CRF after transplantation.

Mustian et al. [25] describe in a meta-analysis that the effect of exercise therapy depends on cancer stage and baseline treatment. Exercise and psychological interventions were significantly more effective than drug options during and after cancer therapy [25].

So, what hypotheses support the idea that exercise therapy can help with CRF? Repka and Hayward [26] explain that exercise therapy may result in a more robust and significant increase in antioxidant capacity and a decrease in protein oxidation, which has been shown to reduce CRF. A different approach is taken by Chamorro-Viña et al. [27], who suggest that after HSCT, natural killer cell cytotoxicity (NKCC) recovery is important for a good outcome. In a study conducted by them, the ratio of NKCC in their IG was eight times greater than in their CG. Their intervention was performed immediately after HSCT with moderate intensity, unlike Repka and Hayward [26].

Although Gaser et al. [28] did not find significant between-group differences compared to their CG in the Activities Scale for Kids using strength training, the authors used strengthening exercises to improve HRQoL. In contrast to other studies, the exercise sessions in the BISON study lasted longer than 30 min (median 51 min; range 30–60 min). Another difference from other studies was that these interventions began immediately with HSCT preparation.

The improvements in CRF observed in the outpatient setting (phase 2) should be interpreted cautiously. Due to a potential overlapping training effect from inpatient exercise therapy (phase 1) in group 1_nosport, these children still showed moderate values at t_{100} (phase 2) but could no longer improve at t_{200} without exercise. The minimal recovery of CRF in group 3_nosport could indicate spontaneous remission without training in phase 2.

However, not exercising (anymore) after hospital discharge resulted in the lowest recovery from CRF in this study population. The intention-to-treat analysis largely confirmed the results of the as-treated analysis. Regarding TFS, which showed the most significant improvement, the intention-to-treat analysis and the as-treated analysis were 87.5% identical.

For sleep and rest fatigue (SRF) and general fatigue (GF), the intention-to-treat and as-treated analyses at t_{200} showed identical results. The improvement in GF in group 1_nosport at t_{100} in the as-treated analysis may be due to statistical outliers and was leveled out in the intention-to-treat analysis.

If the original two groups (IG and CG) had been maintained in the analysis and evaluation at t_{200} had only included these two groups, significant improvement through exercise therapy compared to CG would have been achieved. After stratification and due to the small number of cases, only a non-significant trend favoring exercise therapy was observed in phase 2.

Nevertheless, these study results align with those of Repka and Hayward [26] and support proposing moderate physical activity as an option for reducing CRF. The data on exercise therapy and HRQoL present some differences. Here, all children showed significant improvement over time from tpost to t_{200}, regardless of exercise therapy. A positive influence of physical activity could not be demonstrated in this sample, which may be attributable to the small number of patients in phase 2. The only statistically significant correlation was between CRF and increased HRQoL.

Beller et al. [29] describe that none of the identified studies reported negative effects of exercise therapy, which the authors of this study can confirm. In addition to positive effects on the immune system, such as reduced risk of infection, the number of days in hospital could be reduced through exercise therapy [29]. All these effects can also have a positive influence on the HRQoL examined here.

Poor compliance in completing and returning the two questionnaires resulted in a high dropout rate and, therefore, was the greatest limitation in the study design.

The striking increase in CRF (indicated by low fatigue values) during inpatient phase 1 can be explained by the discomfort of the stem cell transplantation and the still altered blood values ("cell depth"). The intervention also failed to significantly improve CRF in the group of patients studied here. In this state of increased CRF and in the special situation of being in the isolation room, the patients and their parents reported a significantly reduced quality of life in all dimensions.

The fact that the parents' perspective sometimes showed a greater degree of concern may be due to the fact that the parents of older children and adolescents do not always notice the social networks and opportunities through which their children can engage in emotional, social, and school activities.

A study by Adiguzel et al. [30] showed that parents of children with physical disabilities have a changed anxiety level regarding their children, and this has an influence on their HRQoL. Parents of children with cancer probably also have an increased sense of anxiety because they fear for their children's lives. This causes different answers in the child or parent questionnaire.

In the digital age of the virtual classroom, children and, especially adolescents in hospitals, depending on their state of health, can participate in some teaching activities and almost to the normal extent in their SA via Facebook, Instagram, Snapchat, WhatsApp, etc.

The positive correlation between CRF and HRQoL proves that the increasing perception of reduced fatigue (represented by high CRF values) leads to the perception of increased quality of life.

The fact that all patients in phase 2 reported significant improvements in quality of life over time is not surprising, because increasing recovery from the transplantation process and the associated healing means hospital discharge and return to "normal life".

Limitations

Whereas a significant reduction in CRF was found in our IG only after discharge from the hospital, the impact of exercise therapy on HRQoL was moderate. Nevertheless, improved CRF correlated significantly with increased HRQoL.

Positive effects of exercise therapy during the inpatient phase were not observed for either CRF or HRQoL. In phase 2 of the study, there were too few children in the four study groups. A major limitation of this study was the high number of non-responders among outpatient children due to lack of commitment.

Conclusions

Our data suggest that exercise therapy can help reduce CRF and, therefore, increase HRQoL after pediatric HSCT. The provision of sports to HSCT patients as a non-specific factor represents a helpful aspect of the "return to normality", because exercise is a routine part of daily life for many children and adolescents. This appears to hold greater significance than the direct influence of exercise therapy on health-related quality of life.

Exercise therapy immediately after transplantation can be recommended for a better post-hospital outcome if reducing other side effects in the hospital is not the primary concern. Due to its limited in-hospital effect, other applications may take precedence initially. However, in the outpatient setting, exercise therapy shows a reduction in CRF, possibly due to treatment initiated during hospitalization, highlighting the beneficial role of exercise therapy in pediatric oncology. Although the direct influence of exercise therapy on HRQoL was not clearly demonstrated in this study, the improvement in CRF was significantly correlated with increased health-related quality of life. These findings lead the authors to recommend inpatient sports activities following HSCT, which should be continued after hospital discharge during the rehabilitation phase.

Ethical approval

The research related to human use has complied with all the relevant national regulations and institutional policies, has followed the tenets of the Declaration of Helsinki, and has been approved the Ethics Committee of the Department of Medicine at Goethe University Frankfurt. It is registered at http://www.clinicaltrials.gov with ID-No. NCT01575704.

Informed consent

Informed consent was obtained from all individuals included in this study.

Disclosure statement

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Conflict of interest

The authors declare no conflict of interest.

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