Assessing pulmonary function in children and adolescents after cancer treatment: protocol for a multicenter cohort study (SCCSS FollowUp–Pulmo)

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Abstract

Background: Childhood cancer survivors (CCS) are at risk of pulmonary dysfunction due to cancer treatments, but evidence on prevalence and risk factors remains limited. Most previous studies had small sample sizes or retrospective study designs, little information on treatments, a lack of standardization of pulmonary function tests (PFTs), or limited pulmonary assessments to certain PFTs. Since spirometry mainly assesses the large airways, but cancer therapy also affects peripheral airways, additional functional tests are needed. The nitrogen multiple breath washout (N2MBW) test is sensitive to peripheral airway damage in other patient populations, but its benefit in CCS is unknown. Therefore, comprehensive and standardized evaluation of pulmonary function after cancer treatment in childhood using different PFTs that include N2MBW is needed to address these knowledge gaps and provide insights into possible early stages of pulmonary dysfunction.

Objective: With the Swiss Childhood Cancer Survivor Study (SCCSS) FollowUp–Pulmo, we will comprehensively assess lung function in children and adolescents after treatment for cancer to identify risk factors for pulmonary dysfunction, assess the ability of N2MBW to detect pulmonary dysfunction compared with other PFTs, and investigate the association of functional outcomes from PFTs with self-reported respiratory symptoms.

Methods: The SCCSS FollowUp–Pulmo is a prospective multicenter longitudinal cohort study embedded in routine clinical care that enrolls CCS aged 6?20 years for whom at least one year has passed since childhood cancer diagnosis, who have completed treatment and attend regular pediatric oncological follow-up care. Inclusion criteria comprise any of the following: systemic anticancer treatment (chemotherapy, immunotherapy, or targeted agents), thoracic surgery, thoracic radiotherapy, or hematopoietic stem cell transplantation (HSCT). CCS receive a standardized pulmonary assessment including spirometry, body plethysmography, diffusing capacity of the lung for carbon monoxide (DLCO), and N2MBW, and a questionnaire on respiratory symptoms and lifestyle. Data from previous and subsequent routine care PFTs will be included in the study.

Results: The study started recruitment in June 2022 at the University Children's Hospital Bern, Switzerland. Subsequently, patient recruitment expanded to the University Children's Hospitals in Basel and Geneva, Switzerland. The study continuously enrolls new CCS. By October 2024, we had invited 220 patients of which 201 participated, resulting in a response rate of 91%.

Median age at study was 14 years (interquartile range [IQR] 10-17), and median time since diagnosis 7 years (IQR 4-10).

Conclusions: This study will contribute to a comprehensive understanding of pulmonary function in childhood cancer survivors and assess related risk factors, as well as the utility of N2MBW compared to other PFTs. The results will assist the development more targeted screening and risk-stratified follow-up care. Clinical Trial: ClinicalTrials.gov “NCT04732273”

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Original Paper

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Abstract

Background

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With the Swiss Childhood Cancer Survivor Study (SCCSS) FollowUp–Pulmo, we will comprehensively assess lung function in children and adolescents after treatment for cancer to identify risk factors for pulmonary dysfunction, assess the ability of N_2MBW to detect pulmonary dysfunction compared with other PFTs, and investigate the association of functional outcomes from PFTs with self-reported respiratory symptoms.

Methods

The SCCSS FollowUp–Pulmo is a prospective multicenter longitudinal cohort study

embedded in routine clinical care that enrolls CCS aged 6–20 years for whom at least one year has passed since childhood cancer diagnosis, who have completed treatment and attend regular pediatric oncological follow-up care. Inclusion criteria comprise any of the following: systemic anticancer treatment (chemotherapy, immunotherapy, or targeted agents), thoracic surgery, thoracic radiotherapy, or hematopoietic stem cell transplantation (HSCT). CCS receive a standardized pulmonary assessment including spirometry, body plethysmography, diffusing capacity of the lung for carbon monoxide (DLCO), and N_2MBW, and a questionnaire on respiratory symptoms and lifestyle. Data from previous and subsequent routine care PFTs will be included in the study.

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Significance

This study will contribute to a comprehensive understanding of pulmonary function in childhood cancer survivors and assess related risk factors, as well as the utility of N_2MBW compared to other PFTs. The results will assist the development more targeted screening and risk-stratified follow-up care.

Trial Registration: ClinicalTrials.gov “NCT04732273”

Keywords (3-10): childhood cancer survivors, respiratory function tests, late effects, pulmonary toxicity, multiple breath washout test, cohort study

Introduction

Survival rates and long-term complications

Advances in childhood cancer treatment and supportive care have resulted in survival rates that now exceed 80% in developed countries [1]. Yet even as cancer treatments are curative in targeting cancer cells, they can harm healthy tissue and potentially cause late complications such as second neoplasms and chronic diseases [2,3]. The cumulative incidence of such late effects among childhood cancer survivors (CCS) thus predisposes them to increased morbidity and premature mortality [4]. Among late effects, pulmonary complications are the third leading cause of excess mortality among CCS after second neoplasms and cardiovascular diseases [5].

Pulmotoxic treatments

Several cancer treatment modalities can be pulmotoxic. These include the chemotherapeutic agents busulfan, bleomycin, carmustine, and lomustine, thoracic radiotherapy, thoracic surgery, and hematopoietic stem cell transplantation (HSCT) [6,7]. The underlying mechanisms of pulmonary toxicity involve alveolar, vascular, and parenchymal damage resulting from chemotherapy and radiotherapy, which may progress to lung fibrosis [6–8]. HSCT-related lung damage can result from intensive conditioning regimens, infections, or graft-versus-host disease (GvHD), while surgery to the chest or lungs may reduce lung volumes and impair chest wall compliance [7,9]. However, recently published recommendations for surveillance of pulmonary function among CCS from the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) could not consistently confirm the pulmonary toxicity of all of these treatments, particularly certain chemotherapeutics, due to limited and low-quality evidence [10]. Other

chemotherapeutics, such as methotrexate and cyclophosphamide have also been suspected of causing lung damage [8,11], but findings across studies remain inconsistent [12,13]. Considering that these treatments may harm developing lungs and potentially lead to progressive pulmonary damage [14], it is important to study their effects on lung function.

Prevalence and detection of pulmonary dysfunction

Pulmonary dysfunction in CCS exposed to pulmotoxic treatments has been reported in varying proportions of survivors (44%–77%) depending on study populations and criteria used to define obstructive, restrictive, and diffusion impairments [12,13,15,16]. The lung has a large functional reserve, and early disease may often remain asymptomatic, particularly when it affects the lung periphery [17]. Most studies have used conventional pulmonary function tests (PFTs) such as spirometry, body plethysmography, and diffusing capacity of the lung for carbon monoxide (DLCO) to assess lung function in CCS. However, spirometry and body plethysmography lack the sensitivity to detect changes in small airways [18], which may be damaged first [6]. The nitrogen multiple breath washout (N_2MBW) test, which measures ventilation inhomogeneity of the ventilated lung detecting small airway disease, has been increasingly used in other patient populations, including those treated with allogeneic HSCT [19–21]. In a small prospective study of adult CCS, N_2MBW identified more cases of pulmonary dysfunction than spirometry, even among those who had not been exposed to previously defined pulmotoxic treatments [22]. Though larger prospective studies with standardized assessments still are needed, these findings suggest that N_2MBW could be a valuable complementary test in screening CCS for early pulmonary damage.

Current knowledge gaps

The recently published IGHG recommendations not only summarize existing evidence but

also highlight large knowledge gaps and methodological weaknesses in previous research [10]. These gaps highlight the need for prospective, longitudinal studies with larger sample sizes and broader range of treatment exposures to characterize the onset and progression of treatment-related pulmonary dysfunction. The long-term effects of newer chemotherapeutic and immunotherapeutic agents on lung function are understudied [23]. Evidence on how treatment-related complications, comorbidities, and genetic variants influence lung damage risk is limited as well. Standardization, too, is lacking in pulmonary function testing and in the use of appropriate age- and sex-specific reference values. For example, results should be reported as z-scores rather than just proportions of patients with reduced lung function. Additionally, few studies have assessed diagnostic tests specific to location and type of potential dysfunction, such as N_2MBW for peripheral inhomogeneity in ventilation. More data are also needed on the association between PFT outcomes and clinical symptoms. To address these gaps, we designed the Swiss Childhood Cancer Survivor Study (SCCSS) FollowUp–Pulmo.

Study objectives

The primary objective of SCCSS FollowUp–Pulmo is to longitudinally investigate lung function in children and adolescents after cancer treatment using a comprehensive set of that PFTs also assess small airway disease. Second, the study investigates possible effects of treatment-related risk factors (systemic anticancer agents, thoracic radiotherapy, thoracic surgery, and HSCT), treatment-related complications (pulmonary infections, GvHD), and existing comorbidities (e.g., pulmonary or cardiac disease) on lung function. Third, the study compares examines the ability of the N_2MBW test to detect pulmonary dysfunction in comparison with other PFTs. Fourth, it investigates the association between lung function and self-reported respiratory symptoms.

Methods

Study design and inclusion criteria

SCCSS FollowUp–Pulmo is a multicenter prospective longitudinal cohort study integrated into routine clinical care of several children's hospitals in Switzerland. The study is an interdisciplinary collaboration between the departments of pediatric hematology/oncology and pediatric pulmonology of respective centers, the Institute of Social and Preventive Medicine (ISPM) at the University of Bern, and the Swiss Childhood Cancer Registry (ChCR, www.childhoodcancerregistry.ch). The ChCR is a nationwide, population-based cancer registry that includes Swiss residents diagnosed up to the age of 20 with leukemia, lymphoma, central nervous system tumors, malignant solid tumors, or Langerhans cell histiocytosis, classified according to the International Classification of Childhood Cancer, third edition (ICCC-3) [24]. While the ChCR captures over 95% of children diagnosed in Switzerland [25], the SCCSS FollowUp–Pulmo study also includes a few patients treated and followed up in Swiss clinics who may not be registered in the ChCR due either to registration delays or residency outside of Switzerland.

All CCS aged 6–20 years for whom one year or more has elapsed since cancer diagnosis, who have completed treatment, and are in regular pediatric hemato-oncological follow-up care are eligible for SCCSS FollowUp–Pulmo. These treatment modalities possibly affecting lung function are included: any systemic anticancer treatment (chemotherapy, immunotherapy, or targeted therapy) [26]; thoracic surgery involving the chest or lungs (excluding central line placement) [27]; radiation of the lungs, the chest (axilla, mantle, mediastinal) or scattered radiation from other radiation fields including whole abdomen or any upper abdominal field, spinal doses of 30 Gray or higher, and total body irradiation

(TBI) [27]; or HSCT [28]. Excluded are CCS who were treated only with surgery and/or radiation outside the thorax due to their low risk for pulmonary dysfunction [29], and patients with relapse or in palliative care at the time of recruitment.

Ethical approval was granted by the Ethics Committee of the Canton of Bern, Switzerland (KEK-BE: 2019-00739) and the study is registered on ClinicalTrials.gov (NCT04732273).

Study procedures

The study is coordinated by the ISPM research team, which is responsible for overall study management, monitoring recruitment progress, and handling administrative and financial aspects. Clinical teams at each participating center include pediatric oncologists, pulmonologists, data managers, and study nurses.

Step 1: Selection of eligible survivors

Eligible CCS are identified in two ways: 1) The ChCR provides an initial list of eligible patients to participating hospitals; and 2) a member of the clinical team regularly screens upcoming follow-up appointments, cross-referencing with the ChCR and identifying any additional eligible patients (Figure 1). This process ensures the inclusion of all eligible patients. The treating physician organizes pulmonary function assessments for the upcoming oncological follow-up appointment. Detailed recruitment procedures are developed at each center to take into account clinical workflows.

Step 2: Invitation

The clinical team sends the study information, consent form, and a questionnaire on respiratory health to eligible survivors prior to their next oncological follow-up appointment that will include PFTs. CCS who consent to participation send the documents back or bring

them to the consultation.

Step 3: Clinical assessment

At the oncological follow-up assessment, the patients first meet their pediatric oncologist who obtains a history, performs a physical examination, and refers them to pediatric pulmonology for PFTs. Since the PFTs are scheduled within the follow-up care, they are conducted irrespective of study consent. Patients with pathological results will have repeated PFTs as clinically indicated (Figure 2). The clinical team collects the signed consent form and questionnaire. If patients did not complete the consent form and questionnaire prior to or during the clinical visit, they can still return the documents later. If the patient declines to participate, no data are collected for the study purposes.

Step 4: Data collection and management

The clinical team at the respective study centers and the research team at ISPM extract the data for each consenting participant from medical records, PFTs, and questionnaires. All data are entered into the Research Electronic Data Capture (REDCap; version 14.0.10, Vanderbilt University, Nashville, Tennessee) database. The REDCap database complies with all legal requirements for data security and data protection. Within the database, each patient has a unique REDCap ID.

Exposures and outcomes of interest

Pulmonary function tests

Survivors perform a set of PFTs including spirometry, body plethysmography, DLCO, and N_2MBW according to The American Thoracic Society and the European Respiratory Society (ATS/ERS) recommendations [30,31]. PFTs are conducted in pediatric lung function

laboratories by trained technicians. Standard operating procedures for PFTs are harmonized among centers to ensure comparability, with quality control performed by the lung function technicians. Because N_2MBW is not yet widely used in clinical settings, we additionally perform a centralized quality control to ensure that only high-quality tests and the latest algorithms are included. Specialized software developed by experts at the University Hospital in Bern detects evidence of leaks, insufficient waiting time between tests, early termination of tests, synchronization issues, and abnormal breathing patterns or volumes in accordance with consensus guidelines [32,33]. Experienced pulmonologists interpret and review the results of PFTs.

Since asthma and allergic conditions are common differential diagnoses in young patients, including CCS, most clinics also measure fractional exhaled nitric oxide (FeNO) in those with obstructive patterns on spirometry or asthma-like symptoms [34]. High FeNO levels suggest an asthmatic or allergic etiology, while low levels may indicate noninflammatory causes related to cancer treatment effects.

Textbox 1 shows main outcome measures from PFTs, their interpretation, anatomical correlates, and reference values used for respective PFTs. The study also collects all prestudy PFT data from patients who previously underwent these assessments and subsequent PFTs conducted as part of ongoing clinical care.

Textbox 1 Pulmonary function tests performed in childhood cancer survivors, their interpretation, and anatomical correlates.

Pulmonary function test	Main outcomes	Meaning of abnormal results	Anatomical correlates	Normal values
Spirometry	FVC [L] FEV_1 [L] FEV_1 /FVC $FEF_{25\%-75\%}$	Airway obstruction, reduced dynamic lung volumes	Fibrotic destruction of the lung tissue and large airways, reduced lung compliance	Quanjer et al., ERJ, 2012 [35]
Body plethysmography	FRC SR_{eff} SR_{tot} RV TLC VC	Reduced static lung volumes, hyperinflation	Fibrotic destruction of the lung tissue and large airways, reduced lung compliance	Hall et al., ERJ, 2021 [36]
DLCO	DLCO	Reduced alveolar-capillary gas transfer, reflected by diffusion deficits	Alveolar-capillary membrane damage	Stanojevic et al., ERJ, 2017 [37] Stanojevic et al., ERJ 2020 [38]
N_2MBW	LCI S_{ACIN} S_{COND}	Increased ventilation inhomogeneity of the airways with reduced global, alveolar, and conducting ventilation	Fibrotic damage of small airways	Ramsey et al., ERJ, 2024 [39]
FeNO*	FeNO	Eosinophilic airway inflammation as key component of allergic asthma	Allergic inflammation as alternative cause of pulmonary obstruction	Jacinto et al., Clin Respir J, 2013 [34]

Abbreviations: DLCO, diffusion capacity of the lung for CO; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; $FEF_{25\%-75\%}$, forced expiratory flow at 25-75% of forced vital capacity; FRC, functional residual capacity; FVC, forced vital capacity; GLI, global lung function initiative; LCI, lung clearance index; RV, residual volume; S_{COND}, conductive ventilation inhomogeneity index; S_{ACIN}, acinar ventilation inhomogeneity index; SR_{eff} and SR_{tot}, resistance; TLC, total lung capacity; VC, vital capacity.

* FeNO is measured in CCS with symptoms suggestive of asthma (wheeze, dyspnea, cough) or signs of obstruction in spirometry

Medical and questionnaire data

Information obtained from medical records includes anthropometric measures, respiratory disease history, physical evaluation, PFTs, cancer diagnosis and treatment, and additional data from medical history including comorbidities and significant treatment-related complications (GvHD, pulmonary infections) (Textbox 2).

Survivors complete a detailed questionnaire on respiratory health that includes sections on respiratory symptoms, infectious diseases, exercise-induced problems, allergic and pulmonary diseases, family history of respiratory conditions, lifestyle and environmental factors, and sociodemographic information.

Textbox 2 Description of medical and questionnaire data collected as part of SCCSS FollowUp–Pulmo.

Data from medical records	
Personal information and anthropometric measures	Date of birth, sex, height, weight, BMI
Respiratory history and physical evaluation	Recent history of airway infections, lung auscultation, thoracic inspection, signs of dyspnea, oxygen saturation
Pulmonary function tests	Spirometry, body plethysmography, DLCO, N_2MBW, FeNO (date, test quality, outcomes listed in Textbox 1)
Cancer diagnosis	Date of diagnosis, type of cancer, location, metastases, relapse, second malignant neoplasm
Cancer treatment	Treatment protocol and arm, start and end date Cumulative doses of all individual chemotherapy drugs, targeted agents, and immunotherapies Radiotherapy (cumulative dose, location, duration) Surgery (location, type) HSCT (autologous or allogeneic, donor type and source, conditioning regimens, complications)
Additional data from medical history	GvHD (acute or chronic, affected organs, grade, treatment) Significant pulmonary infections during or after cancer treatment (diagnosis, causing pathogen, duration of hospitalization) Comorbidities
Questionnaire data	
Respiratory symptoms	Cough, wheeze, dyspnea (frequency, duration, triggers)
Infectious diseases	Otitis, sinusitis, pneumonia (recurrence, treatment)
Exercise-induced problems	Frequency, types, triggering situations
Allergic diseases	Allergic rhinitis, hay fever, atopic dermatitis
Pulmonary diseases	Asthma, bronchitis, lung fibrosis, emphysema (treatment)
Lifestyle and environment	Physical activity (physical education and recreational exercise) Active and passive smoking (amount and type of tobacco products)
Sociodemographic data and family history	Citizenship, parental education and profession, family history of asthma, chronic bronchitis, hay fever and atopic dermatitis

Abbreviations: BMI, body mass index; DLCO, diffusing capacity of the lungs for carbon monoxide; N2MBW, nitrogen multiple breath washout test; FeNO, fractional exhaled nitric oxide; HSCT, hematopoietic stem cell transplantation; GvHD, graft-versus-host disease

Sample size calculation

To determine the sample size needed for our study, we based calculations on the study by Schindera et al., which assessed lung function in long-term CCS using spirometry and N_2MBW [22]. This single-center study was conducted in Swiss CCS and applied the same inclusion criteria for treatment exposures, making it a suitable reference. The main outcome from N_2MBW was the lung clearance index (LCI). Mean LCI z-score was 1.37 with a standard deviation (SD) of 2.69. We calculated the number of participants necessary to achieve a statistical significance level of 0.05 and a power of 0.80 while accounting for a 15% dropout rate. This calculation indicated that a minimum of 146 participants would be required to detect a similar deviation in LCI with sufficient statistical power. We plan to include a larger sample size to increase precision, improve our ability to detect smaller deviations, and ensure adequate power to analyze other lung function outcomes and investigate specific subgroups of patients defined by tumor type and treatments received.

Statistical analysis

To compare PFT outcomes with normal values, we will calculate z-scores and percent-predicted values using external Global Lung Initiative (GLI) reference data [35–37,39]. We will define pulmonary dysfunction as z-scores below –1.64 or above +1.64 for respective PFT indices since these thresholds represent deviations from the reference population mean and indicate abnormalities in pulmonary function. To characterize pulmonary function among CCS, we will analyze z-scores for predefined outcomes and assess differences based on characteristics such as treatment exposure, age at treatment, and time since cancer diagnosis. We will assess group differences using appropriate statistical tests based on the type of variable such as t-tests or Mann-Whitney tests for continuous variables and

χ^2 or Fisher's exact tests for categorical variables. For analyses of associations between outcomes and covariates, we will apply regression models adjusted for potential confounders. For longitudinal data, we will use mixed effects models to account for repeated measures over time. We will use Stata (Stata Corp LLC, Texas, USA) and R (Foundation for Statistical Computing, Vienna, Austria) for statistical analyses.

Results

Recruitment started in June 2022 at the University Children's Hospital in Bern, in March 2023 at the University Children's Hospital in Basel, and in March 2024 at the University Children's Hospital in Geneva. The number of new participants per month varies across the centers, depends on clinic capacity, and is steadily growing (Figure 3). As of October 2024, a total of 220 patients had been invited to participate in the study. Among those, 201 patients consented to and performed PFTs, resulting in a response rate of 91%. Bern registered 125 participants, Basel 70, and Geneva 6. The time required to perform all lung function tests and complete the questionnaire was 45-60 minutes per participant.

More than one-half of the 201 participants, 119, were male, median age at study was 14 years (interquartile range [IQR] 10-17), and median time since diagnosis 7 years (IQR 4-10) (Table 1). The most common diagnoses were leukemia, which had been diagnosed in 105 participants (52%); lymphoma, diagnosed in 22 (11%); and neuroblastoma, in 18 (9%). All but two of the participants had been treated with chemotherapy, 25 (13%) received thoracic radiotherapy, and 15 (8%) had had thoracic surgery. In total, 20 participants (10%) had undergone HSCT, with 11 (6%) treated with autologous and 9 (4%) with allogeneic HSCT.

Table 1 Demographic and clinical characteristics of childhood cancer survivors participating in the SCCSS FollowUp–Pulmo study up to October 2024

	N=201	
Demographic characteristics	**n**	**(%)[a]**
Sex		
Male	119	(59)
Female	82	(41)
Median age at study in years (IQR)	14 (10–17)	
Categories of age at study in years		
6-10	47	(23)
11-14	73	(36)
15-18	66	(33)
≥19	15	(8)
Clinical characteristics	**n**	**(%)[a]**
Median age at diagnosis in years (IQR) (range)	5 (3–9) (0.1-17)	
Median time since diagnosis in years (IQR) (range)	7 (4–10) (1-17)	
Categories of time since diagnosis in years		
<5	68	(34)
5-10	83	(41)
11-15	41	(20)
>15	9	(5)
Diagnosis (ICCC-3)		
Leukaemia	105	(52)
Lymphoma	22	(11)
CNS tumour	11	(6)
Neuroblastoma	18	(9)
Retinoblastoma	0	(0)
Renal tumour	15	(8)
Hepatic tumour	2	(1)
Bone tumour	6	(3)
Soft tissue sarcoma	14	(7)
Germ cell tumour	2	(1)
Other tumour[b]	2	(1)
Langerhans cell histiocytosis	4	(2)
Treatment		
Chemotherapy[c]	199	(99)
Pulmotoxic chemotherapy	16	(8)
Thoracic radiotherapy[d]	25	(13)
Thoracic surgery[e]	15	(8)
HSCT[f]	20	(10)
Autologous	11	(6)
Allogeneic	9	(4)
Relapse	15	(8)

[a] Column percentages are given.

[b] Other malignant epithelial neoplasms, malignant melanomas, and other or unspecified malignant neoplasms.

[c] Any chemotherapy alone or combined with other treatments.

[d] Radiotherapy involving chest, abdomen, spine, or total body irradiation alone or combined with other treatments.

[e] Surgery involving thorax or lungs alone or combined with other treatments.

[f] Any hematopoietic stem cell transplantation alone or combined with other treatments.

Abbreviations: BMI body mass index; IQR, inter quartile range; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer - Third Edition; HSCT, hematopoietic stem cell transplantation.

Discussion

This prospective, multicenter cohort study of lung function in children and adolescents after cancer treatment investigates risk factors, compares the detection of pulmonary dysfunction by N_2MBW with conventional PFTs, and examines the association of functional outcomes from PFTs with respiratory symptoms.

Comparison to previous research

Previous studies of pulmonary dysfunction after treatment for childhood cancer have mostly been retrospective, based on chart reviews [14,40–42]. This has entailed methodological weaknesses, particularly a risk of selection bias because CCS for whom PFT results were obtained might overrepresent symptomatic CCS or those treated more intensively. We did identify several prospective studies in pediatric CCS, but like the retrospective ones they mostly recruited specific groups of patients treated with previously defined pulmotoxic treatments such as HSCT [42–44] or thoracic radiation [14,45], or specific tumor types such as leukemia [46] or lymphoma [47,48]. Data on the pulmotoxic effects of individual agents such as busulfan [49], melphalan [50], cyclophosphamide [46,50] and methotrexate [51] remain limited. By including CCS exposed to systemic therapies such as any chemotherapy, targeted agents, or immunotherapy, our study will provide a better understanding of treatment-related pulmonary dysfunction in a broadly representative population of CCS. Continuous recruitment will allow us to collect data on the pulmonary effects of newer treatments used in contemporary protocols, whose impacts remain largely unknown [52]. Detailed information from medical records will allow the investigation of effects of comorbidities and treatment-related complications on PFT outcomes.

Previous studies rarely included sensitive tests like N_2MBW that can detect early changes

in the lung periphery. Most used spirometry, body plethysmography, and DLCO [12,14,15,49]. A study investigating 57 pediatric CCS with median follow-up time of 6.2 years from end of treatment did not find differences in ventilation inhomogeneity measured by N_2MBW compared with healthy controls [53]. In contrast, several studies in patients after allogeneic HSCT reported LCI to be a sensitive measure for early pulmonary complications [20,54,55]. This study will obtain N_2MBW data for CCS exposed to a wide range of treatment modalities and investigate whether N_2MBW is more sensitive than other PFTs in detecting early pulmonary dysfunction.

Another drawback of many existing studies is that they report PFT data using binary cut-offs and describe results as either normal or abnormal [12,15,49]. This reduces statistical power and introduces interpretations based on predefined threshold values. Reporting PFT results as raw data and z-scores based on internationally agreed upon, age-adjusted reference values will allow better comparison and pooling across studies. Data on how lung function correlates with clinical symptoms [10]. The data from questionnaires will allow this study to investigate symptoms and other patient-reported outcomes and their correlation with PFT results.

Collaboration with other ongoing studies

The SWISS-Pearl Study (ClinicalTrials.gov ID: NCT05427136), currently conducted in multiple centers in Switzerland, investigates lung function in pediatric cancer patients. The study includes spirometry, body plethysmography, N_2MBW, magnetic resonance imaging of the lungs, and questionnaires at different points during cancer treatment. We plan to combine that study with ours to create a comprehensive database enabling us to analyze

lung function trajectories in pediatric cancer patients and survivors.

The GECCOS (Genetic Risks for Childhood Cancer Complications Switzerland) study is a nationwide cohort study collecting germline genetic data from childhood cancer patients and survivors in Switzerland [56]. In consenting patients, we will link clinical and PFT data with the genetic data from GECCOS, allowing us to investigate the effects of genetic predisposition on pulmonary toxicity. This will assist the development personalized treatment strategies and risk-adapted long-term care for survivors.

Study limitations

A current limitation of this study is the limited number of participants and the heterogeneity of the study population, which can limit the statistical power for conducting subgroup analyses. For instance, exploring rare tumors or assessing specific effects of individual chemotherapeutic agents may at present be challenging. But we plan to expand the study to more centers and pool data in international collaborations.

Another study limitation is the lack of systematic baseline PFT assessments prior to cancer diagnosis. This makes it challenging to determine for an individual whether any observed pulmonary dysfunction is due to cancer treatments or was preexisting.

Finally, there is a small risk of selection bias because CCS with longer time since the end of treatment who do not experience respiratory symptoms or were not exposed to pulmotoxic treatments may be less likely to participate in the study, potentially leading to underrepresentation of healthy CCS. Yet because the study is embedded in regular follow-up care and supported by oncologists with initial results showing a high participation rate, exceeding 90%, this bias should be minimal.

Conclusion

This multicenter cohort study prospectively investigates pulmonary dysfunction in young CCS. By assessing lung function as an intermediate outcome, rather than established disease or mortality, this study will provide a resource for evaluating pulmonary dysfunction at an earlier stage in the disease trajectory, particularly within the early years post-treatment. The initial response shows that integrating standardized pulmonary evaluations into routine follow-up care in Switzerland is feasible and widely accepted by both survivors and healthcare providers. The findings of this study will provide new insights to inform the development of guidelines and recommendations for pulmonary follow-up care.

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Authors contributions

All authors contributed to the study conception and design. MŽ, CS, GS, and CK wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

Philipp Latzin reports relationships with Vertex, OM Pharma, Vifor, Polyphor, Santhera, Allecra, and Sanofi Aventis. These include grants, consulting fees, payments for lectures, advisory board memberships, and travel reimbursement. None of these relationships are

associated with the current study.

Abbreviations

ATS/ERS	The American Thoracic Society and the European Respiratory Society
CCS	Childhood cancer survivors
ChCR	Swiss Childhood Cancer Registry
DLCO	Diffusing capacity of the lung for carbon monoxide
FeNO	Fractional exhaled nitric oxide
GECCOS	Genetic Risks for Childhood Cancer Complications Switzerland
GLI	Global Lung Function Initiative
GvHD	Graft-versus-host-disease
HSCT	Hematopoietic stem cell transplantation
ICCC-3	International classification of childhood cancer, third edition
IQR	Interquartile range
ISPM	Institute of Social and Preventive Medicine
LCI	Lung clearance index
N_2MBW	Nitrogen multiple breath washout test
PFTs	Pulmonary function tests
REDCap	Research Electronic Data Capture
TBI	Total body irradiation

Data availability

Researchers interested in collaborative work can contact the corresponding author (Claudia

Kuehni; claudia.kuehni@unibe.ch) to discuss planned projects.

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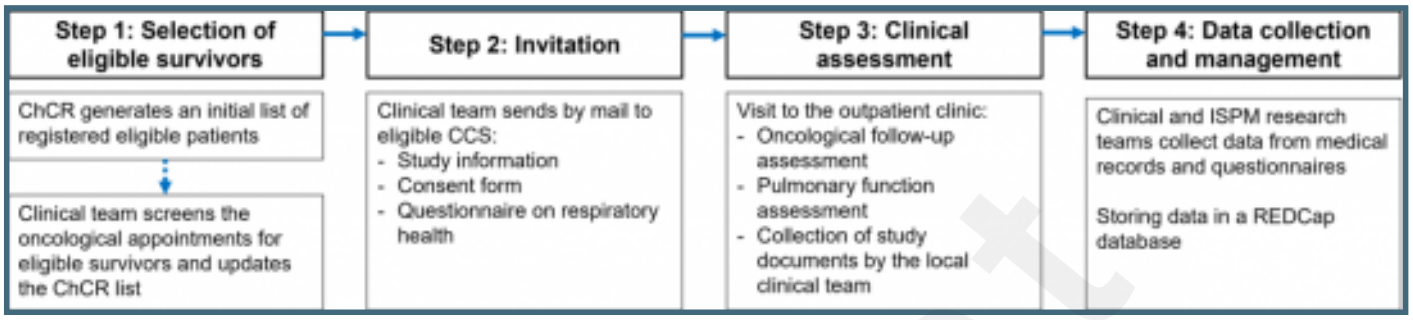
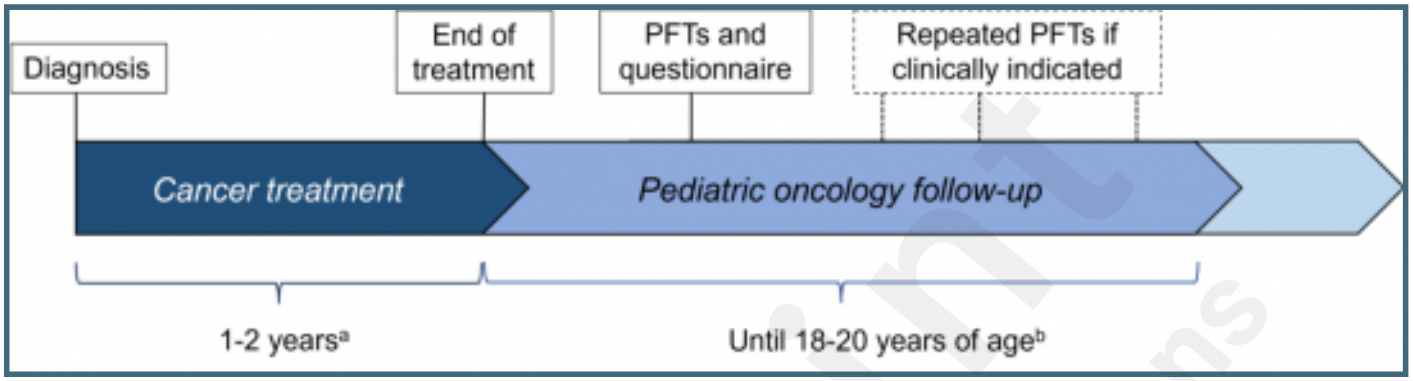
Supplementary Files

Figures

Flowchart of the SCCSS FollowUp–Pulmo procedures. Abbreviations: ChCR, Swiss Childhood Cancer Registry; CCS, childhood cancer survivors; ISPM, Institute of Social and Preventive Medicine; REDCap, Research Electronic Data Capture database.



Timeline of pulmonary function assessments during the SCCSS FollowUp–Pulmo. Abbreviation: PFTs, pulmonary function tests. a The duration of cancer treatment varies based on the specific cancer diagnosis and the corresponding treatment protocol. b The age at which a patient transitions out of pediatric oncology follow-up may vary individually, depending on the cancer treatment protocol and the practices of the respective center.



Number of participants in SCCSS FollowUp–Pulmo since the start of the study.