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Cohort profile: pulmonary early assessment of the lung in paediatric cancer patients (SWISS-PEARL Study)

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Summary

BACKGROUND: Due to the limited sensitivity of conventional lung function tests in detecting small airway abnormalities, cancer treatment-related pulmonary toxicity may be underdiagnosed. It has been suggested that the nitrogen multiple-breath washout test (N_2MBW) might be more sensitive in detecting small airway abnormalities in childhood cancer survivors.

OBJECTIVE: The Pulmonary Early Assessment of the Lung in Paediatric Cancer Patients (SWISS-PEARL) study aims to assess the prevalence and development of early pulmonary toxicity at baseline and longitudinally in paediatric cancer patients using spirometry, body plethysmography, diffusing capacity for carbon monoxide (DLCO), N_2MBW and magnetic resonance imaging (MRI) and to identify treatment-related pulmotoxic risk factors.

METHODS: This prospective, multicentre, cohort study at the University Children's Hospitals of Basel, Bern, Lausanne and Zurich, is enrolling patients aged ≥4 and <22 years at study entry exposed to at least one of the following cancer treatments: chest radiation, chemotherapy or targeted agents, haematopoietic stem cell transplantation and/or thoracic surgery. Participants perform comprehensive lung function testing at baseline (i.e. within 28 days of the start of systemic cancer treatment) and during four follow-up visits until two years after the end of intensive treatment. Respiratory symptoms are also assessed at each time point, and MRI is planned at one and two years post-treatment.

RESULTS: Since May 2022, we have recruited 44 patients and performed 134 lung function tests at baseline. Mean age at diagnosis was 12 years (range 4–18). The most common cancer diagnoses were leukaemia (41%) and lymphoma (23%). Pulmonary assessment was feasible and of good quality in 43/44 (98%) patients for at least one test at baseline; only 4 patients dropped out after baseline measurements.

CONCLUSION: This study will assess the potential development of early pulmonary dysfunction during and post-treatment. Findings from the SWISS-Pearl study may help inform future guidelines for pulmonary surveillance in paediatric cancer patients.

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Introduction

The 5-year survival rate for childhood cancer patients in Switzerland has increased to 87%, according to the Swiss Childhood Cancer Registry [1]. However, treatment-related pulmonary toxicity remains a significant concern [2–4]. Known pulmotoxic treatments leading to pulmonary dysfunction include allogeneic haematopoietic stem cell transplantation, chest radiation, thoracic surgery and chemotherapy agents such as bleomycin, busulfan, carmustine and lomustine [5]. Cancer treatment in children occurs at a sensitive stage of lung growth and development. Due to the lung's large functional capacity, symptomatic lung diseases may arise late [3]. Childhood cancer treatment protocols contain various recommendations for

ABBREVIATIONS

DLCO:	diffusing capacity of the lungs for carbon monoxide
FEV1:	forced expiratory volume in 1 second
FRC:	functional residual capacity
FVC:	forced vital capacity
LCI:	lung clearance index
N_2MBW:	nitrogen multiple-breath washout test
TLC:	total lung capacity

lung function screening based on the type of cancer, the affected region and the treatment modality. Screening timing ranges from during treatment to up to five years after the end of treatment and even later [6–16]. Conventional lung function tests include spirometry, body plethysmography and diffusing capacity of the lungs for carbon monoxide (DLCO). The protocol recommendations differ based on treatment-related pulmonary toxicity, the underlying disease, pulmonary assessment modalities and timing [6–16]. Long-term follow-up guidelines suggest spirometry and DLCO as diagnostic modalities, especially in symptomatic paediatric cancer survivors [17, 18]. For example, the current High-Risk Neuroblastoma Study 2 protocol of SIOP-Europa-Neuroblastoma (SIOPEN), which includes a regimen containing the known pulmotoxic substrate busulfan, recommends lung function tests during consolidation, maintenance, the end of treatment and three years' post-treatment. In the event of pathological test results, follow-up lung function tests are recommended in accordance with local standards, which may include procedures such as chest X-ray, spirometry and oxygen assessment [11]. To improve pulmonary follow-up care in childhood cancer patients, the International Guideline Harmonization Group investigated pulmonary dysfunction in childhood, adolescent and young adult (CAYA) cancer survivors to develop pulmonary surveillance guidelines after cancer treatment. Due to limited studies and insufficient evidence, the expert panel only recommends lung function tests in children with respiratory symptoms or who have received known pulmotoxic treatment [18].

Several cohorts and studies from North America and Europe were conducted to investigate the effects of pulmotoxic treatments. These studies were limited by the fact that they only assessed childhood cancer survivors exposed to pulmotoxic cancer treatment [3, 19–24], leaving a gap in knowledge regarding lung function during cancer treatment. The conventional lung function tests used as monitoring tools in guidelines and cohorts to monitor pulmonary dysfunction, especially spirometry, can mainly detect pathologies in the large airways, and not subtle changes in the small airways [25–27], which limits their ability to detect the early development of pulmonary dysfunction. Washout tests can specifically detect peripheral airway (95% of the lung volume) abnormalities by assessing gas mixing within the entire ventilated lung [28, 29]. However, until now, only a few studies have examined the nitrogen multiple-breath washout (N_2MBW) test as a monitoring modality [22–24].

To better understand the use of the washout test as a monitoring tool, our research group conducted a systematic review exploring the application of studies reporting functional and structural lung abnormalities in paediatric cancer patients and survivors using washout techniques and lung imaging modalities to detect cancer treatment-related pulmonary toxicity [30]. None of the identified studies demonstrated results comparing N_2MBW to spirometry at diagnosis. In addition, no study reported an onset of pulmonary dysfunction during and shortly after childhood cancer treatment [22, 23, 27, 31–39], particularly in non-haematopoietic stem cell transplantation patients. There are currently no systematic, prospective, longitudinal studies using N_2MBW or magnetic resonance imaging (MRI) [22, 23, 27, 31–39] to identify pulmonary toxicity exclusively in paediatric cancer patients.

Given the uncertainty regarding the onset of pulmonary dysfunction in non-haematopoietic stem cell transplantation patients following pulmotoxic treatment, it is important to identify the most sensitive lung function testing modalities for early detection of pulmonary toxicity. Modalities such as washout and radiation-free functional pulmonary MRI may have the potential to detect early, subtle signs of pulmonary toxicity in the peripheral airways, which conventional tests might miss. As previously shown in childhood cancer survivors [27], the N_2MBW test is sensitive in assessing the lung periphery. This test requires minimal cooperation and no forced manoeuvres [40], making it accessible for both young and very ill patients.

We hypothesise that the N_2MBW test is more sensitive than spirometry in detecting the onset of pulmonary toxicity, based on the assumption that first changes after pulmotoxic treatment appear in the small peripheral airways. The Pulmonary Early Assessment of the Lung in Paediatric Cancer Patients (SWISS-PEARL) study addresses knowledge gaps concerning early pulmonary toxicity by comparing the current gold standard – spirometry – with other lung function testing modalities,including N_2MBW, for examining small airway disease. In addition, MRI will be used to gain a comprehensive understanding of the onset of lung abnormalities post-treatment. The standardised respiratory health assessment in this study includes a medical history focused on pulmonary diseases and associated risk factors, findings from physical examinations and a focused questionnaire on lung symptoms. This study will report on potential development of lung abnormalities, as well as their reversibility or progression to lung diseases following pulmotoxic treatments.

Study objectives

The SWISS-PEARL study aims (a) to assess prevalence and development of early pulmonary dysfunction at baseline and longitudinally in paediatric cancer patients using four different lung function tests (spirometry, body plethysmography, DLCO, N_2MBW) and lung MRI, and (b) to identify treatment-related pulmotoxic risk factors. Using different methodologies in parallel may offer a comprehensive understanding of early pulmonary dysfunction during and post-treatment.

Methods

Study design

The SWISS-PEARL Study (https://clinicaltrials.gov/ct2/show/NCT05427136) is a standardised, prospective, multicentre cohort study to assess early pulmonary dysfunction in paediatric cancer patients conducted in Switzerland using the outcome measures lung function tests and lung MRI.

Study population

Inclusion criteria and participating centres

We are recruiting all newly diagnosed paediatric cancer patients immediately after diagnosis at the University Children's Hospitals of Basel, Bern, Lausanne and Zurich, who are aged ≥4 and <22 years at study entry and who will receive at least one of the following cancer treatments: chest radiation, treatment with any kind of chemotherapy or targeted agents, haematopoietic stem cell transplantation and/or thoracic surgery. Only those patients capable of performing at least one of the four planned lung function test modalities within 28 days of initiating systemic cancer treatment are eligible for the study. We exclude patients who will undergo surgery outside the chest as the only cancer treatment, and patients with previous cancer therapy or a relapse. Patients with an oxygen (O_2) saturation below 92% requiring additional oxygen supply or those who are unable to perform a lung function test within the specified timeframe at baseline are also excluded. MRI is not carried out in pregnant study participants, or those who require sedation or have metal in their body, such as a pacemaker. The study can be expanded to further paediatric oncology centres.

Study procedures

Patient identification and recruitment

At each study centre, a dedicated study nurse and oncologist assist with patient recruitment. Patients receive study information, informed consent forms and a consent form for further use of data and biological materials (including genetic samples). Patients are approached during the initial hospital admission for treatment of cancer. To reduce patients' burden, assessments are scheduled during regular clinical visits whenever possible.

Lung assessments

Lung function tests include conventional ones (spirometry, plethysmography and DLCO) and N_2MBW tests. Measurements are carried out according to the American Thoracic Society and the European Respiratory Society joint guidelines [41, 42]. Lung imaging includes functional and structural MRI sequences. The lung function tests and MRI are not part of the routine medical examinations, but are carried out specifically for the SWISS-PEARL study.

The lung function tests are performed in paediatric lung function laboratories by experienced lung function technicians or study nurses. Quality control is ensured through standardised protocols. Spirometry provides information on dynamic flows and volumes [43, 44]. The main outcomes from spirometry are the forced vital capacity (FVC), the forced expiratory volume in 1 second (FEV1) and the Tiffenau Index (FEV1/FVC). Plethysmography assesses static lung volumes and airway resistance. Two main outcomes from body plethysmography are the functional residual capacity (FRC) and total lung capacity (TLC) for the assessment of hyperinflation [45]. Alveolar-capillary gas diffusion deficits are assessed with DLCO or the diffusing capacity divided by the alveolar volume (DLCO /alveolar volume) as main outcomes [46–48]. The main outcome from N_2MBW is the lung clearance index (LCI). The LCI represents the number of functional residual capacity (FRC) lung turnovers needed while breathing 100% oxygen to reach a predetermined percentage of the physiological nitrogen concentration, e.g. LCI 2.5% refers to the number of turnovers to reach 2.5% [29]. Higher LCI values indicate increased ventilation inhomogeneity [29]. The diffusion- and convection-interaction-dependent ventilation inhomogeneity index for the distal regions of the acinus, termed S_{ACIN}, and the convection-dependent ventilation inhomogeneity index of the conducting airways, termed S_{COND}, are two other parameters from the N_2MBW test [29]. At all participating centres, experienced lung function technicians use the same device, the Exhalyzer® by Ecomedics with software version 3.3.1, to perform N_2MBW [49].

To transform FEV1, FVC, FRC and DLCO into age-, height- and sex-standardised z-scores we use the Global Lung function Initiative (GLI) equations 2021, version 2.0 [43, 45, 46, 50, 51]. For the outcomes where GLI does not exist, the following reference values are used:

- TLC reference equations by Zapletal et al. [52] for children aged 4–17 years, and reference equations by the European Community of Coal and Steel (ECCS) for individuals aged 18 years or over [43, 53]
- LCI z-scores are calculated using normative values from Kentgens et al. [54]
- S_{COND} and S_{ACIN} z-scores are calculated using normative values from Husemann et al. [55]

Abnormal lung function tests are defined as a z-score < −1.64 for all lung function outcomes [47] except LCI, for which an abnormal test is defined as a z-score > +1.64 [56, 57].

MRI includes structural and functional measurements using a 1.5 Tesla whole-body MR system. Structural MRI of the lung is based on breath-hold or respiratory-gated acquisitions. Functional pulmonary MRI is performed primarily by employing non-contrast dynamic time-resolved scans during free breathing, which rely on a dedicated rapid MRI acquisition scheme with automated post-processing [58–61]. Based on the characteristic signal modulations of the acquired time-series data, voxel-wise maps of fractional ventilation and perfusion can be extracted, allowing regional lung function assessment. Outcome parameters of the automated post-processing pipeline are the lobar and whole-lung defect percentages calculated by thresholding the fractional ventilation and perfusion maps, providing a quantitative measure of lung function impairment. Average ventilation and perfusion defect percentages in the right and left lung are reported and evaluated. Furthermore, the structural MRI data are assessed based on standard radiological scoring of the most frequently encountered lung alterations in cancer patients after treatment [34–36] (supplementary material "MRI scoring system" in the appendix), according to 0 (normal), 1 (mild changes <50% of lobe involved) and 2 (moderate changes >50% involved) in six regions (lung lobes including lingula), thus employing a similar scoring principle as proposed previously for cystic fibrosis [62, 63], but with adapted parameters. Scoring is performed by two experienced thoracic radiologists who are blinded to clinical and demographic characteristics.

Respiratory symptoms are assessed by a standardised questionnaire at the same time a lung function test is done.

Schedule of assessments

Lung function tests are done at the baseline visit and during four follow-up visits until approximately two years post-treatment [64]. Each visit includes four lung function tests (supplementary material "Lung function test criteria" in the appendix). During each assessment, participants complete a combined questionnaire (self-reported and assisted by medical staff as needed) to record detailed information concerning hospitalisation (supplementary material "Questionnaire baseline+ and "Questionnaire follow-up" in the appendix). A timeline with all procedures of the SWISS-PEARL Cohort is summarised in table 1 and figure 1. MRI scans are scheduled approximately one and two years after the completion of intensive cancer treatment (supplementary material "MRI scoring system" in the appendix). The overall duration of the scheduled assessments depends on the cancer treatment protocol and poses particular challenges for scheduling visits, especially for assessments scheduled during the intensive phase. Therefore, we have compiled standardised measurement points for the most common childhood cancer protocols to improve comparability and harmonisation between different cancer treatment protocols (see appendix). The 1st assessments at baseline are scheduled from the time of diagnosis until a maximum of 28 days after start of treatment, ideally before the first therapeutic intervention, depending on the medical condition of the patient. A lung MRI at diagnosis is only performed if clinically indicated for cancer staging. The 2nd visit is carried out as the 1st follow-up, during the intensive cancer treatment, which may include assessments before high-dose chemotherapy, surgery or chest radiation. The 3rd visit is carried out as the 2nd follow-up, scheduled immediately after the end of intensive treatment. Maintenance chemotherapy is excluded from the intensive treatment phase as side-effects are less expected [6]. The 4th visit is carried out as the 3rd follow-up, scheduled at 12 months post-intensive treatment, including a lung MRI whenever possible. The 5th visit is carried out as the 4th follow-up, occurring 24 months after intensive treatment, including a lung MRI whenever possible. After the 5th visit and therefore approximately two years after the end of cancer treatment, patients are followed up according to their lung health and aftercare plan, their clinical complaints and according to their individualised Passport for Care®.

Our study is collaborating with Genetic Risks for Childhood Cancer Complications Switzerland (GECCOS), a study addressing genetic risk factors that may increase susceptibility to pulmotoxic treatment [65]. Therefore, we collect deoxyribonucleic acid (DNA) samples from the oral mucosa of each patient for future analysis. These samples are stored at room temperature in the Germline DNA Biobank in Geneva.

Collected information

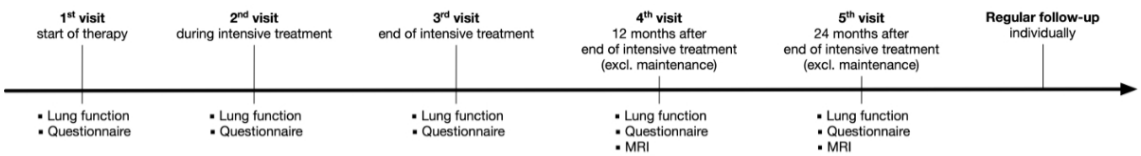
The data collected for the SWISS-PEARL cohort are summarised in table 2. At the beginning of each appointment, patients are handed a questionnaire for the assessment of pre-existing lung morbidities, risk factors and respiratory symptoms, in order to identify factors that may influence the main outcomes of interest (table 2). The baseline questionnaire differs from the follow-up questionnaires as shown in table 2. Except for the question on lung diseases/hospitalisation (appendix SM 2, page 4), all questions are self-reported regarding respiratory symptoms. The clinical parameters and the cumulative doses of pulmotoxic treatments are collected from medical records: chemotherapy, radiotherapy, haematopoietic stem cell transplantation and thoracic surgery are documented in the patient files using the Standardised Electronic Chemotherapy Prescription,

Table 1:
Timeline of study visits.

Visit number	Visit name	Time point of visit	Measurement		
			Lung function	MRI	Questionnaire
1	Baseline	Start of therapy	X		X
2	Follow-up 1	During intensive treatment	X		X
3	Follow-up 2	End of intensive treatment	X		X
4	Follow-up 3	12 months after end of intensive treatment (excl. maintenance)	X	X	X
5	Follow-up 4	24 months after end of intensive treatment (excl. maintenance)	X	X	X
6	Regular clinical follow-up	Individually	X*		

* Timing and frequency depend on the treatment regimen, the respective childhood cancer protocols and on respiratory health; 1st visit: baseline measurement before and up to a maximum of 28 days after start of treatment; 2nd visit during intensive treatment (before haematopoietic stem cell therapy [haematopoietic stem cell transplantation], surgery, chest radiation); 3rd visit after intensive treatment; 4th and 5th visits at 12 and 24 months after intensive treatment. Lung function includes spirometry, body plethysmography, diffusing capacity of the lungs for carbon monoxide (DLCO) and nitrogen multiple-breath washout (N_2MBW).

Figure 1: Timeline of study visits. 1st visit: baseline measurement before or up to a maximum of 28 days after start of treatment; 2nd visit during intensive treatment (or before haematopoietic stem cell therapy [haematopoietic stem cell transplantation], surgery, chest radiation); 3rd visit after intensive treatment, excluding maintenance; 4th and 5th visits at 12 and 24 months after the end of intensive treatment. Lung function includes spirometry, body plethysmography, diffusing capacity of the lungs for carbon monoxide (DLCO) and nitrogen multiple-breath washout (N_2MBW).



cato®, and are stored within a REDCap® (Research Electronic Data Capture) database.

Study database, software and data access

The lung function technicians, study nurses and PhD students from the SWISS-PEARL research team store coded raw data including those from lung function measurements and lung imaging on each measurement device at each site. The data are then stored within the REDCap® database. A limited number of study members have REDCap® access for data input and data extraction. Each member who enters data into the database REDCap® has their own login and changes are tracked. Within the database, each patient has a unique anonymised REDCap® ID from their centre. The electronic key for each patient identification is kept on a password-protected server at Inselspital in Bern, and is accessible by a limited number of research team members. Electronic data are stored on password-protected servers. Consent forms are kept in a locked cabinet in a designated research office at the local sites. For N_2MBW measurements, all centres use the Exhalyzer D device (Ecomedics AG, Dürnten, Switzerland) with Spiroware version 3.2.1 and 3.3.1. Raw data (A-files) are stored and used for later quality control and data analysis. Data from spirometry, body plethysmography and DLCO are stored in SentrySuite™ [66] and raw data are also used for later quality control and data analysis.

Ethics and data protection

We received approval (2021-01206) from the ethics committee Northwestern and Central Switzerland (EKNZ) and the local ethics committees (Bern, Geneva, Lausanne, and Zurich) in May 2022. Data protection is implemented in accordance with the standards approved in Switzerland and has been authorised by the ethics committees. The study has received ethical approval for 10 years, with potential extension.

Sample size

Based on Swiss Childhood Cancer Registry data from 1976 to 2018 [67], we expect an average of 79 new cases aged 5 to 20 years across the four participating Swiss Paediatric Oncology Group (SPOG) centres fulfilling our inclusion criteria per year. Considering the feasibility of recruitment and the logistics of performing the tests, we anticipate a participation rate of 60%. With this rate, approximately 106 patients would meet our inclusion criteria nationwide each year. However, as currently only four of the nine oncology centres in Switzerland are participating, the number of patients potentially recruited is estimated to be around 47 per year from all four centres.

Results

Current status and initial baseline results: a two-year overview

The current study protocol includes baseline data reporting up to the end of May 2024. Figure 2 shows the respective study start dates of the individual centres. In Bern, recruitment began in May 2022, followed by Zurich, Lausanne and Basel. The study is ongoing, with recruitment of new patients and the collection of further follow-up data continuing.

Study population

The study started in May 2022 (figure 2, table 3) and as of May 2024 the cohort comprised 44 paediatric cancer patients. According to our sample size calculations, we expected to recruit about 70 patients from May 2022 to May 2024 across all centres. However, several factors have impacted the success of this recruitment. The COVID-19 pandemic was present during the early stages of our study, leading to reduced recruitment. Additionally, we chose not to recruit patients with a poor prognosis or brain tumour patients from Zurich, as they qualify for other studies with greater patient benefit. Similarly, we individually decided to exclude patients with additional diagnoses, such as those on the autism spectrum. This decision was made to avoid an additional burden at the time of cancer diagnosis. Additionally, based on the local resources in each study centre except Bern, recruitment is limited to individuals aged 6 years or over. Of the 59 patients who were invited to participate, 44 (75%) consented (2 Basel, 24 Bern, 6 Lau-

Table 2:
Description of data collected for the SWISS-PEARL study.

Source		Baseline	Follow-up
Patient data	Personal information (date of birth, sex, ethnicity)	X	
Questionnaire data	Contact information (current and past address, apartment level)	X	X
	Lifestyle and environment (physical activity, smoking, pets, living on a farm)	X	
	Perinatal factors (pregnancy complications, gestational age, birth weight and length, breastfeeding)	X	
	Origin and family (citizenship, siblings, parental education, family history of chronic diseases and tumours, smoking habits)	X	
	Respiratory symptoms (colds, infections, coughing, wheezing, whistling, asthma, medication intake)	X	X
	Hospitalisation due to respiratory problems (cause, treatment, oxygen requirement, ICU treatment)		X
Data from medical records	Disease (primary diagnoses, metastases, relapse, second malignancies)	X	X
	Treatments (chemotherapy agents, radiation, haematopoietic stem cell transplantation, cumulative dosages, application modality, intrathoracic surgery), pulmonary complications	X	X
Pulmonary assessment	Measurements (weight, height, lung function tests [N_2MBW, spirometry, body plethysmography, DLCO], laboratory tests [blood cell count])	X	X
	Imaging (MRI)	(X)	X
Biological samples	Samples (DNA)	X	

DLCO: diffusing capacity of the lungs for carbon monoxide; ICU: intensive care unit; N_2MBW: nitrogen multiple-breath washout.

sanne, 15 Zurich). There are 59% (26/44) male participants. Median age at diagnosis was 11 years (interquartile range 8–15). Mean age at diagnosis was 12 years (range 4–18). Using the International Classification of Childhood Cancer, Third Edition (ICCC-3), the most common cancer diagnoses were leukaemia (41%) and lymphoma (23%) (table 4). Other diagnoses – each accounting for smaller percentages ranging from 2% to 16% – were central nervous system (CNS) neoplasms, renal tumours, malignant bone tumours, soft tissue sarcomas, germ cell tumours and "Other" malignant neoplasms.

Lung function test results

In total, 44 participants underwent 134 lung function tests at baseline and measurement results were acceptable in 43 of them. Among these 43 patients, lung function was normal in 33 or 77% (20 without respiratory symptoms, 13

Figure 2: Number of participants in the SWISS-PEARL Cohort (SWISS-PEARL), from study start in May 2022 to May 2024.

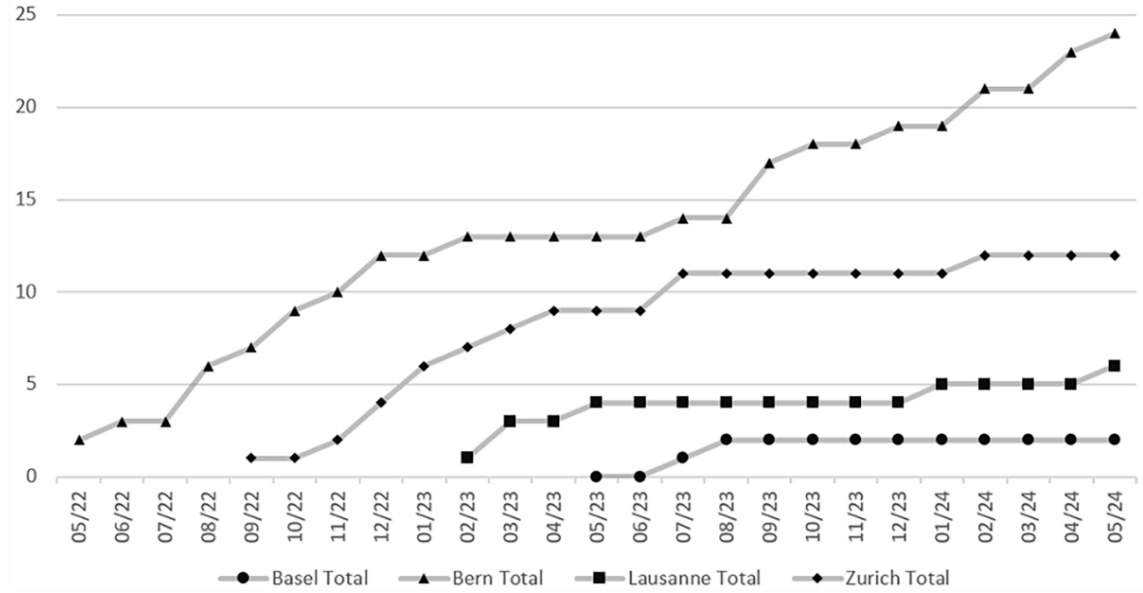


Table 3:
Overview of SWISS PEARL study recruitment by centre and in total as of May 2024.

May 2024		Basel	Bern	Lausanne	Zurich
Months of participation		13	25	16	21
Number of patients	…who met the inclusion criteria	8	39	27	96
	…handed an informed consent form	5	33	6	15
	…who consented to the study	2	24	6	12
	…who dropped out after at least one measurement	0	0	0	3
Number of patients who underwent lung function testing at …	Baseline	2	24	6	12
	Follow-up 1	2	20	4	9
	Follow-up 2	1	15	4	4
	Follow-up 3	0	6	1	1

1st visit: at baseline, before start of treatment to 28 days after start of treatment; 2nd visit: follow-up 1, during intensive treatment (before haematopoietic stem cell therapy [haematopoietic stem cell transplantation], surgery, radiation); 3rd visit: follow-up 2, after completion of intensive treatment; 4th visit: follow-up 3, 12 months after completion of intensive treatment.

Table 4:
Characteristics of participants in the SWISS-PEARL cohort as of May 2024.

Sociodemographic characteristics		n = 44
Sex	Male	26 (59%)
Cancer-related characteristics	Median age at diagnosis in years (IQR)	11 (8–15)
Primary cancer diagnosis as per ICCC-3	I. Leukaemia	18 (41%)
	II. Lymphoma	10 (23%)
	III. CNS neoplasms	2 (5%)
	VI. Renal tumour	2 (5%)
	VIII. Malignant bone tumour	7 (16%)
	IX. Soft tissue sarcomas	2 (5%)
	X. Germ cell tumour	2 (5%)
	XI. Other malignant neoplasms	1 (2%)

ICCC-3: International Classification of Childhood Cancer, Third Edition [74]; IQR: interquartile range.

with respiratory symptoms) and abnormal in 10 or 23% (8 without respiratory symptoms, 2 with respiratory symptoms). Table 5 shows the number of measurements conducted per lung function modality. N_2MBW measurements were almost entirely normal, with only 1 of 32 (3%) patients having an abnormal LCI, and normal results for S_{COND} and S_{ACIN}. For spirometry, FEV1 was abnormal in 3 of 37 (8%) patients and FVC was abnormal in 3 of 33 (9%) patients. Of the 3 patients with an abnormal lung function measurement, 2 had no respiratory symptoms at the time of lung function testing. For body plethysmography, FRC was normal in all patients, but 3 of 24 (13%) had an abnormal TLC value. For DLCO measurements, 5 of 28 (18%) patients had an abnormal test result, of whom 4 had no respiratory symptoms. Pulmonary assessment was well accepted even during intensive cancer treatment, with only 4 patients dropping out.

Respiratory symptoms

We documented data on respiratory symptoms collected from questionnaires (cold, coughing, wheezing and hospitalisation due to respiratory symptoms) and information on respiratory complications from medical records up to 2 weeks prior to the lung function tests. Table 5 shows the number of measurements conducted per lung function modality with and without respiratory symptoms. Of the total $n_{acc.}$ of 43 patients, 15 (35%) showed respiratory symptoms at cancer diagnosis of whom 2 had at least one abnormal test. Of the 32 patients with an acceptable LCI measurement from N_2MBW, 31 had normal LCI values. Among these, 12 of 31 (39%) had respiratory symptoms. For spirometry, of those with normal FEV1 (34/37) and FVC (30/33) values, 13 of the 34 (38%) and 11 of the 30 (37%) had respiratory symptoms.

Discussion

Missing and non-harmonised recommendations for lung function tests leave a gap in the understanding and management of early pulmonary toxicity after cancer treatment [18]. This prospective, multicentre cohort study is investigating the early prevalence of pulmonary dysfunction and its risk factors in paediatric cancer patients and survivors. We assess pulmonary toxicity using spirometry, body plethysmography, diffusing capacity of the lungs for carbon monoxide (DLCO) and nitrogen multiple-breath washout test (N_2MBW) to assess small airway disease with the first lung functional assessment at start of treatment.

Table 5:
Baseline data from the nitrogen multiple-breath washout test, spirometry, body plethysmography and diffusion capacity of the lung for carbon monoxide as of May 2024 (n = 44).

		n $_{tot}$	**n** $_{acc}$	**n** $_{acc}$ **normal lung function**		**n** $_{acc}$ **abnormal lung function**		**n** $_{acc}$	**n** $_{acc}$	**Reference population**
				No symptoms	**Symptoms**	**No symptoms** (asymptomatic pulmonary dysfunction)	**Symptoms** (symptomatic pulmonary dysfunction)	**Absolute value mean (SD)**	**z-score* mean (SD)**	
N_2MBW		33	33	20	12	1	0			
	LCI 2.5 (turnover)	33	32	19	12	1	0	6.23 (0.34)	−0.18 (0.85)	Kentgens et al., 2022 [54]
	S_{COND} × VT	21	20	14	6	0	0	0.04 (0.02)	0.22 (0.59)	Husemann et al., 2014 [55]
	S_{ACIN} × VT	21	20	14	6	0	0	0.07 (0.03)	0.31 (0.98)	Husemann et al., 2014 [55]
Spirometry		41	38	23	14	2	1			Quanjer et al., 2012 [43]
	FEV1 (l)	41	37	21	13	2	1	2.49 (1.08)	−0.25 (1.15)	
	FVC (l)	36	33	19	11	2	1	2.81 (1.33)	−0.31 (1.26)	
	Tiffeneau Index (FEV1/FVC × 100)	36	33	21	12	0	0	0.90 (0.06)	0.18 (0.86)	
Body plethysmography		30	26	18	7	2	1			Hall et al., 2021 [45]
	FRC (l)	29	24	17	7	0	0	2.20 (0.67)	0.23 (1.12)	
	TLC (l)	29	24	16	5	2	1	4.16 (1.36)	−0.34 (1.20)	
DLCO		30	29	21	6	4	1			Stanojevic et al., 2017 [46]
	DLCO (mmol/min/kPa)	30	28	18	5	4	1	7.32 (2.59)	−0.26 (1.22)	
	DLCO / alveolar volume (mmol/min/kPa/l)	29	28	21	6	1	0	1.81 (0.20)	0.17 (0.82)	

acc.: acceptable test after quality control; Baseline: 1st visit done before start of treatment to 28 days after start of treatment; DLCO: diffusing capacity of the lung for carbon monoxide, corrected for haemoglobin; DLCO/alveolar volume: diffusing capacity divided by the alveolar volume; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; l: litre; LCI: lung clearance index; n_{acc}: n after quality control; S_{ACIN}: acinar ventilation inhomogeneity index; S_{COND}: conductive ventilation inhomogeneity index; SD: standard deviation; TLC: total lung capacity; VT: tidal volume.

* An abnormal finding was defined (a) by the lower limit of normality by a z-score lower than −1.645 for FEV1, FVC, Tiffeneau Index, FRC, TLC and DLCO; these z-scores were calculated according to the Global Lung Function Initiative (GLI) (b) by an upper limit of normality by a z-score higher than +1.645 for LCI; this z-score was calculated according to the normative values from Kentgens et al. (2022) [54].

Functional and structural abnormalities are assessed using MRI. The current baseline results have demonstrated good lung health at the time of childhood cancer diagnosis in paediatric patients. The baseline data, derived from the information collected to date, show no significant deviation from the established reference values for the Caucasian population in the respective lung function tests, as presented in table 5. The DLCO measurement has so far been the most sensitive method for detecting asymptomatic patients with abnormal values, in one of the four different lung function measurements. Due to the small sample size, the results cannot be definitively interpreted.

Due to the high survival rate of children with cancer, current research focuses increasingly on cancer treatment-related pulmonary toxicity, especially in childhood cancer survivors (CCS) [23, 68, 69]. International [19, 20] and ongoing national [24, 70] cohort studies evaluate lung function after childhood cancer treatment, but none of these studies performed lung function testing before treatment. Further, the N_2MBW test for assessment of small airway disease was not used, limiting comparability with our study. For example, the St. Jude Lifetime Cohort Study (SJLIFE) for childhood cancer survivors [20] was established in 2007 but did not collect data prospectively from the onset of childhood cancer. Findings from the SJLIFE showed that 65.2% of survivors exposed to known pulmotoxic cancer treatments had abnormal lung function. The highest prevalence was observed in those who received lung radiation (74.4%), followed by those treated with bleomycin (73.3%) and thoracotomy (53.2%) [71]. Further, the lung function test used to monitor pulmonary toxicity is only spirometry, so comparability with our study is limited. In a large cohort from Amsterdam, The Netherlands, it was shown that among childhood cancer survivors treated with potentially pulmotoxic therapy with a minimal follow-up of 5 years, 44% (85/193) had developed pulmonary function impairment at a median follow-up of 18 years. The most common impairments were restrictive lung disease (17.6%) and decreased DLCO (39.9%). Pulmonary radiotherapy, particularly when combined with bleomycin or surgery, was identified as the most important risk factor for developing pulmonary function impairment [3]. In a recent retrospective study from Switzerland, pulmonary function tests were investigated only in childhood cancer survivors and mild-to-moderate lung function impairment was reported [69].

None of these previous studies performed conventional lung function measurements or N_2MBW tests at the time of diagnosis [3, 19, 20]. Therefore it is not entirely known whether some children already had impaired lung function before cancer treatment – this is an important aspect to bear in mind when interpreting these results. The Swiss Childhood Cancer Survivor Follow-Up Pulmo (SCCS) study started in 2022 to assess pulmonary toxicity after childhood cancer treatment using spirometry and the N_2MBW test. Lung function from the start of treatment is also not assessed given that the first lung function test is done after the end of intensive cancer treatment; however the study uses the N_2MBW test to detect pathologies in the small airways [70]. There is an established collaboration between our study and the SCCS study, aiming to analyse lung function trajectories in childhood cancer survivors.

Some previous studies, mainly conducted in haematopoietic stem cell transplantation patients, used washout tests to assess small airway damage. A retrospective cohort study from Germany found no abnormalities in lung function tests before haematopoietic stem cell transplantation in 9 childhood cancer patients, with a mean follow-up time of 5.2 years (range 1.92–13.58) while 4 of 9 eligible patients post-haematopoietic stem cell transplantation treatment had an elevated mean (range) lung clearance index (LCI) of 13.85 (6.51–19.3) [22]. In a cross-sectional study of childhood cancer survivors conducted in Switzerland [24], N_2MBW results were more often abnormal than spirometry data, even in those exposed to medication not known to be pulmotoxic. Mean LCI increased to 7.77 (SD 1.64), z-score 1.37 (SD 2.69), after a median time since diagnosis of 20 years. Further, LCI was more frequently abnormal in survivors exposed to known pulmotoxic treatment (9/15 or 60%) compared to those non-exposed (6/26 or 23%). In a case-control study conducted in Catania, Italy, in children after treatment, within a subgroup of 38 survivors of acute lymphoblastic leukaemia, an association was found between more frequent abnormal LCI and the time elapsed since the end of treatment [23]. To summarise, several of these studies identified pulmonary dysfunction ranging from mild to severe in childhood cancer survivors. These studies primarily focused on adult populations and were conducted several years after cancer treatment, leaving a knowledge gap on pulmonary dysfunction soon after the initiation of childhood cancer treatment. Further, most of the previous studies are retrospective, single-centre and focus only on subgroups that received known pulmotoxic treatments. They are limited by the lack of comprehensive baseline assessments or longitudinal data to outline the onset and trajectory of lung function [22–24]. The SWISS-PEARL study additionally collects exact cumulative treatment doses of all systemic cancer treatments for better comparability, including non-haematopoietic stem cell transplantation patients and those who received suspected or unknown pulmotoxic treatments.

We acknowledge some limitationsof our study concerning data collection and analysis. Diagnoses may vary and every disease is treated following a different treatment protocol with variable treatment duration [6–15, 72]. Therefore, the dataset is heterogeneous and only subgroups can be directly compared. To overcome this limitation, we collect cumulative drug doses for each agent independently of the cancer diagnosis. With an increasing number of study participants, we will also be able to compare lung function between the different treatment regimens. Future international collaborations may help to further increase patient numbers. Recruitment is challenging because of the high psychosocial impact of a childhood cancer diagnosis on the entire family. Participating in a study may be perceived as an additional burden by the patients and the affected families [73]. Empathy, cooperation and teamwork in the study team and good communication between hospitals at a national level is crucial to motivate patients for recruitment in a study at the time of cancer diagnosis. In the SWISS-PEARL study, we interact with patients with considerable empathy and determine when participation in a voluntary study is inappropriate. Additionally, after study consent, we are flexible in postponing assessments when

the general condition, infections or the mood of the patient prevents testing.

One of the strengths of our study is that it collects lung function after childhood cancer treatment in a longitudinal design from the time of cancer diagnosis including N_2MBW testing, allowing assessment of timing and development of pulmonary dysfunction. Various lung function tests are combined with imaging and respiratory symptoms to enable a comprehensive assessment of early lung damage. We are also collecting detailed information on treatment. Therefore, our study may help to better understand the pulmotoxic dose effect of different cumulative treatments and, thanks to the study design, we will be able to assess occurrence of reversible and irreversible lung abnormalities. Another strength of our study is the use of MRI instead of CT, which eliminates exposure to ionising radiation. Using MRI to identify lung damage in children post-cancer treatment is a novel approach that can reduce exposure to radioactive radiation. Additionally, the N_2MBW test is feasible even in critically ill children, and detects abnormalities in the small peripheral airways which may increase our understanding of early detection of pulmonary damage within the paediatric cancer population. This study will contribute to a better understanding of early pulmonary dysfunction, its risk factors and its developmental course during and post-cancer treatment in Switzerland. Our findings may support better surveillance of patients at risk, which can lead to earlier and more effective treatment decisions and ultimately improve lung health in this vulnerable patient population.

Key features of the SWISS-PEARL study for closing knowledge gaps concerning paediatric cancer patients and survivors

Longitudinal study design and assessments

- Multicentre cohort study focusing on early pulmonary effects in paediatric cancer patients and survivors, with processes harmonised across different centres in Switzerland.
- Includes children with newly diagnosed cancer, with baseline data captured within 28 days of the start of treatment.
- Incorporates longitudinal investigations with baseline assessments.
- The onset and progression of lung function impairment could provide important information for timing, screening interval, at-risk patients and the best lung function testing modality during and after paediatric cancer treatment.

Data collection and analysis

- Data collected on suspected pulmotoxic agents (cyclophosphamide, methotrexate, targeted agents, immunotherapy).
- Genetic samples obtained to identify risk factors affecting pulmonary toxicity of cancer treatments (collaborative project).

Lung function testing and standardisation

- Standardisation of lung function measurements: The study incorporates four lung function tests, MRI, questionnaires and hospital record data for systematic baseline and follow-up data collection including cumulative treatment doses.
- Lung function testing is performed and quality-controlled according to standardised protocols, such as those from the American Thoracic Society and the European Respiratory Society (ATS/ERS).
- Use of raw data from lung function tests for analyses where possible, reporting of z-scores.

Modality use and collaborations

- Assessment of pulmonary toxicity in paediatric cancer patients with the N_2MBW test and MRI.
- Close collaboration among oncologists, pulmonologists and radiologists.

Data management

The database REDCap® has been designed so that it can be used for future data collection in similar projects.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Jochen Rössler is currently an employee of Novartis Pharma Basel. No other potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

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