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# Characteristics and feedback of adult survivors of childhood cancer seen in Swiss comprehensive follow-up clinics led by general internists: a prospective cohort study

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## ABSTRACT

**Objectives** In our study, we aimed to characterise adult childhood cancer survivors (ACCS), assess their health issues, gauge health-related quality of life (HRQOL) and evaluate visit satisfaction.

**Design** Prospective cohort study using data from clinical visits and questionnaires.

**Setting** Interdisciplinary follow-up programme for ACCS based on the long-term follow-up (LTFU) guidelines of the Children's Oncology Group and overseen by internists in two Swiss hospitals.

**Participants** ACCS attending our LTFU clinics between April 2017 and January 2022 were eligible.

**Interventions** We documented medical history, current health status and assessed HRQOL using Short Form-36 V.2, comparing it with Swiss general population (SGP) norms (T mean=50, SD=10; age stratified). 3 months post visit, a feedback questionnaire was distributed.

**Main results** Among 102 ACCS (mean age: 32 years (range: 18–62 years), 68% women), 43 had no prior follow-up (36 ACCS>28 years, 7 ACCS≤28 years). A notable 94% had health issues, affecting an average of 6.1 (SD=3.3) organ systems. HRQOL was lower in ACCS>28 years than the SGP>28 years (physical: 44.8 (SD=11.65) vs 49.3 (SD=10.29), p=0.016; mental: 44.4 (SD=13.78) vs 50.53 (SD=9.92), p=0.004). Older ACCS (>28 years) reported inferior physical (44.8 vs 50.1 (SD=9.30), p=0.017) and mental HRQOL (44.4 vs 50.3 (SD=7.20), p=0.009) than younger ACCS. The majority of respondents reported high levels of satisfaction with the consultation, exceeding 90%.

**Conclusion** ACCS attending LTFU clinics face diverse health issues impacting multiple organ systems and exhibit lower HRQOL compared with the SGP. Thus, internist-led LTFU clinics are crucial for optimising follow-up care.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study's strength lies in the comprehensive collection of cancer history data for all adult childhood cancer survivors (ACCS) in our cohort, establishing a solid foundation for analysis. This model of follow-up is based on a detailed cancer history, a current health questionnaire and well-established follow-up guidelines (Children's Oncology Group long-term follow-up guidelines), all of which are integrated into interdisciplinary clinical visits led by general internists.

⇒ These clinics, albeit small in scale, signify a pioneering effort to cater to the specific needs of older ACCS, a neglected cohort in Swiss healthcare research. Despite their size, the clinics provide a unique opportunity for in-depth examination of the healthcare requirements and outcomes of ACCS, offering a valuable platform for future research and intervention development in this underexplored area of survivorship care.

⇒ Modest cohort size: the study is limited by a relatively modest cohort size, which could impact the generalizability of the findings to a broader population of ACCS.

⇒ Two-centre study: the inclusion of data from only two centres may introduce potential centre-specific biases and restrict the broader applicability of the study's results.

⇒ Older ACCS were not actively recruited but rather voluntarily sought specialized follow-up care or were referred by caregivers, introducing potential selection bias.

## INTRODUCTION

The lifelong follow-up of childhood cancer survivors (CCS) is crucial.[1] We now understand that CCS face numerous health issues, which worsen with age,[2] leading to higher mortality rates compared with their peers.[3 4] These health problems can impact every organ system. While the spectre of secondary cancers looms large and significantly contributes to the elevated mortality

among CCS, organ toxicity presents a more burdensome daily challenge.[2] The Swiss Childhood Cancer Survivor Study (SCCSS) has provided valuable insights into the well-being of younger CCS in Switzerland,[5–7] showing they generally have a better health-related quality of life (HRQOL) than the average Swiss citizen. However, research on the HRQOL of older adult CCS (ACCS) remains limited. The increasing number of ACCS is a reflection of improved curative prospects for paediatric and adolescent cancer patients, with over 7000 ACCS currently residing in Switzerland.[8]

While evidence on optimal ACCS follow-up strategies remains limited,[9] established guidelines outline key components of such follow-ups.[10] Among these, the Children's Oncology Group long-term follow-up (COG-LTFU) Guidelines stand out as the most comprehensive, tailored to the unique treatments CCS underwent.[11] These guidelines are complemented by the 'Passport for Care' (PFC), facilitating individualised examination schedules based on a CCS's treatment details.[12] However, Kadan-Lottick *et al*[13] found that having such individualised guidelines does not guarantee adequate follow-up: CCS under the care of general practitioners received fewer recommended tests compared with specialised follow-up clinics, leading to fewer diagnoses. Currently, most Swiss ACCS receive medical care from adult oncology services or their general practitioners.[14]

To enhance care for potentially multimorbid ACCS, we have established two multidisciplinary LTFU clinics, led by experienced general internists and paediatric oncologists. Here, we outline the characteristics of the ACCS Cohort served in our LTFU clinics and evaluate their HRQOL. We explore the relationship between ACCS health problems, treatment intensity and HRQOL. Additionally, we assess whether structured follow-up visits, including detailed health risk information, offer a positive experience for ACCS.

## Methods

### Study design

The study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology checklist for cohort studies (https://www.strobe-statement.org/checklists/).

### Setting and structure of the LTFU programme

We established two LTFU clinics: one at the Cantonal Hospital of Baselland in Liestal in 2017 and the other at the Inselspital, University Hospital of Bern in 2018. The Cantonal Hospital of Baselland is a tertiary hospital without a paediatric unit but offers comprehensive adult care. Inselspital is one of Switzerland's largest university hospitals, including a paediatric oncology centre providing all treatments except allogeneic stem cell transplantation (SCT).

In collaboration between internists and paediatric oncologists, we created a unique follow-up model for ACCS in Switzerland. We analysed oncological records to generate survivorship passports summarising diagnoses, treatments and other relevant data. These were entered into the PFC application to develop individualised follow-up plans according to COG-LTFU guidelines. ACCS completed a comprehensive health questionnaire. Using this, COG-LTFU guidelines and ACCS's health concerns, we planned their initial clinic visit. This visit included a detailed medical history, clinical examination by an internist, necessary evaluations and a discussion with the paediatric oncologist about the treatment received during childhood or adolescence, its associated risks and recommended lifelong follow-up.

To ensure comprehensive care, we forged collaborations with various in-hospital specialists, including cardiologists, dermatologists, radiologists, fertility specialists, pulmonologists, gastroenterologists, orthopaedists, psycho-oncologists, endocrinologists and social workers.

Following the initial visit, ACCS chose annual follow-up at our clinic or with their general practitioner. They received personalised PFC-access and comprehensive letters summarising findings and COG-LTFU guideline recommendations. These letters were sent to their general practitioners, with copies sent to the ACCS. If the ACCS did not have a general practitioner, the letter was sent directly to the ACCS. Our LTFU clinics did not replace primary medical care. Approximately 3 months later, ACCS provided feedback via a questionnaire. See figure 1 for the pathway and online supplemental table S1 for a sample clinic visit schedule.

### Participants

We enrolled ACCS who attended our follow-up clinics starting from 2017 (Liestal) or 2018 (Bern) if they were 18 years or older at the time of their first visit and had received a cancer diagnosis before the age of 20 years. ACCS younger than 18 years at their initial visit and those who did not provide informed consent were excluded from the study. For this report, we exclusively analysed data collected up to January 2022, encompassing information from the first clinic visit and feedback questionnaire.

ACCS fall into two distinct categories: younger ACCS, who transitioned directly from paediatric oncology clinics, and older ACCS, most of whom did not receive guideline-based follow-up care following their 5–10 years of follow-up at the paediatric oncology centre where they were initially treated. To differentiate between these groups, we employed an age cut-off of 28 years as a proxy (younger group: aged 28 years or younger at the follow-up visit, and older group: over 28 years). ACCS>28 years certainly had not been followed in a paediatric setting within the last 5 years. They were recruited through various channels, including information provided by other study groups such as the Cardiac Care for Survivors Study, local press releases, workshops organised by Childhood Cancer Switzerland, word of mouth or referrals from primary care physicians.

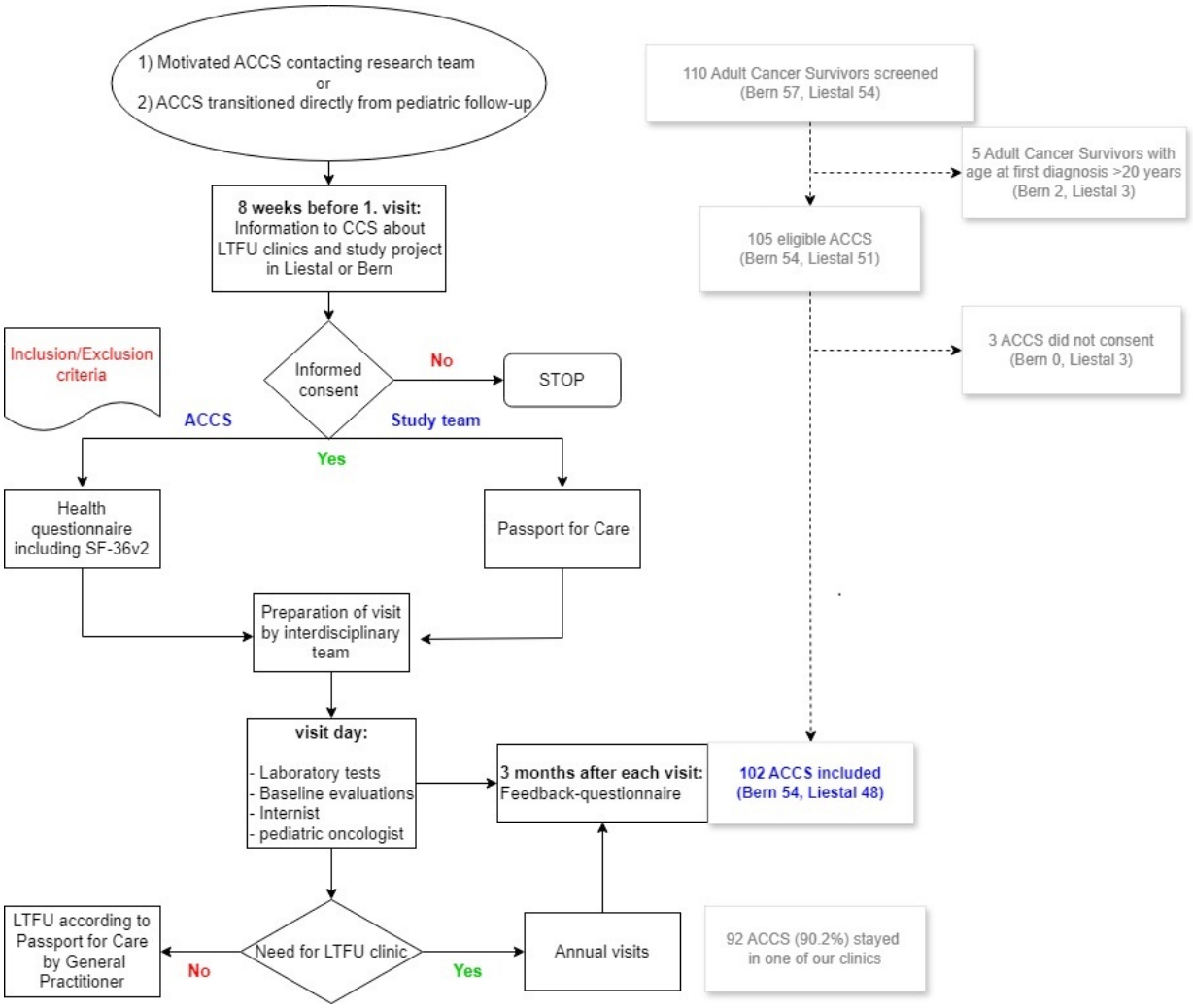


**Figure 1** Flow chart: patient pathway and study population. ACCS, adult childhood cancer survivors; CCS, childhood cancer survivors; LTFU, long-term follow-up.

## Measurements

### *Questionnaire based*

We gathered data on subjective physical and mental health, life circumstances (employment, marital status) and lifestyle factors (tobacco, alcohol use) before the initial clinic visit. We employed a slightly adapted questionnaire used by the SCCSS from 2007 to 2011 for comparability.

### Primary disease and treatment/treatment intensity

In preparation for the clinic visit, we compiled a 'PFC', encompassing the ACCS's oncological history, including primary diagnoses, relapses and second malignancies. We documented the specifics of their oncological treatment. To assess chemotherapy intensity, we computed the cumulative anthracycline dose, measured in mg/m$^2$, and the cyclophosphamide equivalent dose, in g/m$^2$. Evaluating radiotherapy, we tallied the number of anatomical fields irradiated and recorded the highest cumulative dose administered in gray. We also documented instances of high-dose chemotherapy followed by SCT and categorised surgeries based on type whenever feasible in the PFC application (eg, central venous catheter placement, neurosurgery and laparotomy).

### Current health problems

We documented all instances of health issues reported by the ACCS. These issues were subsequently categorised based on the number of occurrences per organ system. To ensure comprehensive assessment, we employed the Common Terminology Criteria for Adverse Events (CTCAE), modified according to the St. Jude LIFE framework,[15] when specific CTCAE data was unavailable for a particular health problem, we used CTCAE V.5.0[16] as an alternative reference. Notably, we employed a scoring system, classifying issues with a score of ≥3 as indicative of severe health problems and those with a score of <3 as less burdensome concerns.

### Current HRQOL

To assess HRQOL, we used the validated Short Form-36 V.2, comprising 36 items across 8 health domains: physical functioning (10 items), physical role functioning (4 items), bodily pain (2 items), general health perception

(5 items), vitality (4 items), social role functioning (2 items), emotional role functioning (3 items) and mental health (5 items). Summary measures, namely the Mental Component Score (MCS) and the Physical Component Score (PCS),[17] were derived from these responses, ranging from 0 to 100, with higher scores indicating better HRQOL. These summary scores were transformed into T Scores and compared to 2015 reference scores from the Swiss general population (SGP), which had a mean of 50 and a SD of 10.[18]

### Feedback following clinic visit

Approximately 3 months post clinic visit, ACCS were invited to complete a feedback questionnaire, originally designed to assess outpatient satisfaction in oncology,[19] which we adapted to the LTFU context. Our study examined patient satisfaction with the detailed explanation of their individual health risks from cancer therapy and the recommended follow-up plan, as well as overall satisfaction with the consultation. We also investigated whether ACCS experienced heightened health-related worries or fears post visit. Two key questions, 'Since the visit, I have been more worried about my health status than before' and 'Since the visit, my fears are greater than before', offered response options of strongly agree, agree, disagree or strongly disagree (see online supplemental figure S1 for details).

### Statistical analysis

We commenced our analysis by profiling our ACCS Cohort, distinguishing between younger (≤28 years) and older ACCS (>28 years) using descriptive statistics. Binary variables were presented as absolute and relative frequencies, while normally distributed continuous variables were expressed as mean±SD, and non-normally distributed continuous variables as median/IQR. Age group comparisons were executed using the Student's t-test, Mann-Whitney U test and Pearson's $\chi^2$ test, as appropriate. We applied a similar approach to characterise responders and non-responders to the feedback questionnaire.

To explore further, we employed multivariable regression models to investigate the relationship between treatment intensity and key outcomes: the number of current health problems, PCS and MCS, adjusting for sex and age. Given the tendency of the CTCAE Grading system to assign high scores (≥3) for secondary cancer and infertility, we focused on the overall number of health problems as the primary outcome, disregarding CTCAE scores. Variable selection included age, sex, treatment intensity (eg, irradiated fields, maximal radiation dose, cumulative anthracycline and cyclophosphamide equivalent chemotherapeutic doses) and health problems linked to vital organ systems (cardiovascular, gastrointestinal/hepatic, neurological, pulmonological and renal). The analysis of HRQOL (MCS and PCS) incorporated the number of affected organ systems as an additional predictor. To ensure robustness, we applied sample size constraints, requiring a minimum of 10 participants per predictor variable.[20]

Predicted values for each variable are presented per one unit increase, with all other variables held constant at the mean (for continuous variables) or the reference category (for categorical variables).

ACCS HRQOL was compared with age-matched peers from the SGP,[18] focusing on disparities between younger and older ACCS subgroups and their respective Swiss counterparts (aged≤28 years and >28 years). Hypothesis testing followed the conventional significance threshold of p values<0.05, with statistical analysis conducted using R V.4.1.2.[21]

### Patient and public involvement

Before starting the study, the study team worked with ACCS to refine the feedback questionnaire's clarity and relevance and to gather insights on setting up follow-up clinics. ACCS in the study were invited to provide free-text feedback, including thoughts on the questionnaire's burden. Additionally, the team joined workshops with ACCS and parents, hosted by Childhood Cancer Switzerland and the Swiss Cancer League AYA programme, to share study findings and foster collaborative engagement within the survivor community.

## Results

We enrolled 102 patients in our study (figure 1). The mean age was 31.7 years (range: 18.2–61.8 years at the first visit). Approximately half (n=50, 49%) belonged to the younger group at the first visit, representing ACCS who had recently transitioned from paediatric to adult care. Table 1 summarises the characteristics of the study population.

ACCS presented with various initial cancer diagnoses, with lymphoma (25%), leukaemia (23%), sarcoma (20%) and Central Nervous System (CNS) tumour (17%) being the most common primary diagnoses, 12.7% had experienced relapses. No significant difference in cancer diagnoses was observed between younger and older ACCS (online supplemental table S2).

### Treatment/treatment intensity

Nearly all ACCS (94%) had received chemotherapy and 93% had undergone surgery (86% in ACCS>28 years vs 100% in ACCS≤28 years, p=0.022). Radiotherapy had been administered to 54% of ACCS, with a significantly higher percentage in ACCS>28 years (37% vs 62%, p=0.018). SCT had been performed in 12% of cases (n=12; 2 allogeneic, 10 autologous), with no significant age-related differences (see table 1).

### Current health problems

ACCS with health problems had an average of 6.1 (SD=3.3, range 1–15) affected organ systems. Only six ACCS (6%) reported no health problems (ACCS>28 years: 1, ACCS≤28 years: 5). Among the 45 ACCS≤28 years with health problems, the average number of health problems in different organ systems was 4.93 (SD=3.02), significantly lower

**Table 1** Baseline characteristics of adult childhood cancer survivors

| Characteristics | | Age≤28 | Age>28 | P value |
|---|---|---|---|---|
| Total ACCS, n (%) | 102 (100) | 50 (49.02) | 52 (50.9) | |
| Age (years), mean (SD) | 31.69 (11.0) | 22.05 (2.8) | 40.96 (7.4) | |
| Range (years) | 18.2–61.8 | 18.2–27.8 | 29.9–61.8 | |
| Gender | | | | 0.775 |
| Female (%) | 69 (67.6) | 35 (70) | 34 (65.4) | |
| Male (%) | 33 (32.4) | 15 (30) | 18 (34.6) | |
| Participants | | | | **<0.001** |
| Bern (%) | 54 (52.9) | 39 (78) | 15 (28.85) | |
| Liestal (%) | 48 (47.1) | 11 (22) | 37 (71.15) | |
| Follow-up before (n=89) | | | | **<0.001** |
| Yes (%) | 30 (33.7) | 27 (62.8) | 3 (6.5) | |
| No (%) | 59 (66.3) | 16 (37.2) | 43 (93.5) | |
| Body mass index classes (n=92) | | | | 0.164 |
| <18.5 kg/m$^2$ (%) | 7 (7.7) | 3 (7.1) | 4 (8.2) | |
| 18.5–24.9 kg/m$^2$ (%) | 54 (59.3) | 30 (71.4) | 24 (49) | |
| 25–29.9 kg/m$^2$ (%) | 17 (18.7) | 5 (11.9) | 12 (24.5) | |
| >30 kg/m$^2$ (%) | 13 (14.3) | 4 (9.5) | 9 (18.4) | |
| Partnership (n=93) | | | | **0.004** |
| Yes (%) | 49 (53.3) | 16 (36.4) | 33 (68.8) | |
| No (%) | 43 (46.7) | 28 (63.8) | 15 (31.2) | |
| Civil status (n=93) | | | | **<0.001** |
| Single (%) | 70 (75.3) | 43 (97.7) | 27 (55.1) | |
| Married (%) | 22 (23.7) | 1 (2.3) | 21 (42.9) | |
| Divorced (%) | 1 (1.1) | 0 (0) | 1 (2) | |
| Nationality (n=92) | | | | 1.000 |
| Switzerland (%) | 86 (93.5) | 42 (93.3) | 44 (93.8) | |
| Foreigner (%) | 6 (6.5) | 3 (6.7) | 3 (6. 2) | |
| Country of birth (n=91) | | | | 1.000 |
| Switzerland (%) | 87 (94.6) | 42 (95.5) | 45 (95.7) | |
| Other country (%) | 4 (5.4) | 2 (4.5) | 2 (4.3) | |
| Lifestyle behaviour | | | | |
| ≥1 sunburn last summer (n=92) (%) | 41 (44.6) | 26 (57.8) | 15 (31.9) | **0.022** |
| Alcohol consumption (n=93) | | | | |
| Daily (%) | 3 (3.2) | 2 (4.5) | 1 (2) | 0.414 |
| Weekly (%) | 33 (35.5) | 18 (40.9) | 15 (31.9) | |
| None/rare (%) | 57 (61.3) | 24 (54.5) | 33 (67.3) | 0.376 |
| Current smoker (n=92) (%) | 14 (15.2) | 7 (15.5) | 7 (14.9) | 0.930 |
| Smoking≥10 cigarettes per day (%) | 5 (5.4) | 2 (2.5) | 3 (2.6) | 0.682 |
| Oncological treatment | | | | |
| Chemotherapy, n (%) | 96 (94.12) | 46 (92.0) | 50 (96.0) | 0.638 |
| Vinca alkaloids, n (%) | 78 (81.2) | 34 (73.9) | 44 (88.0) | 0.132 |
| Alkylating antineoplastic agents, n (%) | 74 (77.1) | 35 (76.1) | 39 (78.0) | 1.000 |
| Anthracyclines, n (%) | 67 (69.8) | 35 (76.1) | 32 (64.0) | 0.286 |
| Corticosteroids, n (%) | 51 (53.1) | 21 (45.7) | 30 (60.0) | 0.229 |
| Cisplatin, n (%) | 26 (27.1) | 14 (30.4) | 12 (24.0) | 0.632 |

Continued

Table 1 Continued

| Characteristics | | Age≤28 | Age>28 | P value |
|---|---|---|---|---|
| Cumulative dose of cyclophosphamide equivalent* (g/m$^2$), median (IQR) | 6.8 (3.3–16.78) | 6.72 (3.18–13.96) | 10.21 (3.66–20.42) | 0.473 |
| Cumulative dose of Anthracyclines†, (mg/m$^2$), median (IQR) | 178.50 (120.00–304.90) | 150.00 (117.00–325.90) | 181.75 (124.12–273.25) | 0.421 |
| Surgery, n (%) | 95 (93.2) | 50 (100) | 45 (86.5) | **0.022** |
| Central venous catheter, n (%) | 54 (54.7) | 38 (76.0) | 16 (35.6) | **<0.001** |
| Neurosurgery, n (%) | 17 (17.9) | 13 (26) | 4 (8.9) | 0.057 |
| Laparotomy, n (%) | 28 (29.5) | 11 (22.0) | 17 (37.8) | 0.145 |
| Thoracic surgery, n (%) | 12 (12.6) | 8 (16.0) | 4 (8.9) | 0.464 |
| Nephrectomy, n (%) | 3 (3.2) | 2 (4.0) | 1 (2.2) | 1.000 |
| Enucleation, n (%) | 1 (1.1) | 1 (2.0) | 0 (0.0) | 1.000 |
| Limb sparing procedure, n (%) | 9 (9.5) | 3 (6.0) | 6 (13.3) | 0.385 |
| Splenectomy, n (%) | 3 (3.2) | 0 (0.0) | 3 (6.7) | 0.205 |
| Amputation, n (%) | 5 (5.3) | 3 (6.0) | 2 (4.4) | 1.000 |
| Pelvic Surgery, n (%) | 4 (4.2) | 1 (2.0) | 3 (6.7) | 0.536 |
| Oophorectomy, n (%) | 1 (1.1) | 1 (2.0) | 0 (0.0) | 1.000 |
| Thyroidectomy, n (%) | 2 (2.1) | 0 (0.0) | 2 (4.4) | 0.429 |
| Other, n (%) | 63 (66.3) | 29 (58.0) | 34 (75.6) | 0.112 |
| Radiotherapy, n (%) | 56 (54.9) | 21 (37.5) | 35 (62.5) | **0.018** |
| Number of radiation fields per ACCS mean (SD) | 2.32 (1.78) | 2.81 (2.02) | 2.03 (1.58) | 0.113 |
| Maximum dosage median (IQR) | 40.25 (25.62–54.00) | 51.3 (22.95–54.00) | 40.00 (26.25–51.90) | 0.554 |
| Stem cell transplantation, n (%) | 12 (11.8) | 5 (10) | 7 (13.5) | 0.814 |
| Autologous | 10 (83.3) | | | |
| Allogeneic | 2 (16.66) | | | |
| Allogeneic matched related | 1 (8.3) | | | |
| Allogeneic matched unrelated | 1 (8.3) | | | |

Significant differences between ACCS aged≤28y and ACCS aged>28y marked in bold print
*Cyclophosphamid equivalent dose.[31]
†Doxorubicin equivalent dose.[11 26]
ACCS, adult childhood cancer survivors.

than the average of 7.2 affected organ systems (SD=3.17) reported by the 51 ACCS>28 years (p<0.001). There were no significant differences between men and women (men mean 5.5, SD=3.13; women 6.5 SD=3.3, p=0.408) (online supplemental table S3). All organ systems were affected (figure 2). Approximately half of ACCS (n=55; 53 %) had at least one health problem with a CTCAE grade≥3, with 60% of these individuals being older and 40% younger.

Multivariable linear regression revealed significant associations between age (p=0.001) and cumulative cyclophosphamide equivalent dose (p=0.023) with an increase in chronic health problems in vital organ systems, defined as cardiovascular, gastrointestinal/hepatic, neurological, pulmonological and renal (table 2): The model predicts 1.62 chronic health problems in a subject 10 years older than the population mean age and 1.25 chronic health problems in a subject with 1 g higher cumulative cyclophosphamide equivalent dose, ceteris paribus. Approximately a quarter of ACCS (23%) developed secondary malignant neoplasms (SMNs), with skin cancers accounting for the majority (29% of SMNs) (see online supplemental table S4).

### Current HRQOL

HRQOL (physical and mental) in ACCS was significantly lower than in the SGP. Mean T scores for physical HRQOL were lower in older ACCS than in younger ACCS: physical HRQOL (44.83 (SD=11.65) vs 50.08 (SD=9.30)). This is in concordance with the decline in physical HRQOL seen in the SGP (>28 years n=1081, T score 49.25 (48.63–49.88), SD=10.29; 18–28 years, n=128, T score 55.14 (53.99–56.28), SD=6.2).[17]

Only younger ACCS reported a higher mental HRQOL than their same-age peers (mean T Score 50.31 vs 46.33, p=0.007) (online supplemental table S5).[17] Older ACCS exhibited lower mental HRQOL than younger ACCS (>28

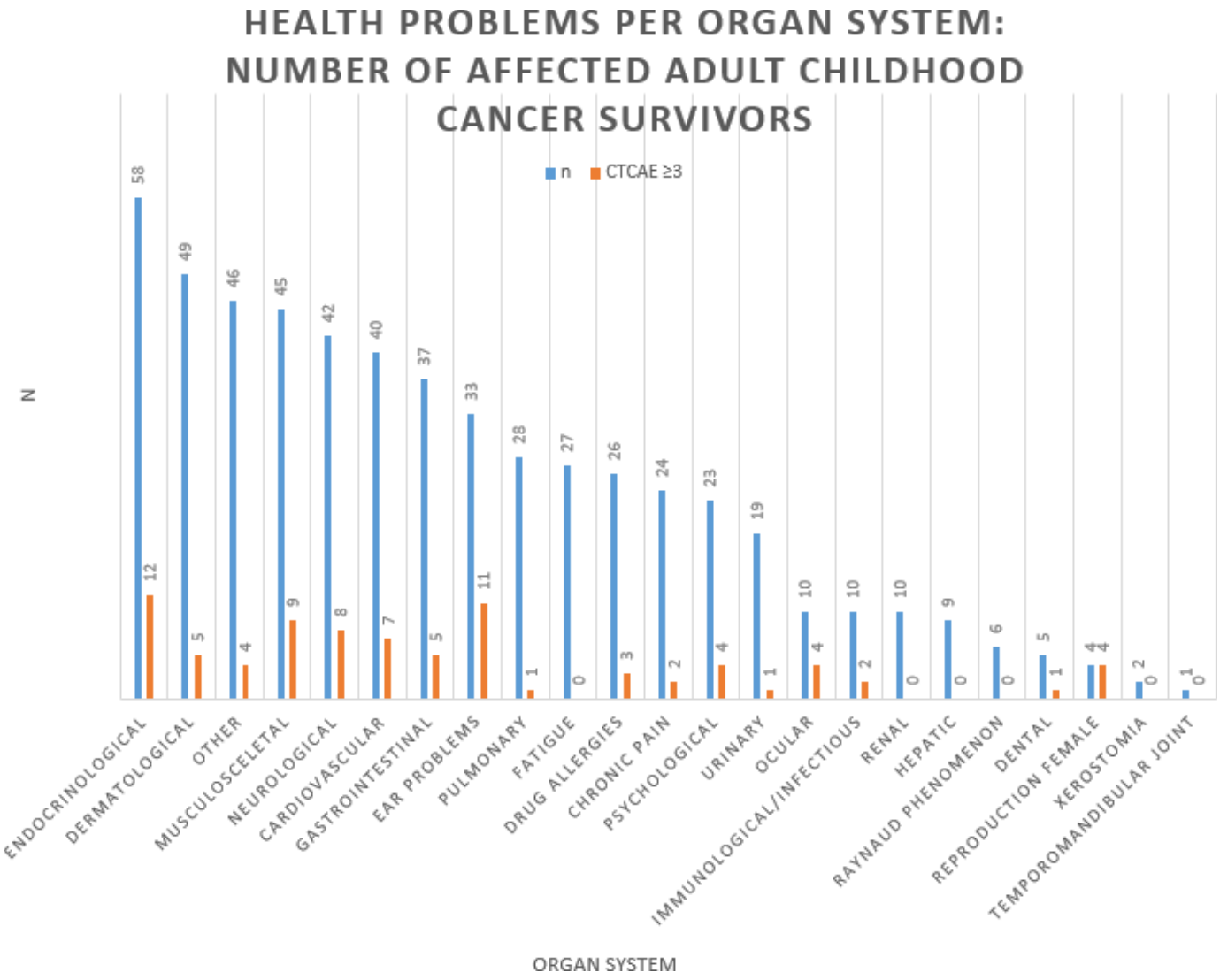


**Figure 2** Number of organ systems affected by health problems. CTCAE, common terminology criteria for adverse events.

years: 44.39 (SD=13.78) vs <28 years: 50.31 (SD=7.20)), in contrast to the trend observed in the SGP (>28 years: 50.53 (SD=9.92) vs 18–28 years: 46.33 (SD=9.66)).

Lower physical HRQOL was significantly associated with a higher number of health problems (p<0.001) (table 3): For a subject with one additional health problem compared with the average, the predicted PCS was 44.27, ceteris paribus. There was a slight but significant effect of cumulative anthracycline dose (marginally worse physical HRQOL) and cumulative dose of cyclophosphamide

**Table 2** Multivariable linear regression for total number of affected vital* organ systems

| Factor | Predicted | Coefficient (95% CI) | P value |
|---|---|---|---|
| Intercept | 1.22 | −0.57 (−1.77 to 0.63) | 0.349 |
| Age | 1.62 (+10 years) | 0.04 (0.02 to 0.06) | 0.001 |
| Sex | 1.47 (female) | 0.25 (−0.27 to 0.77) | 0.347 |
| Number of irradiated fields | 1.34 (+1 field) | 0.12 (−0.05 to 0.29) | 0.169 |
| Maximal radiation dose | 1.24 (+10 gray) | 0 (−0.01 to 0.01) | 0.709 |
| Cumulative dose of anthracyclines† (mg/m$^2$) | 1.27 (+100 mg) | 0 (0 to 0) | 0.566 |
| Cumulative dose of cyclophosphamide equivalent‡(g/m$^2$) | 1.25 (+1 g) | 0.03 (0 to 0.05) | 0.023 |

*Vital organ systems defined as cardiovascular, gastrointestinal/hepatic, neurological, pulmonological and renal.
†Doxorubicin equivalent dose.[11 26]
‡Cyclophosphamid equivalent dose.[31]

Table 3 Multivariable linear regression for physical and mental health related quality of life

| | Physical Component Score | | | Mental Component Score | | |
|---|---|---|---|---|---|---|
| Factor | Predicted | Coefficient (95% CI) | P value | Predicted | Coefficient (95% CI) | P value |
| Intercept | 45.92 | 59.02 (49.59 to 68.45) | <0.01 | 52.19 | 59.06 (47.55 to 70.56) | <0.01 |
| Age | 45.01 (+10 years) | −0.09 (−0.28 to 0.10) | 0.341 | 51.05 (+10 years) | −0.11 (−0.34 to 0.12) | 0.325 |
| Sex | 46.79 (female) | 0.86 (−3.39 to 5.12) | 0.687 | 49.27 (female) | −2.92 (−8.11 to 2.27) | 0.266 |
| Number of irradiated fields | 45.8 (+1 field) | −0.12 (−1.51 to 1.27) | 0.863 | 51.9 (+1 field) | −0.29 (−1.98 to 1.40) | 0.733 |
| Maximal radiation dose (gray (Gy)) | 45.76 (+10 Gy) | −0.02 (−0.11 to 0.08) | 0.73 | 52.32 (+10 Gy) | 0.01 (−0.10 to 0.13) | 0.825 |
| Cumulative dose of anthracyclines* (mg/m$^2$) | 44.28 (+100 mg) | −0.02 (−0.03 to 0) | 0.03 | 52.57 (+100 mg) | 0 (−0.01 to 0.02) | 0.679 |
| Cumulative dose of cyclophosphamide equivalent† (g/m$^2$) | 46.18 (+1 g) | 0.26 (0 to 0.46) | 0.016 | 52.22 (+1 g) | 0.03 (0.22 to 0.28) | 0.806 |
| Cumulative number of health problems | 44.27 (+1) | −1.66 (−2.29 to −1.02) | <0.001 | 51.51 (+1) | −0.68 (−1.45 to 0.10) | 0.085 |

*Doxorubicin equivalent dose.[11 26]
†Cyclophosphamid equivalent dose.[31]

equivalent chemotherapy, with improved HRQOL at higher doses. This association remained when adjusting for age, sex and treatment intensity. Mental HRQOL showed no significant associations with the factors examined (see table 3).

### Feedback after the clinic visit

Most ACCS (n=68, 67%, not all answered each question) responded to the feedback questions, including fear (n=59), worries (n=56), satisfaction with PFC conversation with doctor (n=57), understanding of the plan (n=68), satisfaction with consultation (n=58) and preference for annual follow-up (n=68). No significant differences were found between responders and non-responders in terms of gender, age-group, age and HRQOL (mental, physical). ACCS with a greater number of health problems responded significantly more frequently to questions about fear and worries (details in online supplemental table S6). Most ACCS in our cohort preferred continuing their follow-up in our clinics (younger: 66%, older: 81%) (online supplemental figure S1). Nearly all ACCS were satisfied with the consultation as a whole (younger: 96%, older: 94%) and the briefing about their individual health risks based on their oncological therapy and recommended follow-up (younger: 96%, older: 97%). They believed they understood the information provided (younger: 93%, older: 97%). Although the majority of respondents reported that worries about their health and general fears did not increase after the follow-up visit, there was a significant difference between older and younger ACCS, with a higher proportion of older ACCS reporting increased worries (younger: 17%, older: 44%; p=0.04).

## Discussion

### Principal findings

Even at a young age, ACCS attending our clinics manifested multiple health issues encompassing all organ systems, associated with a notable decline in their HRQOL, particularly regarding physical HRQOL. While the younger ACCS in our cohort exhibited a superior mental HRQOL compared with their age-matched counterparts in the SGP, older ACCS experienced significantly worse mental HRQOL. ACCS expressed satisfaction with the comprehensive, internist-led multidisciplinary follow-up and detailed health risk information provided by our clinics.

We noted differences between ACCS in our clinics and those in the SCCSS Cohort. Our attendees were older, predominantly women and had undergone more intensive treatments than their SCCSS counterparts.[6] Additionally, they had a higher incidence of relapses of their primary oncological disease and SMNs, SMNs occurring at more than double the rate reported in the Childhood Cancer Survivor Study (CCSS) (30-year cumulative incidence of 9.3%).[22] Notably, one-third of the SMNs of our ACCS were skin cancers, while the CCSS excluded non-melanoma skin cancer.

### Strengths and limitations of the study project

Our study has significant strengths, notably thorough documentation of cancer histories among ACCS. Additionally, our diverse cohort spans various age groups and includes ACCS treated for lymphoma, leukaemia, sarcoma and CNS tumours, reflecting the heterogeneous spectrum of childhood cancer diagnoses. Some limitations merit attention. Our study includes a small cohort from just two centres, potentially impacting the generalisability of our findings. Notably, older ACCS in our sample were not actively recruited but rather sought specialised follow-up care voluntarily or were brought by concerned caregivers. Thus, this sample may not entirely reflect the broader population of older ACCS in Switzerland. Despite these limitations and the potential for selection bias, we consider it important to report our results due to the scarcity of research on this age group and their associated health concerns.

### Comparative analysis

The higher proportion of women in our cohort aligns with the observation that women generally exhibit a higher degree of health consciousness and engagement in preventive health behaviours compared with men.[23]

Our cohort, in contrast to the ACCS Cohort analysed in the SCCSS study with an average age of 25 years, exhibits a higher mean age at 31.5 years. This age difference highlights a significant point: many ACCS in our study, especially older ones, had not received regular follow-up care before their first visit to our LTFU clinic. This gap could be attributed to the historical practice of deeming ACCS cured of their oncological disease without the need for further follow-up, a practice that may have been more prevalent in previous decades.[5] Data from various European clinics underscore this trend, indicating that a significant number of paediatric institutions transition CCS to either general practitioners or adult oncology services at a median age of 18 years.[24]

Over half of our ACCS received radiotherapy, compared with the younger cohort studied in the SCCSS (25.8%).[6] SCT is the most intense treatment used in paediatric oncology. In our cohort, approximately 1 in 10 ACCS underwent SCT, primarily using autologous stem cells. This rate is double that reported in the SCCSS Cohort (5.5%).[6] These differences may arise from the appeal of our LTFU programme to heavily treated ACCS with multiple chronic health issues, who attend our clinic more than those with fewer or less severe morbidities. The higher rates of relapse of their primary oncological disease and SMNs within our cohort further support this hypothesis. In the CCSS Cohort, CCS had a cumulative relapse rate of 6.2% after primary diagnosis, which is half the rate observed in our cohort.[25] SMNs were not the main cause of reduced physical health in our study cohort since almost all ACCS had been cured of their SMNs before being seen in our clinic.

On average, ACCS in our study experience six health problems, ranging from 0 to 15, with older ACCS exhibiting more issues than younger counterparts. They also demonstrate signs of premature ageing and illnesses typically associated with older age in the general population. Over half of ACCS in our cohort face severe health problems (CTCAE grade≥3), with nearly two-thirds of older ACCS having at least one severe health problem. The St. Jude cohort shows a similar distribution of organ system involvement with a CTCAE grade≥3.[26] Data from the St. Jude Lifetime Cohort Study revealed that by age 50, survivors had an average of 17.1 chronic health problems, with 4.7 of them being CTCAE grade≥3, compared with community controls with 9.2 and 2.3 chronic health problems, respectively.[2] Studies consistently demonstrate elevated morbidity and mortality among ACCS compared with peers.[27] Regular follow-up and lifestyle modification guidance can mitigate this risk over time.[3] Without dedicated follow-up clinics, ACCS often receive uncoordinated care, leading to inefficiencies and increased costs.[1] Health problems stemming from cancer treatment can affect all organ systems. Experienced physicians specialising in internal medicine are well equipped to manage patients with multiple health issues and optimise their care, making them suitable leaders for specialised follow-up clinics for ACCS. Collaboration with a paediatric oncologist for preparation and guidance is essential to ensure that general internists can effectively address relevant health risks. Our cohort generally reported a lower HRQOL compared with research data from the SGP,[18] with the exception of mental HRQOL in younger ACCS. These findings align with international data: the CCSS reports poorer HRQOL compared with healthy populations,[28 29] while the SCCSS[7] indicates better HRQOL in this younger ACCS Cohort compared with the SGP. The improved mental HRQOL among young ACCS could potentially signify post-traumatic growth.[30]

It is plausible that individuals with a lower quality of life may be more inclined to take advantage of LTFU visits, potentially leading to an overestimation of the negative long-term effects on HRQOL resulting from oncological therapy. Our multivariable regression analysis revealed a significant association between physical HRQOL and the cumulative doxorubicin equivalent dose, as well as the cumulative number of health problems. In our cohort, mental HRQOL was significantly lower in older ACCS compared with their younger counterparts. This observation is noteworthy as, in the general population, physical HRQOL tends to decline with age, while mental HRQOL typically improves.[18]

In our cohort, older ACCS showed more concern about their health status post visit compared with younger counterparts. We attribute this to younger ACCS often perceiving themselves as healthier, leading to less postvisit apprehension. The comprehensive LTFU plan, explained by our paediatric oncologist (EMET in both centres), was well understood by most ACCS. Despite being presented with an extensive list of potential late effects during this discussion, ACCS from both age groups expressed satisfaction with over 80% reporting no heightened fear post

visit. While the desire for annual follow-up at the LTFU clinic was slightly more pronounced among older ACCS, the difference was not statistically significant. This reflects their greater demand for access to specialised follow-up due to pre-existing chronic health conditions. Importantly, nearly all ACCS in both age groups expressed satisfaction with the PFC discussion and consultation, indicating a high level of contentment with attending our LTFU clinics.

### Implication for clinical practice

The specialised follow-up clinics demand effort and time. In Switzerland, reimbursement for the extensive preparatory work and extended clinical consultations remains insufficient. Approximately one-third of the expenses must be covered through alternative sources such as research funds and foundations. Due to the substantial workload and financial constraints, these clinics are constrained in the number of ACCS they can accommodate annually. Consequently, a potential solution could involve establishing similar clinics in various regions across Switzerland.

### Implication for research

Further research is essential to demonstrate the cost-effectiveness and enhanced clinical outcomes associated with specialised follow-up settings. Future analyses of our data should explore the adherence of ACCS transitioning directly from paediatric care, without self-selection, to LTFU over time. Additionally, conducting in-depth qualitative studies is warranted to assess whether our LTFU clinic model effectively meets ACCS' needs without generating undue concerns.

To gauge therapy intensity, we used cyclophosphamide and doxorubicin equivalent doses. Our study demonstrated a positive correlation between higher exposure to cyclophosphamide equivalent chemotherapeutics and a greater number of health problems. This finding warrants further investigation in larger ACCS cohorts.

## CONCLUSION

Our study shows that, given the complex health problems affecting their HRQOL and the great needs of ACCS, internist-led LTFU clinics are a promising approach. Offering a specialised follow-up clinic is feasible in a large university hospital as well as in a smaller cantonal hospital. Essential in the set-up is the motivation of the interdisciplinary team and a close collaboration between paediatric oncology providing the knowledge about childhood cancer treatments and known risks for late-effects and experienced internists who think broadly enough to assess the diverse health problems seen in ACCS and initiate treatment if necessary.

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**Ethics approval** This study involves human participants and was approved by ethics committee of Northwestern and Central Switzerland (EKNZ, 2017-00109). Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available upon reasonable request. Data are available on reasonable request. Data can be made available to collaborating researchers on request and decision in the steering committee. The data are not publicly available due to containing information that could compromise the privacy of adult childhood cancer survivors participating in our research project.

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