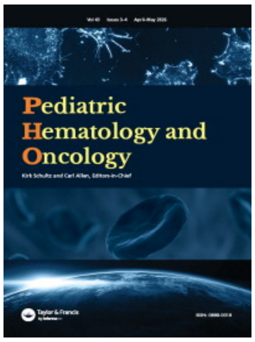

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Feasibility and Validity of the 6-Minute Cycling Test in Childhood Cancer Patients

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ABSTRACT

The 6-min cycling test (6MCT), a submaximal endurance test, has not yet been applied in pediatric oncology. This study evaluates its feasibility and validity in 71 childhood cancer patients (9.6 ± 4.0 years). For validation, 46 patients additionally underwent cardiopulmonary exercise testing (CPET). Performance in the 6MCT (total revolutions) was correlated with peak oxygen uptake (VO_{2peak}) and peak work rate (WR_{peak}) using Spearman's correlation. Linear regressions assessed the predictive value of VO_{2peak} and WR_{peak} on 6MCT performance. Sixty-six participants (93%) successfully completed the 6MCT, averaging 550 ± 129 revolutions. Revolutions correlated moderately with VO_{2peak} ($\rho = 0.46$, $p = 0.001$) and strongly with WR_{peak} ($\rho = 0.64$, $p < 0.001$). VO_{2peak} significantly predicted 6MCT performance ($p = 0.001$, $R^2 = 0.214$), whereas WR_{peak} explained more variance ($p < 0.001$, $R^2 = 0.488$). The results demonstrate that the 6MCT is a feasible, valid endurance assessment in this population, offering a promising alternative when gold standard testing is not available.

Abbreviations: 6MCT: 6-minute cycling test; 6MWT: 6-minute walk test; A6MCT: Assisted 6-minute cycling test; CPET: Cardiopulmonary exercise testing; RPE: Rate of perceived exertion; VO_{2peak}: Peak oxygen uptake; WR_{peak}: Peak work rate

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Cardiorespiratory fitness; childhood cancer; exercise oncology; exercise testing; validation study

Background

As a consequence of advances in therapeutic modalities, an increasing number of children and adolescents are surviving their cancer into adulthood.[1,2] However, there are often long-term physical and psychological effects.[3] It is therefore becoming more important to consider the side effects of medical therapy and the disease itself.[2] In recent years, there has been a notable increase in the number of scientific studies investigating the physical performance of childhood cancer patients.[4,5] The findings

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indicated that patients not only showed reduced performance during intensive cancer treatment,[4,6]but also throughout survivorship.[7,8] Accurate assessment of the physical performance of children and adolescents during and after cancer treatment is essential not only for continuous monitoring of current fitness capacities, but also for adapting exercise programs to individual performance levels.

Cardiorespiratory fitness is particularly important, as it has been shown to be an effective indicator of physical and mental performance in both healthy and diseased populations.[9,10] The gold standard for assessing cardiorespiratory fitness is the measurement of maximal oxygen uptake by cardiopulmonary exercise testing (CPET).[11] However, CPET is not always routine in clinical practice, as the test is time-consuming and requires expensive equipment and specially trained staff.

In previous studies of children and adolescents with oncological diseases, the 6-min walk test (6MWT) was commonly used to assess functional exercise capacity, offering a simpler and less exhausting alternative to CPET.[12–15] However, there are some limitations to this test in clinical practice: the test may be impractical in inpatient settings because patients often require infusion lines or isolation due to their treatment. Furthermore, the limited availability of space in hospitals often restricts its use. Additionally, patients with impaired coordination due to chemotherapy-associated polyneuropathies face an increased risk of falling during a gait test. In these patients, the test may primarily assess walking ability, with limited insight into cardiorespiratory function. These limitations could result in misinterpretations of a patient's actual endurance capacity, which could in turn lead to incorrect conclusions when personalizing their exercise training or rehabilitation program.

For these reasons, there is a need to investigate alternative tests to assess cardiorespiratory fitness in childhood cancer patients, tailored to the specific needs of these patients.

Jansen et al.[16] developed a motor-assisted submaximal endurance test for both legs and arms for children with neuromuscular diseases, the assisted 6-min cycling test (A6MCT). In healthy boys, the A6MCT for the legs showed a positive correlation ($r = 0.58$, $p < 0.01$) with the 6MWT and a high test-retest reliability (ICC = 0.88, 95% CI 0.72–0.95).[16] Furthermore, the feasibility of the A6MCT has been demonstrated in other patient groups[17–19] and has been employed as an outcome measure in training intervention studies.[20]

The duration of the A6MCT test is comparable to that of the 6MWT, with the protocol also based on the 6MWT. In contrast to the 6MWT, however, the A6MCT can be conducted in a limited space and with an infusion line. In addition, the risk of falls is minimal, and due to the light workload, the test can also be performed by patients with muscular limitations. This makes the test an appropriate option for childhood cancer patients.

In order to facilitate its utilization in childhood cancer patients, the test was adapted to the needs of these patients and to the prevailing conditions at the Childhood Cancer Center in Mainz. The objective of this study was to investigate the feasibility and validity of this adapted 6-min cycling test (6MCT) as a clinical indicator of cardiorespiratory fitness in children and adolescents with cancer. For that purpose, the feasibility of the test was evaluated in a sample of childhood cancer patients. Furthermore, an additional CPET was conducted to assess the validity of the test.

Methods

Participants

This study was conducted on a sub-sample of subjects who participated in either the FORTEe randomized controlled trial (NCT05289739) or the Kolibri longitudinal cohort study (NCT05867186). The sub-sample consisted of patients from the Childhood Cancer Center of the University Medical Center of the Johannes Gutenberg-University Mainz in Germany. According to the main studies, they were considered eligible for the validation study if they met the following criteria: 1) oncological disease according to the International Classification of Childhood Cancer (ICCC-3), 2) 4–21 years of age, and 3) during or within the first five years after completion of anti-cancer treatment (chemo- and/or radiotherapy and/or surgery) at the University Medical Center Mainz. Exclusion criteria were: 1) the patient is assessed by the treating team (pediatric oncologist, exercise professional, etc.) as unsuitable to participate, e.g. due to medical or psychological reasons; 2) the patient (and the legal guardians) has/have insufficient knowledge of the German or English language so that it is not possible to carry out both the informed consent and the exercise testing; and 3) the patient is in a terminal phase of the disease.

Procedures

This publication is part of a series of publications investigating cardiorespiratory fitness in children with cancer, using the same methodology. The study design has been approved by the local ethics review committee of the Rhineland-Palatinate Chamber of Physicians under the application number 2021-15904 on 04.08.2021 and under the application number 2022-16726 on 17.03.2023. All procedures performed in this study are in accordance with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the legal guardians in the case of minor participants and from all study participants older than 16 years of age.

The physical examinations were performed in a standardized order. Where feasible, the CPET and 6MCT were conducted at least one day apart. For patients during aftercare who were no longer attending the hospital regularly, the two tests were performed on the same day. In this instance, the interval between the two endurance tests was ≥30 min to ensure adequate recovery, which is consistent with previous studies that have also chosen a minimum interval of 30 min between endurance tests.[21]

Cardiorespiratory fitness

6mct

The 6MCT was conducted in accordance with the protocol established by the working group of Jansen et al.[16] However, it was decided to use an electronically braked cycle ergometer (Corival Pediatric, Lode BV, Groningen, Netherlands, or Corival CPET, Lode

BV, Groningen, Netherlands) instead of a motor-assisted mobility trainer. This offers the advantage of precise control and monitoring of test conditions, taking advantage of the wide availability and ease of use of standard cycle ergometers in clinical settings. To make the test suitable even for frail patients, the resistance was set to the lowest available initial workload of 7 watts for all participants and maintained throughout the entire test duration.

The cycle ergometer was adjusted according to the patient's height. Subsequently, the patients underwent a familiarization phase, during which they became acquainted with the cycle ergometer. Participants were given standardized instructions to complete as many revolutions as possible in 6 min. During the test, participants received verbal encouragement every 15 s to maintain attention and perform the test with the best possible effort (see Supplement 1). If participants needed to take a break due to exhaustion, they were allowed to rest. In such cases, they were verbally motivated to continue the test as soon as possible.[16]

Heart rate was recorded continuously using an upper arm sensor (Polar Verity Sense, Polar, Kempele, Finland). The maximum heart rate was predicted using an age-based equation,[22,23] and the measured heart rate values were then compared with these predicted values. The rate of perceived exertion (RPE) was assessed every minute using the Borg scale 6–20.[24] A three-step scale was used for children up to and including the age of 8.[25] The primary outcome was the number of revolutions achieved in 6 min. The cumulative revolutions per minute achieved and the number of rest periods were also recorded.

Participants' compliance in the 6MCT was rated on a scale of 1–5 (1 = very high compliance; 5 = very low compliance) by the therapists who administered the tests.

CPET

CPET was performed on the same electronically braked cycle ergometer (Corival Pediatric, Lode BV, Groningen, Netherlands, or Corival CPET, Lode BV, Groningen, Netherlands) using a modified Godfrey protocol.[26] Starting with an initial load of 6, 20, or 40 W, depending on the patient's height, age, and ability, the workload was gradually increased by 10 W/min (respectively 20 or 30 W/min) to voluntary exhaustion, and the cadence was maintained at a steady 60–80 rpm. Gas exchange data were constantly measured breath-by-breath by the means of a wearable metabolic system (K5, COSMED, Rome, Italy), calibrated according to the manufacturer's instructions before each test. Heart rate was monitored throughout the test with a 12-lead ECG (Quark T12x, COSMED, Rome, Italy).

Peak oxygen uptake (VO_{2peak}) was assessed as the highest 30-second average during exercise and expressed in relation to body weight ($mL\cdot min^{-1}\cdot kg^{-1}$). Peak work rate ($WR_{peak}$) was defined as the highest work rate and was also reported in relation to body weight ($W\cdot kg^{-1}$).

As there are no standard criteria established in pediatric oncology for recognizing the validity of a test, various objective (heart rate, respiratory exchange ratio) and subjective (signs of intense exertion) criteria from previous studies in childhood cancer patients[14,27,28] and healthy children[11] were considered. As these criteria led to different results in terms of the number of 'valid' tests, data from all patients were included in the analysis, regardless of the fulfillment of individual criteria, to allow for a comprehensive interpretation.

Anthropometric and medical parameters

Participants' height and weight were assessed using standardized procedures and instruments. Information on diagnosis and cancer treatment was collected from medical records.

Statistics

Given the relatively small sample size, both the mean ± standard deviation (SD) and the median (first quartile, third quartile [Q1, Q3]) are presented in the descriptive statistics to capture both robust and average values and to minimize distortions due to outliers. Categorical variables are reported as the actual number of test subjects, along with the corresponding percentage in relation to the absolute number.

In line with the criteria of Dirks et al.,[18] the 6MCT was considered successful if the patient completed the test for the full six minutes without taking breaks longer than 15 s and without complications.

To assess validity, the results of the 6MCT were correlated with the gold standard for assessing endurance performance, the CPET results (VO_{2peak}, WR_{peak}). Due to the robustness of the Spearman correlation coefficient in the presence of outliers, the association between VO_{2peak}, WR_{peak} and the results of the 6MCT were analyzed using the Spearman correlation coefficient (ρ). The strength of the relationship was interpreted according to Cohen's guidelines.[29]

Subsequently, a linear regression analysis was conducted to ascertain the predictive impact of cardiorespiratory fitness (assessed by VO_{2peak} or WR_{peak}) on the 6MCT outcome. The assumptions underlying the linear regression were verified by inspecting residual versus fitted value plots for homoscedasticity and utilizing Q–Q plots to ascertain the normality of residuals. Effect sizes were calculated and interpreted according to Cohen.[29,30]

The statistical analyses were conducted using IBM SPSS Statistics for Windows (Version 27), while the graphs were created with GraphPad Prism (Version 10.0). The significance level was set at 5% for all tests.

Results

Participant characteristics

A total of 71 participants (46.5% female) aged 4 – 20 years were recruited to perform the 6MCT. The most prevalent cancer types were leukemia (47.9%), central nervous system tumors (16.9%), and lymphomas (9.9%). Of the participants, 47.9% were undergoing intensive cancer treatment, 4.2% were receiving maintenance therapy, and 47.9% were in aftercare. Participant characteristics are presented in Table 1.

Feasibility and results of the 6MCT

The 6MCT was successfully completed in 66 out of 71 patients (93.0%). One patient refused to participate in the test, and two patients were unable to perform the test due to medical reasons: One patient had a malignant bone tumor in the lower

Table 1. Baseline characteristics of participants ($N = 71$).

	Mean ± SD (median [Q1, Q3])
Age at study (years)	9.6 ± 4.0 (9 [7, 12])
Height (m)	1.39 ± 0.23 (1.38 [1.20, 1.57])
BMI ($kg \cdot m^{-2}$)	19.0 ± 4.4 (17.6 [15.90, 22.72])
	n (%)
Sex, male	38 (53.5)
Cancer type	
Leukemias	34 (47.9)
Lymphomas	7 (9.9)
CNS and miscellaneous intracranial and intraspinal neoplasms	12 (16.9)
Neuroblastoma and other peripheral nervous cell tumors	3 (4.2)
Renal tumors	2 (2.8)
Malignant bone tumors	3 (4.2)
Soft tissue and other extraosseous sarcomas	5 (7.0)
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	2 (2.8)
Other and unspecified malignant neoplasms	3 (4.2)
Therapy stage at study	
Intensive cancer treatment	34 (47.9)
Maintenance therapy	3 (4.2)
After care	34 (47.9)

Continuous values are presented as mean ± standard deviation (Median [Q1, Q3]), categorical values are presented as *n* (%).

Table 2. Results of 6MCT and CPET.

	n	Mean ± SD	Median (Q1, Q3)
6MCT			
Revolutions after 6 min	66	550 ± 128	555 (481, 619)
RPE (BORG 6-20)	64	15 ± 4	15 (13, 18)
HR after 6 min (bpm)	59	157 ± 25	161 (134, 177)
HR after 6 min (% of predicted HR_{max})	59	78.0 ± 12.8	80.7 (67.5, 88.6)
Compliance	66	1 ± 1	1 (1, 1)
CPET			
VO_{2peak} ($mL \cdot min^{-1} \cdot kg^{-1}$)	46	30.7 ± 9.0	31.8 (24.1, 36.8)
RPE (BORG 6-20)	42	16 ± 3	16 (14, 18)
HR_{peak} (bpm)	46	187 ± 10	187 (181, 194)
HR_{peak} (% of predicted HR_{max})	46	93.1 ± 5.0	93.4 (89.7, 96.5)
RER_{peak}	46	1.27 ± 0.12	1.26 (1.17 – 1.32)

6MCT, 6-min cycling test; CPET, cardiopulmonary exercise testing; RPE, rate of perceived exertion; HR, heart rate; bpm, beats per minute; VO_{2peak}, peak oxygen uptake; RER, respiratory exchange ratio.

extremities, and the other had metastases from a solid tumor in the spine. Both patients were undergoing intensive cancer treatment at the timepoint of testing. In two young patients (4 and 5 years old) undergoing intensive cancer treatment, the test was terminated prematurely. In both cases, the reason for termination was motivational issues in cycling for six minutes at a time.

No adverse events occurred during or after the 6MCT.

The results of the participants' performance are presented in Table 2. The mean number of revolutions achieved by the patients in six minutes was 550 ± 128, with an average RPE of 15 ± 4. The mean heart rate at the end of the test was 157 ± 25, which corresponds to 78.0% of the predicted maximum heart rate.

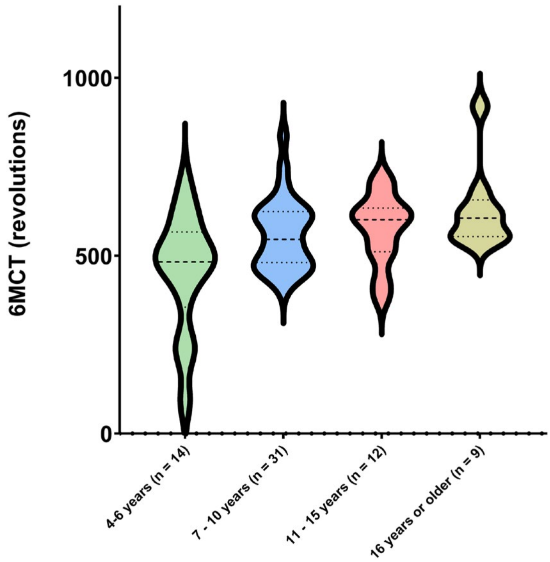

Figure 1. Distribution of revolutions at the end of the 6MCT across different age groups.

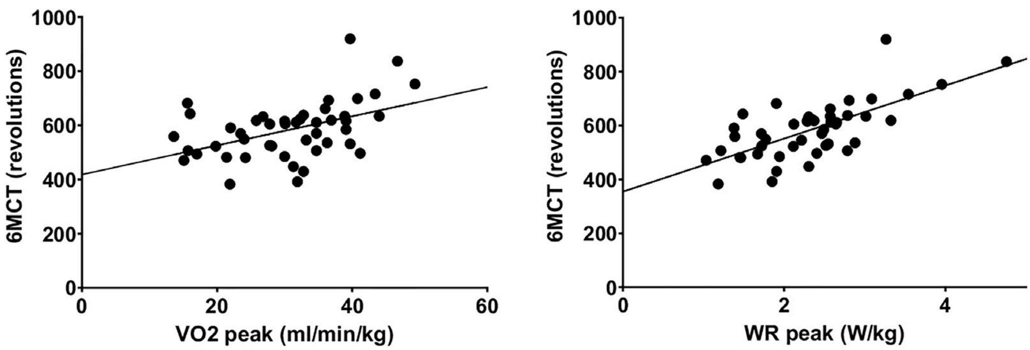

Figure 2. Relationship between the peak oxygen consumption (VO_{2peak}) attained at the CPET and the revolutions at the end of the 6MCT (left) and the relationship between the peak work rate (WR_{peak}) attained at the CPET and the revolutions at the end of the 6MCT (right).

The distribution of the number of revolutions shows 2 upward outliers and 3 downward outliers. The outliers were not eliminated from the analysis; rather, they were included to ensure that the entire range of observed performance was taken into account, thereby providing a more comprehensive representation of the distribution.

Figure 1 shows the distribution of results of the 6MCT across different age groups. It can be observed that the older children tend to achieve a higher result than the younger ones. A downward outlier is evident in the age group of 4 to 6-year-olds. Upward outliers are present in the age groups 7-10 years and 16 years and older.

Validity of the 6MCT

A total of 46 participants underwent CPET in addition to 6MCT. The reasons for not performing an additional CPET were as follows: medical reasons ($n = 1$), logistics/organizational issues ($n = 15$) and refusal of CPET/low compliance ($n = 6$).

There was a moderate positive correlation between revolutions at the end of the 6MCT and VO_{2peak} ($\rho = 0.46$, $p = 0.001$) and a large positive correlation between revolutions at the end of the 6MCT and WR_{peak} ($\rho = 0.64$, $p < 0.001$).

The results of the linear regression indicate that both the VO_{2peak} ($F(1,44) = 11.975$, $p = 0.001$) and the WR_{peak} ($F(1,44) = 41.936$, $p < 0.001$) exert a significant impact on the result of the 6MCT. For each 1 $mL \cdot min^{-1} \cdot kg^{-1}$ increase in VO_{2peak}, the number of revolutions in the 6MCT increases by 5.371. For each 1 $W \cdot kg^{-1}$ increase in WR_{peak}, the number of revolutions increases by 98.465. The VO_{2peak} explains 21% of the variance in the 6MCT, while the WR_{peak} explains 49% of the variance in the 6MCT. According to Cohen,[29] these figures correspond to a large effect in each case.

The scattergrams showing the relationships between 6MCT and VO_{2peak}, and 6MCT and WR_{peak} are presented in Figure 2.

Discussion

The objective of this study was to examine the feasibility and validity of the 6MCT in children and adolescents with cancer. The findings indicate that the test is feasible in childhood cancer patients aged 4–20 years. Of the 71 participants recruited, 66 (93%) were able to successfully complete the test, and no adverse events were observed.

The test was found to be feasible for patients undergoing cancer treatment and for those receiving aftercare. Furthermore, the 6MCT proved to be feasible for all cancer entities analyzed. Limitations were observed in patients with bone tumors or metastases in the lower extremities or spine during intensive cancer treatment. However, these patients are also unable to perform other conventional endurance tests on the cycle ergometer, treadmill, or walking tests. Alternative endurance tests using a hand-crank ergometer[16,18] could be employed to assess endurance capacity in this patient group.

In general, even very young patients were able to comprehend the instructions for the test and perform it in an appropriate manner. This is particularly positive, as the determination of endurance capacity in this age group is often described as challenging due to limited cooperation skills.[11,31] Nevertheless, the sole two participants to terminate the test prematurely were two of the youngest participants (4 and 5 years old, respectively) who terminated the test due to motivational issues. Despite these uncertainties, 87.5% of participants in the 4–6-year age group successfully completed the test to the end, which lends support to the feasibility of the test in this age group.

Older children tended to perform better on the 6MCT than younger children. Nevertheless, further studies involving a larger number of older patients are required to make more precise statements in this regard. The fact that older children achieve better or higher results compared to younger children has also been proven in other submaximal endurance tests.[32,33] On the one hand, better performance can be attributed to physiological factors such as more efficient oxygen uptake[34,35] and higher cardiovascular efficiency.[35,36] Additionally, more developed motor skills[37] may also contribute to a more efficient running or cycling technique.

The distribution of 6MCT test results shows several outliers, both up and down. These outliers may indicate that the test is capable of identifying patients with markedly high or low cardiorespiratory fitness within the sample. However, as the downward outliers originate from patients who did not undergo additional CPET, it is uncertain whether the patients in question truly exhibited such low endurance capacity or whether coordination or motivation issues may have contributed to the low number of repetitions.

The results demonstrate that the 6MCT is a valid measure of the endurance capacity of childhood cancer patients, exhibiting a significant positive correlation between the number of revolutions achieved in the 6MCT and the results of CPET. However, the VO_{2peak} exhibited only a moderate correlation with the 6MCT test result. The results of the linear regression indicate that only 21% of the variance can be explained by the VO_{2peak}. In contrast, the WR_{peak} demonstrated a substantial correlation with the 6MCT test result, with 49% of the variance being explained by the WR_{peak}. One potential explanation for these discrepancies is that hematotoxicities (e.g. anemia) resulting from cancer treatment or the disease itself[38] may have influenced oxygen uptake.[39,40] This would lend support to the assertion that VO_{2peak} has a relatively low explanatory power in comparison to WR_{peak}. Furthermore, other factors, such as leg strength, which is frequently diminished in childhood cancer patients,[4,8] coordinative aspects of cycling; or treatment-associated cardiotoxic effects,[41] may have contributed to the test result. It would be beneficial for future studies to investigate the influence of additional predictors on the 6MCT in greater detail.

Nevertheless, the test represents a practical alternative to maximal exercise testing, particularly in patients who are unable to perform CPET for medical reasons or due to a lack of compliance or if CPET cannot be performed for logistical or cost reasons. Furthermore, the heart rate and RPE after 6 min in the 6MCT indicate a submaximal exercise test,[42] which consequently represents a low burden for patients in comparison to tests of maximal exhaustion. Accordingly, the test is also suitable for frail patients.

To the best of our knowledge, there are no published reference values for the 6MCT on a conventional cycle ergometer with which we could compare our data. In our adapted test on the cycle ergometer, the patients achieved a heart rate of 157 ± 25 bpm, which is similar to the A6MCT published by Jansen et al.[16] In this test, healthy boys achieved a heart rate of 161 ± 22 bpm, while boys with Duchenne muscular dystrophy achieved a heart rate of 155 ± 18 bpm. Therefore we conclude that the physiological response observed in our test is similar to that of the already validated A6MCT.[16]

The results of the CPET demonstrate that the participants in our study exhibit a diminished cardiorespiratory fitness when compared to the established reference values for healthy children.[43–46] Nevertheless, the VO_{2peak} of 30.7 ± 9.0 $mL \cdot min^{-1} \cdot kg^{-1}$, as determined by our research team, is consistent with the findings of earlier investigations in childhood cancer patients. A study of childhood cancer patients during or shortly after treatment reported a VO_{2peak} of 31.7 ± 9.2 $mL \cdot min^{-1} \cdot kg^{-1}$,[47] while a study of pediatric patients with acute lymphoblastic leukemia within five years after completion of treatment demonstrated a median VO_{2peak} of 30.4 $mL \cdot min^{-1} \cdot kg^{-1}$.[48] The aforementioned findings suggest that the sample under examination is representative of childhood cancer patients in terms of cardiorespiratory fitness.

Perspectives and implications for practice

The findings indicate that the 6MCT is an accurate and valid method for estimating the endurance capacity of children and adolescents with cancer. Consequently, the results may be used to assess current cardiorespiratory fitness and to control the appropriate level of training intensity. As the test does not require special equipment or particular expertise, it could be a suitable option for use in primary care or physiotherapy to assess cardiorespiratory fitness, which is of particular importantance in children and adolescents with cancer[49,50] due to its prognostic significance.[51,52]

The subsequent step would be to establish an equation based on the 6MCT for predicting VO_{2peak}. This would entail conducting a further study with a larger patient sample and including other predictors, such as leg strength or hemoglobin level. Thus, the 6MCT could be employed to assess endurance performance with greater accuracy if the gold standard for assessing cardiorespiratory fitness is not available. Furthermore, the test could be evaluated in other clinical populations as a simple alternative to CPET.

Limitations

The sample was notably heterogeneous, encompassing not only a range of diagnoses and cancer treatments but also a diversity of age. This heterogeneity precluded direct comparisons across clinical characteristics. Furthermore, the majority of patients were aged between 4 and 11 years, whereas adolescents were substantially underrepresented. Future studies should therefore specifically analyze adolescents.

A further limitation is the relatively small sample size, which is a consequence of the low prevalence of childhood cancer. Furthermore, it was not possible to carry out CPET with all patients in addition to the 6MCT, which limits the ability to draw conclusions regarding the validity of the 6MCT.

Furthermore, it was not possible to assess the reliability of the test through repeated measures in this study due to the inherent variability in the medical and physical conditions of childhood cancer patients. Such variability affects the comparability of measurements and limits reliable assessment of test consistency.

Conclusions

The 6MCT was found to be a feasible and valid method for assessing endurance capacity in children and adolescents with cancer. The test is therefore recommended as a simple and cost-effective method of assessing exercise capacity, particularly suited to immunocompromised and therefore isolated patients, in cases of lack of space or patients at risk of falling. However, further studies with larger and more homogeneous samples are required to confirm the present results. These should also focus on developing an equation for estimating VO_{2peak} from the test results in order to enable more accurate assessments of cardiorespiratory fitness and increase the clinical value of the test.

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Author contributions

CRediT: **Lena Wypyrsczyk**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing; **Mareike Kühn**: Conceptualization, Formal analysis, Investigation, Methodology, Writing – review & editing; **Elias Dreismickenbecker**: Conceptualization, Methodology, Supervision, Writing – review & editing; **Marie A. Neu**: Conceptualization, Supervision, Writing – review & editing; **Heidi Diel**: Conceptualization, Writing – review & editing; **Joerg Faber**: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Disclosure statement

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This research was approved by the local ethics review committee of the Rhineland-Palatinate Chamber of Physicians under the application number 2021-15904 on 04.08.2021 and under the application number 2022-16726 on 17.03.2023. All procedures performed in this study are in accordance with the 1964 Declaration of Helsinki and its later amendments. All participants were informed of the purpose, content, and potential risks and benefits of the study, and written informed consent was obtained from legal guardians for minors and from all participants over the age of 16.

Consent for publication

Not applicable.

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Data availability statement

The data supporting the findings of this study contain personal information that cannot be made publicly available due to data protection regulations, but are available from the corresponding author upon reasonable request.

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