

Health-related quality of life in adolescent and young adult cancer survivors

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ABSTRACT

Purpose Today survival rates for adolescent and young adult (AYA) cancer patients exceed 80%. However, cancer and treatment leave many patients suffering from chronic conditions. These late effects may impair their health-related quality of life (HRQoL). We aimed to (1) compare HRQoL of AYA cancer survivors with the Swiss general population and (2) investigate socio-demographic and cancer-related characteristics associated with poor HRQoL.

Methods AYA cancer survivors (age 16-25 at diagnosis; ≥ 5 years survival) who had been identified through the Cancer Registry Zurich and Zug, Switzerland filled out a questionnaire. We assessed HRQoL using the Short-Form 12 (SF-12), producing two scores: Physical Component Summary score (PCS, physical health) and Mental Component Summary score (MCS, mental health). We used multivariable logistic regression analyses to investigate associated characteristics.

Results We compared 155 survivors with 350 controls. Survivors had significantly lower physical health than controls (mean=52.5 vs. mean=54.7, $p < 0.001$). Male survivors reported better mental health than controls (55.2 vs. 53.3, $p = 0.078$) and females slightly worse (49.8 vs. 51.8, $p = 0.285$). Poor physical health was strongly associated with having a migration background (OR=4.63, $p = 0.008$) and unemployment (OR=7.66, $p = 0.005$). Poor mental health was associated with female sex (OR=2.69, $p = 0.057$), suffering from late effects (OR=5.91, $p < 0.001$) and a migration background (OR=5.82, $p = 0.004$).

Conclusions Results emphasize the need for individualized support services to improve survivors' HRQoL in vulnerable subgroups. We recommend adapted care for women and migrants, in addition to educational and employment support systems.

Keywords Adolescent, Young adult; Cancer; Survivor; SF-12; Health-related quality of life

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INTRODUCTION

With increasing survival rates of adolescent and young adult (AYA) cancer in Europe, exceeding 80% today [1,2], the question on the quality of survival in this growing population arises. This population of AYA cancer survivors encounters a high risk for adverse late outcomes (late effects) [3], including second malignancies, cardiovascular and pulmonary conditions, endocrine dysfunction, neurological disorders, infertility, as well as psychological and social problems [4-7,3]. More than 60% of survivors report having at least one chronic condition and over one third of them report having at least two [6].

AYAs find themselves in a challenging state of development between childhood and adulthood. A diagnosis of cancer might interfere with these developmental milestones and thus have an important impact on their health related quality of life (HRQoL). Later on, the presence of late effects may further affect their HRQoL

HRQoL is a complex construct mainly defined by an individual's perception of his or her physical and mental health over time [8,9]. HRQoL has been widely studied in childhood cancer survivors [10-13], whereas AYA cancer

survivors' HRQoL has only recently come to the focus of attention [14-16,7]. In some studies with childhood cancer survivors, findings suggest that survivors' HRQoL is comparable to the norm population [10,11,13], while another study found survivors reporting significantly poorer HRQoL [12]. Cancer relapse and chronic problems have been strongly associated with poorer HRQoL in the areas *well-being* and *physical health* [10,12]. Despite experiencing impairments, childhood cancer survivors also demonstrate resilience and higher psychological well-being than their peers [11,13].

AYAs have emerged as a unique group in the clinical setting that requires specialized and cautious care and practice guidelines when facing the specific challenge of cancer diagnosis [17,18]. The previously limited amount of studies on AYAs has recently been increasing, examining not only their HRQoL and health behaviors, but also psychosocial outcomes [19,20]. HRQoL in AYAs has already been studied in Germany [21], the United Kingdom [22] and the United States [23]. However, to address quality of survivorship internationally, it is essential to expand the scope of countries reporting on survivors' quality of life. Therefore, we aimed to (1) compare HRQoL of AYA cancer survivors to the Swiss general population, and (2) investigate socio-demographic and cancer-related characteristics associated with poor HRQoL

METHODS

Sample and procedure

We identified eligible AYA cancer survivors in the population-based Cancer Registry Zurich and Zug. Participants were eligible for our study if they were diagnosed between January 1990 and December 2005 at age 16 to 25 years, and survived ≥ 5 years. To allow for a comparison with an associated study including childhood cancer survivors the sample was limited to the following diagnoses: central nervous system (CNS) tumors, germ cell tumors, lymphomas, leukemias, neuroblastomas, renal, hepatic, and bone tumors, as well as soft tissue sarcomas [24]. The Cancer Registry Zurich and Zug provided addresses of all eligible survivors. If necessary the addresses were updated using web search and by contacting the community where the survivors had resided last.

Eligible survivors received a cover letter, study information, informed consent form, questionnaire, and prepaid return envelope. Four weeks later, non-responders received another copy of the questionnaire. Data collection took place between August 2010 and January 2012.

The control group consisted of a subgroup of a random sample of the Swiss general population, who participated in a study on health and well-being in Switzerland. Eligible participants of this study were 18-75 years of age and resident in Switzerland. Their information was collected between 2015 and 2016. For direct comparison only those in the same age-group (20-47 years) as the AYA cancer survivors were included in the analyses.

The study was approved by the Cantonal Ethics Committee of Zurich (Ref No. EK: 2010-0228/2), and participants gave informed consent.

Measurements

The questionnaire assessed information on attendance and preferences for the organization of follow-up care, quality of life, and psychological distress.

Outcome health-related quality of life

HRQoL was assessed by the SF-12 [25]. The SF-12 questionnaire has been developed to provide a shorter but valid alternative to the SF-36 and is a good and useful instrument successfully used across different countries to assess HRQoL in both healthy and chronically ill populations [26-29]. The SF-12 questionnaire uses weighted subscales to produce two summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Raw scores were converted into T-scores (mean=50, SD=10) according to age- and sex-stratified norm data from the Socio Economic Panel study standardized German population norm [27,25]. Higher scores indicate better HRQoL. The control group completed the SF-36 and we used the respective twelve items from the SF-12 to calculate their SF-12 scores.

With health status and health perception being age dependent, PCS and MCS tend to vary over life span. Therefore age-specific means indicate the average health for a specific age group. An individual's HRQoL can be best interpreted when knowing whether that person's score is above or below average. Therefore cut-off points for individual scores have been established using statistical methods [30]. Having a score that is below the cut-off indicates that this person has significantly worse HRQoL than his or her comparison group. The PCS difference score for poor health was defined as 6.97 points below the age-specific group mean (i.e. $PCS \leq 45.5$), and the MCS difference score for poor mental health as 6.24 points below the mean (i.e. $MCS \leq 47.5$) [30]. We thus created binary variables indicating poor physical health when $PCS \leq 45.5$, and poor mental health when $MCS \leq 47.5$, respectively.

Socio-demographic characteristics

We assessed *sex*, *age* and *educational achievement* (compulsory education: up to ninth grade; vocational education: vocational training/apprenticeship, high school degree, or teacher's college; upper secondary education: college and university of applied science; university degree [31,32]). In the university education category no one reported having poor physical or poor mental health. Therefore we combined upper secondary education and university degree. Further we assessed *employment* (employed/unemployed), *relationship status* (survivors were asked whether they had a partner or not: (yes/no)), and *migration background* (yes/no). The definition of *migration background* was adapted from the Swiss Federal Statistical Office's definition [33]: Not being Swiss citizen, or not Swiss citizen since birth, or not born in Switzerland, was coded as having a migration background.

Cancer-related characteristics

Participants were asked whether they were suffering from *late effects* of the former cancer diagnosis or treatment (yes/no) and had the possibility to specify them. Further, we asked whether they had been diagnosed with a *relapse* (yes/no), or a *second malignancy* (yes/no).

The Cancer Registry Zurich and Zug provided information on *diagnosis* (classified according to the International Classification of Childhood Cancer, third edition) [34]. For the regression analyses we grouped diagnoses into six major groups: lymphoma, germ cell tumor, sarcoma, leukemia, CNS tumor, and other, following the ranking of the most common cancers in our study population and the AYA cancer population in general [17,35,1]. Furthermore the registry provided information on survivors' age at diagnosis (16-20 years; 21-25 years); time since diagnosis (5-10 years; 11-15 years; 16+ years), and *treatment* (surgery only; chemotherapy: may have had surgery but not radiotherapy; radiotherapy: may have had surgery and/or chemotherapy).

Statistical analysis

For the comparison between participants and non-participants we used descriptive statistics and chi-square tests for proportions. To account for differences between survivors and controls for aim 1 we standardized the controls on sex, age at study and migration background according to the marginal distribution of the survivors. The mean PCS and MCS scores were compared using t-tests (significance threshold $p \leq 0.05$). For proportion comparison of poor physical and poor mental health between survivors and controls we used adjusted Wald chi-square tests (significance threshold: $p \leq 0.05$). For aim 2 (to investigate demographic and clinical characteristics associated with

poor HRQoL), we ran univariable and multivariable logistic regression. Only characteristics associated at $p \leq 0.10$ in the univariable logistic regression were included in the multivariable logistic regression. Likelihood ratio tests delivered global p -values for the multivariable logistic regression (significance threshold: $p \leq 0.1$). All analyses were performed using Stata version 14.2 (StataCorp, College Station, TX, USA).

Table 1: Study population characteristics, comparing participants, non-participants and a sample of the general population

	General population		Participants		Non-participants		<i>p</i> -value ^a
	N	%	N	%	N	%	
Total	350	100	155	100	309	100	
Sociodemographic characteristics							
Sex ^b							0.151
Female	210	40.0	59	38.1	96	31.0	
Male	140	60.0	96	61.9	210	68.0	
Age at study (years)							0.548
20-29	91	26.0	42	27.1	74	24.0	
30-39	153	43.7	82	52.9	180	58.2	
40+	106	30.3	31	20.0	55	17.8	
Migration Background							
No migration background	275	78.6	122	78.7	n/a	n/a	
Migration background	75	21.4	33	21.3	n/a	n/a	
Partnership ^b							
No partner	66	18.9	35	22.6	n/a	n/a	
Partnership	272	77.7	120	77.4	n/a	n/a	
Education ^b							
Compulsory education	10	2.9	12	7.7	n/a	n/a	
Vocational training	150	42.9	73	47.1	n/a	n/a	
Upper Secondary education	58	16.6	50	32.3	n/a	n/a	
University education	114	32.6	19	12.3	n/a	n/a	
Employment ^b							
Not employed	37	11.0	14	9.0	n/a	n/a	
Employed	301	89.0	141	91.0	n/a	n/a	
Clinical characteristics							
Diagnosis							0.170
Lymphoma	n/a	n/a	59	38.1	91	29.5	
Germ cell tumor	n/a	n/a	45	29.0	117	37.9	
Sarcoma	n/a	n/a	14	9.0	17	5.5	
Leukemia	n/a	n/a	13	8.4	28	9.1	

RESULTS

Characteristics of the study population

In total, 469 survivors were eligible to participate in the study, of which 389 (100%) had a current address and could be contacted (Figure 1). Of those contacted, 160 (41%) filled in the questionnaire, and 155 completed the SF-12 items (40%; 96 (62%) males). Participants and non-participants did not differ regarding their socio-demographic and cancer-related characteristics (Table 1). Participants' mean age at study was 34.0 years. Mean age at diagnosis was 21.6 years, and mean time since diagnosis was 12.4 years. Lymphomas (38%) and germ cell tumors (29%) were the most common diagnoses. Of all participants, 22 (14%) reported having had a relapse, 11 (7%) a second malignancy, and 41 (27%) reported having at least one late effect.

The control population (n=350; 140 (40%) males) had a mean age of 35.5 years.

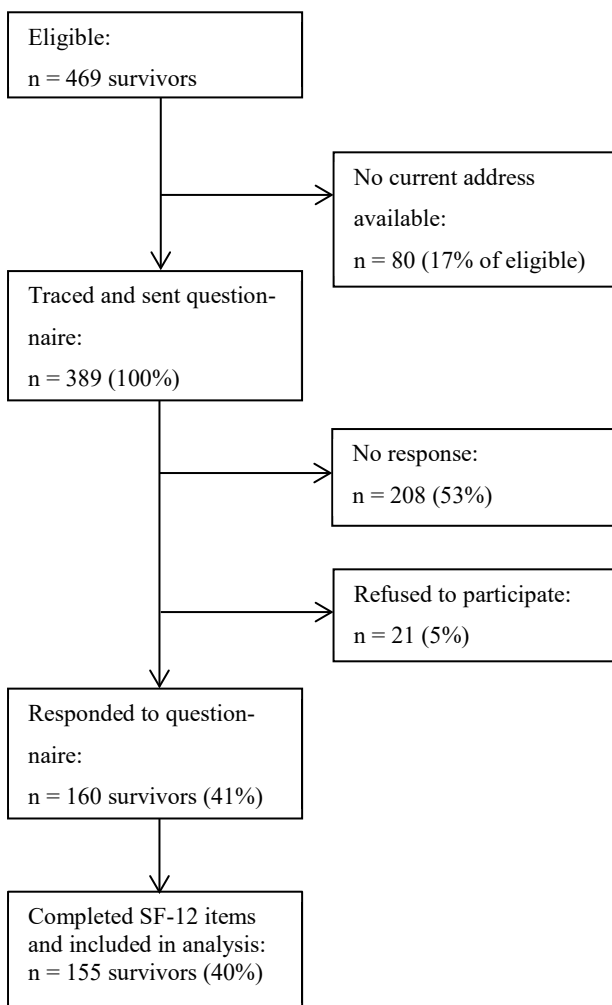


Fig. 1 Flow chart of our study participants

Eligible survivors had been diagnosed with central nervous system tumor (CNS), germ cell tumor, lymphoma, leukemia, neuroblastoma, renal, hepatic, and bone tumor, as well as soft tissue sarcoma, between 1990 and 2005, aged between 16-25 years at the time of diagnosis and were ≥ 5 years after diagnosis at time of study

Table 1 (continued)

	General population		Participants		Non-participants		<i>P</i> -value ^a
	N	%	N	%	N	%	
CNS tumor	n/a	n/a	13	8.4	36	11.7	
other	n/a	n/a	11	7.1	20	6.5	
Treatment ^b							0.507
Surgery only	n/a	n/a	54	34.8	108	35.0	
Chemotherapy ^c	n/a	n/a	31	20.0	63	20.4	
Radiotherapy ^d	n/a	n/a	39	25.2	59	19.1	
Age at diagnosis (years)							0.439
16-20	n/a	n/a	67	43.2	122	39.5	
21-25	n/a	n/a	88	56.8	187	60.5	
Time since diagnosis (years)							0.971
5-10	n/a	n/a	57	36.8	111	35.9	
11-15	n/a	n/a	50	32.3	99	32.0	
16+	n/a	n/a	48	31.0	99	32.0	
Relapse							
No relapse	n/a	n/a	133	85.8	n/a	n/a	
Relapse	n/a	n/a	22	14.2	n/a	n/a	
Second malignancy							
No second malignancy	n/a	n/a	144	92.9	n/a	n/a	
Second malignancy	n/a	n/a	11	7.1	n/a	n/a	
Late effects ^b							
No late effects	n/a	n/a	111	71.6	n/a	n/a	
Late effects	n/a	n/a	41	26.5	n/a	n/a	
Type of late effect							
Psychological late effect	n/a	n/a	4	9.8	n/a	n/a	
Somatic late effect	n/a	n/a	28	66.3	n/a	n/a	
Both	n/a	n/a	9	22.0	n/a	n/a	
	Mean	SD	Mean	SD	Mean	SD	<i>P</i> -value ^e
Age at study (years)	35.5	7.21	34.0	5.87	34.2	5.62	0.722
Age at diagnosis (years)	n/a	n/a	21.6	2.89	21.7	2.92	0.727
Time since diagnosis (years)	n/a	n/a	12.4	4.74	12.5	4.78	0.831

^a *p*-values from chi-square test

^b Missing values; percentages are based on the total number of participants/non-participants/general population

^c Chemotherapy (may have had surgery but not radiotherapy)

^d Radiotherapy (may have had surgery and/or chemotherapy)

^e *p*-value from two sample t-test

Aim 1: Comparison of HRQoL with general population

Survivors had significantly lower PCS scores than controls (mean: 52.5 vs. 54.7, $p < 0.001$), both in males (52.7 vs. 54.9, $p = 0.004$), and females (52.1 vs. 54.2, $p = 0.032$, Figure 2). Male survivors reported better mental health than controls (55.2 vs. 53.3, $p = 0.078$) and females slightly worse (49.8 vs. 51.8, $p = 0.285$, Figure 3). The proportions of survivors and controls with poor physical health (11.0% vs. 9%, $p = 0.554$) or poor mental health (24.0% vs. 21%, $p = 0.412$) did not differ.

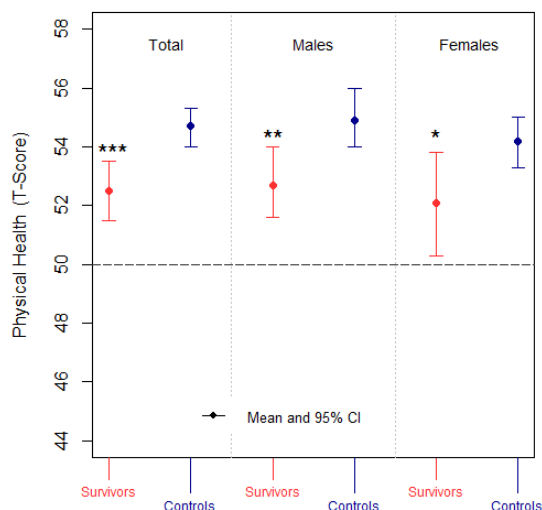


Fig. 2 Comparison of physical health measured by the Physical Component Summary (PCS) in AYA cancer survivors and the general population (mean scores and 95% confidence intervals)

Abb.: AYA, adolescent and young adult, CI, Confidence Interval, HRQoL, health related quality of life, PCS, Physical Component Summary. Higher scores indicate better physical health

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

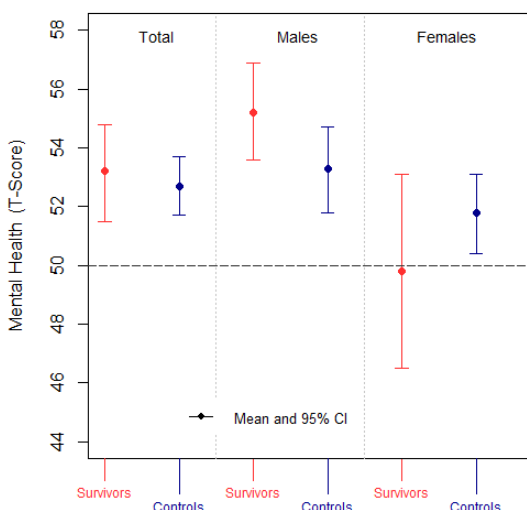


Fig. 3 Comparison of mental health measured by the Mental Component Summary (MCS) in AYA cancer survivors and the general population (mean scores and 95% confidence intervals)

Abb.: see Fig.2, MCS, Mental Component Summary

Aim 2: Characteristics associated with poor HRQoL

Poor physical health

In univariable logistic regression, survivors with a migration background (odds ratio (OR) = 5.34, 95% confidence interval (CI): 1.87-15.26, $p = 0.002$), those who were unemployed (OR=8.86, CI: 2.61-30.16, $p < 0.001$) and those with late effects (OR=2.75, CI: 1.00-7.67, $p = 0.054$) were more likely to report poor physical health (Table 2). Survivors who had compulsory education only, compared to higher education, tended to be more likely to report poor physical health (OR=2.37, CI: 0.54-10.42, $p = 0.253$). No age-dependent difference in reported HRQoL at study was found. There was no difference in physical health regarding age at diagnosis, type of cancer diagnosis, treatment, relapse or second malignancies.

In multivariable regression, only migration background (OR=4.63, CI: 1.50-14.28, $p = 0.008$) and unemployment (OR=7.66, CI: 1.93-30.34, $p = 0.005$) remained significantly associated with poor physical health.

Poor mental health

In univariable regression, females (OR=3.74, CI: 1.73-8.09, $p = 0.001$), those with a migration background (OR=4.53, CI: 1.97-10.37, $p < 0.001$), the unemployed (OR=7.26, CI: 2.26-23.38, $p = 0.001$) and those reporting late effects (OR=8.02, CI: 3.49-18.42, $p < 0.001$) were more likely to report poor mental health (Table 3). Additionally, survivors who had been diagnosed with germ cell tumors were less likely to report poor mental health (OR=0.24, CI: 0.08-0.71; $p = 0.010$) than lymphoma survivors.

In multivariable regression, being female (OR=2.69, CI: 0.87-7.51, $p = 0.057$), having a migration background (OR=5.82, CI: 1.98-17.07, $p = 0.004$) and reporting late effects (OR=5.91, CI: 2.16-16.14, $p < 0.001$) remained significantly associated with reporting poor mental health.

DISCUSSION

Our findings show that overall, AYA cancer survivors have significantly worse physical health than the general population. Poorer physical health was reported among those with a migration background and those who were unemployed. Survivors reported similar mental health as the general population. Male survivors reported better mental health, whereas female survivors reported slightly worse mental health than controls. Survivors with a migration background and those reporting late effects were at particular risk to have poor mental health.

Table 2: Characteristics associated with poor physical health in AYA cancer survivors (low physical health if SF-12 Physical Component Summary (PCS) score $\leq 45.5^a$)

	Survivors reporting poor health		Univariable regression			Multivariable regression ^b		
	N	% ^c	OR ^d	[95% CI] ^e	<i>p</i> -value	OR ^d	[95% CI] ^e	<i>p</i> -value ^f
	17	11.0						
Sex					0.421			
Male	9	9.4	1					
Female	8	13.6	1.52	0.55 - 4.18				
Age at study					0.870 ^g			
20-29	5	12.0	1					
30-39	8	9.8	0.80	0.24 - 2.62				
40+	4	13.0	1.10	0.27 - 4.47				
Migration background					0.002			0.008
No	8	6.6	1			1		
Yes	9	27.3	5.34	1.87 - 15.26		4.63	1.50 - 14.28	
Partner					0.271			
No	2	5.7	1					
Yes	15	12.5	2.36	0.51 - 10.85				
Education					0.214			
Compulsory schooling	3	25.0	2.37	0.54 - 10.42				
Vocational training Upper Secondary /university education	9 4	12.3 5.8	1 0.44					
Unemployment					<0.001			0.005
No	11	7.8	1			1		
Yes	6	42.9	8.86	2.61 - 30.16		7.66	1.93 - 30.34	
Diagnosis					0.518 ^g			
Lymphoma	5		1					
Germ cell tumor	3		0.77	0.17 - 3.41				
Sarcoma	2		1.80	0.31 - 10.41				
Leukemia	2		1.96	0.34 - 11.45				
CNS tumor	2		1.96	0.34 - 11.45				
Other ^h	3		4.05	0.81 - 20.31				
Treatment					0.485			
Surgery	7	13.0	1					
Chemotherapy	5	16.0	1.29	0.37 - 4.48				
Radiotherapy	3	7.7	0.56	0.14 - 2.32				
Age at diagnosis					0.736			
16-20	8	11.9	1					
21-25	9	10.2	0.84	0.31 - 2.30				

Table 2 (continued)

	Survivors reporting poor health		Univariable regression			Multivariable regression ^b		
	N	% ^c	OR ^d	[95% CI] ^e	<i>p</i> -value	OR ^d	[95% CI] ^e	<i>p</i> -value ^f
Time since diagnosis					0.922			
5-10 years	7	12.3	1					
11-15 years	5	10.0	0.79	0.24 - 2.68				
16+ years	5	10.4	0.83	0.25 - 2.81				
Relapse					0.319			
No	16	12.0	1					
Yes	1	4.5	0.35	0.04 - 2.77				
Second malignancy					0.837			
No	16	11.0	1					
Yes	1	9.0	0.80	0.10 - 6.67				
Late effects					0.054			0.397
No	9	8.0	1			1		
Yes	8	19.5	2.75	1.00 - 7.67		1.67	0.52 - 5.39	

^a Cut-off calculated by deducting 6.97 points from the age-specific mean as indicator for poor physical health

^b In the multivariable model, we included all variables that were significantly associated ($p \leq 0.1$) with low PCS in the univariable logistic regression model

^c Percentage of survivors reporting poor health in specific subcategory

^d Odds ratio (OR for scoring 6.97 points below the age-specific mean (Physical Component Summary Score ≤ 45.5))

^e 95% confidence interval

^f Global *p*-value calculated with likelihood ratio test (multivariable regression)

^g Global *p*-value calculated with chi-square test (univariable regression)

^h Other malignant cancers ranking below the top five most common cancers in the AYA population

p-values ≤ 0.1 are depicted in bold

Our findings are in line with findings from a recent systematic review on the quality of life in AYA cancer patients and survivors [15] and findings from an additional study on AYA cancer survivors' HRQoL in the US [23]. The studies in the systematic review assessed quality of life with a variety of validated tools like the Pediatric Quality of Life Inventory, the European Organization for Research and Treatment of Cancer's quality of life questionnaire, the Quality of life Behavioral Risk Factor Surveillance System and the Functional Assessment of Cancer Therapy-Bone Marrow Transplant, but also with their own instruments [15]. Nineteen studies used quantitative methods, 13 studies used qualitative methods and a mixed-methods approach was used by three studies [15]. Both the systematic review and the study from the US,

using the SF-12, concluded that, overall, in comparison to the general population AYA cancer survivors were more likely to have poor or impaired quality of life. The impaired HRQoL was observable early on after diagnosis. In contrary, a study from the UK comparing AYA cancer survivors' HRQoL with normative data concluded that physical and mental health measured by the SF-12 were comparable in both groups [22]. A possible explanation why the survivors' mental health in our study was not significantly worse but comparable with the norm population's mental health could be the link between cancer survival and post-traumatic growth and resilience in cancer survivors [36,12].

Table 3: Characteristics associated with poor mental health in AYA cancer survivors (low mental health if SF-12 Mental Component Summary (MCS) score $\leq 47.5^a$)

	Survivors reporting poor health		Univariable regression			Multivariable regression ^b		
	N	% ^c	OR ^d	[95% CI] ^e	<i>p</i> -value	OR ^d	[95% CI] ^e	<i>p</i> -value ^f
	37	24.0						
Sex					0.001			0.057
Male	14	14.6	1			1		
Female	23	39.0	3.74	1.73 - 8.09		2.69	0.87 - 7.51	
Age at study					0.709 ^g			
20-29	12	29.0	1					
30-39	18	22.0	0.70	0.30 - 1.64				
40+	7	22.6	0.73	0.25 - 2.14				
Migration background					<0.001			0.004
No	21	17.2	1			1		
Yes	16	48.5	4.53	1.97 - 10.37		5.82	1.98 - 17.07	
Partner					0.104			
No	12	34.3	1					
Yes	25	20.8	0.50	0.22 - 1.15				
Education					0.112			
Compulsory schooling	5	41.7	1.89	0.54 - 6.66				
Vocational training	20	27.4	1					
Upper Secondary / university education	11	16.0	0.50	0.22 - 1.15				
Unemployment					0.001			0.133
No	28	19.9	1			1		
Yes	9	64.3	7.26	2.26 - 23.38		3.66	0.87 - 15.47	
Diagnosis					0.039			0.114
Lymphoma	20	54.0	1					
Germ cell tumor	5	14.0	0.24	0.08 - 0.71		0.25	0.05 - 0.89	
Sarcoma	1	3.0	0.15	0.02 - 1.23		0.07	0.00 - 1.35	
Leukemia	4	11.0	0.87	0.24 - 3.17		0.49	0.09 - 2.63	
CNS tumor	3	7.0	0.59	0.14 - 2.37		0.43	0.80 - 2.35	
Other ^h	4	11.0	1.11	0.29 - 4.26		0.92	0.18 - 4.76	
Treatment					0.398			
Surgery	11	20.4	1					
Chemotherapy	6	19.4	0.94	0.31 - 2.85				
Radiotherapy	11	28.0	1.54	0.59 - 4.02				
Age at diagnosis					0.702			
16-20	17	25.4	1					
21-25	20	22.7	0.87	0.41 - 1.82				

Table 3 (continued)

	Survivors reporting poor health		Univariable regression			Multivariable regression ^b		
	N	% ^c	OR ^d	[95% CI] ^e	<i>p</i> -value	OR ^d	[95% CI] ^e	<i>p</i> -value ^f
Time since diagnosis					0.346 ^g			
5-10 years	15	26.0	1					
11-15 years	14	28.0	1.09	0.46 - 2.56				
16+ years	8	17.0	0.56	0.21 - 1.46				
Relapse					0.687			
No	31	23.0	1					
Yes	6	27.0	1.23	0.44 - 3.42				
Second malignancy					0.259			
No	36	25.0	1					
Yes	1	9.0	0.30	0.04 - 2.43				
Late effects					<0.001			<0.001
No	14	13.0	1			1		
Yes	22	54.0	8.02	3.49 - 18.42		5.91	2.16 - 16.14	

^a Cut-off calculated by deducting 6.24 points of the age-specific mean as indicator for poor mental health

^b In the multivariable model, we included all variables that were significantly associated ($p \leq 0.1$) with low MCS in the univariable logistic regression model

^c Percentage of survivors reporting poor health in specific subcategory

^d Odds ratio (OR for scoring 6.24 points below the age-specific mean (Mental Component Summary Score ≤ 47.5))

^e 95% confidence interval

^f Global *p*-value calculated with likelihood ratio test (multivariable regression)

^g Global *p*-value calculated with chi-square test (univariable regression)

^h Other malignant cancers ranking below the top five most common cancers in the AYA population

p-values ≤ 0.1 are depicted in bold

In our study, a strong determinant of poorer physical and mental health was having a migration background. Similar to our findings, the above mentioned study from the US found that it was more likely to have poor physical health among participants with a different ethnic background, namely Hispanic responders, compared to Whites [23].

Even though it is difficult to make general statements about the health status of migrants because of the population's diversity, data from the National Health Report in Switzerland in 2015 showed that the population with migration background had overall a worse health status than the native Swiss population [37]. Despite using interpreting resources and the health professionals' language skills, cultural differences in understanding and meaning making of health and sickness may persist [38,39]. Cultural differences and individual characteristics may contribute to the different outcomes between those with migration background and those without. In addition to that, two US studies found that physical health in cancer survi-

vors was also affected by having a lower educational degree [23,40], which is a tendency that can be observed in our findings..

HRQoL was also affected by employment status. Those being unemployed had significantly poorer physical and mental health than those who were employed. This is in accordance with data from the Swiss National Health Report 2015 showing that the number of people who perceive their health status as (very) good is lower in the unemployed and they additionally suffer more from modest to severe depression than those who were employed [37]. Employment status and health affect each other in many and bidirectional ways and due to non-availability of further information from our participants on the reasons for unemployment, we are not able to draw conclusions on the causality path. A possible explanation could be the healthy worker effect [37,41], i.e. with better health a survivor is more likely to get employed. Another explanation could be that the survivors' HRQoL was negatively affected by their unemployment, which is in line with findings where unemployment at age 26-55 was found to have

major effect on HRQoL, compared to younger or older age [41].

In general males scored higher than females with a significant difference in mental health. This is in line with gender-specific differences found by Geue et al. in 2012 in short-term survivors of young adult cancer [21] and results from the German Socio Economic Panel (SOEP) survey from 2002 [27]. The gender-specific difference persists across the whole population, independent of age and health status [27]. This might explain why in our and a study from the US, female survivors and females in the norm population scored lower in their physical and mental health than males [40]. Sex differences may persist due to the diverse impact of health outcomes such as concerns on body appearance, questions on fertility and sexual functioning, physical, psychological, and psychosocial late effects [11].

Similar to our findings, other studies found a strong association between more late effects and poorer physical and mental health (though not statistically significant for physical health in our study) [22]. In accordance with these findings, studies from the US found a strong association between having symptoms and an increased likelihood to report poorer physical and mental health [23,40]. In addition, our findings were also consistent with studies among childhood cancer survivors, where physical and psychological late effects were strong determinants of poorer HRQoL [5,10-13].

Regarding diagnosis, studies show different results. Our results are similar to the UK study findings where survivors diagnosed with germ cell tumors overall reported better HRQoL than others [22]. One study from the US found that former germ cell tumor patients were more likely to report better physical than mental health [23]. However, studies agree that the more intense the received treatment and the higher the number of late effects a survivor has, the worse the HRQoL [23,40]. More intense treatments like chemotherapy and/or radiotherapy have been associated with poor mental health and are risk factors for a diverse number of late effects [17,40,3]. Our study results suggest that there might be an association between treatment and mental health, by showing an elevated odds ratio for radiotherapy (may have had surgery and/or chemotherapy) compared to chemotherapy (may have had surgery; Table 3). However, our results did not reach significance level, which might be ascribed to a reduced accuracy of effect estimates in subgroup analyses due to a small sample size of our study population.

Our findings complement other studies pointing out aspects in need of intervention or additional support, such as reducing disparities due to migration background, and support and counseling in education and employment issues. Improved outcomes may be achieved by providing culturally adapted brochures, information material, and services in modern and acceptable format for AYAs, such as online-platforms, social networks and events. Our results also indicate that females may be in need for more psychological support and counseling than what has been provided until today. Follow-up targeting gender-specific outcomes and provision of multidisciplinary services may be helpful. Health promotion and guidance against risky health behaviors can help improve physical and mental health and lead to better HRQoL [18,14,7].

Limitations and strengths

The relatively small sample size of AYA cancer survivors participating in our study limits the effect-accuracy of our statistical analyses, especially in subgroup analyses. The response rate of 40% may indicate that those who were in worse condition did not want to participate in the study. These limitations are comparable to those of other studies using questionnaires. The restriction of our study population in regard to specific diagnostic groups limits the generalizability of our findings. Another limitation is the cross-sectional design which prevents us from drawing any causal explanations.

A major strength was the use of population-based data combined with clinical information from the Cancer Registry Zurich and Zug, and the comparison with an adequate Swiss control group within the same age range. Another strength is the use of the prominently used and validated SF-12 questionnaire in combination with specifically calculated cut-offs for our study population.

Conclusion

Our results show that most of the AYA cancer survivors report satisfactory HRQoL. However there are relevant subgroups at higher risk for poor HRQoL and in need for adequate and specialized care. It is necessary to re-evaluate the existing support and consultation services with respect to the vulnerable subgroups. Additionally, mental health in particular was associated with several socio-demographic and cancer-related characteristics. Further research in AYAs is of uttermost importance in order to improve health related and psychological outcomes in this continuously growing population.

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COMPLIANCE WITH ETHICAL STANDARDS All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.”

CONFLICT OF INTEREST The authors declare that they have no conflict of interest.

INFORMED CONSENT Informed consent was obtained from all individual participants included in the study.

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