

Life Satisfaction in Young Adults 10 or More Years after Hematopoietic Stem Cell Transplantation for Childhood Malignant and Nonmalignant Diseases Does Not Show Significant Impairment Compared with Healthy Controls: A Case-Matched Study

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Patients undergoing hematopoietic stem cell transplantation (HSCT) may experience physical and psychological deterioration that impairs their life satisfaction (LS). This study focused on LS in long-term survivors at 10 or more years after HSCT. Fifty-five patients (39 males, median age 25 years) undergoing allogeneic HSCT for childhood malignant (n = 52) or nonmalignant diseases (n = 3) were enrolled. A control group of 98 young adults (59 males, median age 24 years) was considered. A questionnaire with a modified Satisfaction Life Domain Scale was administered. We assessed such domains as education, employment, leisure time, social relationships, and perception of physical status with a 30-item questionnaire. To investigate the association between the domains and the probability of diminished LS, we performed a logistical procedure using the maximum likelihood method. Predictive factors of LS were adjusted for sociodemographic variables. In the multivariate analysis, the participant's level of LS was not significantly correlated with sociodemographic factors or with HSCT status. The same analysis showed a slight trend in favor of the control group ($P = .06$) for body perception. Our data suggest that the patients who undergo HSCT in childhood have no significant difference in long-term LS compared with healthy controls.

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INTRODUCTION

The majority of previous clinical trials concerning childhood malignant and nonmalignant diseases have shown great improvement in short-term and long-term outcomes after chemotherapy or hematopoietic stem cell transplantation (HSCT) in recent years. In particular, studies conducted in the last decade have in-

dicated that total cure can be achieved in 60%-90% of pediatric patients with acute lymphoblastic leukemia or acute or chronic nonlymphoblastic leukemia [1-4]. Thus, there has been a strong interest in national and international studies on late effects after HSCT [5,6] and, more recently, on cognitive and behavioral outcomes [7]. HSCT recipients are an important group to consider for late physical and psychological deterioration that impairs quality of life (QOL) or life satisfaction (LS). LS is a subjective measure of satisfaction related to physical, cognitive, emotional, social functioning, and well-being [7,8].

Although some previous QOL and LS studies have been conducted with adult HSCT recipients [8,9-16], few well-documented reports have focused on these issues in childhood HSCT [17-19]. The principal purpose of the present pilot study was to evaluate health status and LS in young adult HSCT survivors to assess whether they are participating normally in social, family, educational, and employment contexts. A comparison with a healthy control group was used for clinical interpretation of the results and to identify specific

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risk factors that could impair the HSCT recipients' long-term LS.

PATIENTS AND METHODS

All patients diagnosed with a malignant or nonmalignant disease and treated by allogeneic HSCT in our center between 1985 and 1998 were contacted by mail or e-mail to elicit their participation in the study. The recruitment period was limited to 2 years.

Patients were eligible for enrollment who were disease-free after HSCT performed at least 10 years before the start of this study. Eligibility criteria also included any stem cell source or donor, as well as patient or parent/guardian written consent. Adolescents or young adults who met all of the inclusion criteria were approached to participate in the study at a scheduled checkup. In our center, a checkup is generally scheduled every 2 years for patients who survive for more than 10 years after HSCT. Medical and demographic parameters extracted from medical records included age, sex, type of HSCT, type of stem cell source and donor, conditioning regimen, and post-HSCT complications, including graft-versus-host disease (GVHD) and late effects. Patients were given a written questionnaire after signing an informed consent that was explained by the senior physician providing care at the time of HSCT.

Health and LS were self-assessed using a questionnaire based on the patient's level of satisfaction using the Satisfaction with Life Domains Scale (SLDS-BMT) [12] adapted by our center and approved by our Institutional Ethics Committee. The questionnaire covered 5 core domains identified as likely the most important for adolescents and young adult HSCT survivors.

The domains were as follows: 1, schooling (level of education, school performance, relationship with teachers and classmates, future plans); 2, employment (relationship with colleagues, future projects); 3, leisure time and physical functioning (sport activities, hobbies, other); 4, relationships and social functioning (family relationships, friendships, girlfriend/boyfriend interaction, social participation); and 5, body image (perception of subjects' physical status, including sexuality and long-term post-HSCT sequelae). Details of the questionnaire are presented in Table 1.

The domains contained 2-10 items each, for a total of 29 questions. Answers were evaluated by a single psychologist at our center. Some questions were formulated with answers on a 4-point scale: insufficient, sufficient, good, or very good. Higher scores (≥ 3) indicated greater LS. A series of open-ended answers at the end of each domain were included. The patient was asked to provide a final comment concerning satisfaction with the helpfulness of our HSCT center's personnel in terms of psychological and healthcare support.

Healthy young adults visiting our hospital for blood donation at the same time as the HSCT recipi-

Table 1. Questionnaire for LS Self-Assessment of Patients Undergoing HSCT

School domain
1) Which level of education (elementary, secondary, university)?
2) Any school performance and /or education failure? (please specify yes/no and how many times)
3) Which kind of difficulties? please specify whether difficulties have been solved or not
4) Which learning efficiency? (*)
5) Which attendance grade? (*)
6) Any pleasure in obtaining efficient education? (*)
7) Any discomfort or not with schoolmates? (*)
8) Which relationship with teachers? (*)
9) Any causes of discomfort with schoolmates or teachers?
10) Which future projects do you have?
Job domain
11) Which kind of job and for how long?
12) Is the actual job in line with your own aspirations? (*)
13) Do you like your job? (*)
14) Are you comfortable or not with your colleagues? (*)
15) Are you comfortable with your superiors? (*)
16) Did you change frequently your job and if yes how many times and why
17) Do you have future projects?
Leisure time domain
18) Which kind of sport, when and how many times (†)
19) Do you like Music? (indicate any kind of instrument you use or prefer †)
20) Which Hobbies do you like and for how long? (†)
21) Any other activities?(†)
Relationship domain
22) With relatives and your own family
23) With your own boy or girlfriend, if any
24) Marriage: what about it, since when, and are you satisfied
25) Any life difficulties after HSCT? (specify if difficulties have been solved or not)
26) Did you undergo psychosocial support (if yes, for how long)
27) Any psychologic impact of previous disease or HSCT on normal relationship?
27) Are you satisfied with your body perception including sexuality and fertility? (*)
28) Are there any physical activities that are not allowed to you and if yes why
General comments
29) Are you satisfied for the assistance received in your HSCT center (*)
30) Any other comments?

*Score 1-4 (insufficient, sufficient, good, very good).

†Score 1-4 (once, twice a week, a fortnight, never).

ents were visiting for checkups were chosen as the age- and sex-matched control group. The individuals in this control group were asked to provide informed consent. The questionnaire was administered to the control group in the same manner as in the HSCT recipients.

Statistical Analysis

We set up a case-control study (ratio 1:2) to assess LS. This study was based on the analysis of a 30-item questionnaire, with 10 of 30 items set in a quantitative ordinal scale (ie, teacher, family relationships, and so on) contributing to the overall score, that is, the dependent variable in our statistical model. The other 20 items were on a nominal scale (qualitative, ie, sex, education level, hobbies) and did not contribute to the overall score, but were considered independent variables in the statistical model.

We evaluated the probability of LS through a multivariate analysis according to the logistical procedure (SAS version 8; SAS Institute, Cary, NC) using the method of maximum likelihood. Logistic regression

allowed us to investigate the relationship between a categorical outcome (satisfaction, yes/no) and a set of variables (prognostic factors). Our logistical procedure was similar to other regression procedures, but with a dichotomous outcome as a dependent variable; binary responses were LS (yes/no). LS included a limited number of domains: work/school problems, family relationships, leisure time, and body perception. Ratings were made on a 4-point scale for each domain, and the items were then summed to give an overall LS score. The overall score was calculated by subject, not by items (ie, variables), so each subject with a score above or below the 75th percentile among all subjects was classified as “satisfied” or “not satisfied”, respectively [20]. We dichotomized the dependent variable (overall score) because the assumptions for the model with the score in a continuous numeric scale (linear regression model) were not satisfied. This explains our choice to use a logistical model.

We used the stepwise effect selection method to identify the prognostic factors for LS. Effects were entered or removed from the model according to a significance level of 0.30 for a variable to be both placed into and remain in the model and a significance level of 0.30 for a variable to stay in the model. The stepwise selection process was terminated if no further effect could be added to the model, or if the effect that had just entered the model was the only one removed in the subsequent backward elimination [20].

The relationship between the independent and dependent variables was expressed in terms of odds ratio with 95% confidence interval, computed as the exponential of the parameter estimate. The predictive ability of the model was assessed using the Somer D index, which is the difference between the percentage of concordant and discordant pairs of predicted probability and observed responses, divided by 100. Prognostic factors, such as age (as a continuous variable), sex, HSCT, case versus control, level of education, work, free time, and life projects, were evaluated to define the probability of LS of all the subjects studied. A χ^2 test statistic was used to assess the association between transplantation status (transplanted–controls) and domains. An unpaired 2-sample *t*-test was used for continuous variables.

RESULTS

Of 160 recipients of allogeneic HSCT performed between 1985 and 1998, 116 young adults were alive, without evidence of disease and eligible for this study. Fifty-six of the 116 eligible patients had a checkup at our HSCT center between June 2008 and June 2010. Only 1 of these 56 patients refused to participate in the study. Completion of the questionnaire took an average of 18 minutes for the HSCT recipients and 21 minutes for the controls. Characteristics of the patient and control groups are summarized in Table 2.

Out of 56 enrolled patients (39 males), 53 had a malignant disease and 3 had a nonmalignant disease. The median age was 5.2 years (range, 0.8–14.9 years) at diagnosis, 9.0 years (range, 1.1–17.9 years) at HSCT, and 25 years (range, 18–40 years) at the time of the study.

The median follow-up from the time of HSCT was 12.2 years (range, 10.2–17.1 years). Of the 55 patients assessed, 51 had undergone related donor HSCT, 3 had undergone unrelated marrow donor HSCT, and 1 had undergone unrelated cord blood donor HSCT. Thirty-six of the 55 patients had received a pretransplantation conditioning regimen including fractionated total body irradiation.

Acute GVHD occurred in 41 patients (10 with grade III and over), and limited chronic GVHD occurred in 11 patients. Two patients experienced extensive chronic GVHD resembling a diffuse sclerodermic pattern. All the patients were off GVHD treatment and GVHD-free throughout the study period.

Late effects occurring after HSCT were detected in 42 of the 55 patients. Fifteen of these 42 patients presented with late effects in more than one organ. These late effects included hypergonadotropic hypogonadism (*n* = 29), actinic amenorrhea (*n* = 6), subclinical hypothyroidism (*n* = 15), non–insulin–dependent diabetes mellitus (*n* = 5), cataracts (*n* = 29), secondary malignancies (follicular thyroid carcinoma, *n* = 2), mild pulmonary restrictive syndrome (*n* = 16), mild pulmonary obstructive syndrome (*n* = 3), arterial hypertension (*n* = 4), severe cardiomyopathy (*n* = 1), severe osteoporosis (*n* = 1), hepatic nodular hypertrophy (*n* = 2), and chronic hepatitis C virus infection (*n* = 6). Hormone replacement therapy was provided whenever needed.

In our univariate analysis of factors associated with LS (Figure 1), the only significant difference between the patient and control groups was in educational level. At the time of the study, 79% of the patients were attending secondary school compared with 54% of controls

Table 2. Characteristics of Patients and Controls

	Cases	Controls
Enrolled subjects, <i>n</i>	56	98
Evaluable subjects, <i>n</i>	55	98
Sex, M/F, <i>n</i>	39/17	59/39
Malignant disease, ALL/CML/AML/ NHL, <i>n</i>	52 (31/7/11/2)	
Nonmalignant disease, MDS/SAA, <i>n</i>	3 (2/1)	
Age at diagnosis, years, median (range)	5.2 (0.8–14.9)	
Age at HSCT, years, median (range)	9.0 (1.1–17.9)	
HSCT type, FD/URD/CB, <i>n</i>	51/3/1	
Conditioning regimen, TBI/no TBI, <i>n</i>	36/19	
Acute GVHD, grade I–II/III–IV, <i>n</i>	41/101	
Chronic GVHD, limited/extended, <i>n</i>	1/2	
Time after HSCT, years, median (range)	12.2 (10.2–17.1)	
Age at study, years, median (range)	25 (18–40)	24.5 (18.1–38.8)

ALL indicates acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CB, cord blood; CML, chronic myelogenous leukemia; FD, family donor; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; SAA, severe aplastic anemia; TBI, total body irradiation; URD, unrelated donor.

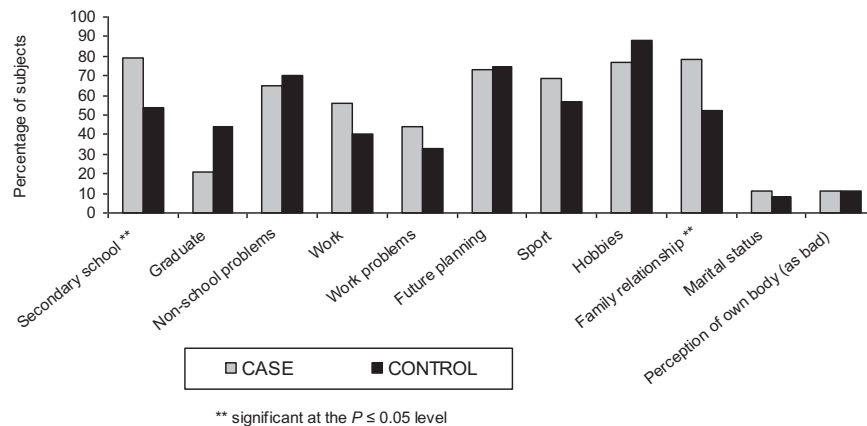


Figure 1. Comparison of domains by univariate analysis.

($P < .0001$). Only 8 of the 55 patients refused to attend secondary school, and 3 of those 8 were unemployed. Twelve patients (21%) graduated, compared with 44 controls (45%). Two patients graduated from a university with a degree in engineering, 2 with a degree in fine arts, 3 with a law degree, 3 with a degree in modern arts, and 2 with a degree in media/language. Thirteen patients were still enrolled at a university, whereas the majority of the controls had graduated. Roughly 30% of the controls who graduated chose a scientific major course, and 70% chose a nonscientific course.

Slightly more patients than controls (44% versus 33%) had some problems keeping a job, but the difference was not statistically significant. Good and/or very good family relationships were recorded in the patient group ($P = .003$). No major differences were found between the 2 groups in terms of leisure time (sports or hobbies). Few members of either group were married, likely owing to the low median age of the participants. The results showed no differences in how sexuality was perceived between the 2 groups.

Multivariate analysis showed that the level of LS was not significantly correlated with sociodemographic factors (eg, sex, age, education, relationships) or HSCT status. A mild trend in favor of the control group was seen in the subjects' body perception factor scores (odds ratio, 1.894; 95% confidence interval, 0.968-3.705; $P = .06$). The Somer D index was 0.64 (percent concordant, 54.0%; percent discordant, 10.0%).

DISCUSSION

The aim of this study was to evaluate health and LS in young adults at 10 or more years after HSCT performed in childhood for malignant or nonmalignant disease. The median follow-up was 12.2 years post-HSCT.

Some limitations of this study should be taken into account, including the relatively small number of patients, the slightly inadequate comparison with controls, and unavailability of sociodemographic background information at the time of questionnaire administration.

Unfortunately, population norms are not readily available and, when available, are not always culturally appropriate [19]. Nonetheless, our data indicate that patients who underwent HSCT in childhood have no significant difference in LS compared with healthy controls once they reach adolescence or young adulthood. Educational level constituted the only significant difference in the univariate analysis, and this was related mainly to the low number of patients still in secondary school or at a university at the time of this study. This was a reasonable finding, given that some of the patients had delayed their education because of their childhood illness. In contrast, the majority of controls had obtained a secondary school diploma or had graduated from a university by the time of the interview.

The 2 groups demonstrated no significant difference in terms of school problems. With regard employment and future planning, the patient group expressed a relatively (but not significantly) greater interest in looking for employment. In particular, 2 patients were seeking a specific job, such as managing a pub or a farm, and 10 other patients were strongly determined to find a job and start a family. In contrast, the majority of the control group expressed more caution about future projects, preferring to attend a school or university instead of looking for a job.

The 2 groups dedicated an almost equal amount of time to sports (in particular, physical activities such as body building). No particular between-group difference was seen in terms of hobbies. Interestingly, some of the HSCT survivors were disposed to original leisure time activities, such as music, painting, or model aircraft construction.

Previous studies have found that a proportion of childhood cancer survivors experience acceptable physical health and exhibit good psychological and social behavior with no difference in terms of depression or self-esteem compared with normal matched controls [21,22]. Difficulties in evaluating LS or QOL in these previous studies were related to the means of validation, with minimal burden on patients and staff or

having sufficient capacity to follow patients for extended periods. Similar findings seem to emerge for patients cured after HSCT, but previous studies have detected a possible bias, related mainly to differences in subject age, number of subjects analyzed, type of transplantation, observation period, type of control [19,23], and difficulty reaching consensus on which LS measures should be used [24-26].

A recent review underscored that, notwithstanding the need for more standardized broad measures of QOL and LS in the healthy population and survivors of childhood cancer, general measures might have the advantage of applicability [7]. We chose this strategy, which is probably less sensitive than a more complex approach, such as the subscales that take multi-item measures into consideration. In addition, a subjective measurement approach, such as the use of a questionnaire, can provide a better fit with a client autonomy model in which the client is viewed as the expert with respect to his or her own life [27].

It is interesting to note that the well-known post-HSCT complications [28,29] had no significant negative impact on the psychosocial outcome of our patients compared with controls. This finding was recently confirmed in a study of adult HSCT survivors [30], contrary to previous reports [7,11].

Our results demonstrate that the majority of HSCT survivors have great appreciation for life, family, and friends. Even the center effect, including strong psychological support from HSCT staff, was relevant to recovery from the negative impact of the transplantation procedures, as evidenced by the patient comments. These findings are in keeping with longitudinal studies that support an early decrease in QOL immediately after allogeneic HSCT [25,30,31], but a consistent recovery to baseline levels thereafter. Different observations have been recorded from post-HSCT survivors of severe congenital immunodeficiency [32], in whom the underlying genetic defect could have some negative influence on the neuropsychological outcome regardless of the posttransplantation course.

We emphasize that in our univariate and multivariate analyses, demographic factors, life aspect factors (eg, school, work, leisure time, family relationships) or emotional outcome factors (eg, body perception) were not associated with a negative impact on LS in either group. In particular, despite a relatively high rate of post-HSCT late effects in our survivors, their body image was very similar to that of controls, except in 1 patient who had significant growth impairment, a less severe complication in the other patients. One possible explanation for this finding is that none of the patients presented with signs and symptoms of GVHD at the time of the study, and, importantly, no increased body-related anxiety was reported. Sanders et al. [23], in a large study of QOL of adult survivors after childhood HSCT, found no correlation between

previous chronic GVHD and long-term physical deterioration.

The high proportion of our patients reporting normal physical, psychosocial, and behavioral function could be due to these patients' increased capacity to bear life's difficulties, as has been described previously [33,34]. Although stronger resilience acquired after a chronic illness could represent a favorable factor for LS after HSCT [35], we did not measure this in the present study and so have no reliable data to support this concept.

Sutherland et al. [36] analyzed the LS of HSCT adult subjects with an age-matched normal population and found that survivors more than 3 years post-HSCT had similar or, in some domains, even higher LS compared with the normal population. Bieri et al. [30] and Bishop et al. [37] recently evaluated the health and screening patterns of HSCT survivors and found similar health and screening behaviors as matched controls.

In terms of sexuality, our findings demonstrate a sufficiently normal pattern in HSCT survivors, probably related to either normal hormone production or replacement therapy. However, the information that the vast majority of HSCT survivors are bound to be infertile [6] has been identified as a burning issue; thus, we have encouraged specific social and psychological support in some cases. In this regard, a comforting message concerning paternity seems to emerge from recent data [38], where patients under age 25 years at the time of HSCT experiencing some reappearance of spermatogenesis years after HSCT, even when conditioned with standard TBI. Finally, we note that there was no difference in marital status between the HSCT survivors and controls.

In conclusion, our research indicates that even if survivors of childhood HSCT experience of some physical discomfort, they are not necessarily at risk for future low level of LS or behavioral disturbances. As a final comment, although most of our cured adolescents could be considered so-called "fortunate survivors," we point out that continuous long-term follow-up is of great importance to detect negative physical or psychological effects whenever these findings emerge. Therefore, we suggest a long-term evaluation of LS in both multicenter and single-center studies that does not exclude a simple methodology such as we have adopted here. The selection of population norms remains one of the most important barriers to measuring LS or QOL after HSCT, and future studies should use more appropriate measures to compare control groups and cancer survivors. Programs including medical, teaching, and psychosocial support must be encouraged, along with screening and preventive practices recently recommended by the European Group for Blood and Marrow Transplantation, Center for International Blood and Marrow Transplant Research, and American Society of Blood and Marrow Transplantation consensus panel [39].

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