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Distress in a Pandemic: Association of the Coronavirus Disease-2019 Pandemic with Distress and Quality of Life in Hematopoietic Stem Cell Transplantation

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ABSTRACT
The global coronavirus disease 2019 (COVID-19) pandemic has drastically disrupted cancer care, potentially exacerbating patients’ distress levels. Patients undergoing hematopoietic stem cell transplantation (HSCT) may be especially vulnerable to this pandemic stress. However, the associations of the COVID-19 pandemic with distress, fatigue, and quality of life (QoL) are not well understood in this population. In a cross-sectional analysis of data from 205 patients undergoing HSCT enrolled in a supportive care trial, we compared baseline pre-HSCT distress symptoms (depression, anxiety, and posttraumatic stress disorder [PTSD]), fatigue, and QoL between enrollees before (ie, March 2019-January 2020) and during (ie, March 2020-January 2021) the COVID-19 pandemic. We used linear regression models adjusting for sociodemographics and cancer diagnosis to examine the associations between enrollment period and patient-reported outcomes. We used semistructured qualitative interviews in 20 allogeneic HSCT recipients who were ≥3-months post-HSCT to understand the impact of the COVID-19 pandemic on their recovery post-HSCT. One hundred twenty-four participants enrolled before COVID-19, and 81 participants enrolled during the pandemic. The 2 cohorts had similar baseline demographics and disease risk factors. In multivariate regression models, enrollment during COVID-19 was not associated with pre-HSCT symptoms of depression, anxiety, PTSD, fatigue, or QoL impairment. COVID-19-era participants reported themes of negative (eg, increased isolation) and positive (eg, engagement with meaningful activities) implications of the pandemic on HSCT recovery. We found no differences in pre-HSCT distress, fatigue, or QoL in patients undergoing HSCT before or during the COVID-19 pandemic; however, patients in early recovery post-HSCT report both negative and positive implications of the COVID-19 pandemic in their lives.

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INTRODUCTION
The global coronavirus disease-2019 (COVID-19) pandemic has drastically disrupted many aspects of life and healthcare in unparalleled ways. For patients with cancer, it has impacted both treatment and recovery trajectories [1,2]. Patients with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT) are especially vulnerable to care changes imposed by the pandemic owing to factors associated with HSCT, including the extensive treatment with a prolonged hospitalization, high burden of physical symptoms due to potential toxic side effects, and quality of life (QoL) challenges in recovery [3–6]. Outside the hospital, HSCT recipients grapple with weeks of social isolation and quarantine requirements from a compromised immune system, contributing to distress and impaired QoL in this population. Although a few studies...
have described the implications of the COVID-19 pandemic for HSCT recipients, previous research has focused on the pandemic’s impact on HSCT logistics and COVID-19 complications [7–9]. However, the associations of the COVID-19 pandemic with patient-reported distress, fatigue, and QoL are not well understood.

Compared with other cancer patient populations, many HSCT recipients travel longer distances for their care and require greater caregiver and social support network involvement to ensure successful acute follow-up care (eg, biweekly clinic visits, medication management) and recovery [10]. In addition, HSCT recipients frequently depend on their caregivers for basic activities of daily living (eg, meal preparation, household cleaning) to reduce the risk of infections while their immune system recovers [11]. Thus, pandemic restrictions on lifestyle and travel might have negatively impacted the size and effectiveness of social support networks for HSCT recipients, intensifying their distress [12].

Despite the widespread idea that the COVID-19 pandemic has exacerbated distress symptoms in patients with cancer [13], data are limited for patients with hematologic malignancies undergoing HSCT, who have well-documented heightened psychological distress, fatigue, and impaired QoL irrespective of a pandemic [14]. Accordingly, we aimed to assess the association of the COVID-19 pandemic with distress, fatigue, and QoL in the HSCT population quantitatively and qualitatively. We hypothesized that the COVID-19 pandemic would be associated with increased distress and fatigue and decreased QoL.

METHODOLOGY

Study Procedures

We conducted a cross-sectional analysis of data from 205 patients with hematologic malignancies undergoing HSCT enrolled in an ongoing multisite, randomized supportive care trial at Massachusetts General Hospital, Duke University Medical Center, and Fred Hutchinson Cancer Research Center (ClinicalTrials.gov identifier NCT03641378). We compared baseline pre-HSCT symptoms of distress (ie, depression, anxiety, and posttraumatic stress disorder [PTSD]), fatigue, and QoL between participants enrolled prepandemic (ie, March 2019-January 2020) and participants enrolled during the COVID-19 pandemic (March 2020-January 2021). This study was approved by the Institutional Review Boards at all participating sites. All participants provided written informed consent.

Participants

Among the 347 eligible participants, 205 (59%) enrolled in the study. Participants were adults (age ≥18 years) with a hematologic malignancy hospitalized for autologous or allogeneic HSCT. Patients who could read and respond to questionnaires in English, Spanish, or with an interpreter were eligible to participate. We excluded patients undergoing HSCT for a benign hematologic condition, those undergoing outpatient HSCT, and those with a major psychiatric or cognitive condition precluding their adherence to study procedures. We considered discrepancies while reviewing interview transcripts to ensure that the coding structure after reading a small number of transcripts several times was consistent. Participants were enrolled during the COVID-19 pandemic, were ≥3 months post-HSCT, and were receiving longitudinal care from their transplant clinicians. We asked participants to reflect on their COVID-19 experience with an open-ended question: “Can you tell us how the COVID-19 pandemic has affected you and your family through your HSCT and recovery?” Follow-up questions (eg, “Can you tell us about how the COVID-19 pandemic has affected your level of stress during your transplant and recovery?”) were asked to obtain more details. All interviews were recorded and transcribed verbatim.

For analysis, we used directed content analysis, a widely used qualitative approach for examining the breadth and scope of patient experiences, and extracted themes from the data using an established framework from the literature [21,22]. Participants’ responses were independently coded verbatim without any interpretations by 2 study team members (HA and LH) to avoid bias. We used complete sentences as the coding unit. Codes were informed by both the interview questions and qualitative interview data. We modified the coding structure after reading a small number of transcripts several times to test the codes. We discussed emerging themes from the codes and adjudicated discrepancies while reviewing interview transcripts to ensure that the themes reflected the original data. In addition to deriving core interview themes, we resolved discrepancies using transcript review, discussion, and consensus. With a sample size of 20 participants and a narrow focus, thematic saturation was achieved.

RESULTS

Demographics and Patient Characteristics

Table 1 summarizes participants’ baseline characteristics. More than one-half (60.5%; n = 124) of the participants were enrolled before the COVID-19 pandemic, and 39.5% (n = 81) were enrolled during the pandemic. Baseline characteristics were similar in the 2 groups. The majority of participants were non-Hispanic (n = 185; 90.2%), white (n = 150; 73.2%), female (n = 131; 63.9%), and married (n = 151; 73.6%) with a mean age of 54.9 ± 11.7 years. Participants had a diagnosis of leukemia (n = 67; 32.7%), multiple myeloma (n = 58; 28.3%), lymphoma (n = 48; 23.4%), or myeloproliferative neoplasms (n = 32; 15.6%).

Associations of COVID-19 Status with Patient-Reported Outcomes

Table 2 summarizes the unadjusted comparison of baseline pre-HSCT patient-reported outcomes between our 2 groups. Depression, anxiety, PTSD symptoms, QoL, and fatigue were not different between the participants enrolled before versus those enrolled during the pandemic.

In multivariate adjusted regression models, enrollment during the COVID-19 pandemic was not associated with pre-HSCT symptoms of depression (B = 0.004; 95% confidence...
interval [CI], -0.018 to 0.025; \( P = .733 \), anxiety (B = 0.008; 95% CI, -0.012 to 0.027; \( P = .443 \)), PTSD (B = 0.004; 95% CI, -0.004 to 0.012; \( P = .348 \)), fatigue (B = -0.001; 95% CI, -0.008 to 0.005; \( P = .732 \)) or QoL (B = -0.001; 95% CI, -0.005 to 0.003; \( P = .570 \)) (Table 3).

### Qualitative Findings

Our qualitative analysis of data from patients in post-HSCT recovery revealed that the COVID-19 pandemic had both negative and positive implications for the patients' HSCT and recovery trajectories (Table 4). Themes of negative implications of the pandemic highlighted by participants include (1) increased isolation during HSCT hospitalization in the setting of

| Characteristic          | Pre-COVID-19 (N = 124) | During COVID-19 (N = 81) | \( P \) Value |
|-------------------------|-------------------------|---------------------------|---------------|
| Age and sex             |                         |                           |               |
| Age, yr, M ± SD         | 54.2 ± 11.8             | 56.0 ± 11.6               | .28           |
| Female, n (%)           | 78 (62.9)               | 53 (65.4)                 | .68           |
| Race, n (%)             |                         |                           | .12           |
| White                   | 85 (68.5)               | 65 (80.2)                 |               |
| African American or Black| 15 (12.1)              | 11 (13.6)                 |               |
| Asian                   | 11 (8.9)                | 2 (2.5)                   |               |
| Hispanic or Latino      | 9 (7.3)                 | 3 (3.7)                   |               |
| American Indian or Alaskan Native | 4 (3.2) | 1 (1.2) |               |
| Other                   | 4 (3.2)                 | 1 (1.2)                   |               |
| Ethnicity, n (%)        |                         |                           | .34           |
| Non-Hispanic            | 113 (91.1)              | 72 (88.9)                 |               |
| Education, n (%)        |                         |                           | .33           |
| High school             | 29 (23.8)               | 19 (23.5)                 |               |
| College                 | 64 (52.5)               | 34 (42.0)                 |               |
| Postgraduate            | 29 (23.8)               | 27 (33.3)                 | .96           |
| Income, n (%)           |                         |                           |               |
| <$25,000                | 20 (16.1)               | 8 (9.9)                   |               |
| $25,000-$50,000         | 11 (8.9)                | 12 (14.8)                 |               |
| $50,000-$100,000        | 32 (25.8)               | 23 (28.4)                 |               |
| $100,000-$150,000       | 28 (22.6)               | 16 (19.8)                 |               |
| >$150,000               | 25 (20.2)               | 15 (18.5)                 | .24           |
| Marital status, n (%)   |                         |                           | .92           |
| Married                 | 90 (72.6)               | 61 (75.3)                 |               |
| Single                  | 19 (15.3)               | 8 (9.9)                   |               |
| Divorced                | 9 (7.3)                 | 5 (6.2)                   |               |
| Widowed                 | 4 (3.2)                 | 5 (6.2)                   |               |
| Diagnosis, n (%)        |                         |                           | .35           |
| Leukemia                | 41 (33.1)               | 26 (32.1)                 |               |
| Multiple myeloma        | 33 (26.6)               | 25 (30.9)                 |               |
| Lymphoma                | 29 (23.4)               | 19 (23.5)                 |               |
| Myeloproliferative neoplasms | 21 (16.9) | 11 (13.6) |               |
| Type of HCT, n (%)      |                         |                           |               |
| Allogeneic              | 70 (56.5)               | 42 (51.9)                 |               |
| Autologous              | 54 (43.5)               | 38 (46.9)                 |               |

### Table 2

| Variable       | Pre-COVID-19, mean ± SD | During COVID-19, mean ± SD | \( t \) Value | \( P \) Value |
|----------------|-------------------------|-----------------------------|---------------|---------------|
| Depression     | 4.47 ± 3.25             | 4.44 ± 3.59                 | 0.07          | .95           |
| Anxiety        | 5.12 ± 3.62             | 5.44 ± 4.05                 | -0.59         | .55           |
| PTSD           | 26.40 ± 9.08            | 27.29 ± 10.10               | -0.65         | .52           |
| QoL            | 108.00 ± 19.47          | 107.50 ± 20.20              | 0.18          | .86           |
| Fatigue        | 35.94 ± 11.07           | 36.03 ± 11.73               | -0.05         | .96           |

### Table 3

| Variable       | Coefficient        | 95% CI            | \( P \) Value |
|----------------|--------------------|-------------------|---------------|
| Depression     | 0.004              | -0.018 to 0.025   | 0.733         |
| Anxiety        | 0.008              | -0.012 to 0.027   | 0.443         |
| PTSD           | 0.004              | -0.004 to 0.012   | 0.348         |
| Fatigue        | -0.001             | -0.008 to 0.005   | 0.732         |
| QoL            | -0.001             | -0.005 to 0.003   | 0.570         |

All models controlled for patient age, sex, race, relationship status, education level, hematologic malignancy, and transplant type.
### Table 4
Qualitative Interview Results: Themes, Description, and Quotes

| Themes                                           | Subthemes                                           | Description                                                                                                                                      | Quotes                                                                                                                                                                                                 |
|--------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Positive implications of the COVID-19 pandemic    | Engagement with meaningful activities and social support | The COVID-19 pandemic forced adaptation of several social activities (eg, religious) to virtual platforms. This virtual adaptation allowed HSCT recipients to continue engagement with meaningful social activities that otherwise would not have been possible in the setting of their required isolation and quarantine during HSCT recovery. | “Otherwise, in terms of COVID and my recovery... It means that lots of people are doing a lot of things online... I’m fortunate to have the technological capacity both that I know how to do things and that I have the devices that I need to be able to participate in a lot.” [ID 12] |
| Ease of enforcement of precautionary behaviors   |                                                     | With state and national mandates for infection control via precautionary behaviors (eg, masking) in the United States, HSCT recipients reported fewer challenges less and stigma in enforcing these required behaviors for their recovery. | “Well, maybe it’s better that COVID’s going on, because other people are wearing a mask and you’re more protected.” [ID 4]                                                                                                                                 |
| Increased availability of family and social support |                                                     | As the COVID-19 pandemic forced most workplaces and educational institutions to go virtual and remote, participants reported increased availability of family and social support networks. | “Fortunately, people have been more hygienically focused during the period, so people are wearing masks. This makes it convenient for myself.” [ID 8]                                                                 |
| Negative implications of COVID-19                 | Increased isolation during transplant hospitalization | Participants reported that hospitals’ visitor policy restrictions during the COVID-19 pandemic increased their isolation during HSCT. | “…So it was really hard. When I was going back to the hospital with all these negative thoughts or worries, and I was going to be with new doctors, and no one that I knew in the hospital. There were no visitors for up to 4 weeks. That seemed like forever to me, and I just didn’t know how I was going to do it.” [ID 5] |
|                                                 | Increased isolation outside the hospital             | Participants reported that safety concerns and state restrictions on social gatherings due to the COVID-19 pandemic resulted in persistent isolation at home after HSCT. | “And I raised hell down in Boston because when we got there for the bone marrow transplant, he said my husband wasn’t allowed in. Well, he’s my rock. I draw strength from him. He says, ‘I’ll tell you what, you don’t make special privileges for him to come in, I’m not staying. I’m going home.’ That was very important... but we had to fight for that. And you’re fighting cancer, you’re tired as all hell, you’re trying to wrap your head around just having the cancer. I don’t want to worry about who’s going to be with me, my husband. I know COVID, yeah, whatever, but you live together, you’re with each other all the time, and all of a sudden it’s like separating. I don’t think so.” [ID 10] |

(continued)
restricted visitor policies, (2) increased isolation at home due to states’ restrictions of social gatherings and global restrictions on travel, and (3) increased perceived distress on caregivers as they worried about transmitting SARS-CoV-2 to patients. Participants expressed the following themes of positive implications of the pandemic: (1) increased availability of social support, as more family members were working or schooling from home; (2) easier enforcement of precautionary behaviors (eg, masking, handwashing) by family and caregivers during the pandemic, because the COVID-19 pandemic made precautionary behaviors commonplace; and (3) decreased stigma associated with precautionary behaviors (eg, masking) as everyone was required to adhere to statewide and nationwide precautionary behaviors.

**DISCUSSION**

In this study, we assessed the associations between enrollment during the COVID-19 pandemic with baseline pre-HSCT distress, fatigue, and QoL in 205 patients undergoing HSCT in different geographic regions throughout the United States. Contrary to the widespread notion and our hypothesis that the COVID-19 pandemic exacerbated symptoms of distress and fatigue and worsened QoL in HSCT recipients, we found no differences in pre-HSCT distress, fatigue, or QoL in our sample before and during the COVID-19 pandemic. However, our qualitative assessment of HSCT recipients’ experiences during the COVID-19 pandemic showed that the pandemic has had both negative and positive implications for participant experiences following HSCT.

Our findings suggest that although the COVID-19 pandemic has altered many aspects and logistics of HSCT and recovery [9,12], it has not worsened pre-HSCT distress, fatigue, or QoL compared with prepandemic levels. Indeed, well-established factors, such as patients’ illness experience, treatment burden, and uncertainty regarding future health and potential HSCT complications, are still the likely driving force behind the distress, fatigue, and QoL challenges in this population [3–6]. Our study’s focus on baseline pre-HSCT assessments likely

| Themes | Subthemes | Description | Quotes |
|--------|-----------|-------------|--------|
| Heightened patients’ distress about being infected by SARS-CoV-2 and overall increased thoughts about mortality | Participants articulated heightened distress (eg, anxiety, fear) specifically pertaining to the COVID-19 pandemic with increased thoughts about COVID-related mortality if they were to contract the coronavirus. | “And I’m afraid to; if I have to do anything, I'm gloved and masked and I get worried about going to the hospital now for my blood transfusions and my doctor's appointments because of the COVID all over the place. … If COVID kills me after all I've been through, I will be totally pissed. Just want to let you know.” (ID 10) “Well, yeah. I mean, I’m super anxious. I don’t want to get sick. I don’t want to get sick with COVID. And considering that I just had a stem cell transplant, I know I’m more vulnerable than others. So that’s one of my biggest fears.” (ID 17) “And I’d say also during the earlier hospitalization, I was very nervous about the nurses and the nursing assistants and everybody was coming close to me all the time and thinking, “Well, I don’t know who they’ve been with and I don’t know what people they live with, who are they seeing.” And the spread of that got me a little bit nervous.” (ID 12) |
| Increased family and caregiver distress and burden | Participants reported increased perceived distress on caregivers as they worried about transmitting COVID-19 to patients. | “And it’s also affecting my family, because they’re limited as to what they could do, so I know that’s been tough on them, too.” (ID 17) “So COVID has complicated things in my family, there’s a lot of extra stress. My wife is a preschool teacher. She works with 12 young kids, so that the whole risk and fear of COVID, infecting her and therefore possibly infecting me is a significant stress for her all the time because I’m immunocompromised. … And it continues today, where she’s constantly worried about my health because of COVID.” (ID 20) |
| Caregiver role in care | The restrictions of the COVID-19 pandemic resulted in some restrictions on family/caregiver involvement with in-hospital care. | “Well, before COVID, my entire family would walk into that office, and every one of my children … So when COVID hit, I then could still have them on the line virtually. I kind of still record the conversations, but it did make it harder on me so that I didn’t have my support team around me to help figure out what was going on and next steps and— in the first few months, there were a lot of questions.” (ID 15) |
captured the true contribution of the COVID-19 pandemic on patient-reported outcomes, accounting for any distress accompanying the HSCT procedure itself. Although peri-transplantation patient-reported outcome screening is limited in the HSCT population [23], screening during this phase of the care cycle may help identify patients at increased risk for distress, fatigue, and QoL challenges that likely are compounded by the treatment itself.

Another potential explanation for the discordance between our findings and the widespread notion of intensified patient distress reported by cancer clinicians is that the COVID-19 pandemic forced the whole world to live like HSCT recipients, which may have given them a psychological advantage to managing pandemic-related restrictions on life [24]. For example, HSCT recipients were already used to precautionary behaviors (eg, wearing face masks in public) and limited interactions with large crowds. Although our findings suggest that the COVID-19 pandemic was not associated with increased pre-HSCT distress, fatigue, and decreased QoL, it is possible that we are missing some longitudinal changes in distress, given the restrictions on visitors during HSCT hospitalizations. Our qualitative findings show that the pandemic indeed had both negative and positive implications for HSCT recipients during their recovery. It is also possible that existing self-report measures that assess distress, fatigue, and QoL in cancer populations do not capture pandemic-specific or COVID-19–specific stressors that are likely existential in nature. Patients spontaneously reported that the ongoing COVID-19 pandemic increased their thoughts and distress about mortality, something not typically elucidated by standard distress screening instruments in cancer populations.

Social support and caregivers play critical roles in the treatment and successful recovery of HSCT recipients [11]. Regardless of a global pandemic that imposes restrictions on travel and social interactions, social isolation during HSCT hospitalization and acute recovery is substantial and contributes significantly to the distress that already accompanies the toxic side effects of HSCT. Thus, it was unsurprising that a constant theme in our findings pertained to the pandemic’s impact on social isolation and changes in the nature and structure of social support. Some participants reported that the pandemic improved access to social support, whereas others reported that the pandemic has been a barrier to needed social support. Furthermore, participants mentioned that the COVID-19 pandemic increased distress symptoms in their caregivers, owing to the caregivers’ concerns that their actions and lifestyle increased the risk of patients contracting COVID-19. This work highlights the need for further research aimed at understanding social support in patients undergoing HSCT and their caregivers during turbulent times like the COVID-19 pandemic.

This study has several limitations. First, the majority of our study participants were non-Hispanic white, married, and educated, all of which may limit the generalizability of our findings, particularly given the disproportionate impact of the COVID-19 pandemic on ethnic minorities and underserved communities [25]. Second, the cross-sectional nature of our analysis limits our ability to comment on the causality of our examined variables. Additional longitudinal assessments of patient-reported outcomes in the setting of a pandemic may be useful for gaining a comprehensive understanding of the impact of the pandemic on this population. Third, although we were able to capture important aspects of distress through widely used self-report measures for the HSCT population, it is likely that we were unable to capture the existential components of distress (eg, increased thoughts about mortality reported qualitatively) [26], which may have been heightened by the pandemic. Fourth, although disease status appeared similar in the 2 groups, the post–COVID-19 cohort reflected a 35% drop in patients from the pre–COVID-19 cohort, and patients who proceeded to HSCT during the pandemic may be fundamentally different than those who underwent HSCT before the pandemic, in terms of both their disease and their psychological status. Fifth, although our sample size is comparable to studies assessing patient-reported outcomes in this population, our null findings may be due simply to our limited power to detect differences in patient-reported outcomes. Sixth, although our study focused only on patients, including direct caregivers’ perspectives from qualitative interviews would provide a more holistic view of the impact of the COVID-19 pandemic on patients’ care experiences and social support. Finally, on average, patients are already quite distressed before undergoing HSCT compared with other medical procedures, and the pandemic might not have increased it further.

In conclusion, we did not find that the COVID-19 pandemic significantly worsened distress, fatigue, and QoL in patients about to undergo HSCT. Nonetheless, our findings highlight the need to comprehensively explore the numerous factors (eg, illness experience, treatment burden) that influence patient-reported outcomes in HSCT recipients irrespective of the COVID-19 pandemic. Our findings also underscore the importance of social support during HSCT recovery, especially during a global pandemic, which imposes further barriers and restrictions on social support networks for vulnerable cancer populations such as HSCT recipients.

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