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# Psychological and Physical Function in Allogeneic Hematopoietic Cell Transplant Survivors with Chronic Graft-Versus-Host Disease

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## Abstract

**Purpose:** Chronic graft-versus-host disease (cGVHD) is a common late complication of allogeneic hematopoietic cell transplantation (HCT). This study comprehensively evaluated physical and psychological function among individuals with cGVHD. Additional aims were to

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Author Contributions

Jenna Hansen analyzed data, interpreted results, drafted manuscript, and revised manuscript. Mark Juckett conceived study, designed methodology, acquired funding, enrolled participants, performed clinical evaluations, interpreted results, and revised manuscript. Mikayla Foster interpreted the results and revised manuscript. Meredith Rumble designed methodology, interpreted results, and revised manuscript. Keayra Morris designed methodology, acquired data, and revised manuscript. Peiman Hematti conceived study, designed methodology, acquired funding, interpreted results, and revised manuscript. Erin Costanzo conceived study, designed methodology, acquired funding (PI), enrolled participants, supervised all data acquisition, analyzed data, interpreted results, drafted manuscript, and revised manuscript.

All authors approved the final version and agreed to be accountable for aspects of the work in ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of the University of Wisconsin-Madison (9/29/14 / 2014–0752).

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent to Publish

The authors affirm that participants provided informed consent for publication of the anonymized data.

investigate relationships between disease severity and psychological and physical function, and to investigate patterns of psychological and physical function by disease site.

**Method:** Adults at least 6 months post allogeneic HCT were enrolled and either had cGVHD ($n$ = 59) or served as a reference sample of HCT survivors with no cGVHD history ($n$ = 19). Participants completed self-report measures of depression, anxiety, fatigue, insomnia, pain, cognition, and sexual function and had a comprehensive clinical evaluation of cGVHD using NIH consensus scoring criteria. Participants with cGVHD were stratified by disease severity and site and compared to the reference group with no cGVHD.

**Results:** Participants with mild cGVHD had comparable psychological and physical symptoms to the reference sample, while participants with moderate cGVHD experienced more severe anxiety and problems with sexual function, and participants with severe cGVHD experienced more severe depressive symptoms and pain compared to the reference sample. Participants with cGVHD manifesting in the skin and GI tract had the most severe symptoms, including mood disturbance, fatigue, and pain.

**Conclusions and Implications for Cancer Survivors:** Results suggest that patients with more severe cGVHD and those with cGVHD manifesting in the skin, GI tract, and lungs are at risk for poorer psychological and physical outcomes and may benefit from proactive interventions to optimize function.

### Keywords

Chronic graft-versus-host disease; hematopoietic cell transplant; depression; anxiety; pain; sexual function

## Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for advanced hematologic cancers, including leukemias and lymphomas. Although HCT can extend survival, the intensive treatment carries a significant risk of morbidity and mortality and can impair quality of life. A common late complication of HCT is chronic graft-versus-host disease (cGVHD) which involves both allogeneic and autoimmune dysregulation [1]. cGVHD occurs in 30–70% of allogeneic HCT and is the primary cause of late non-relapse mortality in HCT patients [2, 3]. cGVHD can range from mild, affecting only a single organ or tissue site, to severe disease, affecting multiple organs and leading to disability and mortality [1]. While symptoms differ based on disease site and severity, those living with cGVHD experience poorer overall health and are at risk for a variety of health comorbidities including endocrine disorders, osteoporosis, cardiopulmonary disease, and neurologic symptoms [4].

A growing body of research suggests that individuals with cGVHD have poorer global, or overall, quality of life [5–11], and more severe cGVHD is associated with poorer quality of life [11–15]. There also is evidence that survivors with cGVHD affecting joints, lungs, skin, and GI tract have greater impairment in quality of life [14, 15]. Most prior research has utilized global quality of life measures as part of larger trials or investigations; consequently, there is limited information about specific domains of quality of life.

In particular, little is known about the psychological sequelae of cGVHD. The physical problems, lifestyle adjustments, and mortality risk associated with cGVHD, along with the effects of routine treatments such as corticosteroids, may cause distress and mood changes. Preliminary research has found survivors with cGVHD report concerns about depression and anxiety [13, 16–19]. However, research has been limited by the use of a single item to evaluate mood changes or lack of a comparison group or reference. Fatigue, sleep disturbance, pain, and problems with cognitive function tend to co-occur in a symptom cluster with psychological distress and are well-documented problems for individuals recovering from HCT [20]; however, few studies have examined these quality-of-life concerns in those with cGVHD [13]. In addition, little is known about the interplay between cGVHD presentations and quality of life domains. The current study evaluated these understudied quality-of-life concerns among individuals with cGVHD using patient-reported measures of psychological and physical function and comprehensive physician assessments of cGVHD.

The primary objective of this study was to conduct a comprehensive evaluation of physical and psychological function among individuals with cGVHD. cGVHD patients' scores on patient-reported outcome measures of depression, anxiety, fatigue, pain, sleep disturbance, cognitive function, and sexual function were compared to a reference group of survivors who had allogeneic HCT but did not develop cGVHD. Additional aims were to examine relationships between cGVHD severity and measures of psychological and physical function and to investigate patterns in psychological and physical function by cGVHD disease site.

## Methods

### Participants

The study was approved by the University of Wisconsin-Madison Institutional Review Board. Participants were adults 18 years of age or older who had received allogeneic HCT for a hematologic malignancy at least 6 months prior to enrollment and were receiving ongoing follow up care at the University of Wisconsin Bone Marrow Transplant Program. Only individuals with active cGVHD or those with no cGVHD history were included; participants with a prior cGVHD diagnosis that had resolved were excluded. All known eligible patients who had an appointment during the 18-month study enrollment period were approached about the study. Prior to enrollment, informed consent was obtained from all individual participants included in the study. Either at enrollment or the subsequent clinic visit, participants had a comprehensive cGVHD clinical evaluation by a hematologist specializing in HCT and completed self-report measures.

Of 102 allogeneic HCT survivors with cGVHD approached in clinic, 84 (82%) consented to participated. Subsequently, 25 participants were excluded either because they failed to complete self-report measures ($n = 16$) or because the clinical evaluation showed resolved cGVHD ($n = 9$). 2 participants with confirmed cGVHD diagnoses had missing or incomplete information on grade and disease site at the time of participation and were therefore excluded from analyses with these variables. Of 28 allogeneic HCT survivors with no cGVHD history approached in clinic, 23 (82%) consented to participate. Of those who consented, 4 failed to complete study measures and were excluded. The final sample

therefore included 59 participants with active cGVHD and 19 participants with no cGVHD history who served as a reference group.

Demographics and medical characteristics for study participants are shown in Table 1. Chi-square analyses showed no significant differences in demographics between groups (all $p > .15$). Those with active cGVHD were less likely to have received grafts from bone marrow and to have nonmyeloablative regimens as compared to the reference group, which are known factors associated with cGVHD incidence. Unexpectedly, the active cGVHD group was more likely to have a matched related donor and less likely to have a matched unrelated donor as compared to the reference sample.

## Measures

**Depression.—**The Inventory of Depression and Anxiety Symptoms (IDAS) was used to measure depression and anxiety disorders based on DSM-V diagnostic criteria [21] and has been used in prior studies of HCT patients [22–24]. The general depression, panic (somatic anxiety symptoms), and traumatic intrusions (cognitive anxiety symptoms) subscales were the focus of the present study. The IDAS showed good internal consistency in the present sample, $\alpha = .90$.

**Fatigue.—**The Fatigue Symptom Inventory (FSI) is a well-validated measure of fatigue that was developed for use with cancer patients [25]. Participants rated their fatigue severity and the extent to which fatigue interfered with 7 activities of daily living over the past week from 0 to 10. A score of 3 or above on the severity subscale has been established as an indicator of clinically significant fatigue [26]. The FSI had good internal consistency in this sample, $\alpha = .92$ (severity) and .94 (interference).

**Pain.—**The Brief Pain Inventory (BPI) is a measure of pain that has been well-validated in cancer patients and other populations [27]. Participants rated their pain severity and the extent to which pain interfered with 7 daily activities over the past week from 0 to 10. The BPI had good internal consistency in this sample, $\alpha = .94$ (severity) and .95 (interference).

**Insomnia.—**The Insomnia Severity Index (ISI) is an 8-item measure of the symptoms, consequences, and patient concern about insomnia [28, 29]. Scores of 8 or above are indicative of clinically significant insomnia, with scores of 15 or above indicating moderate to severe insomnia. The ISI showed good internal consistency in the present sample, $\alpha = .89$.

**Cognition and sexual function.—**The Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Function Abilities (6-item short form) and Sexual Function (2-item sexual satisfaction subscale) were used to measure cognition and sexual function [30–32]. Both scales showed good internal consistency in the present sample, $\alpha = .91$ (cognition) and .95 (sexual function).

**cGVHD Burden.—**The Lee Symptom Scale is a 30-item measure of patient perceived cGVHD burden [33]. Participants with active cGVHD rated how much they were bothered by cGVHD-related symptoms over the past month from 0 (Not at all) to 4 (Extremely). Scores are normalized on a 0–100 scale with higher scores indicating worse cGVHD burden.

A change of 6–7 points in scores is considered a clinically meaningful difference. This scale showed good internal consistency in the present sample, α = .84.

**cGVHD.—**Board-certified hematologists specializing in the care of HCT patients confirmed cGVHD diagnoses and performed a comprehensive clinical evaluation of cGVHD using NIH consensus scoring criteria for cGVHD [34]. Overall cGVHD severity was graded from 0 (no cGVHD) to 3 (Severe cGVHD) based on the number and severity of disease sites. Each cGVHD disease site was carefully evaluated and rated for severity.

### Statistical Analysis

STATA statistical package was used for data analysis. cGVHD participants' scores on physical and psychological function measures were characterized with respect to norms or clinical cut points, where available, and were compared to the reference group of allogeneic HCT recipients with no cGVHD using two-tailed *t* tests. Scores for participants falling into each cGVHD grade (mild-severe) were also compared with the reference group and to one another. Finally, scores for participants with the most frequent cGVHD disease sites (eyes, lungs, skin, mouth, joints, and GI tract) were compared to the reference group.

Due to multiple tests, we used the Benjamini and Hochberg False Discovery Rate (FDR) procedure to control for both the false discovery rate and the family-wise error rate. In brief, the FDR procedure involves ranking *p* values from smallest to largest and requires increasingly low *p* values to reject the null hypothesis as the *p*-value rank decreases [35].

## Results

Participants with cGVHD reported psychological symptoms (IDAS) that were comparable to population norms [21] on measures of depression ($M = 38.4$, $SD = 10.5$), somatic anxiety ($M = 12.7$, $SD = 4.4$), and cognitive anxiety ($M = 5.1$, $SD = 1.6$). There were no differences between participants with cGVHD and the reference group of allogeneic HCT recipients without cGVHD on depression or cognitive anxiety measures. Participants with cGVHD, however, had significantly higher somatic anxiety ($M = 12.7$, $SD = 4.4$) than did the reference group ($M = 10.4$, $SD = 3.2$), $t = -2.05$, $p = .04$, $d = .58$.

Participants with cGVHD reported problems with physical symptoms. Mean fatigue severity (FSI) scores ($M = 3.8$, $SD = 2.0$) exceeded the clinical cut score of 3, with 68% of participants with scores indicating clinically significant fatigue. Similarly, mean insomnia (ISI) scores ($M = 7.8$, $SD = 4.8$) were similar to the clinical cut score of 8, with 54% of participants endorsing clinically significant insomnia symptoms. Patients with cGVHD reported mild pain, on average ($M = 2.4$, $SD = 2.2$). Patients with cGVHD had sexual function scores well below the normative population mean (mean T score = 37.1, $SE = 2.5$, 9$^{th}$ percentile); 58% of patients scored in the "low" sexual function range. Patients with cGVHD had cognitive function scores similar to the population mean (mean T score = 47.4, $SE = 2.9$, 40$^{th}$ percentile); however, 22% of patients had scores indicative of mild cognitive impairment. There were no significant differences on any physical function measures between participants with active cGVHD and the reference group of allogeneic HCT recipients with no cGVHD.

### cGVHD Severity

Table 3 shows mean scores for psychological and physical symptom measures by cGVHD grade. Participants with severe cGVHD reported significantly worse depression ($t = 2.13$, $p = .04$, $d = .72$) and pain intensity ($t = 2.12$, $p = .04$, $d = .72$) as compared to the reference sample of patients with no cGVHD. Similarly, those with severe cGVHD reported significantly worse depression ($t = 2.19$, $p = .04$, $d = .69$), pain intensity ($t = 2.12$, $p = .04$, $d = .68$) and pain interference ($t = 2.53$, $p = .02$, $d = .79$) as compared to patients with mild (grade 1) cGVHD. Participants with moderate cGVHD reported significantly more somatic anxiety ($t = 2.51$, $p = .02$, $d = .81$) and poorer sexual function ($t = -2.55$, $p = .02$, $d = .87$) as compared to the reference sample and worse pain interference than patients with mild cGVHD ($t = 2.10$, $p = .04$, $d = .65$) although the difference in pain interference was no longer significant after the FDR procedure. While there was a clinically meaningful 6-point difference in Lee Symptom Scale scores between patients with mild cGVHD and severe cGVHD, the difference was not statistically significant ($t = 1.55$, $p = .13$, $d = .52$).

### cGVHD Disease Site

Table 4 shows mean scores for psychological and physical function measures by cGVHD disease site; comparisons were made to the reference group only as patients can have more than one disease site (see Table 2). Participants with cGVHD manifesting in the eyes did not differ significantly from the reference group on any measures. Participants with cGVHD in the mouth reported more somatic anxiety ($t = 3.21$, $p = .002$, $d = .97$) and poorer sexual function ($t = -2.93$, $p = .005$, $d = .86$) as compared to the reference sample of allogeneic HCT recipients with no cGVHD history. Participants with skin cGVHD had greater depression ($t = 2.37$, $p = .02$, $d = .72$), fatigue intensity ($t = 2.07$, $p = .045$, $d = .61$) and fatigue interference ($t = 2.20$, $p = .03$, $d = .66$), and pain intensity ($t = 2.32$, $p = .03$, $d = .70$) and pain interference ($t = 2.18$, $p = .04$, $d = .66$) as compared to the reference sample although the difference in fatigue intensity was no longer significant after the FDR procedure. Participants with cGVHD in the lungs reported more somatic anxiety ($t = 2.47$, $p = .02$, $d = .76$), greater fatigue intensity ($t = 2.07$, $p = .044$, $d = .62$), and poorer sexual function ($t = -2.41$, $p = .02$, $d = .73$) as compared to the reference sample although the difference in fatigue intensity was no longer significant after the FDR procedure. Participants with cGVHD manifesting in joints reported greater somatic anxiety ($t = 2.19$, $p = .03$, $d = .69$) and pain interference ($t = 2.04$, $p = .048$, $d = .64$) as compared to the reference sample although the difference in pain interference was no longer significant after the FDR procedure. Participants with cGVHD manifesting in the GI tract reported greater depression ($t = 2.67$, $p = .01$, $d = .88$), somatic anxiety ($t = 3.26$, $p = .003$, $d = 1.06$), fatigue intensity ($t = 2.36$, $p = .02$, $d = .78$) and interference ($t = 2.13$, $p = .04$, $d = .69$), pain intensity ($t = 2.50$, $p = .02$, $d = .82$), and poorer sexual function ($t = -3.82$, $p = .001$, $d = 1.36$) as compared to the reference sample of allogeneic HCT recipients with no cGVHD history.

## Discussion

Little difference in psychological and physical function was seen overall between allogeneic HCT survivors with active cGVHD and those with no cGVHD history. While findings

suggest that the presence of cGVHD itself is not necessarily a risk factor for poorer function above and beyond the impact of allogeneic HCT more broadly, subsets of active cGVHD patients did show poorer physical and psychological function in comparison to those without cGVHD, including those with more severe cGVHD and those with active cGVHD manifesting in the skin and GI tract.

Patients with moderate or severe cGVHD reported more psychological symptoms, pain, and poorer sexual function than patients with no cGVHD. These effects were large and clinically meaningful. For example, those with severe cGVHD had a mean score of 3 (moderate pain) on a 10-point pain severity scale compared to an average score of 1.5 (minimal/mild) for those with no or mild cGVHD. Results are consistent with findings that those with severe cGVHD have poorer quality of life [11–15] but clarify that depression symptoms and pain are particularly problematic with more severe cGVHD. Findings are consistent with prior work from Jim et al. (2016) indicating that greater patient-reported cGVHD severity was associated with greater depression symptoms, replicating this finding for severity based on cGVHD graded by a physician. Jim et al. (2016) also found that patient-reported cGVHD was associated with fatigue. Our results show increasing fatigue scores with increased cGVHD severity, but group differences were not statistically significant. Due to small sample sizes, our study was not sufficiently powered to detect small-to-medium effect sizes. This may also account for the finding of no statistically significant group difference in cGVHD symptom burden, although there was a clinically meaningful difference between those with mild and severe cGVHD.

Findings also highlight minimal additional adverse psychological or physical effects for mild cGVHD beyond what is already seen for allogeneic HCT recipients generally. However, it is important to note that large proportions of allogeneic HCT survivors across all groups experienced clinically significant fatigue and sleep disturbance, even though patients were, on average, 4–5 years past HCT.

Patients with cGVHD affecting the skin or GI tract were especially vulnerable to adverse psychological and physical function. These patients showed more severe depression, fatigue, and pain than HCT survivors without cGVHD. Those with GI tract cGVHD also reported severe somatic anxiety and impaired sexual function. These results extend findings from prior studies [14, 15] demonstrating that cGVHD in the skin and GI tract have an especially adverse impact on global quality of life, clarifying that depression and anxiety symptoms, pain, fatigue, and sexual function are relatively more problematic. Results of the present study further support previous findings [14,15] that patients with cGVHD in the lungs are vulnerable to adverse quality-of-life effects; clarifying particularly adverse effects with respect to somatic anxiety symptoms, fatigue, and sexual function. While it is possible that cGVHD severity could account for some of these differences, with a larger proportion of those with skin cGVHD having moderate or severe disease, most patients with cGVHD in the GI tract had mild disease, suggesting that both severity and disease site are important in understanding psychological and physical function. It is also important to highlight that the effects seen were large in magnitude and clinically meaningful. For example, a large majority of patients with cGVHD affecting skin (71%), GI tract (83%), and lungs (74%)

experienced clinically significant fatigue, compared to about half (58%) of allogeneic HCT survivors with no cGVHD.

Of note, sleep and cognitive function were similar for HCT survivors with and without cGVHD. Cognitive function scores overall reflected normal cognitive function, which is consistent with prior work showing that patients with active cGVHD generally reported healthy levels of cognitive function on the FACT-Cog [18]. Although, it is important to emphasize that both studies used a brief self-report measure; comprehensive neuropsychological testing could reveal more subtle and specific cognitive impacts not captured here. In contrast, sleep disturbance was very prevalent, with about half of patients across all groups reporting clinically significant insomnia symptoms even many years after HCT. The high level of sleep disturbance in the post-HCT population may make it difficult to discern cGVHD specific impacts.

To our knowledge this is one of the first studies to comprehensively evaluate several domains of quality of life among individuals with cGVHD with comprehensive, well validated measures. We were able to characterize scores by comparing to a reference group of allogeneic HCT survivors with no cGVHD history and to population norms and clinical cut points, thus providing greater insight into the previously observed global quality of life impact of cGVHD [5–11, 14, 15]. Results further build on the extant literature by clarifying that cGVHD severity and disease site may be more important risk factors than the presence of cGVHD itself. Limitations of the study include a relatively homogeneous sample with respect to racial and ethnic identity, reflecting the catchment area of our cancer center but limiting generalizability to more diverse populations. In addition, patients were assessed at a single time point; it will be important for future research to evaluate dynamic relationships between cGVHD disease activity and psychological and physical function over time. Finally, our sample size is small, despite enrolling most eligible patients at our center during the study period. This was particularly true for the reference sample, as HCT survivors without complications of cGVHD were less likely to be followed long-term in a comprehensive cancer center. Therefore, the study was not sufficiently powered to detect subtle group differences, especially for disease site and severity subgroups. We have attempted to address this limitation in part by providing mean scores for all subgroups in Tables 3 and 4.

Findings suggest that HCT survivors with moderate-to-severe cGVHD and those with cGVHD affecting the skin, GI tract, and lungs may benefit from routine assessment of psychological and physical symptoms together with proactive, tailored interventions. Depression, anxiety, pain, insomnia, and fatigue tend to co-occur and are also responsive to cognitive-behavioral and mindfulness-based interventions, physical activity, and bright light therapy [22, 36–39]. Pharmacologic interventions may also be beneficial but tend to be more symptom specific [20, 36]. Identifying and proactively managing psychological and physical symptoms is important in providing comprehensive cGVHD care to optimize quality of life and health outcomes.

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## Data Availability

The dataset generated during and/or analyzed during the current study are not publicly available because, even after stripping the final dataset of identifiers, the possibility of deductive disclosure of participants remains given the relative rarity of the diagnoses, single study site, brief enrollment window, and small sample size. A combination of data from the medical record including diagnosis and treatment regimen, together with demographic data, could make it possible to identify individuals. Therefore, data are available from the corresponding author under a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes and not to identify any individual participant; (2) a commitment to securing the data using appropriate computer technology; and (3) a commitment to destroying or returning the data after analyses are completed.

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**Table 1.**

Patient Demographics and Medical Characteristics

| Patient Information | Active cGVHD (*n* = 59) | No cGVHD Reference Sample (*n* = 19) |
|---|---|---|
| Mean Age | 59.0 | 50.4 |
| Female Sex, No. (%) | 22 (37.29) | 6 (31.58) |
| Race/Ethnicity, No.(%) | | |
| Caucasian/ White | 57 (96.61) | 18 (94.74) |
| Latina/Latino | 1 (1.70) | 0 (0) |
| Other | 1 (1.70) | 0 (0) |
| No response | 0 (0) | 1 (5.26) |
| Relationship Status, No. (%) | | |
| Married/living with partner | 49 (83.05) | 14 (73.68) |
| Divorced | 3 (5.09) | 3 (15.79) |
| Single | 6 (10.17) | 2 (10.53) |
| Widowed | 1 (1.70) | 0 (0) |
| Education, No. (%) | | |
| Less than 12 years | 1 (1.70) | 0 (0) |
| High School | 14 (23.73) | 5 (26.32) |
| Trade School | 10 (16.95) | 1 (5.26) |
| Some College | 17 (28.81) | 2 (10.53) |
| College Graduate | 13 (22.03) | 8 (42.11) |
| Post-graduate Degree | 4 (6.78) | 2 (10.53) |
| No response | 0 (0) | 1 (5.26) |
| Employment Status, No. (%) | | |
| Full-time | 9 (15.25) | 5 (26.32) |
| Part-time | 12 (20.34) | 2 (10.53) |
| Student | 0 (0) | 1 (5.26) |
| Disabled | 16 (27.12) | 3 (15.79) |
| Homemaker | 1 (1.70) | 0 (0) |
| Retired | 20 (33.90) | 6 (31.58) |
| No response | 1 (1.70) | 2 (10.53) |
| Annual Income, No. (%) | | |
| Less than $10,000 | 1 (1.70) | 0 (0) |
| $10,001–$25,000 | 7 (11.86) | 1 (5.26) |
| $25,001–$40,000 | 7 (11.86) | 6 (31.58) |
| $40,001–$55,000 | 12 (20.34) | 1 (5.26) |
| $55,001–$70,000 | 6 (10.17) | 1 (5.26) |
| $70,001–$85,000 | 7 (11.86) | 2 (10.53) |
| $85,001–$100,000 | 8 (13.56) | 5 (26.32) |
| More than $100,000 | 7 (11.86) | 2 (10.53) |
| No response | 4 (6.78) | 1 (5.26) |
| Time Since HCT (Months) | 61 (11–147) | 42 (9–100) |

| Patient Information | Active cGVHD (*n* = 59) | No cGVHD Reference Sample (*n* = 19) |
|---|---|---|
| Diagnosis, No. (%) | | |
| ALL | 3 (5.08) | 2 (10.53) |
| AML | 24 (40.68) | 5 (26.32) |
| Aplastic Anemia | 0 (0) | 1 (5.26) |
| CLL | 2 (3.39) | 1 (5.26) |
| CML | 8 (13.56) | 2 (10.53) |
| Hodgkin Lymphoma | 0 (0) | 1 (5.26) |
| MDS | 9 (15.25) | 4 (21.05) |
| Non-Hodgkin Lymphoma | 10 (16.95) | 1 (5.26) |
| Other | 3 (5.08) | 2 (10.53) |
| DRI Score, No. (%) | | |
| Low | 26 (44.07) | 6 (31.58) |
| Intermediate | 25 (42.37) | 9 (47.37) |
| High | 7 (11.86) | 2 (10.53) |
| Very High | 0 (0) | 0 (0) |
| N/A | 1 (1.70) | 2 (10.53) |
| Donor Female, No. (%) | 26 (44.07) | 5 (26.32) |
| Unknown | 4 (6.78) | 1 (5.26) |
| Graft Source | | |
| Bone Marrow | 5 (8.47) | 1 (5.26) |
| Cord Blood | 0 (0) | 4 (21.05) |
| Peripheral Blood | 54 (91.53) | 14 (73.68) |
| Graft Match, No. (%) | | |
| Full Matched Unrelated | 21 (35.59) | 10 (52.63) |
| Mismatched Unrelated | 2 (3.39) | 3 (15.79) |
| Matched Relative | 30 (50.85) | 4 (21.05) |
| Mismatched Relative | 4 (6.78) | 0 (0) |
| Unknown | 2 (3.39) | 2 (10.53) |
| Conditioning Regimen, No. (%) | | |
| Myeloablative | 23 (38.98) | 5 (26.32) |
| Non-Myeloablative | 24 (40.68) | 13 (68.42) |
| TBI | 26 (44.07) | 14 (73.68) |
| Unknown | 3 (5.09) | 2 (10.53) |
| GVHD Prophylaxis | | |
| CNI + methotrexate | 49 (83.05) | 8 (42.10) |
| CNI + other | 4 (6.78) | 6 (31.58) |
| Other / unknown | 4 (10.17) | 5 (26.32) |
| Acute GVHD, No. (%) | 23 (38.98) | 0 (0) |

**Table 2.**

Grade and Disease Site for Participants with Active cGVHD

| cGVHD Site | All active cGVHD (*n* = 59) | Grade 1(*n* = 23) | Grade 2 (*n* = 19) | Grade 3 (*n* = 15) |
|---|---|---|---|---|
| Eyes | 47 | 23 | 19 | 5 |
| Mouth | 31 | 25 | 6 | 0 |
| Skin | 28 | 7 | 11 | 10 |
| Lungs | 27 | 16 | 10 | 1 |
| Joints | 24 | 14 | 9 | 1 |
| GI tract | 18 | 15 | 2 | 1 |

**Table 3.**

Mean Symptom Scale Scores by cGVHD Grade

| Symptom Scales | No cGVHD Reference (*n* = 19) | Mild (*n* = 23) | Moderate (*n* = 19) | Severe (*n* = 15) |
|---|---|---|---|---|
| IDAS | | | | |
| Depression | 35.1 | 35.6 | 37.5 | **43.3** * + |
| | (8.7) | (8.1) | (9.7) | (13.7) |
| Panic | 10.4 | 11.8 | **14.0** * | 12.1 |
| | (3.2) | (4.0) | (5.2) | (3.7) |
| Intrusive Thoughts | 4.6 | 5.1 | 5.3 | 5.1 |
| | (1.0) | (1.1) | (2.0) | (1.9) |
| FSI | | | | |
| Intensity | 3.0 | 3.5 | 3.6 | 4.1 |
| | (2.0) | (2.0) | (1.7) | (2.3) |
| Interference | 1.5 | 1.6 | 2.2 | 2.7 |
| | (1.9) | (1.9) | (2.3) | (2.5) |
| BPI | | | | |
| Intensity | 1.5 | 1.6 | 2.6 | **3.0** * + |
| | (1.9) | (1.8) | (2.3) | (2.3) |
| Interference | 1.3 | 1.1 | 2.4+ | **2.9** + |
| | (1.9) | (1.5) | (2.3) | (2.7) |
| ISI | | | | |
| Total | 8.0 | 6.7 | 8.7 | 8.1 |
| | (6.2) | (4.6) | (5.1) | (4.8) |
| PROMIS | | | | |
| Cognition | 20.5 | 21.1 | 21.4 | 21.1 |
| | (5.7) | (4.0) | (4.5) | (5.3) |
| Sexual Function | 2.7 | 2.1 | **1.2** * | 1.4 |
| | (1.9) | (2.1) | (1.6) | (1.8) |
| Lee Symptom Scale | | | | |
| Total | N/A | 48.6 | 49.2 | 54.5 |
| | | (11.4) | (11.2) | (11.7) |

Note. Standard deviations are shown in parentheses.

*= $p < .05$ for comparison between reference and subgroup. Bolded values are statistically significant after FDR procedure.

+= $p < .05$ for comparison between grade 1 group and subgroup. Bolded values are statistically significant after FDR procedure.

**Table 4.**

Mean Symptom Scale Scores by cGVHD Disease Site

| Symptom Scales | No cGVHD Reference (*n* = 19) | Eyes (*n* = 47) | Mouth (*n* = 31) | Skin (*n* = 28) | Lungs (*n* = 27) | Joints (*n* = 24) | GI Tract (*n* = 18) |
|---|---|---|---|---|---|---|---|
| IDAS | | | | | | | |
| Depression | 35.1 | 37.2 | 38.6 | **42.4** * | 40.7 | 42.3 | **43.4** * |
| | (8.7) | (9.4) | (8.9) | (11.4) | (12.0) | (13.4) | (10.4) |
| Panic | 10.4 | 12.4 | **14.3** * | 12.9 | **13.4** * | **13.3** * | **15.3** * |
| | (3.2) | (4.4) | (4.6) | (4.6) | (4.6) | (4.9) | (5.7) |
| Intrusive Thoughts | 4.6 | 4.9 | 5.1 | 5.5 | 5.1 | 5.5 | 5.6 |
| | (1.0) | (1.3) | (1.5) | (2.0) | (1.5) | (2.2) | (1.8) |
| FSI | | | | | | | |
| Intensity | 3.0 | 3.6 | 3.9 | 4.1 * | 4.2 * | 4.1 | **4.4** * |
| | (2.0) | (1.9) | (1.8) | (1.9) | (2.0) | (2.2) | (1.8) |
| Interference | 1.5 | 1.8 | 2.3 | **2.9** * | 2.7 | 2.8 | **2.9** * |
| | (1.9) | (2.2) | (2.3) | (2.3) | (2.5) | (2.4) | (2.1) |
| BPI | | | | | | | |
| Intensity | 1.5 | 2.0 | 2.6 | **2.9** * | 2.6 | 2.8 | **3.2** * |
| | (1.9) | (2.1) | (2.3) | (2.3) | (2.3) | (2.7) | (2.3) |
| Interference | 1.3 | 1.9 | 2.4 | **2.8** * | 2.4 | 2.9 * | 2.8 |
| | (1.9) | (2.3) | (2.4) | (2.4) | (2.5) | (2.9) | (2.5) |
| ISI | | | | | | | |
| Total | 8.0 | 7.3 | 8.3 | 9.4 | 8.6 | 9.3 | 9.1 |
| | (6.2) | (4.9) | (5.0) | (4.4) | (5.7) | (4.7) | (4.4) |
| PROMIS | | | | | | | |
| Cognition | 20.5 | 21.1 | 20.7 | 19.3 | 21.4 | 20.5 | 18.9 |
| | (5.7) | (4.2) | (4.4) | (4.5) | (4.6) | (4.2) | (4.1) |
| Sexual Function | 2.7 | 1.7 | **1.2** * | 1.6 | **1.3** * | 1.6 | **0.6** * |
| | (1.9) | (1.8) | (1.6) | (1.9) | (1.9) | (2.0) | (1.1) |
| LSS | | | | | | | |
| Total | N/A | 50.2 | 53.0 | 54.6 | 52.4 | 56.0 | 56.5 |
| | | (11.3) | (10.5) | (11.2) | (12.8) | (11.3) | (12.0) |

Note. Standard deviations are shown in parentheses. Disease sites are not mutually exclusive. Some participants are in more than one disease site category.

*= $p < .05$ for comparison between reference and subgroup. Bolded values are statistically significant after FDR procedure.