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# Factors Associated with Social Functioning Among Long-Term Cancer Survivors Treated with Hematopoietic Stem Cell Transplantation as Adolescents or Young Adults

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## Abstract

**Objective:** Hematopoietic stem cell transplantation (HSCT) can compromise long-term health and social functioning. We examined the impact of physical and social-emotional factors on the social functioning of long-term adolescent and young adult (AYA) HSCT survivors.

**Methods:** This cross-sectional analysis included HSCT recipients from the INSPIRE trial [NCT00799461] who received their first transplant between ages 15-39. Patient-reported outcome measures included the Short Form-36v2, Fatigue Symptom Inventory, Cancer and Treatment Distress, and the ENRICHD Social Support Inventory. We used hierarchical multiple linear regression to identify physical and social-emotional factors associated with social functioning at the baseline assessment, with the first block including sociodemographic and clinical factors

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Conflict of Interest

The authors have no conflicts of interest to declare.

Human Subjects and Ethics

The Fred Hutchinson Cancer Research Center Institutional Review Board approved the study [Institutional review file #: 6743]. The study conforms to standards in the Declaration of Helsinki and US Federal Policy for the Protection of Human Subjects.

Data Availability

The data that support the findings of this study are available from the study principal investigator (senior author: KLS) upon reasonable request.

significant at $p$=<0.10 in univariate testing, the second block including fatigue and physical function, and the third block including social support and distress.

**Results:** Participants (N=279) were 52% male and 93.5% white, non-Hispanic, with a mean age of 30.3 (SD 6.6) at first transplant. Social Functioning mean was 48.5 (SD 10.5), below age-adjusted norms (t=−13.6, $p$=<0.001). In the first block, current chronic graft-versus-host disease accounted for 5.5% of the variance ($p$=<0.001). Adding fatigue and physical function explained an additional 46.6% of the variance ($p$=<0.001). Adding distress and social support explained an additional 7.7% of the variance ($p$=<0.001). The final model explained 59.8% of the variance; distress, fatigue, and physical function were significantly associated with social functioning.

**Conclusions:** Distress, fatigue, and physical function are associated with social functioning and interventions targeting these symptoms may help to improve SF among long-term cancer survivors treated with HSCT as AYAs.

**Clinical Trial Registration—**Internet-Based Program with or without Telephone-Based Problem-Solving in Helping Long-Term Survivors of Hematopoietic Stem Cell Transplant Cope with Late Complications [NCT00799461].

### Keywords

Adolescent and young adult; AYA; Cancer; cancer survivorship; distress; fatigue; hematologic malignancy; hematopoietic stem cell transplantation; Psycho-Oncology; social functioning

## Background

Cancer patients treated with hematopoietic stem cell transplantation (HSCT) as adolescents or young adults (AYAs; ages 15-39) face complex psychosocial stressors (e.g. school and career disruptions, social isolation) and treatment-related toxicities (e.g. infertility, subsequent malignancies) that can compromise their long-term health and social functioning [1, 2]. Hematopoietic stem cell transplants (HSCT) are used to replace immune cells after the immune system has been damaged by disease or intentionally eradicated by chemotherapy and/or radiation therapy [3]. In an autologous transplant, the stem cells are collected from the patient during remission and reinfused after the patient is treated for disease. In an allogeneic stem cell transplant, stem cells are used from a donor whose tissue type closely matches the patient [3]. In 2017, about 17% of hematopoietic cell transplants performed in the United States were with AYAs between ages 11-40 [4]. AYA HSCT recipients experience higher rates of treatment related mortality and late relapses, contributing to inferior overall outcomes compared to children [2]. Persistent health needs after HSCT can cause physical, social, and financial setbacks that disrupt AYA development towards independence and self-sufficiency [5].

Graft versus host disease (GVHD) is a potentially serious complication of allogeneic stem cell transplantation. GVHD occurs when the donor’s T cells from the graft view the patient’s healthy cells as foreign, and attack and damage them. Chronic GVHD (cGVHD) occurs any time after 100 days post-HSCT and is a syndrome that may involve a single organ or several organs. cGVHD is one of the leading causes of medical complications and death after

allogeneic stem cell transplantation [6]. Rates of cGVHD are significantly higher in adults compared with children [7].

Fatigue, a subjective sense of physical, emotional, and/or cognitive exhaustion that is disproportional to recent activity and interferes with functioning, is one of the most frequently reported symptoms of HSCT survivors and does not appear to resolve with time [8]. Fatigue levels have exceeded population norms in long-term survivors at 3-5 years and matched controls a mean of 10 years post-HSCT [9]. AYAs experience increased fatigue from effort required to participate in school and/or work [10]. Fatigue can compromise healthy lifestyle choices, such as maintaining adequate exercise and nutrition [10]. In comparison between AYA allogeneic HSCT recipients (median age 29) with non-AYAs (median age 52), AYAs report higher physical functioning and physical role functioning, as well as higher physical well-being and activity scores [11].

HSCT is one of the risk factors for poorer health-related quality of life and social functioning among AYA cancer survivors [12]. Distress ranges from common feelings of vulnerability, fear of cancer recurrence, stresses related to perceived demands after treatment such as with family or health needs, or sadness to clinically significant depression, anxiety, or PTSD [13]. Persistently stressed social and family relationships can increase risk for adjustment challenges post-treatment [14]. Social functioning, as assessed in the Short Form Health Survey-36 version 2 (SF-36v2), involves *to what extent* and *how much of the time* physical health or emotional problems *interfere with* normal social activities with friends, family, neighbors or groups [15]. Many AYA HSCT survivors experience declines in social competence and self-concept [2]. Social support can be variable and age-dependent, such that older AYAs may have less family support and may be more reliant on their partner and/or friends [2]. Up to at least two years post-diagnosis, approximately 32% of AYA cancer survivors of mixed diagnoses demonstrate consistently low social functioning [16]. Physical symptoms, psychological distress, and less perceived social support at baseline are associated with low social functioning [16]. Similarly, AYA cancer survivors of mixed diagnoses within the first year post-treatment who report impairments in social functioning also describe physical complications from treatment, mental health concerns, and/or social isolation due to distance traveled to receive treatment [17].

Building upon existing research examining the psychosocial sequelae of HSCT [2,8,10] and the social functioning of AYA cancer survivors [5,16], we aimed to assess the impact of physical and social-emotional factors on the social functioning of long-term cancer survivors treated with HSCT as AYAs. We hypothesized that, after controlling for relevant demographic and clinical factors, fatigue and physical functioning would explain significant variance in social functioning, and that social-emotional factors, such as perceived social support and cancer and treatment-related distress, would explain additional variance in social functioning.

# Methods

## Participants and Procedures

Survivors of a hematologic malignancy who were between 3-18 years post-HSCT, able to communicate and complete patient-reported outcome (PRO) measures in English, and with internet and email access were recruited from a single transplant center for the INSPIRE randomized controlled trial [NCT00799461] [18, 19]. The Fred Hutchinson Cancer Research Center Institutional Review Board approved the trial. All eligible survivors were approached by two mailed letters and follow-up calls to determine interest. They were sent a URL in the letters and by email if interested, and could go to the study website and provide informed consent and immediately complete the online PRO measures. Study staff were available by toll-free study phone line and email to respond to any questions or difficulties. This secondary, cross-sectional analysis included only participants who received their first transplant between the ages of 15-39, met study inclusion criteria, and completed the SF-36v2 social function subscale at baseline.

## Measures

PRO measures completed at baseline and included in this secondary analysis are the Short Form-36 (SF-36v2) social function and physical function subscales, Fatigue Symptom Inventory (FSI), Cancer and Treatment Distress (CTXD), and ENRICHD Social Support Inventory (ESSI). Participants self-reported sociodemographic characteristics and cGVHD status. We gathered diagnosis and treatment factors using medical record data.

**Short Form-36 version 2 (SF-36v2)—**The SF-36v2 is a widely used health-related quality of life measure. Age- and gender-specific norms are available for the United States [20]. The measure provides standardized T scores for eight domains and a physical and mental component summary score, with excellent internal consistency, validity among different medical groups, and test–retest reliability [20, 21, 22]. In this analysis, we used the continuously valued SF-36v2 social function subscale T-scores as our outcome variable and the SF-36v2 physical function subscale T-scores as a factor tested for association with social function. All items are scored so that a high score indicates a more favorable health state.

**Fatigue Symptom Inventory (FSI)—**The Fatigue Symptom Inventory score is a 14-item self-report measure designed to assess the severity, frequency, and daily pattern of fatigue as well as its perceived interference with quality of life. Evidence supports its reliability and validity with cancer patients [23, 24]. Lower scores correspond to less fatigue.

**Cancer and Treatment Distress (CTXD)—**The CTXD scale assesses distress specific to cancer and its treatment, as distinct from general anxiety or depression [25, 26]. The CTXD score used in this analysis is a mean of 20 items rated 0=mild distress to 3=severe distress, from four subscales including health burden, identity, uncertainty and interference. Items assess how much distress or worry interfered (from 0=not at all to 3=a lot) with general activities, work, sleep, enjoyment of life, and relations with other people over the past week. Higher scores indicate greater distress. Reliability in this sample is $\alpha$=0.94.

**ENRICHD Social Support Inventory (ESSI)—**The ESSI is a 7-item self-report scale developed for the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) study regarding structural (partner), instrumental (tangible help), and emotional (caring) support previously found to be predictive of mortality individually in cardiovascular patients [27]. Individual items are summed for a total score, with higher scores indicating greater social support.

### Statistical Analyses

We used frequencies, percentages, means, standard deviations (SD) and ranges to describe the study sample. Univariate analysis examined the variables and candidate covariates to be included in the model. To compare social functioning scores on the SF-36v2 with the normative mean score for age and gender adjusted data for a general population ages 25-44 [20], we tested the difference using a single sample t test. We used hierarchical multiple linear regression to identify the unique contributions of physical and social-emotional factors on the social functioning of long-term cancer survivors treated with HSCT as AYAs. We checked the assumptions of normality, linearity, homoscedasticity, and the absence of multicollinearity. Using a predicted probability plot, we first confirmed that the residuals were normally distributed and homoscedastic. To check multicollinearity, we used variance inflation factor (VIF) values. In the first block we included sociodemographic and clinical factors significant at $p$=<0.10 in univariate testing. In the second block we added fatigue and physical function. In the final block, we added social support and distress. We used IBM SPSS Statistics version 26.

## Results

Table 1 describes the sociodemographic and clinical characteristics of the study participants and baseline scores on the PRO measures. Of 1322 eligible HSCT survivors approached for the INSPIRE study, 771 (58%) enrolled, and N=279 of these were AYAs (36% of the participants). Participants were 52% male and 93.5% white, non-Hispanic, with a mean age at the time of first transplant of 30.3 years (SD 6.6). Participants were on average 10 years post-transplant (SD=4.55) at the time of study approach. Most participants had received an allogeneic transplant (86.0%). Of those who had received an allogeneic transplant, 6.5% reported current cGVHD at the time of the assessment. The majority of participants had at least a 4-year college degree (57.7%) and were married/living with a partner (65.2%). About half of participants (48%) had an income of greater than $80,000/year. Social functioning mean was 48.5 (SD 10.5), below the age-adjusted norms for 25-44 year old males and females ($50^{th}$ percentile = 56.40, SD 9.50; t=−13.6, $p$=< 0.001).

Table 2 provides univariate associations with social functioning. None of the sociodemographic factors reached significance of $p$=<0.10. However, sex reached p=0.10 but did not add to the model so was not included in the final regression model. Current cGVHD at the time of assessment was significantly associated with social functioning ($t$=3.94, $p$=<0.001). Similarly, fatigue ($r$=−0.71), physical functioning ($r$=0.54), cancer and treatment-related distress ($r$=−0.72), and social support ($r$=0.29) were significant at the $p$=<0.001 level and so were retained in the regression model.

Table 3 presents intercorrelations between the variables retained in the regression model and their associations with social functioning.

Table 4 presents the hierarchical regression analysis. We confirmed that the residuals were normally distributed, linear and homoscedastic. No variables were multicollinear as indicated by VIF values below 3.00. In the first block for the regression, current cGVHD contributed significantly to the model ($p$=<0.001) and accounted for 5.5% of the variance in social functioning. Introducing fatigue and physical function in the second block explained an additional 46.6% of the variance and this change in $R^2$ was significant ($p$=<0.001), although cGVHD was no longer significant ($p$=0.68). Adding cancer and treatment-related distress and social support in the final block explained an additional 7.7% of the variance in social functioning ($p$=<0.001). In the final regression model, only three factors remained significantly associated with social functioning: fatigue, cancer and treatment-related distress, and physical function. Social support did not explain significant variance in the model when adjusted for other factors. Together, all variables in the final model explained 59.8% of the variance in social functioning.

## Discussion

In this study of long-term recipients of AYA HSCT, survivors reported lower social functioning on average than age and gender-matched general population norms by more than half of a standard deviation, suggesting a clinically meaningful decrement in the survivors' social function. Consistent with our hypothesis, fatigue, physical function and distress explained a majority of the variance in social functioning for these long-term AYA HSCT survivors. Notably, contrary to prediction, social support did not further explain variance in social functioning, nor was cGVHD significant in the model after including fatigue and physical function. AYA survivors report fatigue as one of the most prevalent, severe, distressing, and persistent symptoms and a significant barrier to participation in social activities [28]. Among hematologic cancer survivors treated with HSCT, 42% report fatigue [29]. This may help to explain why cGVHD is not significant, with the variance being covered by the more broadly experienced fatigue and physical dysfunction.

Among long-term HSCT survivors, known risk factors for impaired physical functioning include younger age, higher body mass index, no or part-time employment, more comorbid diseases, and cGVHD [30]. Interestingly, in research comparing AYA allogeneic HSCT recipients (median age 29) with non-AYAs (median age 52), AYAs describe higher quality of life regarding physical role functioning but social role functioning is comparable between groups [11] suggesting that in AYAs higher physical functioning may not necessarily equate with better social role functioning.

Cancer and treatment-related distress in the model was strongly associated with social functioning even after controlling for health-related factors. AYA HSCT survivors have high levels of unmet psychological needs that appear to remain relatively stable following treatment completion [31]. Among long-term survivors of HSCT, lower resilience scores have been associated with higher odds of having psychological distress [32]. Our finding that higher levels of distress are associated with lower social functioning is consistent with

research among AYA cancer patients of mixed diagnoses [16]. Younger age in allogeneic HSCT recipients has also been associated with distress and fear of cancer progression in particular [33].

Contrary to our hypothesis, social support did not contribute to explaining social functioning in the final model. Previous research with AYA cancer survivors suggests that less perceived social support is associated with lower social functioning [16], as we also found in univariate analysis. However, perceived social support may not mitigate interference from fatigue and distress in involvement in normal social activities, even a decade post-transplant. In addition to the role of social support, recent research has examined the impacts of social constraint, defined as social conditions contributing to individuals modifying or refraining from sharing stress or trauma-related concerns such as fear of recurrence [34]. Social support was more strongly associated with cancer-specific positive outcomes of well-being while social constraint was more strongly associated with cancer-specific negative outcomes such as distress [34].

Future longitudinal research could help to clarify these distinct pathways by examining the social functioning of young adult HSCT recipients along the care trajectory to identify facilitators and barriers to social functioning in AYA survivors. Risk-based predictive models that identify both positive factors that support growth and negative factors that inhibit recovery could be used to tailor supportive care services and could be used in the design of interventions, either augmenting social support or reducing social constraints depending on gaps for individuals. With awareness that AYAs experience the psychosocial impacts of cancer long after treatment has ended, supportive care needs should be assessed throughout the cancer care trajectory. AYAs prefer supportive care resources that reduce feelings of loneliness, create a sense of community, and provide opportunities to meet other AYA patients [35]. We recommend AYA involvement in the design and development of supportive care resources. Digital modalities, such as mobile apps, websites, and social media, can help to enhance the availability and desirability of supportive care services for AYAs.

## Strengths and Limitations

This analysis contributes to the emerging literature examining the social functioning of AYAs post-HSCT. This AYA cohort, consistent with a large proportion of the population with access to HSCT, is a relatively homogeneous sample of white, non-Hispanic individuals with a majority having high levels of socioeconomic resources. All study participants needed internet and email access, as well as adequate English skills to complete the baseline assessment, limiting the generalizability of the findings to those groups, although internet usage is almost ubiquitous among young adults in the United States [36]. Survivors with low socioeconomic resources may have been lost to follow-up and not reached by the mailed approach letter.

Although the reliability and validity of the SF-36v2 is well established, a broader measure of social function that includes social competence, perceived social support, satisfaction with social roles and activities, and social isolation, would be more informative. As can be expected with the use of self-report measures, there are risks of social desirability bias and

recall bias. Given the cross-sectional design, this precludes drawing causal inferences from these data about social functioning and physical and social-emotional factors.

## Clinical Implications

Our findings support the long-term value of building stamina, reducing fatigue, and maintaining active symptom and distress management for long-term cancer survivors who received HSCT as young adults. Studies have found that exercise had a beneficial impact on fatigue and emotional functioning [37, 38] while telephone-based cognitive behavioral therapy [39] and problem-solving treatment (PST) telehealth calls [40] were helpful in reducing distress in HSCT survivors. Psychosocial interventions that provide age-specific social support, such as recreational opportunities to connect with peers and vocational support, as well as assist with post-treatment symptom management and psychological distress help foster healthy social reintegration [16].

## Conclusions

Cancer and treatment-related distress explained the majority of variance in social functioning in this sample of long-term cancer survivors treated with HSCT as young adults. Fatigue and physical function also interfered with involvement in normal social activities. AYAs long-term social reintegration success may depend on increased availability of psychosocial interventions to help manage psychological and physical late effects.

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## Table 1

Characteristics of Adolescent and Young Adult Participants (N=279)

| Variables and Categories | n (%) or Mean (SD, Range) |
|---|---|
| Age at Assessment, Mean (SD, Range) | 40.5 (7.99, 21.31-56.94) |
| Sex, n (%) | |
| Male | 146 (52.3) |
| Race, n (%) | |
| White/Caucasian | 261 (93.5) |
| Asian | 7 (2.5) |
| American Indian/Alaska Native | 3 (1.1) |
| More than one race | 4 (1.4) |
| Black or African American | 1 (0.4) |
| Unknown | 3 (1.1) |
| Rural Residence, n (%) | |
| Rural/Super rural | 53 (19.0) |
| Education, n (%) | |
| High School/GED or less | 17 (6.1) |
| Some vocational or college credit | 51 (18.3) |
| 2 year college or trade degree | 29 (10.4) |
| 4 year college degree | 94 (33.7) |
| Graduate degree | 67 (24.0) |
| Unknown | 21 (7.5) |
| Income, n (%) | |
| Below $40,000 per year | 45 (16.1) |
| $40,000-$79,999 per year | 70 (25.1) |
| $80,000 and above per year | 134 (48.0) |
| Unknown | 30 (10.8) |
| Marital Status, n (%) | |
| Married/Living with a partner | 182 (65.2) |
| Single/Separated/Divorced/Widowed | 78 (28.0) |
| Unknown | 19 (6.8) |
| Age at first transplant, Mean (SD, Range) | 30.3 (6.6, 15.26-39.97) |
| Years after first transplant, n (%) | |
| 3 to 9 years | 159 (57.0) |
| 10 to 18 years | 120 (43.0) |
| Diagnosis | |
| Acute Leukemia | 111 (39.8) |
| Chronic myelogenous leukemia | 103 (36.9) |
| Hodgkin lymphoma | 21 (7.5) |
| Multiple myeloma | 2 (.7) |
| Myelodysplasias | 14 (5.0) |
| Non-Hodgkin lymphoma | 23 (8.2) |

| Variables and Categories | n (%) or Mean (SD, Range) |
|---|---|
| Other | 5 (1.8) |
| Type of transplant, n (%) | |
| Autologous | 39 (14.0) |
| Allogeneic for one or more transplants | 240 (86.0) |
| Chronic graft versus host disease at time of assessment, n (%) | 257 (92.1) |
| None-Mild | 18 (6.5) |
| Moderate-Severe | 4 (1.4) |
| Unknown | |
| SF-36v2 Social Functioning T-score, Mean (SD, Range) | 48.50 (10.51, 13.22-56.85) |
| Fatigue Symptom Inventory, Mean (SD, Range) | 2.59 (2.01, .00-9.23) |
| SF-36v2 Physical Functioning T-score, Mean (SD, Range) | 49.80 (9.64, 17.05-57.03) |
| Cancer & Treatment Distress, Mean (SD, Range) | 0.70 (0.60, 0-2.70) |
| ENRICHD Social Support Inventory, Mean (SD, Range) | 18.99 (5.07, 1.00-24.00) |

**Table 2**

Univariate Associations with Social Functioning

| **Variables** | ***p* value** |
|---|---|
| Age at Assessment | 0.78 |
| Sex | 0.100 |
| Race | 0.23 |
| Rural Residence | 0.43 |
| Education | 0.65 |
| Income | 0.110 |
| Marital Status | 0.49 |
| Age at first transplant | 0.99 |
| Years after first transplant | 0.61 |
| Diagnosis | 0.46 |
| Type of transplant | 0.57 |
| Chronic graft versus host disease at time of assessment | <0.001 |
| Fatigue Symptom Inventory | <0.001 |
| SF-36v2 Physical Functioning T-score | <0.001 |
| Cancer & Treatment Distress | <0.001 |
| ENRICHD Social Support Inventory | <0.001 |

**Table 3**

Correlations between Variables Retained in Regression and with Social Functioning (N=270)

| Variable | 1. History of cGVHD | 2. Fatigue | 3. Physical Functioning | 4. Cancer and Treatment Distress | 5. Social Support |
|---|---|---|---|---|---|
| Social Functioning | t=3.943, *p*=<0.001 | r=−0.704, p=<0.001 | r=0.529, *p*=<0.001 | r=−0.724, *p*=<0.001 | r=0.290, p=<0.001 |
| Predictors | | | | | |
| 1. cGVHD at time of assessment † | _____ | t=−4.202, p=<0.001 | t=6.390, p=<0.001 | t=−4.446, p=<0.001 | t=1.030, p=.304 |
| 2. Fatigue | | _____ | r=−0.569, p=<0.001 | r=0.740, p=<0.001 | r=−0.302, p=<0.001 |
| 3. Physical Functioning | | | _____ | r=−0.530, p=<001 | r=0.191, p=.001 |
| 4. Cancer & Treatment Distress | | | | _____ | r=−0.326, p=<.001 |
| 5. Social support | | | | | _____ |

† cGVHD = chronic graft versus host disease; cGVHD is dichotomous variable (yes/no) consequently t test was used to determine relationships with other variables; other tests were Pearson correlations.

**Table 4**

Hierarchical Regression for Factors Associated with Social Functioning Among Young Adult Participants

| Variable | β | β/SE | *p* | $Sr^2$ | $R^2$ | $\Delta R^2$ | *p* of $\Delta R^2$ |
|---|---|---|---|---|---|---|---|
| Step 1 | | | | | 0.055 | 0.055 | <0.001 |
| cGVHD at time of assessment† | −9.891 | −0.234 | <0.001 | −0.234 | | | |
| Step 2 | | | | | 0.521 | 0.466 | <0.001 |
| Current cGVHD | −0.808 | −0.019 | 0.676 | −0.018 | | | |
| Fatigue | −3.117 | −0.595 | <.001 | −0.489 | | | |
| Physical Functioning | 0.201 | 0.184 | .001 | 0.145 | | | |
| Step 3 | | | | | 0.598 | 0.077 | <0.001 |
| Current cGVHD | 0.038 | 0.002 | 0.983 | 0.001 | | | |
| Fatigue | −1.675 | −0.320 | <.001 | −0.204 | | | |
| Physical Functioning | 0.135 | 0.123 | 0.015 | 0.096 | | | |
| Cancer and Treatment Distress | −7.195 | −0.411 | <.001 | −0.267 | | | |
| Social Support | 0.076 | 0.037 | 0.378 | 0.034 | | | |

*Note.* N=270

† cGVHD: chronic graft versus host disease