

The impact of infertility and physical late effects on psycho-social well-being of long-term childhood cancer survivors: A cross-sectional study

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ARTICLE INFO

Keywords:

Childhood cancer survivors
Late effects
Infertility
Psychosocial functioning
Health Related Quality of Life

ABSTRACT

Introduction: Describe how physical late effects, and particularly fertility, impact on the psycho-social well-being (anxiety, depression and perception of HRQoL) in a cohort of childhood cancer survivors (CCS).

Methods: Eligibility criteria: a) cancer diagnosis at age < 18 years; b) off-therapy > 5 years; c) age at the time of the study > 18 years and < 35 years. CCS with severe cognitive impairment, psychiatric disorders, or conditions otherwise hampering the participation to the study were excluded. Psychological evaluation included Hamilton Rating Scale for Anxiety (HAM-A), Montgomery-Asberg Depression Scale (MADRS), Satisfaction-Profile (SAT-P) and Short Form Health Survey (SF-36). Late effects have been grouped using the St Jude Lifetime Cohort Study-modified version of the National Cancer Institute's CTCAE version 4.03.

Results: 205 CCS were included (response rate: 80.08%; 58.05% male, 40.00% between 18 and 24 years at the time of the study, 74.36% diagnosis of hematologic malignancies). Moderate or severe anxiety was found in only 3.90% of CCS. More than 35% reported depressive symptoms. The prevalence of any grade of anxiety or depression increases with the increasing of the number of late effects (from 4.08% to 17.14% and from 24.49% to 42.86%, respectively). At least mild depressive symptoms have been reported by 56.33% of CCS affected by reproductive/genital late effects. Reproductive/genital late effect ($p = 0.001$) and female gender ($p = 0.002$) significantly predict the risk of depression. CCS with 2 or more late effects and those with reproductive/genital late effects reported a reduced satisfaction in psychological and physical function.

Discussion: CCS globally show a satisfactory psychological health, but infertility or a high number of physical late effects enhance the risk of depression and impaired HRQoL.

1. Introduction

Recent improvements in medical procedures have contributed to increase considerably the survival of childhood cancer, allowing today

an overall 5-year survival rate of about 85% [1]. Despite this success of pediatric oncology, Childhood Cancer Survivors (CCS) are at increased risk of developing long-term medical conditions mostly caused by their curative therapies [2–7].

Abbreviations: CCS, Childhood Cancer Survivors; CLME, Categories of system-based chronic and Late Medical Health Events; HAM-A, Hamilton Rating Scale for Anxiety; MADRS, Montgomery-Asberg Depression Scale; SAT-P, Satisfaction Profile; SF-36, Short Form Health Survey; HRQoL, Health Related Quality of Life; PCS, Physical health Component Score; MCS, Mental health Component Score.

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<https://doi.org/10.1016/j.ejcped.2023.100025>

Received 7 April 2023; Received in revised form 25 July 2023; Accepted 4 August 2023

Available online 6 August 2023

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Beside physical late effects, a growing number of reports focus on the long-term impact of pediatric cancer on CCS' psychological status and social outcome. Although most CCS have a good psychosocial functioning, some subgroups refer symptoms related to depression, anxiety, distress, somatization, and post-traumatic stress disorder [8–13]. Additional critical issues involve low self-esteem, social relationships, educational achievements, employment status, and lifestyle, which represent crucial factors for independence and individuality development [8,14–18].

Several studies investigated the impact of childhood cancer on the survivors' Health Related Quality of Life (HRQoL) and mental health, but the different and heterogeneous methodologies used make it difficult to clearly identify the causal factors affecting HRQoL of CCS [17,19,20].

Specific factors associated with poor mental health in CCS are diagnosis of brain tumor, older age at cancer diagnosis, the number of late effects or the presence of some specific late effect [9,15,17,19,21,22]. Despite such evidence, the mutual interconnections between the actual health condition (late effects) and the psychological outcome of CCS still need to be further elucidated [8,11,23–28].

Several studies report that suspected or confirmed infertility is often experienced by CCS as a top concern and a source of worry, involving various negative emotions as distress and anxiety [29–32]. Moreover, establishing or maintaining a romantic relationship can be hindered by infertility due to the fear of or the actual rejection from partners [29,33]. Some CCS also have distorted beliefs about their fertility situation: some may continue to have hope even if infertility has been diagnosed, while others are still anxious despite being fertile [29,30,34]. Finally, there is a gender difference about fertility in CCS. Indeed, females are more likely than males to report emotional distress and lower HRQoL because of their risk of fertility. Conversely, males are more likely to receive clear information about the potential impact of cancer therapies on fertility, and for them fertility testing - through semen analysis - is relatively more certain [29,30,32].

Based on these evidences, the aim of this study is to identify the factors correlated with psycho-social vulnerability in our cohort of CCS. Particularly, our hypothesis for this study is that having reproductive/genital late effects (e.g. infertility) impact worse on psycho-social wellbeing (explored in terms of anxiety, depression and self-perception of HRQoL) than having a higher number of late effects.

2. Methods

2.1. Study design and participants

CCS were enrolled between September 2018 and September 2019 at the Transition Unit for Childhood Cancer Survivors, Città della Salute e della Scienza Hospital in Turin, Italy. Demographic and clinical characteristics of this cohort have been previously published [7]. All clinical data (cancer diagnosis, therapies, relapses, second tumors, late toxicities, etc.) of CCS followed at the Transition Unit are recorded in a dedicated database, which is regularly updated during follow-up visits [7].

The eligibility criteria for this study were: a) cancer diagnosis at age < 18 years; b) off-therapy > 5 years; c) age at the time of the study > 18 years and < 35 years. Survivors with severe cognitive impairment, severe psychiatric disorders, or conditions otherwise hampering the participation to the study (e.g., blindness) were excluded.

The present research complies with the Declaration of Helsinki and was approved by the competent Ethical Committee Ethical Committee of A.O.U. Città della Salute e della Scienza di Torino (protocol number 0098534, 24th September 2018). A written informed consent was obtained from all participants.

2.2. Measures

During routine follow-up visits, after the collection of informed consent, a psychologist administered two questionnaires (*Hamilton Rating Scale for Anxiety* and *Montgomery-Asberg Depression Scale*). After that evaluation, the survivor filled two more questionnaires by himself (*Satisfaction Profile* and *Short Form Health Survey*).

The *Hamilton Rating Scale for Anxiety* (HAM-A), a standardized clinical scale designed to assess the severity of anxiety symptoms by an evaluator. The scale is composed of 14 items, scored on a scale from 0 (not present) to 4 (severe). Scores < 17 indicate mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe. Cronbach's α and the intraclass correlation measure of interrater reliability for the HAM-A were 0.86 and 0.92 respectively [35].

The *Montgomery-Asberg Depression Scale* (MADRS), a standardized clinical scale, which measures the patients' general level of depression exploring several symptoms. Each item of the scale is scored by a clinical evaluator between 0 and 6. Usual cut-off scores are: 0–6 (normal/symptom absent), 7–19 (mild depression), 20–34 (moderate depression), and > 34 (severe depression). Cronbach's α and the intraclass correlation measure of interrater reliability for the MADRS were 0.84 and 0.78 respectively [36].

The *Satisfaction Profile* (SAT-P), a questionnaire which investigates the subjective satisfaction among several domains of daily life. It is composed of 32 items and 5 subscales: Psychological functioning, Physical functioning, Work, Sleep/eating/leisure, and Social functioning. For each item the subject must evaluate their personal satisfaction in the last month on a 10-cm horizontal scale, ranging from "extremely dissatisfied" to "extremely satisfied". It provides an analytic scoring (32 scores, one for each item) and a factorial scoring (5 scores, one for each subscale). Higher scores indicate better satisfaction of life (range 0–100) [37–39].

The *Short Form Health Survey* (SF-36), a questionnaire widely used to assess health-related quality of life (HRQoL), well-being, and general health. It has also been validated and already used in population of long-term childhood cancer survivors [22,24,40]. The SF-36 consists of 36 items and eight related subscales that can be summarized in two indexes: the physical health component score (PCS) and the mental health component score (MCS). Higher scores in subscales indicate a better HRQoL (range 0–100) [10,22,24,40–42].

2.3. Statistical methods

The participants' socio-demographic and clinical characteristics were summarized using absolute and relative frequency.

Late effects have been grouped in categories of system-based chronic and late medical health events (CLME), using the St Jude Lifetime Cohort Study (SJLIFE) modified version of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, as follows: cardiovascular, endocrine, musculoskeletal, neurologic, pulmonary, reproductive/genital, and other late effects (which include auditory-hearing, gastrointestinal, hepatobiliary, hematologic, immunologic, infectious, ocular/visual, and renal/urinary late effects). Late effects' severity has been classified in mild (grade 1), moderate (grade 2), severe or disabling (grade 3), life-threatening (grade 4), or death (grade 5) [31]. Despite the low impact on health compared to that on emotional well-being, we separately analyzed the impact of reproductive/genital late effects on psycho-social well-being.

In order to describe associations between late effects and physical, social, and psychological well-being we reported:

- absolute and relative frequencies of anxiety level (defined by HAM-A) and of depression level (defined by MADRS) according to the presence of late effect;
- the median and interquartile range of the HAM-A, MADRS, and SAT-P scale and SF-36 components according to the late effects.

To explore the impact of the number of organs/systems affected by late effects (in terms of CLME) on depressive mood, we estimated crude and adjusted odd ratios (ORs) by logistic models. We considered sex, age at interview, and age at the first cancer diagnosis as confounders, and we included them in the model, beyond the presence of late effect.

3. Results

Two hundred ninety-one subjects underwent regular follow-up visits at the Transition Unit for Childhood Cancer Survivors between September 2018 and September 2019. Thirty-five survivors (12.03%) did not meet the inclusion criteria, while fifty one (17.52%) refused to participate to the study, so the final sample consisted of 205 CCS (response rate: 80.08%) (Fig. 1). The survivors' characteristics according to the participation in the study are reported in Supporting Information S1.

The mean age of CCS at the time of the study was 26.6 ± 4.6 years. Almost half of them were single, about 60% were still living with their family of origin, and 62.93% of them were employed. The most frequent cancer diagnoses were hematologic malignancies (74.63%). One hundred and fifty-six of our CCS (76.1%) had at least one late effect. The participants' demographic and clinical characteristics are detailed in Table 1.

As reported in Table 2, almost 90% (n = 184) of the sample did not refer anxiety. Anxiety was found to be mild in 6.34% (n = 13) of participants and moderate in 2.93% (n = 6), while it was severe only in 2 survivors (0.98%). More than 35% (n = 73) of interviewed CCS reported mild depression, whereas moderate or severe depression was found in 4.88% (n = 10) and in 0.49% (n = 1) of them, respectively (Table 2). Detailed information about answers for each item of HAM-A (panel A) and of MADRS (panel B) are shown in Fig. 2.

Most of participants without late effects had normal levels of anxiety (95.92%; n = 47) and depression (75.51%; n = 37). The prevalence of any grade of anxiety increases from less than 5% in CCS without late effects to 17.14% in those with 2 or more late effects. Also, the prevalence of depressive symptoms increases with the increasing of the number of late effects (from 24.49% to 42.86%).

As for reproductive/genital late effects, more than one half of affected CCS (n = 40, 56.33%) had at least mild depressive symptoms.

Indeed, CCS with reproductive/genital late effect showed higher median MADRS score (8 vs 4 when compared to CCS without late effects; 8 vs 5 when compared to CCS with at least one late effect (p = 0.002) (Table 2). Lowest median scores in psychological and physical functioning subscales of SAT-P were observed in CCS affected by 2 or more

Table 1
Demographic and clinical characteristics.

	No.	%
Sex		
Female	86	41,95
Male	119	58,05
Age at the time of the study (years) – median (26 ± 4.6 y) and interquartile range (23–30 y)		
Age at the time of the study (years)		
18–24	82	40,00
25–29	67	32,68
≥ 30	56	27,32
Relationship status		
Single	102	49,76
Partnership	84	40,98
Married	17	8,29
Separated	2	0,98
Cohabitation		
With family of origin	127	61,95
With own family and/or own partner	45	21,95
With roommates	18	8,78
Alone	15	7,32
Education		
Middle school	32	15,61
High school	129	62,93
University or higher	44	21,46
Employment status		
Student	49	23,90
Unemployed	27	13,17
Employed	129	62,93
Others	9	4,39
Age at the first cancer diagnosis (years) median (9.9 y) and interquartile range (4.7–13.0 y)		
Age at the first cancer diagnosis (years)		
0–4	54	26,34
5–9	49	23,90
10–18	102	49,76
Era of the first cancer diagnosis		
1985–1989	9	4,39
1990–1999	61	29,76
2000–2012	135	65,85
Cancer diagnosis		
<i>Hematologic Malignancies</i>	153	74,63
ALL	73	35,61
Hodgkin Lymphoma	32	15,61
Non- Hodgkin Lymphoma	20	9,76
AML and myelodysplastic syndrome	25	12,20
Others	3	1,46
<i>Brain tumors</i>	18	8,78
<i>Sarcomas</i>	25	12,20
<i>Others</i>	9	4,39
Any radiation	99	48,29
Any surgery	57	27,80
Hematopoietic Stem Cell Transplantation	61	29,76
Reproductive/genital late effects		
No	134	65,37
Moderate	13	6,34
Severe	58	28,29
Endocrine late effects		
No	87	42,44
Moderate	107	52,2
Severe	11	5,37
Cardiovascular late effects		
No	151	73,66
Moderate	53	25,85
Severe	1	0,49
Pulmonary late effects		
No	203	99,02
Moderate	1	0,49
Severe	1	0,49
Neurological late effects		
No	186	90,73
Moderate	15	7,32
Severe	4	1,95
Musculoskeletal late effects		
No	183	89,27
Moderate	17	8,29

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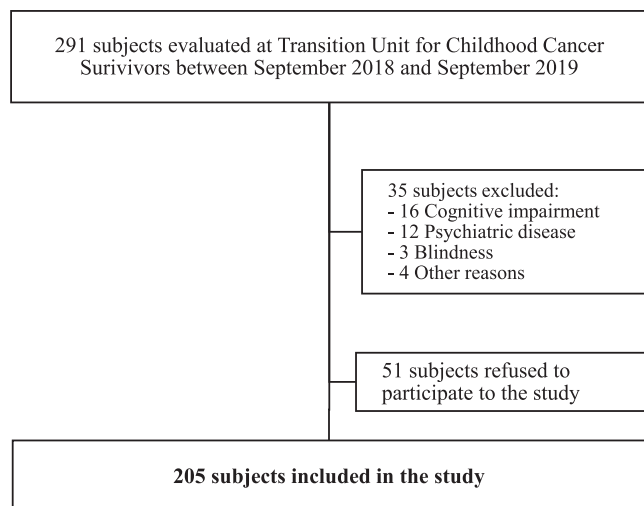


Fig. 1. Inclusion process of participants.

Table 1 (continued)

	No.	%
Severe	5	2,44
Other late effects^a		
No	180	87,8
Moderate	20	9,76
Severe	5	2,44
Number of late effects		
None	49	23,9
1 Late effect	50	24,39
2+ late effects	35	17,07
Second Neoplasms		
No	185	90,24
Yes	20	9,76
Total	205	100

^a Auditory-hearing late effects, gastrointestinal late effects, hepatobiliary late effects, hematologic late effects, immunologic late effects, infectious late effects, ocular/visual late effects, renal/urinary late effects.

late effects and in those with reproductive/genital late effects, whereas no clear differences were observed in the remaining subscales.

Also, MCS synthetic index of SF-36 seemed to be slightly lower in survivors with reproductive/genital late effects compared with those without late effect, whereas no differences in PCS scores were observed (Table 2). Multivariate analysis confirmed the association between depression and the presence of reproductive/genital late effects (OR=4.50, 95% CI 1.91,10.60; p = 0.001) and the association between depression and female gender (OR=2.62 95% CI 1.41,4.88; p = 0.002) (Table 3). We also reported crude ORs of employment (unemployed OR=1.07 95% CI 0.54,2.10; p = 0.847; student OR=2.87 95% CI 1.22,6.77; p = 0.016) and relationship status (partnership OR= 0.44 95% CI 0.24,0.81; p = 0.008; married OR=0.92 95% CI 0.33,2.58; p = 0.880) in Supporting Information S2. These factors were not included in the model because they were associated with the age at interview factor.

4. Discussion

Our study shows that most long-term CCS have a good psychological functioning, but subgroups with emotional impairment were also detected. Moreover, our CCS revealed a good social inclusion, most of them being in a stable relationship, working or studying. These findings

Table 2
HAM-A, MADRS, SAT-P and SF-36 scores according with late effects.

	No late effect		1 late effect		2 or more late effects		Reproductive/genital late effects		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
HAM-A - [N %]										
Less than mild anxiety	47	95,92	44	88,00	29	82,86	64	90,14	184	89,76
Mild anxiety	1	2,04	3	6,00	4	11,43	5	7,04	13	6,34
Moderate anxiety	1	2,04	2	4,00	2	5,71	1	1,41	6	2,93
Severe anxiety	0	0,00	1	2,00	0	0,00	1	1,41	2	0,98
Total	49	100	50	100	35	100	71	100	205	100
MADRS - [N %]										
Normal/symptom absent	37	75,51	33	66,00	20	57,14	31	43,66	121	59,02
Mild depression	11	22,45	13	26,00	13	37,14	36	50,70	73	35,61
Moderate depression	1	2,04	3	6,00	2	5,71	4	5,63	10	4,88
Severe depression	0	0,00	1	2,00	0	0,00	0	0,00	1	0,49
Total	49	100	50	100	35	99,99	71	99,99	205	100
HAM-A - median [iqr]	5	[2;10]	9	[5;14]	6	[3;15]	8	[5;14]	7	[4;13]
MADRS - median [iqr]	4	[1;6]	5	[3;7]	5	[1-11]	8	[4;12]	5	[2;10]
Psychological Functioning (SAT-P) - median [iqr]	74,9	[64.2;79.7]	71,3	[60.2;78.9]	70,9	[56.1;79.5]	65	[51.9;75.4]	70,2	[56.8;78.4]
Physical Functioning (SAT-P) - median [iqr]	70,3	[58.7;79.2]	66,7	[58.0;79.7]	60,4	[50.3;72.0]	62,1	[50.2;76.6]	65,7	[54.5;76.9]
Work (SAT-P) - median [iqr]	72,4	[57.8;83.0]	73,5	[60.2-82.4]	68,6	[54.4;77.2]	71,4	[50.0-83.6]	72,4	[57.8;81.8]
Sleep/Eating/Leisure (SAT-P) - median [iqr]	66,2	[56.2;75.6]	63,7	[52.4;74.2]	65,8	[55.2;80.2]	65,2	[52.2;73.6]	65,2	[53.4;74.8]
Social Functioning (SAT-P) - median [iqr]	79,3	[68.0;83.9]	75	[64.0;85.7]	80,7	[69.0-90.0]	75,7	[63.3;88.7]	77,3	[66.0;88.7]
Physical component summary (SF-36) - median [iqr]	56,3	[53.6;59-1]	56,1	[52.8;58.9]	55,3	[37.8;57.1]	53,9	[47.1;57.1]	55,4	[50.0;58.0]
Mental component summary (SF-36) - median [iqr]	50,9	[45.5;54.6]	47,4	[38.7;53.9]	50,6	[44.7;55.7]	44,3	[36.1;50.6]	47,8	[39.0;53.4]

agree with studies reporting that CCS usually have a favorable psychosocial well-being [11,15,23,24,42].

Despite the overall good adaptation, we found that depressive symptoms are more frequent than anxious ones (over 40% and about 10%, respectively).

Even if previous reports are not univocal in declaring the prevalence of mood or anxiety disorders among CCS [25,43-45], our results can be explained considering that the chronic condition of being a CCS implies long-term periodical clinical controls (due to the risk of late effects), but rarely acute clinical events (potentially triggering anxious symptoms). For those diagnosed with cancer at a younger age, another possible explanation of low levels of anxiety could be that the critical and stressful period of cancer diagnosis and treatment has been faced by parents instead of survivors. Also, the psychological support provided during treatments may have helped patients to cope with the cancer diagnosis and following survivorship phase, minimizing as much as possible anxiety symptoms.

Our study confirms that women are at higher risk of depressive symptoms, similarly to what was reported among the general population [23,46].

A few studies systematically explored the correlation between the number of physical late effects and HRQoL [1,22,24,26-28]. Our initial research hypothesis seems to be confirmed since the cohort of survivors without late effects have lower levels of anxiety and/or depression when compared to those CCS with one or more late effects. Nonetheless, in our sample the presence of reproductive/genital (i.e. infertility) late effects strongly associates with depressive symptoms, confirming our assumption of the particular emotional impact of the infertility among survivors. This result is in line with previous literature that underlines the negative burden of infertility on CCS' psychological well-being [29,30,32] and reveals that the impact of infertility is stronger than that caused by having 2 or more physical late effects. This finding suggests that for CCS reproductive health seems more relevant than other health issues (e.g., cardiovascular disease, endocrinopathies, etc.).

The subjective perception of satisfaction about psychological and physical function seems to be inversely related to the number of late effects and to the presence of reproductive/genital late effects. Since SAT-P has never been used in CCS, we can't compare this result with those obtained in other CCS cohorts. Anyway, SAT-P has been frequently used to assess perception of HRQoL in patients affected by other chronic health conditions (e.g., chronic kidney or liver disease, heart failure)

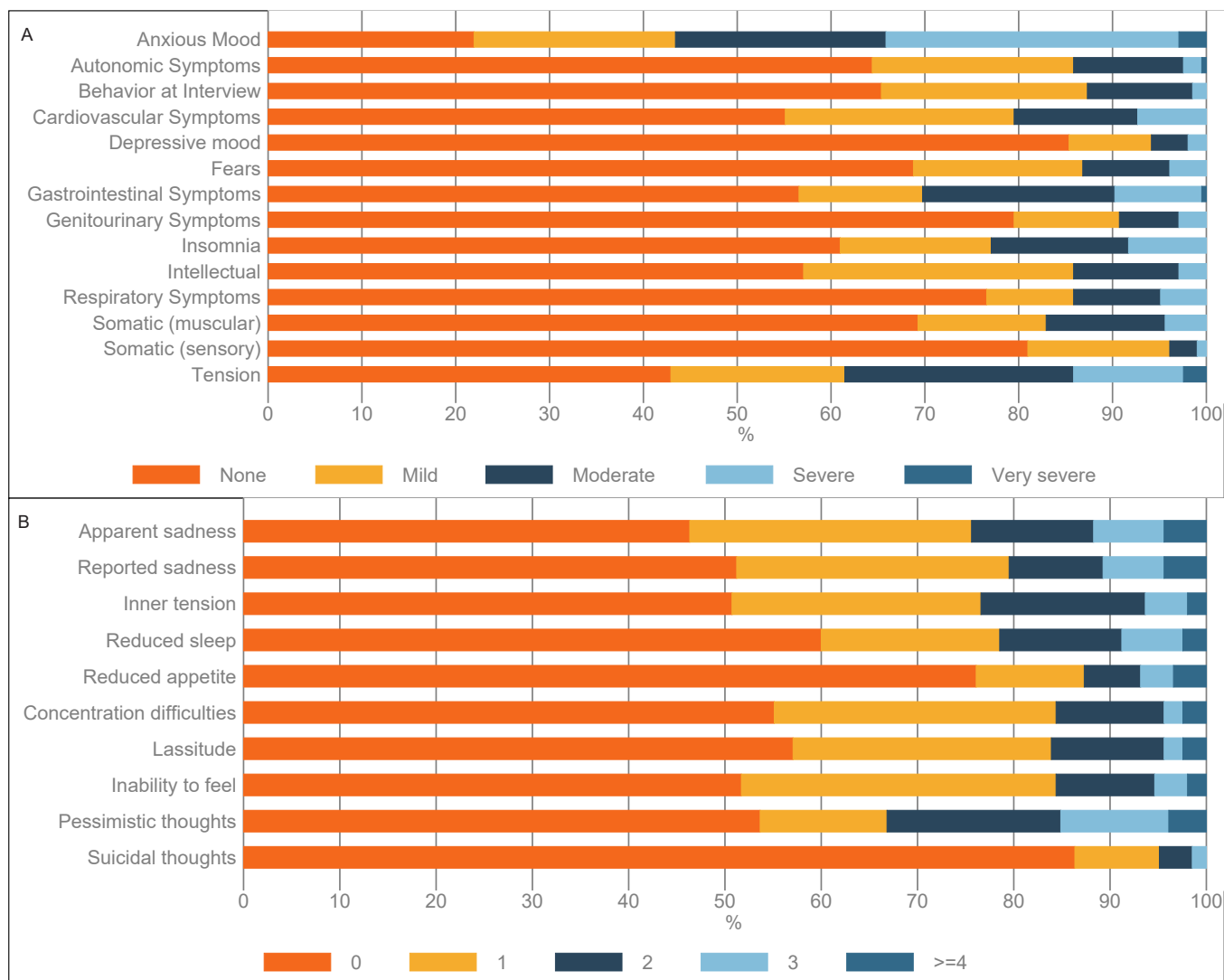


Fig. 2. HAM-A and MADRS results for each item.

Table 3
Crude and adjusted effects on depression.

	Crude effect			Adjusted effect		
	Or	95% CI	p	Or	95% CI	p
Sex (Female vs Male)	2,25	[1.27,3.98]	0,005	2,62	[1.41,4.88]	0,002
Age at time of the study (every 5 years)	1,02	[0.75,1.38]	0,917	0,88	[0.62,1.23]	0,441
Relationship						
Single	1					
Partnership	0,44	[0.24,0.81]	0,008			
Married	0,92	[0.33,2.58]	0,880			
Employment status						
Employed	1					
Unemployed	1,07	[0.54,2.10]	0,847			
Student	2,87	[1.22,6.77]	0,016			
Age at the first cancer diagnosis (years)						
0-4	1			1		
5-9	1,77	[0.79,3.96]	0,163	1,66	[0.70,3.95]	0,252
10-18	1,72	[0.86,3.44]	0,127	1,68	[0.80,3.53]	0,172
Hematopoietic stem cell transplantation	3,52	[1.88,6.58]	< 0.001			
Late effect						
None	1			1		
Reproductive/genital	3,98	[1.78,8.88]	0,001	4,50	[1.91,10.60]	0,001
1 late effect	1,59	[0.66,3.81]	0,300	1,39	[0.56,3.46]	0,476
2 or more late effects	2,31	[0.91,5.88]	0,079	2,07	[0.75,5.71]	0,159

[37,38]. On these bases, we can speculate that the good average levels of satisfaction referred by most of our survivors reflect the good adaptation to the presence of late effects as well as the fact that, for most of them the condition of being a survivor lasted for a long time (i.e., since their childhood).

The SF-36 questionnaire confirms that our CCS have an overall good perception of HRQoL, but the presence of reproductive/genital late effects again negatively impacts on mental health component score. Unfortunately, differences in study conceptions, as well as in the age of participants or follow-up duration, make it difficult to perfectly compare our findings to those of previous studies in which SF-36 was used [10,24,42].

This study has two major limitations, i.e. the impossibility to compare depressive reference values of our population with healthy young Italian population (due to the absence of evaluations performed using the same methods) and its cross-sectional design. Moreover, due to the exclusion of patients with severe neurocognitive disorders, our results likely have low efficacy in describing the psycho-social well-being of brain tumor survivors. Future researcher should consider also these vulnerable subgroups of survivors and the impact of late effects on their subjective well-being.

Nevertheless, the included survivors could be considered representative of the whole cohort of CCS followed at our unit, since we only small and not statistically significant differences in socio-demographic and medical characteristics between participants and not-participants survivors (Supporting Information S1). Also, physical late effects were classified through a validated method. Participants were assessed in both hetero-evaluated and self-administered modality, allowing us to give a global evaluation. Finally, we provide a clinical assessment of the survivors' psychological status and not only a qualitative assessment of their HRQoL [10,22].

In conclusion, we found that our CCS have an overall satisfactory psychological health. Among psychosocial dysfunctions, depressive symptoms are unveiled most frequently than anxious ones and they are heavily conditioned by the presence of reproductive/genital late effects.

Our results highlight the particular impact of late effects, especially infertility, on the psychosocial well-being of survivors. These concerns have to be addressed through dedicated support such as educational activities and conversations about this topic during survivorship care. It is a clinical duty to ensure that survivors are informed of their fertility risks, the availability of fertility preservation options, as well as offering guidance in finding reproductive specialists when needed. Finally, there is the need to involve mental health professionals to cope with the potential impact of late effects on the psychosocial well-being of these subjects.

Funding

No funding was received for this article.

Ethical approval

The present research complies with the Declaration of Helsinki and was approved by the competent Ethical Committee of A.O.U. Città della Salute e della Scienza di Torino (protocol number 0098534, 24th September 2018).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to acknowledge the U.G.I. (Unione Genitori

Italiani contro il tumore dei bambini), for the ongoing support to clinical and research activities of the Transition Unit for Childhood Cancer Survivors.

The authors would also acknowledge Professor Rosalba Rosato for her contribution to data interpretation.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejcped.2023.100025](https://doi.org/10.1016/j.ejcped.2023.100025).

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