

# Health-related quality of life in AYA cancer survivors who underwent HSCT compared with healthy peers

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## Abstract

This study was aimed at comparing adolescent and young adult (AYA) Hematopoietic Stem Cell Transplantation (HSCT) paediatric cancer survivors and a control group of healthy peers in terms of Health-Related Quality of Life (HRQOL) and frequency of posttraumatic stress symptoms (PTSS). The participants were 32 AYA HSCT survivors and 28 matched healthy peers. The survivors were, on average, 19.4 years old ( $SD = 3.8$ ), with an average age of 8.1 years ( $SD = 4.3$ ) at diagnosis, and with a mean time, since treatment was completed, of 8.5 years ( $SD = 3.2$ ). The majority of survivors (78.1%) did not show clinical PTSS, with intrusion symptoms most frequently reported in those who had undergone autologous HSCT ( $F = 3.3$ ;  $df = 2$ ;  $p = 0.05$ ) and relapse presence in their treatment associated with more PTSS avoidance symptoms ( $r = 0.4$ ;  $p = 0.002$ ). Women reported more problems in the SF-36 pain scale ( $t = 2.1$ ;  $df = 31$ ;  $p = 0.04$ ) than men. Additionally, 87.5% of survivors fell below the 25th percentile in the SF-36 general well-being scale, and 70.8% had the same trend for the SF-36 fatigue scale. Survivors reported better emotional well-being ( $t = 2.6$ ,  $df = 27$ ,  $p = 0.01$ ) and fewer limitations than their healthy peers ( $t = 2.5$ ,  $df = 27$ ,  $p = 0.02$ ), while they perceived a lower life satisfaction referring to the past ( $t = -2.8$ ,  $df = 27$ ,  $p = 0.009$ ).

## KEYWORDS

adolescent and young adult childhood cancer survivors, health-related quality of life, healthy peers, hematopoietic stem cell transplantation, posttraumatic stress symptoms

## 1 | INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) had become a primary form of therapy for many childhood cancer diseases, especially when other treatments had failed. The literature on medical and physical sequelae in childhood cancer HSCT survivors was very rich, while the literature on health-related quality of life (HRQOL) and psychological symptomatology as perceived

by patients and/or other observers was more limited (Reinfjell, Tremolada, & Zeltzer, 2017).

Childhood cancer survivors who had undergone HSCT mainly rated their long-term life satisfaction (Uderzo et al., 2012) and their overall HRQOL as comparable with norms or as similar among treatment groups, but bodily pain was reported as higher, while general health and self-esteem were lower (Forinder, Löf, & Winiarski, 2005; Schultz et al., 2014; Tremolada, Bonichini, Taverna, Basso, & Pillon,

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2017), especially by allogeneic recipients and those with active chronic graft versus hospice disease (GVHD) (Armenian et al., 2011). They showed lower educational attainment than their healthy peers (Bebis et al., 2013), especially those who received HSCT for haematological malignancies showed acute and chronic neurocognitive deficiencies (Shah et al., 2008) that could lead to more academic difficulties, resulting in less educational attainment (Freycon et al., 2014; Tremolada, Bonichini, Basso, & Pillon, 2016a).

Childhood HSCT survivors were at higher risk of psychological distress and poor HRQoL in the long term (Sinatora et al., 2017). Moreover, these difficulties appear to be exacerbated by the presence of specific sociodemographic factors, such as: female gender (Brice et al., 2011), older age at transplant (Barrera, Atenafu, & Hancock, 2009; Parsons et al., 2006; Phipps, Dunavant, Lensing, & Rai, 2002; Vrijmoet-Wiersma et al., 2009), lower educational attainment (Barrera et al., 2009; Phipps et al., 2002), lower socioeconomic status (Barrera et al., 2009; Phipps et al., 2002), and unemployment (Sundberg, Wettergren, Frisk, & Arvidson, 2013).

Among the psychological factors identified as associated with lower HRQoL were distress symptoms (Kenzik, Huang, Rizzo, Shenkman, & Wingard, 2015), pre-existing anxiety and/or depression, reduced communication (Felder-Puig et al., 2006), and cancer-related anxiety and fear, which were especially high for unrelated donor HSCT recipients (Armenian et al., 2011). Depressive symptoms impacted on mental HRQoL more than physical HRQoL (Kenzik et al., 2015), especially among allogeneic HSCT survivors (Schultz et al., 2014). Higher scores in psychopathology were reported by childhood cancer survivors for somatic symptoms also comparing with healthy peers, suggesting both the presence of actual long-term somatic sequelae after treatment or a possible decrease in pain tolerance (Zanato et al., 2017).

Most adolescent and young adult childhood cancer survivors were well adjusted. However, in early adulthood, they could show full or partial criteria of posttraumatic stress disorder (PTSD) when compared with healthy peers (Schwartz & Drotar, 2006). Women who were single and with less social support were more at risk for PTSD (Stuber et al., 2011). In an Italian group of AYA paediatric cancer survivors, the prevalence of PTSS was about 21%. Specifically, 10% of ex-patients belonged to a clinical category, while 11% could be classified as subclinical (Tremolada, Bonichini, Basso, & Pillon, 2016b; Tremolada et al., 2016a).

Basing on these findings, we formulated the following hypotheses:

1. We expected that HSCT childhood cancer survivors would show less educational attainment than their healthy peers, following the results on acute and chronic neurocognitive deficiencies that could lead to more academic difficulties, resulting in less schooling years.
2. The range of the PTSS severity percentage in childhood cancer survivors was recognised between 9% and 11% in an Italian sample of childhood cancer survivors, so we wanted to screen these psychopathology indexes in AYA survivors who had undergone HSCT expecting to find higher incidence.

3. We hypothesised that survivors could have a good general satisfaction with their lives, showing a medium-high score measured with the ladder of life questionnaire. The ladder of life is a subjective well-being measure, which in other studies on PTSS in mothers of children with cancer (i.e., Tremolada, Bonichini, Schiavo, & Pillon, 2012) has been significantly associated with other specific symptomatology scales that assessed also depression.
4. We expected an HRQoL comparable with norms, with the exception of physical functioning, bodily pain, general health perception, and physical composite scores, which we hypothesised significantly lower than norms.
5. We expected that the following risk factors could be associated with higher PTSS, lower HRQoL, and ladder of life perceptions: female gender, older age at transplant, unrelated allogeneic donor transplant, haematological diagnosis, less time since HSCT, and lower years of schooling.

## 2 | METHODS

### 2.1 | Patients

All eligible HSCT survivors attending the Pediatric Hematology-Oncologic Clinic at the University of Padua in the period 2008–2012 were asked to take part in this project. Eligibility criteria included being cured for cancer by HSCT in paediatric age, at least 5 years from the stop of the therapies, and being currently 15–25 years old. We excluded childhood cancer survivors treated for brain tumours, those with sensory deficiencies or genetic syndromes, and those who were unable to complete the questionnaires autonomously.

The participants in this study included exclusively adolescent young adult (AYA) HSCT childhood survivors ( $N = 32$ ), recruited during follow-up visits, and matched healthy peers ( $N = 28$ ), recruited from secondary schools, youth groups, and a university in the same geographic area. A clinical researcher showed to the teachers of the schools, to the educators in the youth groups, and to the professors at university the parallel project entitled “Psycho-social wellbeing in adolescents and young adults” during the school meeting of teachers with parents or specific appointments. The principal investigator clarified the objectives of this study to the participants: to have information of psychosocial well-being of healthy adolescents and young adults to compare with those of childhood cancer survivors to implement the psychosocial interventions. Control group participants must have these characteristics: no history of chronic illness or injury and an absence of sensory deficiencies and other pathological aspects. Informed consent was obtained from parents if the adolescents were under 18 years old and directly from young adults aged more than 18 years old.

The participants were all Caucasian and had a mean age of 19.39 years ( $SD = 3.84$ ). Seventeen were men, with an average age of 8.15 years ( $SD = 4.34$ ) at diagnosis and off therapy from an average of 8.53 years. The participants filled in the self-report questionnaires SF-36, ladder of life, and PTSD scale. Sociodemographic

**TABLE 1** Sociodemographic characteristics of the participants

	HSCT childhood survivors (N = 32)		Matched healthy peers (N = 28)			
		Frequency	%	Frequency	%	
Gender	Males	17	53.1	Males	16	57.1
	Females	15	46.9	Females	12	42.9
Diagnosis type	Haematological tumours (Leukaemias, non-Hodgkin lymphomas)	21	65.6			
	Solid tumours (Hodgkin lymphomas, solid tissue, other)	11	34.4			
Education	0–8 years of schooling	9	28.1	0–8 years of schooling	11	39.3
	9–13 years of schooling	21	65.6	9–13 years of schooling	13	46.4
	>13 years of schooling	1	3.1	>13 years of schooling	2	7.1
	Not reported	1	3.1	Not reported	2	7.1
Relationship status	Engaged	19	59.4	Engaged	10	35.7
	Single	6	18.8	Single	17	60.7
	Not reported	7	21.9	Not reported	1	3.6
Economic situation perceived	Low	1	3.1	Low	1	3.6
	Medium	14	43.8	Medium	9	32.1
	High	15	46.9	High	18	64.3
	Not reported	2	6.3	Not reported	0	
Employment	Not working, student	19	59.4	Not working, student	24	85.7
	Looking for a job	4	12.5	Looking for a job	0	14.3
	Part-time	2	6.3	Part-time	4	
	Full-time	7	21.9	Full-time	0	
		<b>Mean</b>	<b>SD</b>		<b>Mean</b>	<b>SD</b>
Age at diagnosis	Range from 0.4 to 16.1	8.1	4.3			
Current age	Range from 14.1 to 25	19.4	3.84	Range from 14.1 to 25	18.9	2.9
Years from end of therapy	Range from 5 to 16	8.5	3.2			

and medical information was also collected. Table 1 illustrates the participants' sociodemographic and medical information.

## 2.2 | Procedure

Ethical approval was obtained from the Hospital of Padua Ethical committee. The day before the follow-up appointment at the Day Hospital of the Clinic, the clinical psychologist telephoned each survivor to explain the study and to obtain verbal participation consent to the study. This was a strategic way to obtain the participation in the present study, as the survivors had the possibility to do all during the same day of their follow-up without needing to come in another specific appointment just for the research. If the HSCT childhood survivors were <18 years old, the psychologist contacted the parent. Upon their arrival at the clinic, a pack that included information about the study, a consent form, and the battery of questionnaires were given to the HSCT childhood survivors. The written consent form was signed by the AYA participants or, in the case of those younger than 18 years of age, by their parents. The participants gave back the questionnaires in

stamped addressed envelopes or electronically using a protected online site.

## 2.3 | Instruments

### 2.3.1 | Medical outcomes study 36-item short-form health survey (SF-36)

This was a short-form health questionnaire with 36 items related to HRQOL. It consisted of eight-scale profile of functional health and well-being. There were also physical and mental health global measures. The eight scales were physical functioning, role limitations resulting from physical health problems, emotional well-being, role limitations resulting from emotional problems, social functioning, fatigue, bodily pain, and general health perception. Scores on each scale range from 0 to 100, with a score of 100 indicating the highest report of health. This questionnaire had been validated for the Italian population, but only for adults. It had not yet been validated for adolescents (15–17 years old), but we adopted it to compare the two groups—HSCT childhood survivors and matched healthy peers—and it was used in other studies

on HRQoL and perceived social support in childhood cancer survivors (Rueegg et al., 2013; Tremolada et al., 2016a).

### 2.3.2 | The PTSD symptom checklist

This was a 17-item checklist assessing the amount of symptoms of PTSD that may be reported in childhood cancer survivors after the experience of a cancer diagnosis. It was an adapted version of Manne, Du Hamel, Gallelli, Sorgen, and Redd (1998) and it was used also in the CCSS cohort (Stuber et al., 2010; Zebrack et al., 2004). Participants reported the presence/absence of their difficult experiences in their lives in the last month. These 17 items were divided into three scales: Intrusion (five items), Avoidance (seven items), and Arousal (five items) symptoms (DSM-V). Cut-off scores for symptom severity were  $\leq 5$  = not diagnostic of the disorder, 6–8 = moderate presence of the disorder, and  $> 9$  = marked severity (Frederick, 1985). Adopting the full continuum of PTSS assessed by a self-report could give more useful information than using PTSD diagnostic criteria. This survey had been administered to Italian parents of children with cancer (Tremolada et al., 2013) and to an Italian cohort of childhood cancer survivors (Tremolada et al., 2016b), demonstrating good internal consistency.

### 2.3.3 | Ladder of life

The participants had to evaluate, filling in a 1–10-point scale, their perceptions of present life, the quality of their life 5 years before, and how satisfying their life will be in the future (5 years later). The instructions given to subjects were the following: "Please imagine a ladder with steps numbered from zero at the bottom to ten at the top. Suppose we say that the top of the ladder represents the best possible life for you and the bottom of the ladder represents the worst possible life for you. If the top step is 10 and the bottom step is 0, on which step of the ladder do you feel you personally stand at the present time/five years ago/in the next five years?"

This instrument was placed in the Childhood Cancer Survivor Study Questionnaires (<https://ccss.stjude.org/tools-and-documents/questionnaires.html>) battery and could give us information about individual life perceptions of the past, the present, and the future. It had been administered to a sample of Italian mothers of children with cancer, demonstrating good global internal consistency (Tremolada et al., 2013).

## 2.4 | Statistical methods

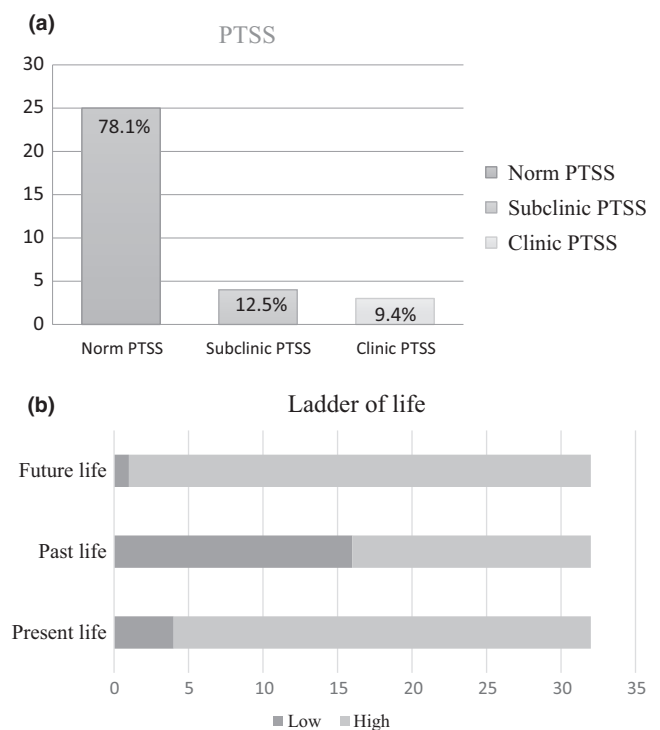
A paired sample *t* test was used to estimate the possible sociodemographic differences between the two samples and to better understand the comparability of the samples. The two groups were matched along gender and age and a file created with the matched clinical and control groups. Descriptive measures of central tendency and variability were computed for all relevant variables and comparisons made between the two groups. Inferential comparisons were made between cancer survivors and control

samples using a paired sample *t* test with a Bonferroni correction. We ran preliminary Pearson bivariate correlations to find the possible significant associations between the examined variables. Then, a series of analysis of variance (independent sample—test or ANCOVAS) was run to identify predictors of HRQOL outcomes, ladder of life perceptions, and PTSS in AYA cancer survivors who had undergone HSCT. The independent fixed variables included in the analysis were type of HSCT (autologous, unrelated unknown donor, related donor), perceived economic situation (low-medium/high), and gender (women versus men). The covariates were off-therapy years, age at diagnosis, and current age. We excluded the variables that did not emerge as significant predictors in the correlations. The dependent variables were the eight HRQOL scales, the three ladder of life scores, and the PTSS sum score. Hierarchical regression analyses were run exclusively for those variables that obtained a preliminary strong significant correlation *r* value. Statistical significance was evaluated at the nominal  $p = 0.05$  level, with adjustments for multiple comparisons, after controlling the normal distribution of the test scores and the homogeneity of variances.

## 3 | RESULTS

### 3.1 | Sociodemographic comparability between the HSCT childhood survivors and the healthy matched peers

Adopting paired-sample *t* tests, no significant differences were found between the two groups along sociodemographic factors,



**FIGURE 1** PTSS (a) and Ladder of life perceptions (b) in HSCT childhood survivors

except for the schooling years ( $t = -2$ ,  $df = 27$ ,  $p = 0.05$ ), with the HSCT childhood survivors showing lower mean frequencies ( $M = 13$ ;  $DS = 2.5$ ) than those of the healthy peers ( $M = 13.8$ ;  $DS = 2.5$ ). This result is in line with the findings of previous studies (Berbis et al., 2013; Freycon et al., 2014; Shah et al., 2008), where the neurocognitive sequelae and academic difficulties in the childhood cancer survivors resulted in less educational attainment.

### 3.2 | Posttraumatic stress symptomatology and life perceptions in HSCT childhood survivors

Most of HSCT childhood survivors showed an absence of marked PTSS severity (78.1%; scoring  $\leq 5$ ), followed by those that entered a subclinic presence of disturbance (12.5%; scoring: 6-8) and those with a clinical profile (9.4%; scoring:  $>9$ ) (Figure 1a).

Ladder of life scores that measured life perceptions were categorised into low (1-5) and high (6-10) levels, and the distribution was principally high in both the present life (90.6%) and the future life (93.7%), while the past life perception was equally distributed between low and high levels (Figure 1b).

### 3.3 | Health-related quality of life reported by HSCT childhood survivors adopting percentiles

The HSCT childhood survivors ( $N = 24$ ) were distributed in their HRQOL reports along three levels, following Italian norms:  $\leq 25$ th percentile, 50th percentile, and  $\geq 75$ th percentile. General health perception, fatigue, and social functioning were the HRQOL scales in which they reported mostly the lower level of  $\leq 25$ th percentile. Additionally, 45.83% of them reported lower levels of emotional well-being and role limitations related to this area,

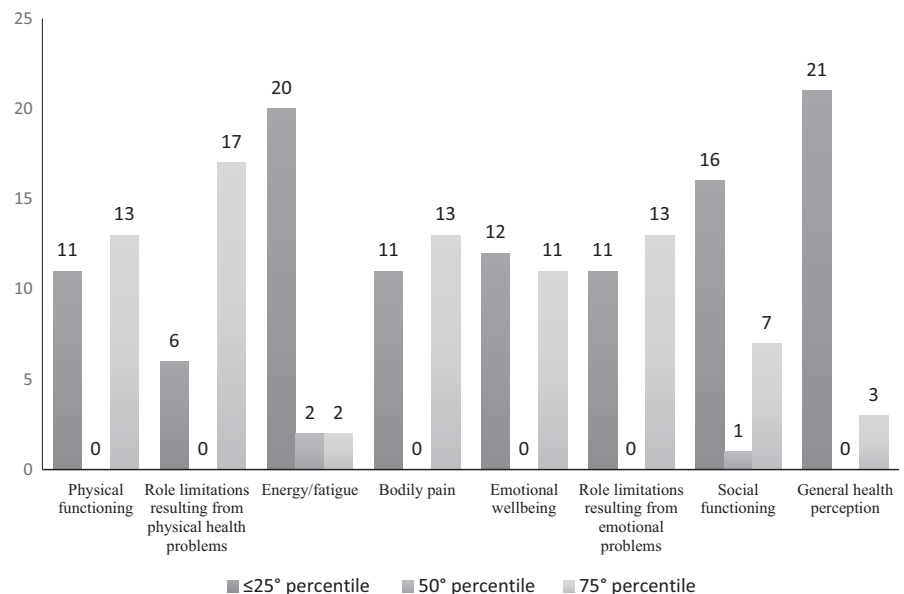
physical functioning, and bodily pain. Figure 2 illustrates HRQOL scales' scores distributed along percentiles.

### 3.4 | Comparison on HRQOL scores and Ladder of life scales between HSCT childhood survivors and healthy peers

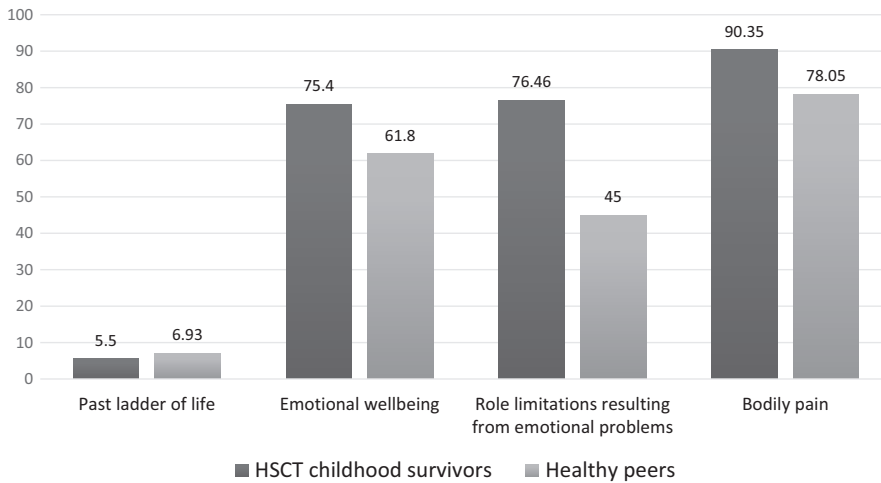
Comparing the HRQOL and ladder of life perceptions of the HSCT childhood survivors with those of healthy peers, there were statistically significant differences in terms of emotional well-being ( $t = 2.6$ ,  $df = 27$ ,  $p = 0.01$ ) and role limitations due to emotional well-being ( $t = 2.5$ ,  $df = 27$ ,  $p = 0.02$ ). HSCT childhood survivors reported better emotional well-being ( $M = 75.4$ ,  $SD = 15.8$ ) and less associated limitations ( $M = 76.4$ ,  $SD = 36$ ) than their healthy peers ( $M = 61.8$ ,  $SD = 17.5$ ;  $M = 45$ ,  $SD = 40.8$ ), even if they reported a worse past life perception ( $t = -2.8$ ,  $df = 27$ ,  $p = 0.009$ ;  $M = 5.5$ ,  $SD = 2.3$ ) than their healthy peers ( $M = 6.9$ ,  $SD = 1.8$ ). HSCT childhood cancer survivors reported also better scores in pain scale ( $t = 2.2$ ;  $df = 27$ ;  $p = 0.03$ ;  $M = 90.3$ ,  $SD = 13.2$ ) than healthy peers ( $M = 78$ ,  $SD = 25.2$ ). Figure 3 shows HRQOL scales' scores and ladder of life scales of HSCT childhood cancer survivors compared with healthy peers.

### 3.5 | Risk factors associated with higher PTSS, lower HRQOL, and ladder of life perceptions in HSCT childhood survivors

Pearson's correlations were run between our variables. Years from the end of therapy were significantly associated with past life perception ( $r = 0.6$ ,  $p = 0.001$ ). Relapse in the treatment cycles of the ex-patients was associated with more PTSS avoidance symptoms ( $r = 0.4$ ,  $p = 0.002$ ).



**FIGURE 2** Health-related quality of life scales' scores reported by HSCT childhood survivors distributed along percentiles



**FIGURE 3** Health-related quality of life scales' scores, ladder of life scales, and education level (schooling years) of HSCT childhood cancer survivors compared with healthy peers

We assessed if there is a significant association between years of schooling and SF36 scales on HRQOL or PTSS, but we did not find any significant association.

Table 2 shows the Pearson's correlations between stable and observed variable.

A significant mean difference using an independent sample *t* test was found regarding HSCT childhood survivors' gender ( $t = 2.1$ ,  $df = 31$ ,  $p = 0.04$ ), with women reporting less bodily pain quality of life ( $M = 84.2$ ,  $DS = 15.6$ ) than men ( $M = 94.1$ ,  $DS = 10.9$ ).

A hierarchical regression analysis was run inserting in the first step the perceived economic situation, gender, and current age, and in the second step, age at diagnosis and years from end of therapy. The dependent variable was SF 36 social functioning scale. The first model was the best ( $R^2 = 0.3$ ;  $p = 0.03$ ) identifying perceived economic situation ( $\beta = 0.6$ ;  $p = 0.001$ ) and gender ( $\beta = -0.3$ ;  $p = 0.003$ ) as the significant predictors on social functioning.

An ANCOVA was run with PTSS intrusion symptoms as the dependent variable and type of HSCT and gender as independent variables. Covariates included in the model were age at diagnosis, actual age, and years since the end of therapy. The type of HSCT was the unique factor significantly associated with PTSS intrusion symptoms ( $F = 3.3$ ,  $df = 2$ ,  $p = 0.05$ ), with HSCT childhood survivors who had undergone unrelated allogeneic HSCT showing less symptoms ( $M = 0.3$ , CI: from  $-0.7$  to  $1.3$ ) than those cured with autologous HSCT ( $M = 1.9$ , CI: from  $1.1$  to  $2.7$ ) or related donor allogeneic HSCT ( $M = 1.5$ ; CI: from  $0.3$  to  $1.6$ ).

## 4 | DISCUSSION

Improvements in the research on, and application of, hematopoietic stem cell transplant (HSCT) for paediatric cancer and blood disorders have led to a concomitant increase in survivorship. But what about the quality of life, the life satisfaction, and the psychological posttraumatic symptoms of healed patients when they become adolescents or young adults? This is a dramatic experience, and it could leave some negative signs in young lives (Bonichini, Tremolada, Pillon, Aloisio, & Messina, 2012).

This study aimed at understanding the HRQOL and life satisfaction in AYA paediatric cancer survivors who had undergone HSCT, comparing their scores with those of matched peers who had no history of serious illness. Possible risk factors associated with poor psychological and quality of life functioning were also identified.

Some findings of this study were partially concordant with the precedent studies on this topic. Some others seemed to take other directions.

First, as reported in the literature (Berbis et al., 2013), the paediatric patients who received HSCT in this study had less educational attainment, assessed with the lower mean of schooling years, probably due to their lower social functioning and higher fatigue perceptions which could lead to more difficulties in the academic performance and to get ahead in their studies. In another Italian study that adopted a narrative approach (Tremolada, Bonichini, Taverna, Pillon, & Basso, 2018), the possible schooling difficulties in attention, socialisation, and fatigue were reported by AYA cancer survivors.

Second, a minority (9.4%) of ex-patients showed a clinical presence of a PTSD symptomatology, even if 12.5% fell in the subclinical category. Around a quarter (22%) of HSCT AYA childhood cancer survivors reported important posttraumatic symptoms due to their cancer experience. This symptomatology percentage is in line with what is reported in precedent studies (Bruce, 2006; Tremolada et al., 2016b).

Third, we assessed the life satisfaction towards the present, the past, and the future. Ladder of life measure is an estimation of own life that could be associated with possible depression symptomatology. Current life satisfaction in this sample was comparable with that of healthy peers, in line with what was reported in the study of Uderzo et al. (2012), except for the past life experience that was lower in the healthy peers. The past 5-year period was associated with the cancer treatment and HSCT experience, so, of course, these adolescent and young survivors reported a lower life perception than healthy peers.

Regarding the hypothesis on HRQOL measures assessed by SF-36 survey, we found that the majority of young adult people cured

**TABLE 2** Pearson's correlations between stable and observed variables (*r* and *p*-value)

	Role limitations			Role limitation			PTSS total	PTSS intrusion	PTSS avoidance	PTSS arousal			
	Physical functioning SF36	Energy-fatigue SF36	Bodily pain SF36	Emotional wellbeing SF36	Social functioning SF36	General wellbeing SF36					Present ladder of life	Past ladder of life	Future ladder of life
Gender	0.043	-0.030	-0.359*	-0.192	0.047	-0.210	0.243	0.208	-0.085	0.223	0.010	0.254	-0.056
	0.814	0.869	0.411	0.291	0.798	0.248	0.180	0.254	0.655	0.219	0.957	0.160	0.761
Present age	-0.127	-0.113	0.081	-0.114	-0.056	-0.236	-0.038	-0.056	-0.001	0.088	0.279	0.027	0.156
	0.488	0.539	0.659	0.535	0.762	0.193	0.837	0.762	0.995	0.634	0.123	0.882	0.393
Age at diagnosis	-0.002	0.271	0.218	0.008	0.177	-0.105	-0.088	-0.521	0.135	-0.006	0.268	-0.010	0.188
	0.992	0.134	0.230	0.966	0.332	0.568	0.630	0.002	0.478	0.976	0.139	0.958	0.303
Diagnosis type	0.132	-0.098	-0.106	-0.182	-0.069	0.069	0.017	-0.305	0.015	0.311	0.137	0.144	0.188
	0.472	0.594	0.818	0.319	0.707	0.709	0.927	0.089	0.937	0.083	0.455	0.432	0.304
Years from end of therapy	-0.141	-0.143	-0.170	-0.014	-0.007	0.149	0.061	0.568**	-0.277	0.058	-0.045	0.076	-0.043
	0.442	0.435	0.351	0.939	0.968	0.416	0.739	0.001	0.139	0.751	0.805	0.677	0.814
Relapse (yes/no)	-0.122	-0.164	-0.077	-0.274	0.065	-0.175	0.116	0.042	0.041	0.262	-0.165	0.403*	-0.048
	0.505	0.371	0.677	0.129	0.725	0.339	0.527	0.820	0.829	0.147	0.366	0.022	0.793

\*Correlation significant at  $p < 0.05$ . \*\*Correlation significant at  $p < 0.01$ .

with HSCT for malignant disease in childhood declared lower health status perceptions compared with norms in SF-36 scales (below 25th percentile), especially with regard to fatigue (83%), social functioning (66.6%), and general well-being (87.5%). These results were in line with in a series of studies about physical and general health limitations (Berbis et al., 2013; Forinder, Löf, & Winiarski, 2006; Schultz et al., 2014). Limited social functioning was found also in some studies reporting weak social relationships (van Dijk et al., 2008) or perceived social support (Tremolada et al., 2016a). However, if compared with a control group of healthy peers, HSCT-healed patients, in this case both adolescents and young adults, reported a higher level of emotional well-being, lower limitations related to this area, and less bodily pain. This was a quite new finding, because most studies showed more bodily pain (Berbis et al., 2013; Forinder et al., 2005), while emotional well-being was usually comparable with norms (Schultz et al., 2014; Uderzo et al., 2012), even though there was found the same result in a recent Italian study on a cohort of childhood cancer survivors (who did not exclusively undergo HSCT) (Tremolada et al., 2016a). HSCT experience was considered as potentially traumatic, even if off-therapy patients could manifest also resilience in coping with painful life events. This capacity could lead to an activation of psychological personal growth and benefit finding in their current lives (Tremolada et al., 2016b). The HSCT childhood cancer survivors could appreciate their lives more and cope better with life's adversities in a way that they could judge more positively their emotional well-being and pain perceptions, despite their effective health conditions.

Regarding the last point, we identified the possible risk factors associated with higher PTSS, lower HRQOL, and ladder of life perceptions. In this study, more years since the therapy time was a favourable factor for judging past life in a better light. A high economic condition and male gender were identified as protective factors in HRQOL perceptions related to social functioning, that represented findings coherent with those reported by several studies (Barrera et al., 2009; Phipps et al., 2002). Probably, the good economic status perception in HSCT childhood cancer survivors could lead to show less worries on social limitations in their lives. Particularly, women could report major expectations in their social relationships so that they could more easily show disappointment towards them. Other studies (Brice et al., 2011; Stuber et al., 2011) found that women reported lower HRQOL perceptions, while in this study only bodily pain was identified as lower domain.

The risk factor for intrusion PTSS identified in this study was to be treated with autologous HSCT rather than with unrelated allogeneic HSCT, while relapse in the treatment cycles impacted avoidance symptoms. Prior studies underlined only unrelated allogeneic donor transplant as associated with poor global HRQOL (Parsons et al., 2006; Phipps et al., 2002), but they did not report a specific significant association with posttraumatic symptoms. Future studies with larger samples could better understand the effect of the type of HSCT experience on psychological well-being, because the type of stress they had to cope with could be different and lead the patients to different psychological conditions, even when they were healed.

The experience of relapse probably led the AYA cancer survivors to have more avoidance symptoms because, inevitably, they perceived stress and negative feelings that could lead them to avoid all the people, things, and communication that could be a reminder of their traumatic experience.

The HRQOL domains (especially emotional well-being, social functioning, and physical well-being) were associated with the PTSS total score. This finding intended that posttraumatic symptomatology was higher in ex-patients who also declared a lower score in the key HRQOL domains: self-perceived health (both emotional and physical) and self-perceived social relationships. Present and future life perceptions were associated with HRQOL emotional well-being, showing how this simple and fast questionnaire could be a valid screening instrument to understand general mental health and intrusion and arousal PTSS. Other variables did not emerge as significant predictors, such as cancer diagnosis, time from the end of therapy, current age, and age at HSCT, as reported in the literature discussed above.

This study had several strengths. It was one of the first Italian studies on this topic; it took deep into consideration the direct reports of AYA cancer survivors; it showed encouraging results in terms of their perceived emotional well-being, while limited functions were reported in the physical area; and, once involving larger samples from different health centres, it could provide a screening questionnaires battery that could be useful to setup specific interventions for patients more at risk, especially in the domains of physical and social functioning, that is, intervening on the social re-entry for patients who end their therapies.

Limitations of the study involved the social desirability in the self-report, especially in adolescents. The use of in-depth interviews could control this limitation in future studies. It was necessary to increase the number of patients in order to better analyse the impact of medical variables (i.e., GVHD, type of HSCT) and to involve other medical centres to have a more homogenous sample throughout all Italian regions.

The final goal was to use that information to provide more targeted and functional intervention to paediatric patients out of therapy who had undergone bone marrow transplantation, identifying those most at risk of perceived problems at both the physical and psychological levels.

Possible interventions could focus on two directions: the first could be the implementing of motor skills functioning on children with cancer both during the treatment phase, when the therapies impacted negatively on their motor performance (Taverna et al., 2017), and also when they were off therapies, adopting a specific rehabilitative programme and paediatric occupational therapy to reduce their fatigue.

The second intervention direction could be to setup specialised psychological support to these patients when they came back to their normal schedules with a specific attention to social relationships and fatigue related to academic performances. Working memory- and attention-powered programmes could help them in their academic achievement. It is important to work also in synergy with residential schools to set up specific educational interventions

focused on survivors, on teachers, and on companions to facilitate a good scholastic re-entry managing the potential isolation and fatigue barriers.

Finally, their emotional strength and resilience could be helpful for overcoming possible posttraumatic symptomatology related to cancer and HCST. Group therapy sessions could be useful to understand better their feelings about the cancer experience, their social behaviours, and their schooling difficulties.

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