

Impact of Pediatric Palliative Care Involvement at Baseline on Symptom Burden in the First
Month Following Hematopoietic Stem Cell Transplantation

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Abstract

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Hematopoietic Stem Cell Transplant (HSCT) is a high-stakes therapy associated with significant symptom burden. Despite known benefits of palliative care in adult HSCT, integration of pediatric palliative care (PPC) in pediatric HSCT is rare. This study investigates if baseline PPC is associated with symptom burden in the first month post-HSCT. This prospective, longitudinal cohort study at 2 pediatric centers assessed HSCT recipients with or without pre-HSCT PPC. Primary outcomes were total number of symptoms, physical symptoms, psychological symptoms, and HPQ-MSAS score at 5 timepoints in the first month reported by patients and parents. Linear mixed models provided estimated marginal means and 95% confidence intervals (CI). Propensity score regression adjustment for PPC was used to reduce confounding by indication and outcomes were compared with absolute mean differences and 95% CI. Fifty-four patients (52.9%) did not have PPC at baseline while 48 (47.1%) did. Most patients received HSCT for hematologic malignancies and patients with baseline PPC were more likely to have had prior HSCT. Total number of symptoms and HPQ-MSAS score peaked at week 1 in both groups. Across all time points, outcomes for patients with baseline PPC involvement either did not differ from, or were slightly worse than, patients without baseline PPC. None of the confidence intervals excluded the null value. Symptom burden was high among pediatric HSCT recipients. Randomized controlled trials with larger populations are needed to better assess the impact of PPC in HSCT.

Introduction

Hematopoietic Stem Cell Transplant (HSCT) is a high-stakes therapy associated with significant symptom burden and long term sequelae.¹ HSCT is pursued with the goal of curing high-risk cancers and other life threatening diseases, such as hemoglobinopathies, immune deficiencies, and metabolic disorders. While advances in HSCT have led to improved survival and clinical outcomes, advances in symptom management, health-related quality of life (HRQoL), psychosocial outcomes, and end of life (EoL) care have lagged.^{2,3}

A substantial proportion of adult and pediatric HSCT patients report post-traumatic stress disorder, depression, and anxiety in addition to physical discomfort as a result of HSCT.^{4,5} These symptoms are typically most pronounced in the acute post-HSCT period; however, even if a patient's underlying disease is cured, HSCT can have chronic effects on every organ system and on the socio-emotional well-being of patients and their families.^{6,7} The distress in HSCT may be modifiable. Early integration of palliative care into adult oncologic and HSCT care has been shown to improve HRQoL and EoL outcomes and is now recommended as the standard of care in adult patients with advanced cancers.^{8,9} In a trial in the adult HSCT population, participants were randomized to receive standard of care versus early, longitudinal involvement of subspecialty palliative care focusing on physical and psychological symptoms during their transplant hospitalization. Among participants randomized to receipt of the palliative care intervention, patient-reported HRQoL was higher and patient-reported anxiety, depression, and symptom burden were lower at both 2 weeks and 3 months post-transplant compared to participants randomized to the standard of care arm.⁵ The intervention also demonstrated sustained effects; at 6 months following HSCT, there was a statistically significant decrease in depression, anxiety, and post-traumatic stress disorder.^{5,8} To date, there have not been randomized controlled trials (RCT) of longitudinal specialty pediatric palliative care (PPC) interventions in pediatric HSCT, however, PPC is uniquely well-suited to partner with pediatric HSCT and offer additional support across domains to address gaps in HSCT care.¹⁰

Pediatric patients receiving HSCT face unique challenge. There are important differences between pediatric and adult HSCT populations with regards to transplant indication, donor source, and survival outcomes with long term physical and psychosocial sequelae that have the potential to impact a child for decades to come.^{11–13} HSCT is often fraught with uncertainty and parents may need to make difficult medical decisions. Parents of pediatric HSCT patients frequently report unmet needs with a high level of distress and there is a complex interplay between patient and parent outcomes.^{14–16} In 2023, the American Society for Transplantation and Cellular Therapy (ASTCT) Committee on Practice Guidelines recommended involvement of PPC pre-HSCT or early in the transplant course for all pediatric patients undergoing HSCT for malignant indications, yet there remains substantial variability in practice with few pediatric institutions implementing universal and longitudinal PPC involvement for HSCT patients.^{17,18} With the recognition that early integration of PPC does not detract from a goal of cure, integration of palliative care is increasing in HSCT.^{18,19} To optimally deploy PPC and achieve maximal benefit, we must understand the impact of PPC. The objective of this study is to assess whether PPC involvement in pediatric patients at baseline is associated prospectively with symptom burden during the first month following HSCT.

Methods

Study design

This was a prospective, longitudinal cohort study of pediatric HSCT recipients followed from admission for HSCT through 6 months post-transplant or until discontinuation of study participation. Participants were enrolled on the HSCT PediQUEST Study (HPQ; Pediatric Quality of Life Evaluation of Symptoms Technology), building on prior PediQUEST studies evaluating symptoms and quality of life in children with advanced cancers.²⁰ Participants were recruited from 2 large pediatric HSCT centers, Dana Farber Cancer Institute/ Boston Children's

Hospital (DFCI/ BCH) and St. Jude Children's Research Hospital (SJCRH), between August 2014 and December 2019. The HPQ study was approved by the institutional review boards (IRB) at both sites. A data use agreement was signed between DFCI and Fred Hutchinson Cancer Center to allow access to and analysis of these data in accordance with IRB policies.

Participants

All patients ≥ 5 years of age undergoing HSCT for any indication (collectively termed "patients") and their parents (or guardians, collectively termed "parents") with age-appropriate written and spoken knowledge of English and ability to complete a computerized survey were eligible. There was no upper age limit for patient participants and patients ≥ 18 years of age could enroll with or without parent enrollment. The specific age and language inclusion criteria were based on the availability of validated instruments. Eligible participants were identified by review of HSCT patient rosters. HSCT physicians who performed the intake consultations for eligible patients confirmed eligibility and introduced the study. The study team then approached interested families to provide more information and obtain informed consent. Patients ≥ 18 years of age and parents of patients under 18 years of age provided signed informed consent, while patients under 18 years provided developmentally appropriate informed assent. Parents also provided informed consent for their own participation.

Data collection

Patient and parent dyads prospectively reported on symptoms and HRQoL on the HPQ survey via a web-based application. Patients received age-appropriate surveys. Surveys could be completed on a computer/ tablet provided by the study team, using the participants' own computer/ tablet with internet access, or on paper (while inpatient). If participants did not have access to an appropriate device, they were provided with a tablet for the duration of the study. For patients unable to operate a computer or read survey questions due to developmental or other considerations, survey questions were read aloud to them and/or they could receive help with use of the computer. All HPQ surveys were auto-assigned by the web-based application. When a survey was assigned and available for completion, participants received a notification email with a link to the survey. Younger patients without their own email addresses accessed their HPQ surveys via their parents' access link. Participants had 2 days to complete assigned surveys with a reminder sent if not complete after 24 hours. Surveys were sent at baseline (study enrollment), day 0 (date of stem cell infusion), and weekly for the first 4 weeks following transplant. In addition to the HPQ surveys, baseline demographic information was collected from participant report and medical record abstraction. Medical record abstraction was completed at multiple timepoints throughout a patient's transplant course to collect transplant characteristics, co-morbidities, and complications post-transplant (e.g., graft versus host disease). Surveys completed on paper and abstracted medical data were entered into REDCap databases.

Measures

Exposure: The primary exposure of interest was PPC involvement at baseline (i.e., prior to HSCT) determined by medical record review at the time of study enrollment. At DFCI/ BCH, patients were referred to PPC based on specific criteria that prompted consult including: receiving second HSCT, not in remission at time of HSCT, high-risk due to co-morbidities, need for additional psychosocial support, or at the discretion of the HSCT team.¹⁸ SJCRH was in the process of expanding PPC for HSCT patients during this study period so patients early in the study were referred to PPC if deemed high risk or receiving allogeneic HSCT while later patients enrolled in this study had near-universal PPC screening consult at baseline with degree of subsequent involvement based on patient need.¹⁸

Outcomes: The primary outcomes of interest were total number of symptoms, number of physical symptoms, number of psychological symptoms, HSCT-PediQUEST Memorial Symptom Assessment Scale (HPQ-MSAS) total score. The HPQ survey assessed patient symptoms, HRQoL, parental activation (e.g., a parents' assessment of their self-efficacy on behalf of themselves and their child), and parental satisfaction with care utilizing 4 instruments embedded in the REDCap application. Outcomes for this analysis relied on the HPQ-MSAS instrument. MSAS reliability is above 0.80 (Cronbach's alpha) with good convergent validity.^{21,22} HPQ-MSAS is a survey adapted from MSAS that captures data on 23 physical and 7 psychological symptoms.^{21,22} Patients 5 to 6 years did not complete HPQ-MSAS and patients 7 to 12 years completed an age-appropriate version containing 9 items. Patients ≥ 13 years and parents completed versions that contained all 30 items.

HPQ-MSAS responses were used to calculate the total number of symptoms, total number of physical symptoms on the physical subscale (comprised of 11 physical symptoms: lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, and dizziness), and total number of psychological symptoms on psychological subscale (comprised of 6 psychological symptoms: sad, worrying, feeling irritable, feeling nervous, difficult sleeping, and difficulty concentrating) (Table 1).^{21,22} Calculated HPQ-MSAS scores measured presence, intensity, frequency, and distress for physical and psychological symptoms in patients in the week prior to questionnaire administration, providing multidimensional information about symptoms. Individual HPQ-MSAS symptom scores were a calculated average of symptom dimensions and the HPQ-MSAS total score was calculated as the average of all HPQ-MSAS symptom scores (excluding bleeding, seizure, and participant write-in symptoms) (Table 1).^{21,22} Scores were calculated if at least 50% of HPQ-MSAS items were answered. For cases where at least 50% of the items were completed but some items are missing, the scores were calculated based on the available data items.

Covariates: Additional covariates include study site, patient and parent age, patient and parent sex, parent education, transplant indication, transplant type, conditioning regimen type, presence of significant pre-transplant co-morbidity, history of prior transplant, and involvement of baseline supportive care services (palliative care, pain service, psychological services).

Statistical Analysis

For patients younger than 13 years, parent data was utilized. For patients 13 years or older, patient reported data was used, however, if patient data were not available at a given time point and parent response was available, parent responses were substituted at that time point. Descriptive measures were used to summarize participant characteristics for both groups. Estimated marginal means and 95% confidence intervals (CI) for total number of symptoms, total number of physical symptoms on physical subscale, total number of psychological symptoms on psychological subscale, and HPQ-MSAS total score were derived from linear mixed models and included all participants at each time point. Timepoint of follow up data was included as a fixed effect and patient was used as random effect to account for repeated measures with exchangeable covariance. Propensity score analysis with propensity score regression adjustment was used to reduce potential bias due to confounding by indication. Propensity scores for palliative care involvement were estimated by fitting a logistic regression model incorporating baseline covariates including site, age, sex, diagnosis type (e.g., transplant indication), transplant type, conditioning type, and presence of significant pre-transplant co-morbidity. This score represents an individual's probability of palliative care involvement given their baseline measures on these covariates. Propensity adjusted marginal means and 95% CIs for total number of symptoms, total number of physical symptoms on physical subscale, total number of psychological symptoms on psychological subscale, and HPQ-MSAS total score were derived from linear mixed models and included all participants at each time point. To account for timepoints nested within patients with repeated measures, patient was included as a

random effect and exposure to palliative care and propensity score were included as a fixed effect to adjust for confounding. Absolute mean differences with 95% CIs were used to compare outcomes between patients who had and had not received PPC.

Results

Participant Characteristics

Study teams screened 649 patients or patient/ parent dyads. Of those, 277 were eligible and 159 patients or patient/ parent dyads enrolled. Participants were followed through 6 months post HSCT. Participants were excluded from this analysis if they did not complete the relevant baseline surveys (n=41) or did not complete surveys from at least one additional timepoint in the first 4 weeks post-HSCT (n=16). One hundred and two patients or patient/ parent dyads met criteria to be included in this analysis. All patients included in this analysis also had a parent participate in this study.

Fifty-four patients (52.9%) did not have PPC involvement at baseline and 48 patients (47.1%) had PPC involvement at baseline (Table 2). The median age of the patients not receiving PPC (12 years) was the same as patients receiving PPC. Patients who did not have PPC at baseline were more likely to be female (52.7%) compared to those who did have baseline PPC (39.6%) (Table 2). The majority of patients who did not have baseline PPC involvement received care at DFCI/ BCH (94.4%) while the majority of patients who had baseline PPC involvement received care at SJCRH (89.6%) (Table 2). Patients who received PPC were more likely to have a history of prior HSCT (20.5%) compared to those who did not receive PPC (3.7%) (Table 2). The majority of patients from both groups were receiving HSCT for hematologic malignancies (Table 2). Those who did not receive baseline PPC were more likely to have an unrelated donor if undergoing allogeneic transplant (51.8%) and receive myeloablative conditioning (57.4%) compared to those who did receive PPC (Table 2).

Among the parents of patients who did not have PPC involvement at baseline (n=54), the median age was 46 years, almost all were female (97.6%), and 96.3% spoke English as their primary language (Table 2). Among the parents of patients who did have PPC involvement at baseline (n=48), the median age was 42 years and the majority (85.4%) were female, however, a smaller fraction (83.3%) reported speaking English as their primary language (Table 2). In both groups, the majority of parents graduated from college and/or graduate school (Table 2).

Symptom Burden and HPQ-MSAS Trajectories

The number of participants who received and did not receive PPC that responded to the HPQ-MSAS questionnaire decreased at progressive timepoints (Table 3). Physical and psychological symptom burden were high throughout the first month post HSCT, typically peaking around week 1 when patients were still experiencing effects of their conditioning regimen and awaiting engraftment. In the unadjusted analysis, predicted mean total number of symptoms, number of physical symptoms, and total HPQ-MSAS score peaked at week 1. Psychological symptoms did not follow this trend.

Following propensity adjustment, predicted mean total number of symptoms and total HPQ-MSAS score peaked at week 1 in the group that did not have PPC involvement at baseline (Figure 1). Means and 95% CIs were 11.2 (9.3, 13.2) and 22.2 (17.4, 26.9) at week 1, respectively (Table 4). Mean number of physical symptoms peaked at day 0 (mean 6.2, 95% CI 5.3, 7.1) and mean number of psychological symptoms was highest at baseline and day 0 (mean 2.3, 95% CI 1.5, 3.0) (Figure 1, Table 4). In the group that had baseline PPC involvement, predicted mean total number of symptoms, number of physical symptoms, and total HPQ-MSAS score peaked at week 1 (Figure 1). Mean scores and 95% CIs were 12.8 (10.8, 14.8), 7.0 (6.0, 7.9), and 26.8 (21.9, 31.7), respectively (Table 4). Mean number of psychological symptoms was highest at baseline and day 0 at 2.4 (95% CI 1.7, 3.2) (Table 4).

Association between PPC and Symptom Burden

Propensity adjusted mean differences between groups and associated 95% CIs are shown in Table 4. Across all time points, the outcome variables (total number of symptoms, number of physical symptoms, number of psychological symptoms, and HPQ-MSAS total score) in the patients that received PPC either did not differ from, or were slightly to somewhat worse than, patients that did not receive PPC. None of the CIs on the difference between the patients receiving and not receiving PPC for any outcome excluded the null value.

Discussion

Pediatric patients receiving HSCT reported a high burden of physical and psychological symptoms in the first month following transplant with elevated HPQ-MSAS scores representing high symptom intensity, frequency, and distress. Psychological symptoms were highest at the start of transplant while physical symptoms typically peaked around week 1. After propensity adjusted analysis, there were no differences in symptom outcomes between patients who did not have PPC involvement at baseline and patients who did.

In adult HSCT patients, early palliative care interventions during the transplant hospitalization were associated with improved HRQoL, symptom burden, and psychological outcomes 2 weeks post HSCT with sustained effects following transplant.^{5,8} A multisite RCT of an early PPC intervention for oncology patients is currently underway, however, this study excludes patients receiving HSCT and there have not been any randomized studies of PPC in patients undergoing HSCT specifically.²⁴ Observational studies in pediatrics have reported improved end of life outcomes when PPC was involved for patients who received HSCT and did not survive.²⁵ Research on the impact of PPC for the majority of HSCT patients who do survive is limited. We therefore conducted the first study reporting on symptom burden in the first month post HSCT comparing groups with and without baseline PPC involvement. In this study, we observed that pediatric HSCT patients with baseline PPC involvement were more likely to be male, have an underlying oncologic diagnosis, and have a history of prior HSCT compared to patients who did not have baseline PPC. To account for differences and address confounding by indication (e.g., patients with higher likelihood of poor outcome based on diagnosis or co-morbidity may have been more likely to have PPC involvement at baseline), propensity score adjustment was used. However, this approach cannot adjust for unobserved confounders and there could have been differences between the groups that were not accounted for.

Notably, there were no significant differences in symptom burden during the first 4 weeks following HSCT between the two groups. This suggests that baseline PPC involvement in pediatric HSCT may not impact symptom outcomes as hypothesized. One consideration in the interpretation of these results is the possibility of non-differential misclassification of the exposure, which could bias towards the null.

In RCTs of palliative care interventions in adults, the palliative care intervention is typically well-defined with specific team members seeing patients at pre-specified intervals and with an emphasis on the domains within palliative care that are perceived to be most impactful in that population.^{8,26,27} This degree of precision with the exposure was not possible in this observational study and the 2 institutions where this study was completed may have had different approaches to PPC when it was made available to patients. For example, some PPC programs focus more on psychosocial support versus symptom management and there are different permutations of a multidisciplinary PPC team.²⁸ The “dose” of palliative care required for effect on outcomes has not been quantified, and the degree of involvement by PPC was not captured in our data. We determined exposure to PPC at baseline medical record abstraction pre-transplant, however, there could be non-differential exposure misclassification if PPC was consulted after enrollment but early in the transplant course. To better quantify the involvement of PPC in this observational study, future work could include chart review of PPC encounters to

explore which PPC team members saw patients at which timepoints and key themes of those discussions. Qualitative interviews with patients and families could also elucidate whether the extra layer of support provided by PPC offered benefits not captured in symptom reporting.

Pediatric patients receiving HSCT and their parents report that there is a high degree of suffering from symptoms in the first month and that there should be more attention paid to quality of life from the start of transplant.³⁰ In the initial PediQUEST study collecting symptom and quality of life data in pediatric patients with advanced cancers, there was a cohort of patients who completed MSAS surveys reporting symptoms in the last 12 weeks of life, when patients would presumably have a high symptom burden.²⁹ Patients and parents reported a mean total MSAS score of 9.3.²⁹ In this study population at 1 week post-transplant, pediatric HSCT patients without baseline PPC involvement reported a mean total HPQ MSAS score of 25.4 (95% CI 21.8, 28.9) and pediatric HSCT patients with baseline PPC involvement reported a mean total HPQ MSAS score of 23.4 (95% CI 19.8, 27.0). This suggests a staggering burden of symptom presence, frequency, severity, and distress in pediatric recipients of HSCT in the first month following transplant.

Despite these findings, patients and parents note barriers to addressing symptoms that can detract from solution-oriented approaches.³¹ A study on barriers to adequate symptom management in pediatric patients with advanced cancers reported that patients, parents, and clinicians (including PPC providers) all described the “normalization” of symptoms which hindered intervention and resulted in the perception that symptoms were expected and nothing more could be done to improve symptoms despite underutilization of multimodal symptom management resources.³¹ Given the intensity and cure-orientation of pediatric HSCT, this phenomena is likely pervasive. If healthcare providers, patients, and families perceive distressing symptoms as an inevitable and uninfluenceable component of HSCT, it makes it harder to move the needle. Education for HSCT and PPC providers and robust anticipatory guidance for patients and families are needed to address these perceptions and change attitudes to optimize the use and effect of symptom management interventions.

This study has several limitations. One substantial limitation is the near complete confounding of baseline PPC exposure by study site as these variables were highly correlated. Study site was included in our multivariable analysis, however, residual confounding is likely. Had there been a difference between groups in this study, it would not have been possible to discern whether those differences were attributable to PPC or other elements of site. Site is unlikely to explain the absence of differences between groups in this analysis. Pediatric HSCT for any indication is rare with most pediatric transplant centers performing 30 to 100 transplants per year, limiting enrollment and ability to detect a statistical difference in outcomes between groups. However, given limited knowledge about the impact of PPC on the post-HSCT trajectory, this study addresses a substantial research gap. Participants who did not complete baseline surveys and surveys from at least one additional timepoint in the acute post-transplant phase were excluded, however, missingness may be non-random if patients with more severe complications from HSCT were unable to respond to follow-up surveys. This could bias our results towards a healthier subset of patients receiving HSCT leading to underestimation of negative outcomes. The inter- and intra-institution variability in PPC and HSCT services, practices, and norms, could impact outcomes and the 2 sites in this study may not reflect all pediatric centers. On the other hand, the 2 institutions included in this study are representative of diverse approaches to transplant and PPC. Patients were cared for by multiple multidisciplinary team members throughout their transplant admission, so these data are capturing the results of a broad spectrum of practice approaches, which helps to enhance generalizability.

Pediatric HSCT patients report a high burden of physical and psychological symptoms in the first month following transplant. There were no differences in symptom burden between those who had PPC involved at baseline and those who did not. These findings, nonetheless,

highlight a need for enhanced symptom management and robust patient and family support during the HSCT process. While PPC was not associated with reduced symptom burden, there are other dimensions of quality of life, distress, and well-being that could have been impacted by PPC but were not explored in this study. Both adult and pediatric transplant recipients and their caregivers have reported limited knowledge about palliative care, however, their perceptions of palliative care are generally positive and they are open to early palliative care integration in HSCT.^{30,32,33} Given the effects seen in adult patients undergoing HSCT, PPC integration in pediatric HSCT merits further exploration. RCTs of well-defined, specialty PPC interventions are needed in the pediatric HSCT population.

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Table 1. Symptoms included on HPQ MSAS questionnaire

Symptom
Physical Symptoms
<i>Anorexia</i>
<i>Pain</i>
<i>Fatigue</i>
<i>Drowsy</i>
<i>Constipation</i>
<i>Dry mouth</i>
<i>Nausea</i>
<i>Vomiting</i>
<i>Taste changes</i>
<i>Weight loss</i>
<i>Dizziness</i>
Cough
Shortness of breath
Difficulty swallowing
Diarrhea
Problems with urination
Numbness/ tingling
Swelling of arms or legs
Sweats
Itching
Changes in skin
Seizure*
Bleeding*
Psychological Symptoms
<i>Sadness</i>
<i>Worrying</i>
<i>Irritable</i>
<i>Nervous</i>
<i>Difficulty sleeping</i>
<i>Difficulty concentrating</i>
Don't look like myself (self-image)
Other
Other (participant write-in symptoms)

Abbreviations: HPQ=HSCT PediQUEST, MSAS = Memorial Symptoms Assessment Scale
Questionnaire assessed presence of symptom as well as frequency, severity, and extent of bother.

Italics signify that symptom was included in relevant physical or psychological symptom subscale

*Excluded from HPQ MSAS Total Score as these items were not included and validated as part of original MSAS questionnaire

Table 2. Selected Characteristics of Participants, by Receipt of Pediatric Palliative Care

Patient Characteristic	PPC at Baseline	
	No N= 54 n (%)	Yes N=48 n (%)
Age at baseline (years), median (range)	12 (5-24)	12 (5-23)
Female sex	29 (52.7%)	19 (39.6%)
English is primary language	53 (98.1%)	42 (87.5%)
Diagnostic Indication for HSCT***		
Hematologic Malignancy	30 (55.6%)	29 (60.4%)
Solid tumor (peripheral or central nervous system)	9 (16.7%)	10 (20.8%)
Non-malignant hematologic/ Metabolic/ Immunodeficiency/Other	15 (27.8%)	9 (18.8%)
Transplant type		
Autologous	11 (20.4%)	10 (20.8%)
Allogeneic related donor (matched or mismatched)	15 (27.8%)	22 (45.8%)
Allogeneic unrelated donor	28 (51.8%)	16 (33.3%)
Myeloablative conditioning	31 (57.4%)	20 (41.7%)
Pre-HSCT co-morbidities present	5 (9.3%)	6 (12.5%)
History of Prior HSCT	2 (3.7%)	12 (25.0%)
Additional support service at baseline		
Pain service	10 (18.5%)	3 (6.3%)
Psychosocial service	43 (79.6%)	40 (83.3%)
Site		
DFCI/BCH	51 (94.4%)	5 (10.4%)
St Jude	3 (5.6%)	43 (89.6%)
Parent/ Caregiver Characteristic	N= 54	N=48
Age in years at baseline, median (range)	46 (34-58)	42 (26-59)
Female sex	43 (97.6%)	41 (85.4%)
Missing*	4 (7.4%)	2 (4.2%)
Relationship to patient		
Mother	43 (79.6%)	41 (85.4%)
Father	6 (11.1%)	5 (10.4%)
Missing*	5 (9.3%)	2 (4.2%)
English is primary language	52 (96.3%)	40 (83.3%)
Highest level of school completed		
High school graduate/equivalent (GED) or less	6 (11.1%)	2 (4.2%)
Some college or technical school	7 (13.0%)	11 (22.9%)
College graduate (associate or bachelor's degree)	25 (46.2%)	21 (43.8%)
Graduate or professional school (e.g., Masters, PhD, JD)	9 (16.7%)	10 (20.8%)
Missing*	7 (13.0%)	4 (8.3%)

Abbreviations: PPC = pediatric palliative care, HSCT = hematopoietic stem cell transplant

***Diagnosis categories: Hematologic malignancy (acute lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphoma), Solid tumor (brain tumor, germ cell tumor, neuroblastoma, other solid tumor), Non-malignant hematologic (Congenital amegakaryocytic thrombocytopenia, Diamond Blackfan anemia, Fanconi anemia, paroxysmal nocturnal hemoglobinuria, severe aplastic anemia, Shwachman-Diamond syndrome, sickle cell disease, thalassemia), Metabolic (other metabolic), Immunodeficiency (hemophagocytic lymphohistiocytosis, Wiskott-Aldrich, other immunodeficiency), Other (dyskeratosis congenita, osteopetrosis)

*Missing values that exceeded 5% are presented as percentages

Table 3. Unadjusted marginal estimates of symptom burden (with 95% CI) at Baseline and 5 timepoints during the first month post-HSCT, by Receipt of Pediatric Palliative Care (N at each timepoint)

Timepoint/Symptom Measure	PPC at Baseline	
	No	Yes
Baseline	N=54	N=48
Total number of symptoms	7.8 (6.4, 9.1)	6.4 (5.0, 7.8)
Physical symptoms	3.2 (2.6, 3.8)	3.1 (2.5, 3.8)
Psychological symptoms	2.8 (2.3, 3.3)	1.9 (1.3, 2.4)
Total HPQ MSAS score	13.0 (9.8, 16.3)	10.9 (7.5, 14.3)
Day 0	N=44	N=38
Total number of symptoms	12.6 (11.2, 14.0)	9.8 (8.3, 11.2)
Physical symptoms	6.7 (6.0, 7.4)	5.9 (5.1, 6.6)
Psychological symptoms	2.8 (2.3, 3.3)	1.9 (1.3, 2.4)
Total HPQ MSAS score	23.4 (20.0, 26.9)	17.1 (13.5, 20.7)
Week 1	N=38	N=40
Total number of symptoms	12.8 (11.4, 14.3)	11.2 (9.7, 12.7)
Physical symptoms	6.5 (5.8, 7.2)	6.5 (5.7, 7.2)
Psychological symptoms	2.5 (2.0, 3.1)	1.7 (1.2, 2.3)
Total HPQ MSAS score	25.4 (21.8, 28.9)	23.4 (19.8, 27.0)
Week 2	N=39	N=36
Total number of symptoms	12.1 (10.7, 13.6)	10.0 (8.5, 11.5)
Physical symptoms	6.1 (5.4, 6.8)	5.6 (4.8, 6.3)
Psychological symptoms	2.7 (2.2, 3.3)	1.5 (1.0, 2.1)
Total HPQ MSAS score	21.9 (18.4, 25.4)	19.0 (15.4, 22.7)
Week 3	N=37	N=34
Total number of symptoms	11.7 (10.2, 13.2)	8.2 (6.7, 9.7)
Physical symptoms	6.0 (5.3, 6.7)	4.9 (4.1, 5.7)
Psychological symptoms	2.7 (2.1, 3.3)	1.0 (0.4, 1.6)
Total HPQ MSAS score	21.7 (18.1, 25.2)	15.0 (11.3, 18.7)
Week 4	N= 25	N=29
Total number of symptoms	9.4 (7.7, 11.0)	7.3 (5.7, 8.9)
Physical symptoms	4.9 (4.1, 5.8)	4.2 (3.4, 5.0)
Psychological symptoms	1.9 (1.3, 2.6)	1.4 (0.8, 2.0)
Total HPQ MSAS score	16.2 (12.2, 20.2)	12.3 (8.36, 16.2)

Abbreviations: HSCT = hematopoietic stem cell transplant, PPC = pediatric palliative care, CI = confidence interval, HPQ=HSCT PediQUEST, MSAS = Memorial Symptoms Assessment Scale

Marginal mean estimates and 95% CIs derived from linear mixed models that included all participants at each time point. Timepoint was included as a fixed effect and participant were used as random effect to account for repeated measures with exchangeable covariance.

Total number of symptoms: based on 28 symptoms which excluded: seizures, bleeding, and other (participant write-in symptoms)

Physical symptoms: physical subscale comprised of 11 physical symptoms including lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, and dizziness

Psychological symptoms: psychological subscale comprised of 6 psychological symptoms including sad, worrying, feeling irritable, feeling nervous, difficult sleeping, and difficulty concentrating

Total HPQ-MSAS score: MSAS total score is a calculated average of symptom dimensions for all reported symptoms (including frequency, severity, and distress sub-items).

Table 4. Propensity adjusted marginal estimates of symptom burden (with 95% CI) at Baseline and 5 timepoints during the first month post-HSCT, by Receipt of Pediatric Palliative Care (N at each timepoint)

Timepoint/Symptom Measure	PPC at baseline		Adjusted mean difference (95% CI)
	No	Yes	
Baseline	N=54	N=48	
Total number of symptoms	6.2 (4.4, 8.0)	8.0 (6.1, 9.9)	-1.8 (-5.0, 1.35)
Physical symptoms	2.7 (1.9, 3.6)	3.6 (2.7, 4.5)	-0.9 (-2.4, 0.5)
Psychological symptoms	2.3 (1.6, 3.0)	2.4 (1.7, 3.2)	-0.2 (-1.4, 1.1)
Total HPQ MSAS score	9.9 (5.37, 14.4)	14.2 (9.5, 18.9)	-4.3 (-12.3, 3.5)
Day 0	N=44	N=38	
Total number of symptoms	11.0 (9.1, 12.9)	11.4 (9.4, 13.3)	-0.4 (-3.6, 2.9)
Physical symptoms	6.2 (5.3, 7.1)	6.3 (5.4, 7.3)	-0.1 (-1.6, 1.4)
Psychological symptoms	2.3 (1.5, 3.0)	2.4 (1.7, 3.2)	-0.2 (-1.4, 1.1)
Total HPQ MSAS score	20.2 (15.5, 24.9)	20.5 (15.6, 25.3)	-0.3 (-8.4, 7.9)
Week 1	N=38	N=40	
Total number of symptoms	11.2 (9.3, 13.2)	12.8 (10.8, 14.8)	-1.6 (-4.9, 1.7)
Physical symptoms	6.0 (5.1, 6.9)	7.0 (6.0, 7.9)	-1.0 (-2.5, 0.6)
Psychological symptoms	2.0 (1.2, 2.7)	2.3 (1.5, 3.1)	-0.3 (-1.6, 0.9)
Total HPQ MSAS score	22.2 (17.4, 26.9)	26.8 (21.9, 31.7)	-4.6 (-12.8, 3.6)
Week 2	N=39	N=36	
Total number of symptoms	10.6 (8.7, 12.5)	11.7 (9.7, 13.6)	-1.1 (-4.3, 2.2)
Physical symptoms	5.6 (4.7, 6.5)	6.0 (5.1, 7.0)	-0.4 (-1.9, 1.1)
Psychological symptoms	2.2 (1.4, 2.9)	2.1 (1.3, 2.9)	0.1 (-1.2, 1.3)
Total HPQ MSAS score	18.8 (14.1, 23.4)	22.4 (17.4, 27.3)	-3.6 (-11.8, 4.5)
Week 3	N=37	N=34	
Total number of symptoms	10.2 (8.3, 12.1)	9.8 (7.8, 11.8)	0.4 (-2.9, 3.7)
Physical symptoms	5.5 (4.6, 6.5)	5.4 (4.4, 6.3)	0.2 (-1.4, 1.7)
Psychological symptoms	2.2 (1.4, 2.9)	1.6 (0.8, 2.3)	0.6 (-0.7, 1.9)
Total HPQ MSAS score	18.5 (13.7, 23.2)	18.3 (13.4, 23.2)	0.2 (-8.0, 8.4)
Week 4	N= 25	N=29	
Total number of symptoms	7.8 (5.7, 9.9)	8.9 (6.8, 11.0)	-1.1 (-4.6, 2.3)
Physical symptoms	4.4 (3.4, 4.5)	4.7 (3.7, 5.7)	-0.2 (-1.9, 1.4)
Psychological symptoms	1.4 (0.5, 2.2)	2.0 (1.2, 2.8)	-0.6 (-2.0, 0.7)
Total HPQ MSAS score	12.9 (7.8, 18.1)	15.6 (10.5, 20.7)	-2.7 (-11.2, 5.9)

Abbreviations: HSCT = hematopoietic stem cell transplant, PPC = pediatric palliative care, CI = confidence interval, HPQ=HSCT PediQUEST, MSAS = Memorial Symptoms Assessment Scale

Marginal mean estimates and 95% CIs derived from linear mixed models that included all participants at each time point. Timepoint was included as a fixed effect and participant were used as random effect to account for repeated measures with exchangeable covariance. Propensity score weighting for palliative care involvement estimated using logistic regression incorporating baseline covariates including site, patient age, patient sex, diagnosis type (e.g., transplant indication), transplant type (e.g., donor source), conditioning type, and presence of significant pre-transplant co-morbidity. This score represents an individual's probability of baseline palliative care involvement given their baseline measures on these covariates.

Total number of symptoms: based on 28 symptoms which excluded: seizures, bleeding, and other (participant write-in symptoms)

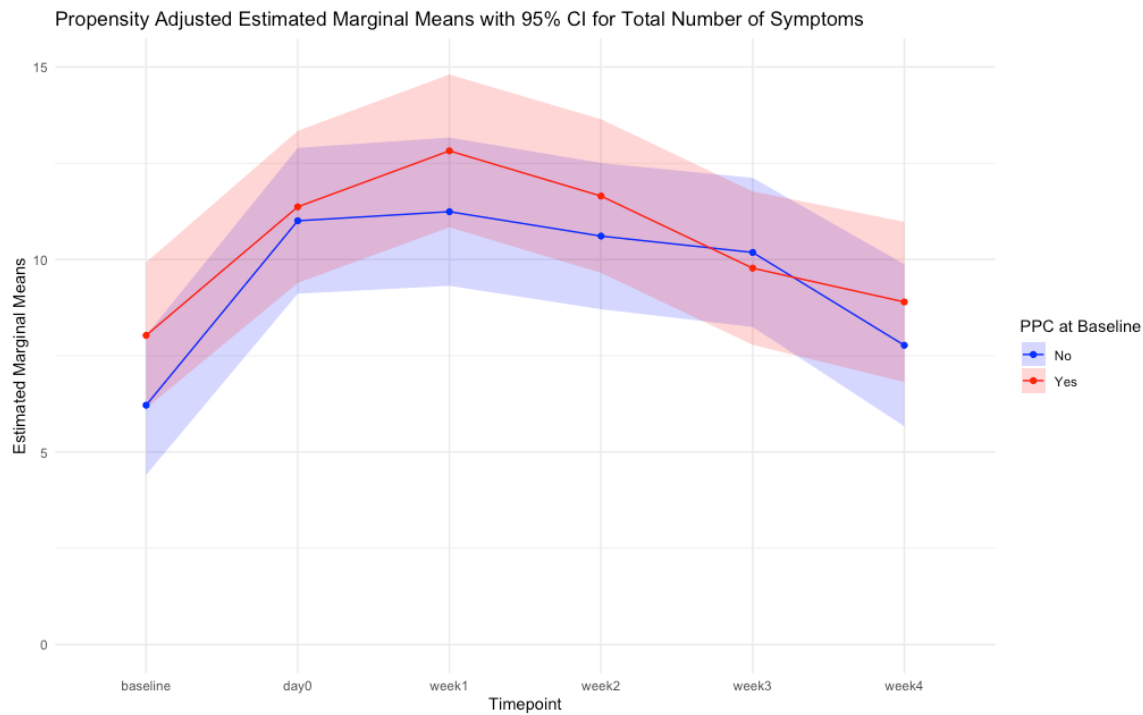
Physical symptoms: physical subscale comprised of 11 physical symptoms including lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, and dizziness

Psychological symptoms: psychological subscale comprised of 6 psychological symptoms including sad, worrying, feeling irritable, feeling nervous, difficult sleeping, and difficulty concentrating

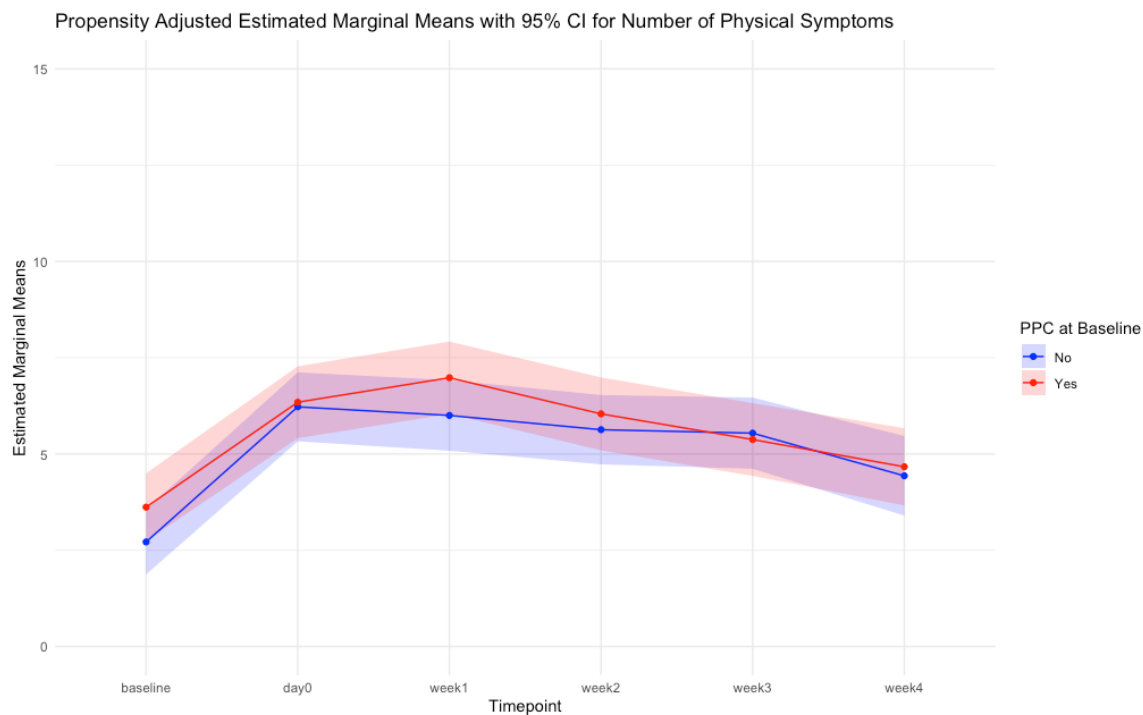
Total HPQ-MSAS score: MSAS total score is a calculated average of symptom dimensions for all reported symptoms (including frequency, severity, and distress sub-items)

Figure 1. Propensity-adjusted marginal estimates (with 95% CI) of A) total number of symptoms, B) number of physical symptoms, C) number of psychological symptoms, and D) total HPQ MSAS Score at Baseline and 5 timepoints during the first month post-HSCT, by Receipt of Pediatric Palliative Care

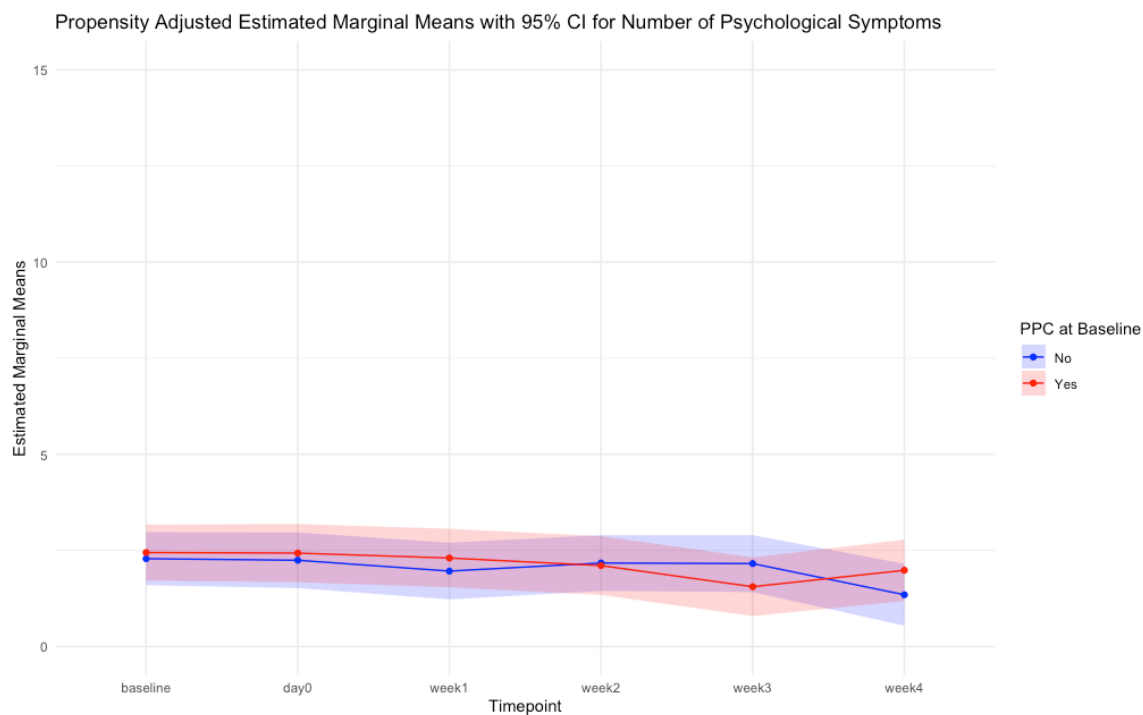
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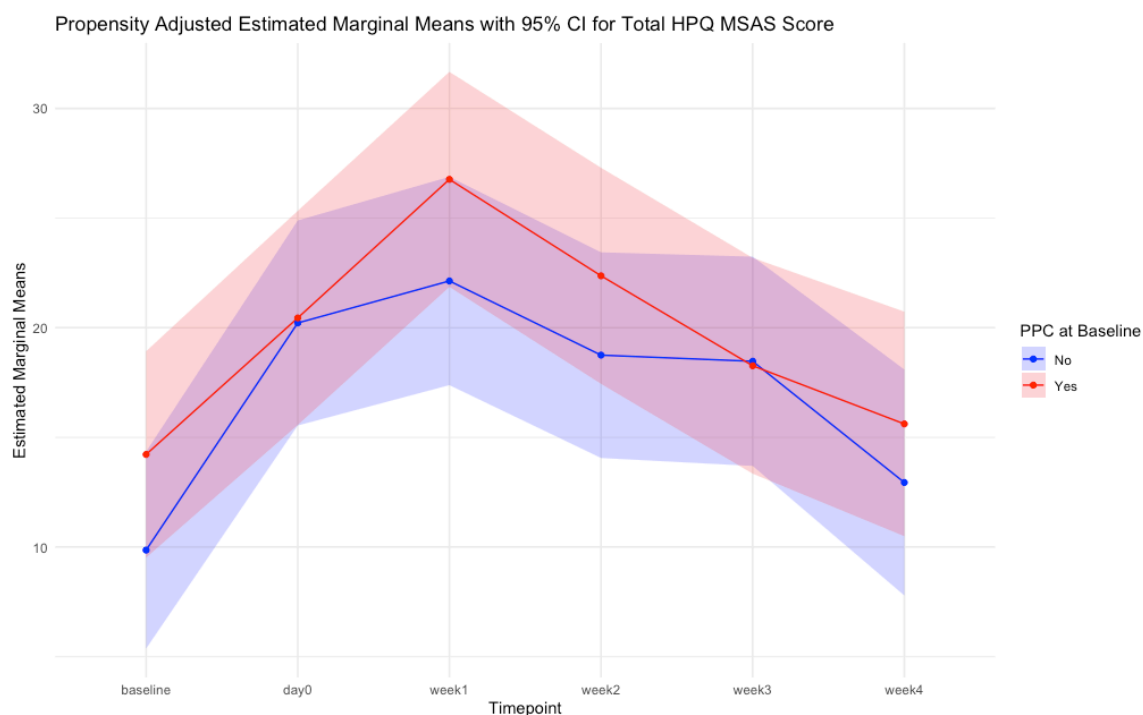
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Abbreviations: HSCT = hematopoietic stem cell transplant, PPC = pediatric palliative care, CI = confidence interval, HPQ=HSCT PediQUEST, MSAS = Memorial Symptoms Assessment Scale