Biol Blood Marrow Transplant 25 (2019) 2234–2242

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Quality of care

Coping and Modifiable Psychosocial Factors are Associated with Mood and Quality of Life in Patients with Chronic Graft-versus-Host Disease

Jamie M. Jacobs[1,2,*], Sarah Fishman[1], Robert Sommer[1], Isabella Sereno[1], Alyssa Fenech[1], Amanda L. Jankowski[1], Lara Traeger[1,2], Joseph A. Greer[1,2], Julie Vanderklish[3], Chrisa Hunnewell[3], Meredith Saylor[3], Yi-Bin Chen[2,3], Thomas Spitzer[2,3], Zachariah DeFilipp[2,3], Jennifer S. Temel[2,3], Areej El-Jawahri[2,3]

[1] *Center for Psychiatric Oncology and Behavioral Sciences, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts*
[2] *Harvard Medical School, Boston, Massachusetts*
[3] *Department of Medicine, Division of Hematology & Oncology, Massachusetts General Hospital, Boston, Massachusetts*

Article history:
Received 11 February 2019
Accepted 24 June 2019

Keywords:
Chronic GVHD
Quality of life
Depression
Anxiety
Coping

A B S T R A C T

Chronic graft-versus-host disease (GVHD) is one of most common complications following allogeneic hematopoietic cell transplantation (HCT) and the most significant contributor to morbidity and nonrelapse mortality. The physical burdens and psychosocial difficulties of these patients have not been described systematically. An exploration into the rates and correlates of mood and quality of life (QOL) in patients with chronic GVHD is necessary to develop a clinically relevant, evidence-based intervention to promote well-being. From July 2015 to July 2017, adult allogeneic HCT survivors with established moderate to severe chronic GVHD (N = 52) enrolled in a prospective, longitudinal study at a tertiary academic center. We examined the rates and correlates of depression and anxiety symptoms (Hospital Anxiety and Depression Scale) and explored whether constructs including coping strategies (Coping Inventory for Stressful Situations), symptom burden (Lee Symptom Assessment Scale), physical functioning (Human Activity Profile), and perceived social support (Medical Outcomes Study Social Support Survey) predicted QOL trajectory over time (Functional Assessment of Cancer Therapy–Bone Marrow Transplant) at the baseline, 3-month, and 6-month follow-up. Analyses adjusted for age, sex, chronic GVHD severity, and time since chronic GVHD diagnosis. At the baseline, 3-month, and 6-month follow-up, 32.7%, 31.1%, and 37.8% of patients reported clinically significant depression symptoms, and 30.8%, 20.0%, and 36.4% reported clinically elevated anxiety symptoms, respectively. Adjusting for covariates, greater use of negative emotion-oriented coping ($\beta = 0.20$, $P = .002$), less use of task-oriented coping ($\beta = -0.10$, $P = .021$), worse physical functioning ($\beta = -0.07$, $P = .004$), and higher symptom burden ($\beta = 0.07$, $P = .002$) were independently associated with depression symptoms at baseline. Greater use of negative emotion-oriented coping ($\beta = 0.28$, $P < .001$) and worse physical functioning ($\beta = -0.05$, $P = .034$) were independently associated with anxiety at baseline. Patients who used more negative emotion-oriented coping ($\beta = -0.58$, $P = .035$), had less task-oriented ($\beta = 0.40$, $P = .028$) and social diversion-oriented coping ($\beta = 0.35$, $P = .039$), and had higher symptom burden ($\beta = -0.30$, $P = .001$), worse physical functioning ($\beta = 0.32$, $P < .001$), and lower perceived social support ($\beta = 6.47$, $P = .003$) at baseline reported poorer QOL over time. The unmet physical and psychosocial needs of patients with chronic GVHD are substantial and warrant investigation into evidence-based interventions that may improve QOL and mood by targeting modifiable psychosocial constructs identified in this study.

INTRODUCTION

The development of chronic graft-versus-host disease (GVHD) following allogeneic hematopoietic cell transplantation (HCT) is increasingly common, affecting approximately 40% to 60% of HCT survivors and generally occurring between 3 and 18 months after transplant [1]. Chronic GVHD is one of the most common complications following transplant and the most significant contributor to morbidity and nonrelapse mortality [1,2]. Patients living with chronic GVHD may experience significant limitations and quality-of-life (QOL) impairment regardless of the affected organ, with more severe chronic GVHD precipitating a greater degree of QOL impairment [3].

HCT survivors experience difficulties with mood, with up to 40% reporting depression symptoms and 18% endorsing

Financial disclosure: See Acknowledgments on page 2241.

* Correspondence and reprint requests: Jamie M. Jacobs, PhD, Massachusetts General Hospital Cancer Center, 55 Fruit Street, Yawkey Center, Suite 10B, Boston, MA 02114.
E-mail address: jjacobs@mgh.harvard.edu (J.M. Jacobs).

https://doi.org/10.1016/j.bbmt.2019.06.024
1083-8791/

anxiety symptoms [4-7]. Although chronic GVHD is considered a risk factor for depression after transplantation [6], the prevalence and severity of anxiety and depression symptoms in patients with chronic GVHD are largely unknown. In addition, how patients cope with illness plays a major role in QOL and is related to symptom burden, mood (ie, depression and anxiety), physical functioning, and social support as patients adapt to the limitations imposed by a chronic disease state [8,9]. Coping is an active process by which patients manage, adjust, and adapt to a stressful situation [10], choosing, for example, to engage in actionable efforts to manage their situation (ie, task-oriented coping) or to distance themselves from the stressor (ie, avoidance-oriented coping) [11]. Importantly, a patient's coping style has consequences for psychosocial and physical well-being; for example, men with prostate cancer who default to a more avoidant coping style experience more negative psychologic adjustment and worse physical health [12], and the use of denial and self-blame coping strategies is associated with more depression and anxiety and worse QOL in patients with incurable cancer [9]. To date, however, studies examining the use of coping strategies in patients with chronic GVHD are lacking.

Furthermore, although relationships among coping strategies, mood, and QOL over time have been described by researchers in the context of solid malignancies [8] and autoimmune diseases [13,14] in an effort to understand trajectories of psychologic well-being, the temporal relationships among symptom burden, functional impairment, coping, social support, and QOL in patients with chronic GVHD are unknown. An understanding of the rates and correlates of depression and anxiety and temporal relationships among the aforementioned factors will provide a comprehensive understanding of the psychosocial needs of patients with chronic GVHD, help identify at-risk patients, and highlight potential factors that may buffer inherent declines in QOL over the course of the disease. Moreover, as interventions addressing the psychosocial needs of patients with chronic GVHD are woefully lacking, the identification of modifiable factors may guide the development of a clinically relevant intervention to improve QOL in patients with GVHD.

Therefore, we conducted a longitudinal, observational study of patients with chronic GVHD to identify the rates of clinically significant depression and anxiety over time, correlates of depression and anxiety, and predictors of QOL over time, with a focus on coping, symptom burden, physical functioning, and social support. We hypothesized that patients with less adaptive coping strategies, higher symptom burden, lower physical functioning, and less perceived social support at baseline would have higher depressive and anxiety symptoms at baseline. Furthermore, we hypothesized that less adaptive coping strategies, higher symptom burden, lower physical functioning, and less perceived social support at baseline would predict QOL over time.

MATERIALS AND METHODS

Study Design

From July 2015 to July 2017, patients with an established diagnosis of moderate to severe chronic GVHD after allogeneic HCT participated in a prospective longitudinal study assessing anxiety, depression, QOL, symptom burden, physical functioning, social support, and coping strategies. Patients were recruited from outpatient clinics at the Massachusetts General Hospital Cancer Center in Boston, Massachusetts. The Dana Farber/Harvard Cancer Center Institutional Review Board approved the study.

Participants

Eligible patients were eligible at any time post-HCT and required to have a diagnosis of moderate to severe chronic GVHD for the first time, as defined by the National Institutes of Health Consensus Criteria [15]. We did not include patients who had progressed from a milder severity of chronic GVHD. Additional eligibility criteria included (1) age ≥18 years and (2) the ability to read and respond to questions in English or with minimal interpreter assistance. Patients with significant psychiatric or other comorbid disease were not eligible if the treating clinician determined that this would interfere with informed consent or study participation.

Procedure

Study staff identified potentially eligible patients by querying the electronic health record (EHR) for HCT recipients receiving their care at the Massachusetts General Hospital Cancer Center and identified those with moderate to severe chronic GVHD based on clinician assessment of chronic GVHD severity documented in the EHR. Clinicians are mandated to conduct an assessment of chronic GVHD and record related documentation at each clinical encounter at our institution. After obtaining permission from the primary treating transplant physician, a clinical research coordinator (Sarah Fishman) approached patients who met inclusion criteria. Study staff described the study procedures, and eligible and interested patients signed a written informed consent form to enroll in the study. Participants completed self-report assessments at baseline within 72 hours of enrollment as well as at 3 and 6 months postenrollment. Assessments were completed during participants' regularly scheduled clinic visits using tablet computers with a Research Electronic Data Capture (REDCap) online survey tool or paper questionnaires compliant with the Health Insurance Portability and Accountability Act.

Measures

Sociodemographic and Clinical Factors

Participants reported sociodemographic information such as age, sex, race, ethnicity, and education. We collected information about diagnosis, clinical characteristics, and transplant type from the EHR.

Anxiety and Depression

We used the Hospital Anxiety and Depression Scale (HADS) to measure symptoms of depression and anxiety. The HADS is a valid and reliable 14-item measure that has shown strong psychometric properties in oncology patient studies [16-18]. On a 4-point Likert scale, participants rated how they have felt in the past week. Subscales were examined continuously as well as with a cut-off of 8 or higher indicating clinically significant anxiety or depression.

QOL

We used the Functional Assessment of Cancer Therapy–Bone Marrow Transplant [19] to assess QOL, which has been used in previous GVHD research [20]. The Functional Assessment of Cancer Therapy–Bone Marrow Transplant consists of 4 subscales (physical, functional, emotional, and social) and items specific to HCT. This measure consists of 47 items on a 5-point Likert scale, with higher scores corresponding to better QOL.

Symptom Burden

To assess chronic GVHD symptom burden, we used the Lee Symptom Assessment Scale [21]. This 30-item symptom assessment measures the negative effects of chronic GVHD on skin, vitality, lung, nutritional status, psychologic functioning, and eye and mouth symptoms, with higher scores indicating greater symptom burden. The Lee Symptom Assessment Scale is well validated [22] and frequently used in chronic GVHD research [23].

Physical Functioning

The Human Activity Profile (HAP) was administered to assess patients' physical fitness. The HAP is a 94-item self-report assessment of physical fitness and energy expenditure [24]. Participants are asked to assess their physical functioning on a 3-point scale, with higher scores corresponding to better physical functioning. The HAP is a validated measure and has been used with allogeneic HCT survivors [24].

Social Support

We administered the Medical Outcomes Study Social Support Survey to assess perceived social support [25]. The Medical Outcomes Study Social Support Survey consists of 19 items with 4 subscales measuring practical, informational and emotional, positive social interaction, and affectionate support. Participants answer on a 5-point Likert scale, with higher scores demonstrating higher perceived support.

Coping Strategies

Patients' coping strategies were assessed using the revised, 66-item version of the Coping Inventory for Stressful Situation (CISS) [11] with subscales measuring task-oriented coping (eg, purposeful efforts aimed at solving the problem), negative emotion-oriented coping (eg, blaming oneself and self-preoccupation), and avoidance-oriented coping (eg, ignoring the problem or using social activities to divert attention). The avoidance subscale also comprises a distraction and social diversion subscale. The CISS uses a 5-point Likert scale;

higher scores indicate greater use of the respective coping style. The CISS is a valid instrument [26] and has been used in oncology settings [27].

Statistical Analyses

Data were analyzed using Stata software (version 14; StataCorp, LLC, College Station, TX). Patients' sociodemographic, clinical, and treatment-related characteristics at the baseline time point were summarized with measures of central tendency for continuous variables and proportions for categorical variables. We described the rates of clinically significant anxiety and depression symptoms at baseline, 3 months, and 6 months with the proportion of patients scoring above the clinical cutoff. Next, we computed separate adjusted analyses to test the associations of coping strategies, symptom burden, physical functioning, and perceived social support at baseline (independent variables) with anxiety symptoms at baseline (dependent variable). We then repeated each analysis with depression symptoms at baseline as the dependent variable. These models controlled for age, sex, severity of chronic GVHD (moderate versus severe), and time from diagnosis of chronic GVHD to study enrollment.

To assess predictors of longitudinal trends in QOL, we conducted linear mixed-effect models with maximum likelihood to estimate missing data, regressing QOL at all 3 time points on baseline coping, symptom burden, physical functioning, and social support while also adjusting for patient age, sex, chronic GVHD severity, and time since chronic GVHD diagnosis. We did not include anxiety and depression symptoms in this model because of the large overlap of these symptoms with QOL. However, we repeated these analyses with longitudinal anxiety symptoms and depression symptoms as the dependent variable in place of QOL, with the same predictors as previously indicated. For illustration purposes, coping was operationalized as high versus low with a median split. Standardized regression coefficients (βs) and 95% confidence intervals (CIs) were obtained to determine the magnitude of the relationships, alongside a 2-sided $\alpha < .05$ to assess statistical significance. With a sample size of 50 patients, we had 90% power to detect a relationship among the psychosocial predictors and QOL.

RESULTS

Patient Characteristics

We identified 75 patients with moderate to severe chronic GVHD based on screening the EHR between July 2015 and July 2017. Thirteen were excluded because they had mild chronic GVHD (n = 9) or were non-English speaking (n = 4), and 6 were not approached because of physician refusal (n = 3) or missing their appointment (n = 3). A total of 56 eligible patients were approached in clinic, and 93% (52/56) agreed to participate and enrolled in the study. Overall, 86% of patients (45/52)

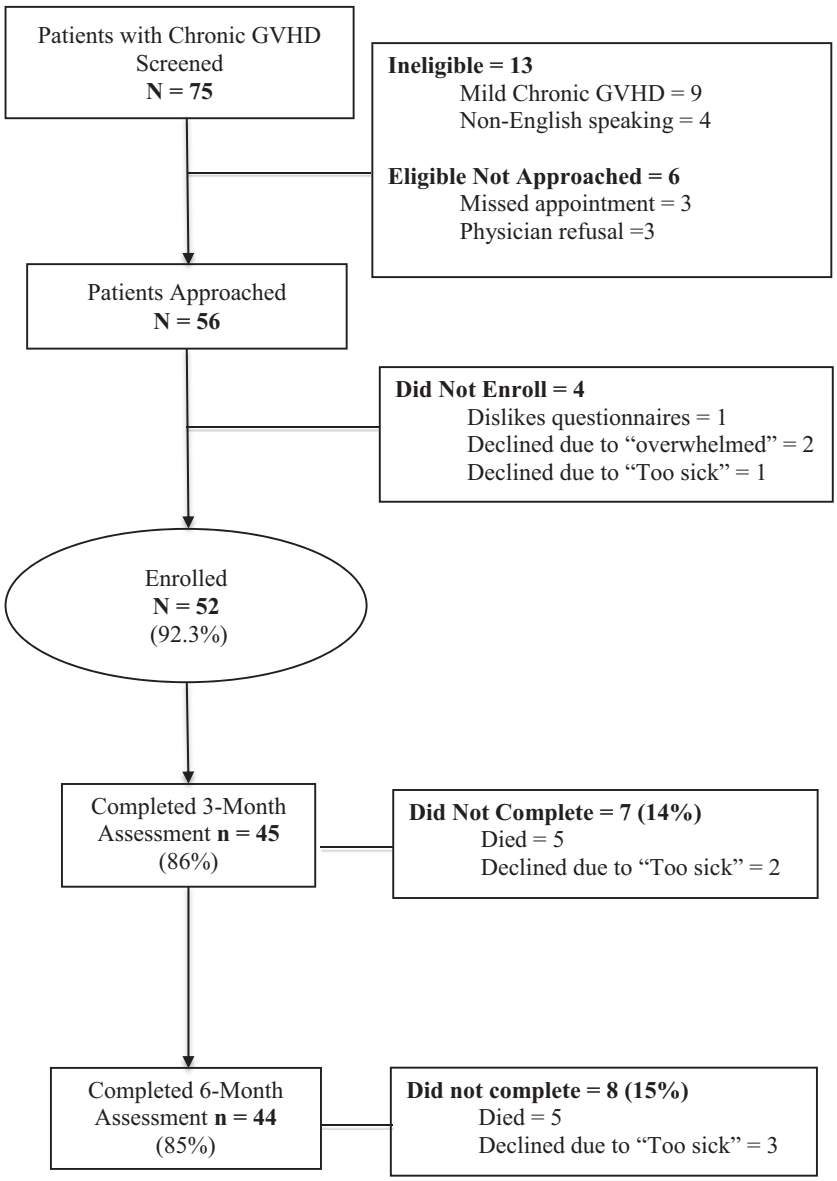

Figure 1. Study flow.

completed the 3-month assessment, and 85% (44/52) completed the 6-month assessment. Reasons for incomplete assessments are described in the study flow diagram (Figure 1). As detailed in Table 1, patients were, on average, 63 years old (range, 27 to 77 years), with the majority being female (59.6%; 31/52), white (92.3%; 48/52), and married or partnered (71.2%; 37/52). Most patients had a diagnosis of moderate chronic GVHD (71.2%; 37/52).

Rates of Depression and Anxiety over Time

As measured by the HADS, 32.7% (17/52) of patients reported elevated depression symptoms at baseline, 31.1% (14/45) at the 3-month assessment, and 37.8% (17/45) at the 6-month assessment. Similarly, 30.1% (16/52) of patients reported clinically significant anxiety symptoms at baseline, followed by 20.0% (9/45) at the 3-month assessment and 36.4% (16/44) at the 6-month assessment (See Figure 2).

Factors Associated with Depression and Anxiety Symptoms at Baseline

Adjusting for age, sex, chronic GVHD severity, and time since chronic GVHD diagnosis, patients reporting greater use of negative emotion-oriented coping ($\beta = 0.20$; $P = .002$; 95% CI, 0.07 to 0.33) and less use of task-oriented coping ($\beta = -0.10$; $P = .021$; 95% CI, −0.19 to −0.02) had greater depression symptoms at baseline. Worse physical functioning ($\beta = -0.07$; $P = .004$; 95% CI, −0.11 to −0.02) and greater symptom burden ($\beta = 0.07$; $P = .002$; 95% CI, 0.03 to 0.11) were also related to more depression symptoms at baseline. Avoidance-oriented coping (including the distraction and social diversion coping subscales) and perceived social support were not associated with depression symptoms.

Patients with greater use of negative emotion-oriented coping ($\beta = 0.28$; $P < .001$; 95% CI, 0.17 to 0.40) and worse physical functioning ($\beta = -0.05$; $P = .034$; 95% CI, −0.10 to 0.002) experienced greater anxiety symptoms at baseline adjusting for age, sex, chronic GVHD severity, and time since chronic GVHD diagnosis. Use of task-oriented or avoidance-oriented coping (including the distraction and social diversion coping subscales) was not associated with anxiety symptom severity at baseline. Level of anxiety at baseline was also not related to symptom burden or perceived social support.

Longitudinal Predictors of QOL Trajectory

Patient-reported QOL remained stable over time ($\beta = -0.34$; 95% CI, −3.2 to 2.53; $P = .815$). We then examined whether coping strategies predicted QOL over time. All statistics corresponding to the following results are displayed in Table 2. Furthermore, although analyses were conducted with a continuous score representing coping strategies, for graphical representation (Figures 3 and 4), we categorized each coping strategy with a median split (high versus low) to show differences in QOL based on high or low use of each coping strategy. Regarding coping strategies predicting QOL over time, patients who used more negative emotion-oriented coping at baseline reported worse QOL over time (Figure 3A). In addition, less use of task-oriented coping was associated with poorer QOL over time (Figure 3B). The relationship between avoidant-oriented coping and QOL was not significant (Figure 4A). Within the avoidance subscale, less use of social diversion-oriented coping was associated with poorer QOL over time (Figure 4B); however, distraction-oriented coping was not associated with QOL over time (Figure 4C).

Table 1
Participant Characteristics (N = 52).

Characteristic	Value
Age, median (range), y	63 (27-77)
Female sex	31 (59.6)
Race	
White	48 (92.3)
Black	1 (1.9)
Multiracial	3 (5.8)
Hispanic ethnicity	7 (13.5)
Relationship status	
Married/partnered	37 (71.1)
Single	7 (13.5)
Divorced	5 (9.6)
Widowed	3 (5.8)
Education	
Some high school or high school graduate	17 (32.7)
Some college or college graduate	26 (50.0)
Postgraduate	9 (17.3)
Diagnosis	
Acute myeloid leukemia/myelodysplastic syndrome	21 (40.4)
Acute lymphoblastic leukemia	8 (15.4)
Non-Hodgkin lymphoma	10 (19.2)
Hodgkin lymphoma	4 (7.7)
Myeloproliferative neoplasms	9 (17.3)
Conditioning intensity	
Myeloablative conditioning	18 (34.6)
Nonmyeloablative conditioning	34 (65.4)
Received total-body irradiation	14 (26.4)
Donor type	
Matched related donor	14 (26.9)
Matched unrelated donor	35 (67.3)
Haploidentical	3 (5.8)
Time from HCT to enrollment, median (range), mo	26 (4-161)
Chronic GVHD severity	
Moderate	37 (71.2)
Severe	15 (28.8)
Chronic GVHD organ involvement*	
Ocular	45 (86.5)
Skin	36 (69.2)
Oral	28 (53.8)
Lung	19 (36.5)
Myofascial	17 (32.7)
Gastrointestinal	13 (25.0)
Other	13 (25.0)
Receiving systemic steroids	43 (82.7)

Values are presented as n (%) unless otherwise indicated.
* Categories are not discrete as patients may have multiple organs involved in chronic GVHD.

Symptom burden, physical functioning, and perceived social support predicted QOL over time, such that patients with higher symptom burden, worse physical functioning, and less perceived support reported poorer QOL over time. All models adjusted for age, sex, severity of chronic GVHD, and time since diagnosis of chronic GVHD. Results were consistent when analyses were repeated with longitudinal depression and anxiety as outcomes in place of QOL.

DISCUSSION

With the increased use of allogeneic HCT, a potentially curative therapy for many patients with hematologic

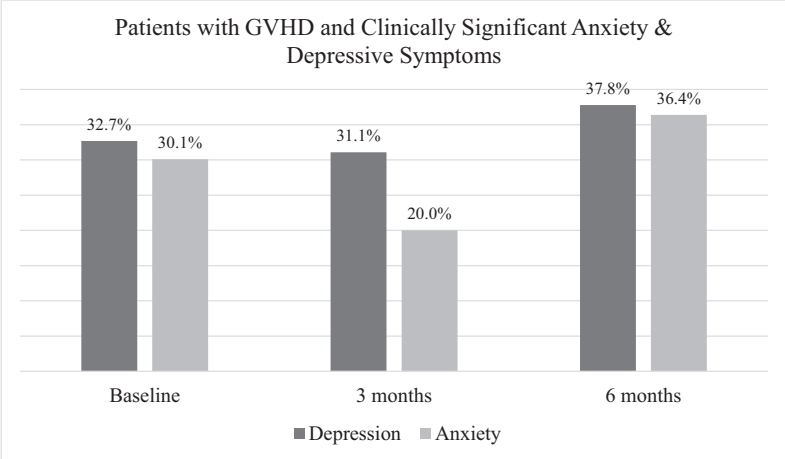

Figure 2. Percentage of patients with chronic GVHD who met criteria for clinically significant anxiety and depressive symptoms across 3 study time points. Clinically significant anxiety and depression indicated by score ≥8 on the HADS.

Table 2
Linear Mixed-Effects Models Predicting QOL Longitudinally in Patients with Moderate to Severe Chronic GVHD

	Quality of Life (FACT-BMT)		
Variable	β	95% CI	*P* Value
Negative emotion-oriented coping (CISS)	−0.58	−1.11 to −0.04	.035*
Task-oriented coping (CISS)	0.40	0.04 to 0.75	.028*
Avoidance-oriented coping (CISS)	0.29	−0.04 to 0.62	.089
Distraction-oriented coping (CISS)	0.04	−0.34 to 0.42	.838
Social diversion-oriented coping (CISS)	0.35	0.02 to 0.68	.039*
Chronic GVHD symptom burden (LSAS)	−0.30	−0.47 to −0.13	.001†
Adjusted activity profile (HAP)	0.32	0.15 to 0.49	<.001†
Social support (MOS-SSS)	6.47	2.27 to 10.68	.003†

Separate models were constructed for each predictor of interest. All models adjusted for age, sex (male versus female), chronic GVHD severity (moderate versus severe), and time from chronic GVHD diagnosis to study enrollment.
FACT-BMT indicates Functional Assessment of Cancer Therapy–Bone Marrow Transplant (range, 0 to 148); CISS, Coping Inventory for Stressful Situations (range, 16 to 80); LSAS, Lee Symptom Assessment Scale (range, 0 to 100); HAP, Human Activity Profile (range, 94 to 282); MOS-SSS, Medical Outcomes Study Social Support Survey (range, 19 to 95).
* $P < .05$.
† $P < .01$.

malignancies, the psychosocial and physical burden of chronic GVHD on allogeneic HCT survivors is ever prominent. The current study is the first prospective observational study to highlight the substantially high rates of depression and anxiety symptoms in patients with moderate to severe chronic GVHD, with approximately one third of patients meeting criteria for clinically significant depression or anxiety. While disruptions in mood are prevalent in HCT survivors [4-7], the incidence of depression and anxiety in survivors who develop chronic GVHD is not well understood. Previous work by our group with cross-sectional data collected through the Chronic GVHD Consortium demonstrated that 19.3% and 22.8% of patients were moderately to extremely bothered by depression and anxiety, respectively [28]. Furthermore, patients with self-reported depression and anxiety in that study had worse QOL, physical functioning, functional status, and survival [28]. We also demonstrated an association between higher depression and anxiety and greater symptom burden in patients living with chronic GVHD [29]. Taken together, these findings highlight the need for screening, referral, and intervention.

Although a somewhat larger body of evidence describes the substantial QOL impairment experienced by HCT survivors with chronic GVHD, this is the first longitudinal study to examine predictors of QOL over time, identifying coping, symptom burden, perceived social support, and physical functioning as related constructs. The development of chronic GVHD is the factor most strongly associated with QOL post-transplantation [5], and the severity of chronic GVHD is directly and inversely related to QOL [3]. Given the long-term psychosocial and physical toll of chronic GVHD, identifying populations at risk of poorer QOL over time is of utmost importance. Even more concerning is the absence of an association between response to treatment for chronic GVHD and patient-reported QOL [30]. This suggests that improving QOL requires a multifactorial approach targeting several underlying correlates of QOL, such as coping strategies, symptom burden, perceived social support, and physical functioning, all of which predicted QOL over time in the current study.

Patients in our study who used negative emotion-oriented coping were more likely to report anxiety and depression symptoms and poorer QOL over time, while patients who used task-oriented coping reported fewer depression symptoms and better QOL over time. Coping style is a modifiable construct that, if altered to be more adaptive in the context of a chronic medical stressor, could potentially change the trajectory of QOL for patients with chronic GVHD. Alternatively,

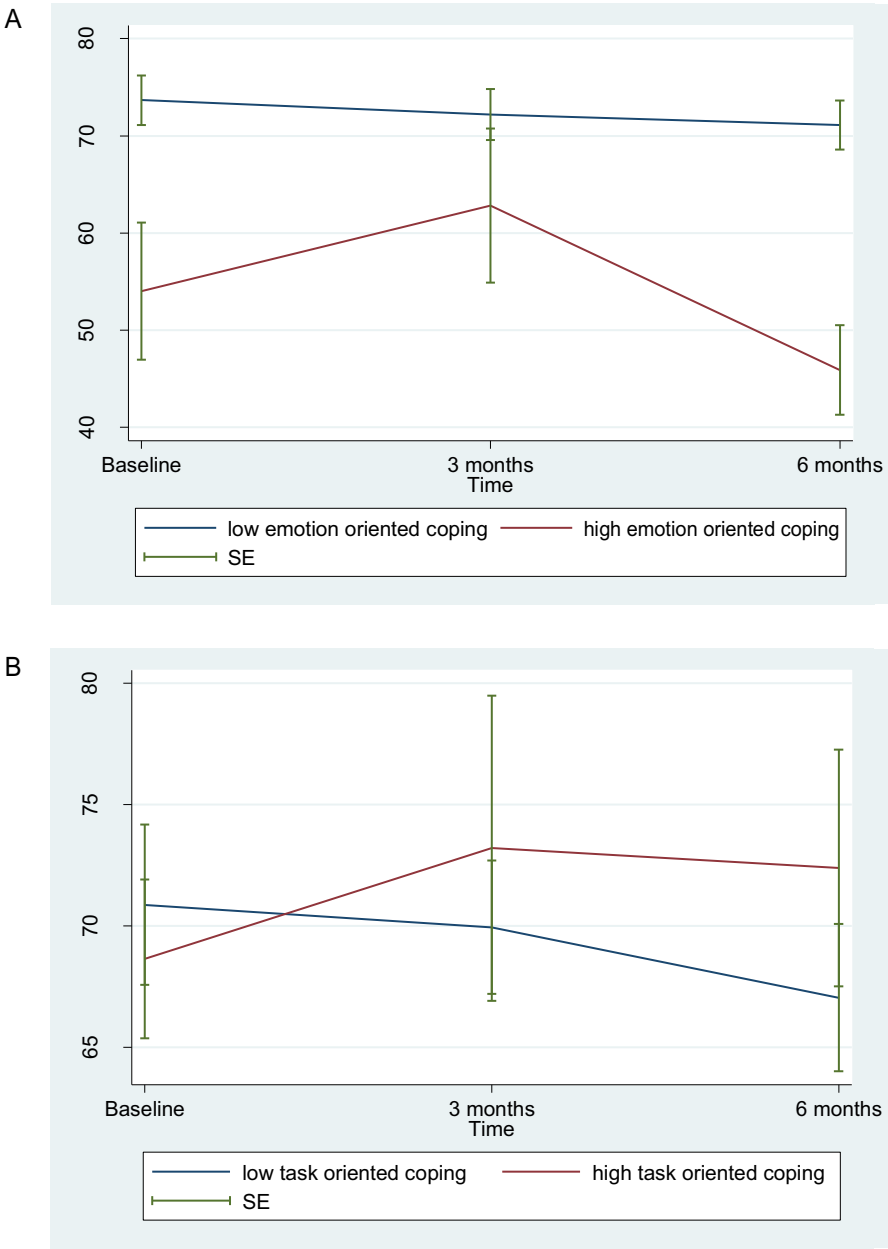

Figure 3. Longitudinal relationship between use of negative emotion-oriented and task-oriented coping strategies (high versus low strategy use) at baseline with QOL over time. (A) High use of negative emotion-oriented coping at baseline predicts poorer QOL over time. (B) Low use of task-oriented coping at baseline predicts poorer QOL over time. These figures operationalize the use of negative emotion-oriented and task-oriented coping strategies as high versus low use with a median split for the purposes of illustration.

management of anxiety and depression may lead to use of more helpful coping strategies and less use of negative emotion-oriented strategies. Although negative emotion-oriented coping includes blaming oneself, negative self-statements, and denial, task-oriented coping seeks to solve a problem, set goals, or gather information. It is notable that patients in this study who used social diversion coping strategies, a subscale of avoidance-oriented coping, had better QOL over time. While avoidance of a problem would generally be viewed as a maladaptive coping style, avoidance in the form of social diversion can be a helpful and healthy approach to manage anxiety and depression in the context of a chronic stressor such as GVHD, which is largely unchanging and minimally controllable. We identified only 1 other study that examined use of coping post-transplantation but not specifically in chronic GVHD. Consistent with our findings, this study demonstrated that patients who turn to less adaptive coping strategies and have transplant-related symptomatology are at higher risk for depression [31].

The results of our study also showed that symptom burden was associated with greater depression symptoms, poorer physical functioning was associated with anxiety, and both symptom burden and physical functioning predicted QOL over time. These findings are consistent with the few studies examining these constructs in patients with chronic GVHD. One study demonstrated that symptom burden in patients with chronic GVHD is associated with lower physical functioning [30]. Furthermore, use of prednisone has been shown to be

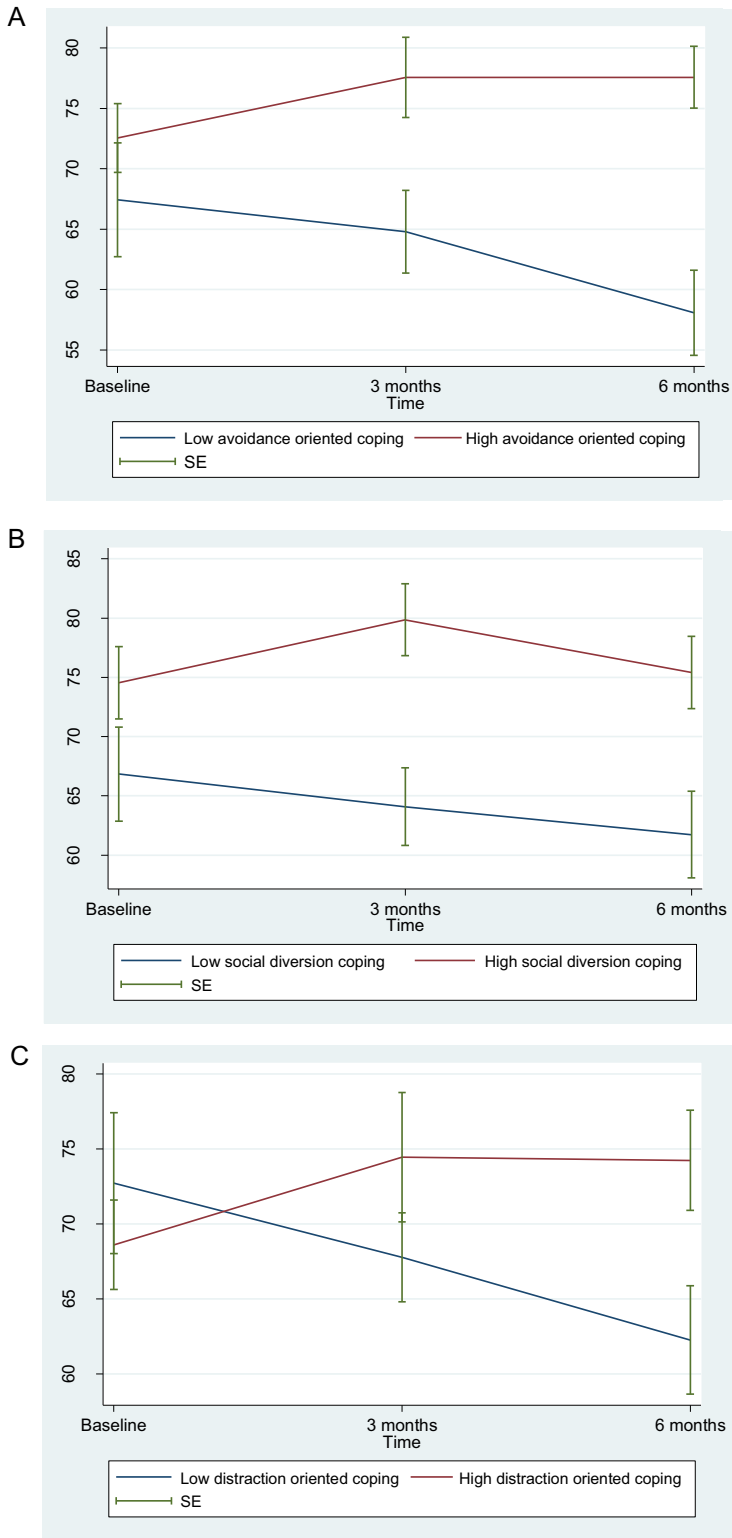

Figure 4. Longitudinal relationship between use of avoidance-oriented coping strategies (high versus low strategy use) at baseline with QOL over time. (A) Low use of avoidance-oriented coping at baseline marginally predicts poorer QOL over time. (B) Low use of social diversion-oriented coping at baseline predicts poorer QOL over time. (C) Use of distraction-oriented coping at baseline does not predict QOL over time. These figures operationalize the use of avoidance-oriented coping strategies as high versus low use with a median split for the purposes of illustration.

associated with higher symptom burden and QOL [30], which is significant as 82.7% of the current sample was receiving systemic corticosteroids. Symptom burden can lead to functional impairments and activity limitations, which affects QOL and overall functional status in patients post-HCT [30,32]. We also demonstrated that patients with lower perceived social support experienced poorer QOL across all time points. We were unable to identify any literature reporting on perceptions of

social support in chronic GVHD, but in 1 study of survivors of autologous transplantation, problematic social support was associated with poorer long-term survival [33]. This finding further supports that recognizing patients with deficits in social support or those receiving problematic support may identify 1 population at risk for poorer QOL across time.

Certain limitations should be considered when interpreting the study results. First, the relatively small sample comprises primarily white, non-Hispanic English-speaking participants, restricting the generalizability of the findings. Second, the analyses did not account for anxiety or depression symptoms or disorders before HCT, which are known to predict the development of mood disorders post-transplant [34]. Furthermore, although the analyses did adjust for age, sex, chronic GVHD severity, and time since chronic GVHD diagnosis, additional disease- and treatment-related factors may confound the relationships among the examined psychosocial factors, such as time elapsed since transplant, other post-transplant complications, medications, infections, or pre-existing medical or psychiatric comorbidities. However, given our limited sample size, we are unable to adjust for all these factors. Although we cannot determine directionality of the relationships between baseline anxiety and depression and baseline coping, symptom burden, physical functioning, and perceived social support, a major strength of the study is the longitudinal examination of anxiety, depression, and predictors of QOL in a prospective cohort. Although there is a noticeable change in anxiety at the second study time point, we are limited in our ability to understand what may be driving that anxiety change and whether this is clinically meaningful. Nonetheless, the study time points are not anchored to a clinical event; patients could enroll at any time following their chronic GVHD diagnosis.

There are unmet psychosocial and physical needs of patients who develop chronic GVHD post-HCT [35], and these findings highlight the substantial need to promote adaptation and enhance effective coping while maintaining or improving QOL and mood. Although poor coping may have downstream effects on mood and QOL, alternatively, the presence of depressive or anxiety symptoms can affect the coping strategies one chooses to engage with. In the short term, patients at risk for poorer QOL and mood disorders warrant expeditious referral to supportive care services such as psychology, psychiatry, and/or social work for proactive management of depression and/or anxiety symptoms. In addition to therapy with a licensed clinical social worker or psychologist, patients may benefit from a pharmacologic approach for mood management with antidepressants or anxiolytics. In the long term, the correlates of anxiety and depression and predictors of QOL identified in the current study (ie, coping strategies, perceived social support, physical functioning, and symptom burden) are modifiable by way of evidence-based psychosocial interventions that can be easily adapted to target the unique needs of patients with chronic GVHD. For example, interventions based on cognitive behavioral therapy are beneficial for improving mood [36] and QOL [37] for cancer survivors and have been used in patients post-HCT [38]. Specifically, skills-based interventions target aforementioned modifiable constructs by teaching patients techniques to (a) employ adaptive coping strategies [39], (b) enhance physical functioning [40], (c) expand social support networks [41], (d) manage symptoms and side effects [42], and (e) improve mood [43], among others. A skills-based cognitive behavioral therapy intervention that is innovatively adapted for patients with chronic GVHD has the potential to substantially enhance the care of patients throughout the trajectory of the disease.

In summary, chronic GVHD can be a debilitating outcome for HCT survivors, with stable and high rates of clinically elevated anxiety and depression symptoms. These findings highlight the substantial psychosocial and physical needs of patients with chronic GVHD and identify distinct and modifiable correlates of depression, anxiety, and QOL such as coping, symptom management, physical functioning, and perceived social support. Although substantial efforts are devoted to better prevent or treat chronic GVHD, future investigation should also focus on innovative, evidence-based interventions that promote skill acquisition and improve post-transplant outcomes by improving mood and maintaining QOL for patients with chronic GVHD.

ACKNOWLEDGMENTS

Financial disclosure: This work was supported by funding from the American Cancer Society-Institutional Research Grant (ACS-IRG, A.E.-J.).

Conflict of interest statement: There are no conflicts of interest to report.

Z.D. received research funding from Incyte. J.S.T. received research funding from Pfizer. The other authors declared no conflicts of interest.

REFERENCES

1. Pidala J, Kurland B, Chai X, et al. Patient reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. *Blood*. 2011;117:4651–4657.
2. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2011;29:2230.
3. Kurosawa S, Oshima K, Yamaguchi T, et al. Quality of life after allogeneic hematopoietic cell transplantation according to affected organ and severity of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2017;23:1749–1758.
4. Lee SJ, Fairclough D, Parsons SK, et al. Recovery after stem-cell transplantation for hematologic diseases. *J Clin Oncol*. 2001;19:242–252.
5. Lee SJ, Loberiza F, Antin J, et al. Routine screening for psychosocial distress following hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2005;35:77.
6. Syrjala K, Chapko M, Vitaliano P, Cummings C, Sullivan K. Recovery after allogeneic marrow transplantation: prospective study of predictors of long-term physical and psychosocial functioning. *Bone Marrow Transplant*. 1993;11:319–327.
7. Syrjala KL, Langer SL, Abrams JR, et al. Recovery and long-term function after hematopoietic cell transplantation for leukemia or lymphoma. *JAMA*. 2004;291:2335–2343.
8. Paterson C, Jones M, Rattray J, Lauder W. Exploring the relationship between coping, social support and health-related quality of life for prostate cancer survivors: a review of the literature. *Eur J Oncol Nurs*. 2013;17:750–759.
9. Nipp RD, El-Jawahri A, Fishbein JN, et al. Factors associated with depression and anxiety symptoms in family caregivers of patients with incurable cancer. *Ann Oncol*. 2016;27:1607–1612.
10. Lazarus RS, Folkman S. *Stress, Appraisal, and Coping*. New York, NY: Springer; 1984.
11. Endler NPD, Parker JDA. *Coping Inventory for Stressful Situations (CISS): Manual*. 2nd ed North Tonawanda, NY: Multi-Health Systems; 1999.
12. Roesch SC, Adams L, Hines A, et al. Coping with prostate cancer: a meta-analytic review. *J Behav Med*. 2005;28:281–293.
13. Vriezekolk JE, van Lankveld WG, Geenen R, van den Ende CH. Longitudinal association between coping and psychological distress in rheumatoid arthritis: a systematic review. *Ann Rheum Dis*. 2011;70:1243–1250.
14. Englbrecht M, Kruckow M, Araujo E, Rech J, Schett G. The interaction of physical function and emotional well-being in rheumatoid arthritis—what is the impact on disease activity and coping? *Semin Arthritis Rheum*. 2013;42:482–491.
15. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11:945–956.
16. Nikbakhsh N, Moudi S, Abbasian S, Khafri S. Prevalence of depression and anxiety among cancer patients. *Caspian J Intern Med*. 2014;5:167–170.
17. Chaturvedi SK. Psychiatric oncology: cancer in mind. *Indian J Psychiatry*. 2012;54:111–118.

18. Boxley L, Flaherty JM, Spencer RJ, et al. Reliability and factor structure of the Hospital Anxiety and Depression Scale in a polytrauma clinic. *J Rehabil Res Dev*. 2016;53:873–880.
19. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11:570–579.
20. Pulewka K, Wolff D, Herzberg PY, et al. Physical and psychosocial aspects of adolescent and young adults after allogeneic hematopoietic stem-cell transplantation: results from a prospective multicenter trial. *J Cancer Res Clin Oncol*. 2017;143:1613–1619.
21. Lee SJ, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2002;8:444–452.
22. Merkel EC, Mitchell SA, Lee SJ. Content validity of the Lee Chronic Graft-versus-Host Disease Symptom Scale as assessed by cognitive interviews. *Biol Blood Marrow Transplant*. 2016;22:752–758.
23. Martires KJ, Baird K, Steinberg SM, et al. Sclerotic-type chronic GVHD of the skin: clinical risk factors, laboratory markers, and burden of disease. *Blood*. 2011;118:4250–4257.
24. Herzberg PY, Heussner P, Mumm FH, et al. Validation of the human activity profile questionnaire in patients after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2010;16:1707–1717.
25. Sherbourne CD, Stewart AL. The MOS social support survey. *Soc Sci Med*. 1991;32:705–714.
26. Cosway R, Endler NS, Sadler AJ, Deary IJ. The Coping Inventory for Stressful Situations: factorial structure and associations with personality traits and psychological health. *J Appl Biobehav Res*. 2000;5:121–143.
27. Shakeri J, Kamangar M, Ebrahimi E, et al. Association of coping styles with quality of life in cancer patients. *Indian J Palliat Care*. 2015;21:298–304.
28. El-Jawahri A, Pidala J, Khera N, et al. Impact of psychological distress on quality of life, functional status, and survival in patients with chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2018;24:2285–2292.
29. El-Jawahri A, Wood B, Cutler CS, et al. Self-reported depression and anxiety by patients with chronic graft-versus-host disease identify a group with worse quality of life, symptoms, and functional status. *Biol Blood Marrow Transplant*. 2016;22:S27.
30. Inamoto Y, Martin PJ, Chai X, et al. Clinical benefit of response in chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2012;18:1517–1524.
31. Barata A, Gonzalez BD, Sutton SK, et al. Coping strategies modify risk of depression associated with hematopoietic cell transplant symptomatology. *J Health Psychol*. 2018;23:1028–1037.
32. Baker KS, Fraser CJ. Quality of life and recovery after graft-versus-host disease. *Best Pract Res Clin Haematol*. 2008;21:333–341.
33. Frick E, Motzke C, Fischer N, Busch R, Bumeder I. Is perceived social support a predictor of survival for patients undergoing autologous peripheral blood stem cell transplantation? *Psychooncology*. 2005;14:759–770.
34. El–Jawahri A, Chen YB, Brazauskas R, et al. Impact of pre–transplant depression on outcomes of allogeneic and autologous hematopoietic stem cell transplantation. *Cancer*. 2017;123:1828–1838.
35. Lee SJ. Have we made progress in the management of chronic graft-vs-host disease? *Best Pract Res Clin Haematol*. 2010;23:529–535.
36. Traeger L, Greer JA, Fernandez-Robles C, Temel JS, Pirl WF. Evidence-based treatment of anxiety in patients with cancer. *J Clin Oncol*. 2012;30:1197–1205.
37. Duncan M, Moschopoulou E, Herrington E, et al. Review of systematic reviews of non-pharmacological interventions to improve quality of life in cancer survivors. *BMJ Open*. 2017;7: e015860.
38. DuHamel KN, Mosher CE, Winkel G, et al. Randomized clinical trial of telephone-administered cognitive-behavioral therapy to reduce post-traumatic stress disorder and distress symptoms after hematopoietic stem-cell transplantation. *J Clin Oncol*. 2010;28:3754.
39. Stanton AL, Luecken LJ, MacKinnon DP, Thompson EH. Mechanisms in psychosocial interventions for adults living with cancer: opportunity for integration of theory, research, and practice. *J Consult Clin Psychol*. 2013;81:318.
40. Bower JE. Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*. 2014;11:597.
41. Gudenkauf LM, Antoni MH, Stagl JM, et al. Brief cognitive-behavioral and relaxation training interventions for breast cancer: a randomized controlled trial. *J Consult Clin Psychol*. 2015;83:677–688.
42. Duijts SF, van Beurden M, Oldenburg HS, et al. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial. *J Clin Oncol*. 2012;30:4124–4133.
43. Greer JA, Traeger L, Bemis H, et al. A pilot randomized controlled trial of brief cognitive-behavioral therapy for anxiety in patients with terminal cancer. *Oncologist*. 2012;17:1337–1345.