Brief Report

Circadian Rhythmicity as a Predictor of Quality of Life in Allogeneic Hematopoietic Cell Transplant Patients

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Abstract

Context. Quality of life (QoL) is increasingly recognized as an important outcome of cancer treatment. Previous studies have examined clinical predictors of QoL, but with the increasing prevalence of wearable sensors that monitor sleep and activity patterns, further investigation into whether these behaviors are predictive of post-treatment QoL is now feasible. Among patients receiving aggressive cancer treatment such as hematopoietic cell transplantation (HCT), analysis of circadian rhythms (24-hour patterns of sleep and activity) via wearable sensors is limited.

Objective. To evaluate the relationship between overall QoL and circadian rhythms in patients receiving allogeneic HCT.

Methods. Patients wore an ActiGraph GT3X (Pensacola, FL) activity monitor for at least 72 hours before the initiation of conditioning chemotherapy and transplantation and completed a QoL (Functional Assessment of Cancer Therapy-General [FACT-G]) assessment. QoL assessments were also completed 1, 3, and 6 months after HCT.

Results. Patients ($n = 45$, M age = 55) were mostly male (66%) with a total FACT-G score of 80.96 (SD = 16.05) before HCT. Mixed models revealed robust cross-sectional associations between overall QoL and multiple circadian rhythmicity parameters, including durations of high physical activity, overall circadian rhythmicity, and earlier starts of daily activity (P's < .01). Recovery of QoL after transplant was predicted by longer pre-transplant durations of high physical activity ($P = .04$) and earlier evening retirement ($P = .04$).

Conclusion. Our findings suggest that wearable sensor information is a promising method of predicting recovery of QoL after HCT. Additional studies are needed to confirm these findings in a larger sample. J Pain Symptom Manage 2019;57:952–960. © 2019 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative treatment for hematologic malignancies, with recent advances in HCT techniques improving transplant-related morbidity, mortality rates, and post-transplant relapse.[1,2] In addition to medical outcomes, quality of life (QoL) has gained increasing attention as an important metric of HCT success for both patients and clinicians. Overall, long-term QoL remains impaired in HCT recipients relative to population norms.[2,3] However, assessing average QoL may obscure heterogeneity in recovery patterns after transplant and may not reflect the varied recovery patterns in QoL as demonstrated by previous longitudinal assessments.[4] Notably, some patients demonstrate preserved physical QoL at

baseline that subsequently declines after HCT with no evidence of QoL recovery by six months after transplant.[4] Several factors, including older age, female sex, and advanced disease, have previously been identified as at-risk indicators for poor recovery of QoL.[3] However, these sociodemographic and disease predictors do not fully explain QoL trajectories after HCT.[4] Thus, novel approaches are needed to identify patients at risk for poor QoL recovery after transplant.

Wearable activity sensors, previously available for research purposes only, are now ubiquitously commercially available and can be used to evaluate patient behaviors before transplant. An actigraph, for example, is a small sensor typically worn on the wrist that uses an accelerometer to infer physical activity (i.e., activity), sleep, and wake cycles.[5] Utilization of actigraphs allows for passive and noninvasive tracking of daily activity and sleep patterns in real time. One objective marker of behavioral patterns that can be derived from wearable sensors is circadian rhythmicity or the consistent timing and magnitude of sleep and activity patterns that follow a daily 24-hour cycle. Circadian rhythmicity is conceptually distinct from separate assessments quantifying objective sleep and physical activity.[6] Individuals with normal circadian patterns tend to be active during the day and inactive at night, with consistent objective sleep and activity patterns. In contrast, cancer patients show dysregulated circadian rhythms, often during cancer treatment,[7] as evidenced by being less active during the day and exhibiting flattened variability in magnitude of daily rest and activity levels[8−10] and having inconsistent patterns of sleep and activity.[9−11] In cancer patients, less-robust circadian rhythms are associated with higher levels of systemic inflammation[12] and an increased risk of disease progression and mortality.[13] In patients with suspected cancer, less-robust circadian rhythms may also predict tumor malignancy.[14]

Although limited, existing literature supports the association between QoL and circadian rhythmicity in cancer patients.[15−19] Rhythmic 24-hour rest/activity periods are associated with higher concurrent QoL in addition to more favorable medical outcomes (e.g., treatment response, survival) in patients with various types of cancer, including breast, colorectal, and lung cancer.[16,17,19−21] These associations have been observed over and above the impact of sex, age, primary tumor, number of metastatic sites, and prior treatment.[17] However, to our knowledge, no studies have examined the predictive value of circadian rhythmicity for identifying recovery of QoL. Furthermore, circadian rhythms in HCT recipients have been largely unexplored. Thus, the goal of this pilot study was to evaluate the relationship between circadian rhythmicity in cancer patients before receiving allogeneic HCT and QoL throughout the transplant course. We hypothesized that increased baseline rhythmicity would be associated with better concurrent QoL before HCT and would predict faster recovery of QoL after HCT.

Methods

Eligible participants were at least 18 years of age, were scheduled to receive allogeneic HCT, had completed vital organ testing for allogeneic HCT, had a hemoglobin value of ≥8 g/dL, had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, and were able to walk unassisted. Written informed consent was obtained before initiation of study procedures. The study was approved by the University of South Florida Institutional Review Board. Following written informed consent, participants filled out a baseline questionnaire assessing QoL. A research coordinator then attached an actigraph to the wrist of patients' choice and explained its use (after completion of vital organ testing and within 30 days of admission for allogeneic HCT). Seven days later, the actigraph was removed by study staff. Participants were asked to complete follow-up questionnaires at 1, 3, and 6 months after transplant.

Measures and Materials

Demographic and Clinical Information. Patient-related variables obtained through medical record review included date of birth, comorbidities, gender, donor source, and primary diagnosis. Comorbidities were calculated using the Hematopoietic Cell Transplantation Comorbidities Index (HCT-CI).[22] Higher scores on the HCT-CI reflect greater comorbidity (e.g., cardiovascular disease, infection).

Circadian Rhythmicity. Daily activity patterns were evaluated using GT3X wrist actigraphs (ActiGraph LLC, Pensacola, FL). Actigraphs have been shown to be valid and reliable measures of circadian patterns[5,21,23] and feasible for patients receiving autologous or allogeneic HCT.[24−26] Each actigraph uses a three-axis accelerometer to assess and record physical movement, which is then averaged over every minute. To maintain consistency across different durations of actigraphic monitoring, and consistent with evidence-based practice parameters,[23] raw continuous accelerometer data from the first 72 hours of consecutive wear time (starting at 12:00 AM) were exported into a comma separated value (.csv) worksheet using ActiLife 6.13.3 (ActiGraph LLC). Time and vector magnitude were then input into a five-parameter extended cosine model with an antilogistic transformation of the standard cosine curve[27] in SAS 9.4 to derive circadian parameters. Selected representative

Table 1
Participant Characteristics ($N = 45$)

Variable	Mean (SD)/Median (Range)/N (%)
Age: mean (SD)	54.8 (13.8)
Comorbidities: median (range)	3 (0−8)
Female: frequency (%)	15 (33.3)
Donor source: frequency (%)	
Umbilical cord blood	1 (2.2)
MMUD	10 (22.2)
MUD	21 (46.7)
MRD	13 (28.9)
Primary diagnosis: frequency (%)	
AML	10 (22.2)
MDS	8 (17.8)
ALL	5 (11.1)
NHL, B-Cell	4 (8.9)
NHL, T/NK-Cell	4 (8.9)
HD	3 (6.7)
MM	3 (6.7)
Other	8 (17.7)

MMUD = mismatched unrelated donor; MUD = matched unrelated donor; MRD = matched related donor; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; ALL = acute lymphocytic leukemia; NHL = non−Hodgkin's lymphoma; HD = Huntington's disease; MM = multiple myeloma.

statistics reported here include width ratio, up-mesor, down-mesor, and f-statistic (Supplemental Table 1). The width ratio characterizes the duration of high activity compared with low activity, with larger numbers indicating longer durations of high activity. The up-mesor refers to the time of day when participants became active, with larger numbers indicating a later daily start of activity. The down-mesor refers to the time of day when participants' activity declined for the evening, with larger numbers indicating a later daily decline of activity. The f-statistic describes "the strength and endurance of a [circadian] rhythm, as a measure of the signal-to-noise ratio,"[28] calculated as "the percentage of the variance accounted for by the fitted cosine model"[28] accounting for the number of observations and parameters in the model.[27] A larger f-statistic indicates a more robust circadian rhythm.[9]

Quality of Life. The Functional Assessment of Cancer Therapy-General (FACT-G),[29] plus a Bone Marrow Transplant-specific subscale (not reported here), was used to assess QoL before HCT and 1, 3, and 6 months after HCT. The FACT-G has been used extensively in HCT recipients. In addition to a total score, this scale includes four subscales: physical well-being (PWB; 7 items), social well-being (SWB; 7 items), emotional well-being (EWB; 6 items), and functional well-being (FWB; 7 items). In this study, we evaluated the total FACT-G score as the primary outcome. Additional

Table 2
Unstandardized Mixed Model Parameter (Beta) Estimates

Circadian Variable	Effect	Total QoL	PWB	SWB	EWB	FWB
Width ratio	Intercept	78.53[a]	20.97[a]	23.56[a]	17.93[a]	15.59[a]
	Time	−1.76	−0.59	−0.56	1.29[b]	−2.39[a]
	Time×time	0.47[c]	0.17	0.09	−0.16[c]	0.47[a]
	Width ratio	4.66[c]	2.13[b]	0.68	1.41[c]	0.63
	Time×width ratio	−4.38[c]	−1.99[c]	−0.14	−1.21[c]	−1.02
	Time×time×width ratio	0.63[c]	0.27[c]	0.01	0.17[c]	0.16
Up-mesor	Intercept	78.40[a]	20.94[a]	23.54[a]	17.88[a]	15.55[a]
	Time	−2.00	−0.70	−0.60	1.23[b]	−2.41[a]
	Time×time	0.51[c]	0.19	0.10	−0.15[c]	0.47[a]
	Up-mesor	−2.30[c]	−0.73	−0.40	−0.78[c]	−0.58
	Time×up-mesor	0.21	−0.05	−0.26	0.17	0.24
	Time×time×up-mesor	<.01	0.03	0.06	−0.01	−0.04
Down-mesor	Intercept	78.65[a]	21.04[a]	23.56[a]	17.96[a]	15.58[a]
	Time	−1.92	−0.65	−0.57	1.24[b]	−2.41[a]
	Time×time	0.50[c]	0.18	0.10	−0.15[c]	0.47[a]
	Down-mesor	1.09	0.76	0.14	0.27	−0.11
	Time×down-mesor	−1.82[c]	−0.94[c]	−0.26	−0.42	−0.27
	Time×time×down-mesor	0.27[c]	0.13[c]	0.05	0.06	0.04
f-statistic	Intercept	78.62[a]	21.00[a]	23.56[a]	17.95[a]	15.62[a]
	Time	−2.08	−0.71	−0.54	1.22[b]	−2.50[a]
	Time×time	0.52[c]	0.19	0.09	−0.15[c]	0.49[a]
	f-statistic	1.04[b]	0.27	0.19	0.13	0.48[b]
	Time×f-statistic	−0.47	−0.17	0.06	−0.02	−0.30[c]
	Time×time×f-statistic	0.07	0.02	−0.01	0.00	0.05[c]

QoL = quality of life; PWB = physical well-being; SWB = social well-being; EWB = emotional well-being; FWB = functional well-being.
Models adjusted for mean-centered age and comorbidities and each covariate×time and covariate×time×time interaction. All outcomes are mean-centered. Width ratio is multiplied by 10, and f-statistic is divided by 100 for ease of interpretation. The intercept represents the value of the outcome before transplant, and the circadian variable effect evaluates whether the circadian rhythmicity parameter was associated with the outcome before transplant. Longitudinal changes are modeled as time and time×time effects, and the associations between each circadian rhythmicity parameter and time are examined using the effect×time and effect×time×time interaction, which account for baseline QoL.
[a]$P < .001$.
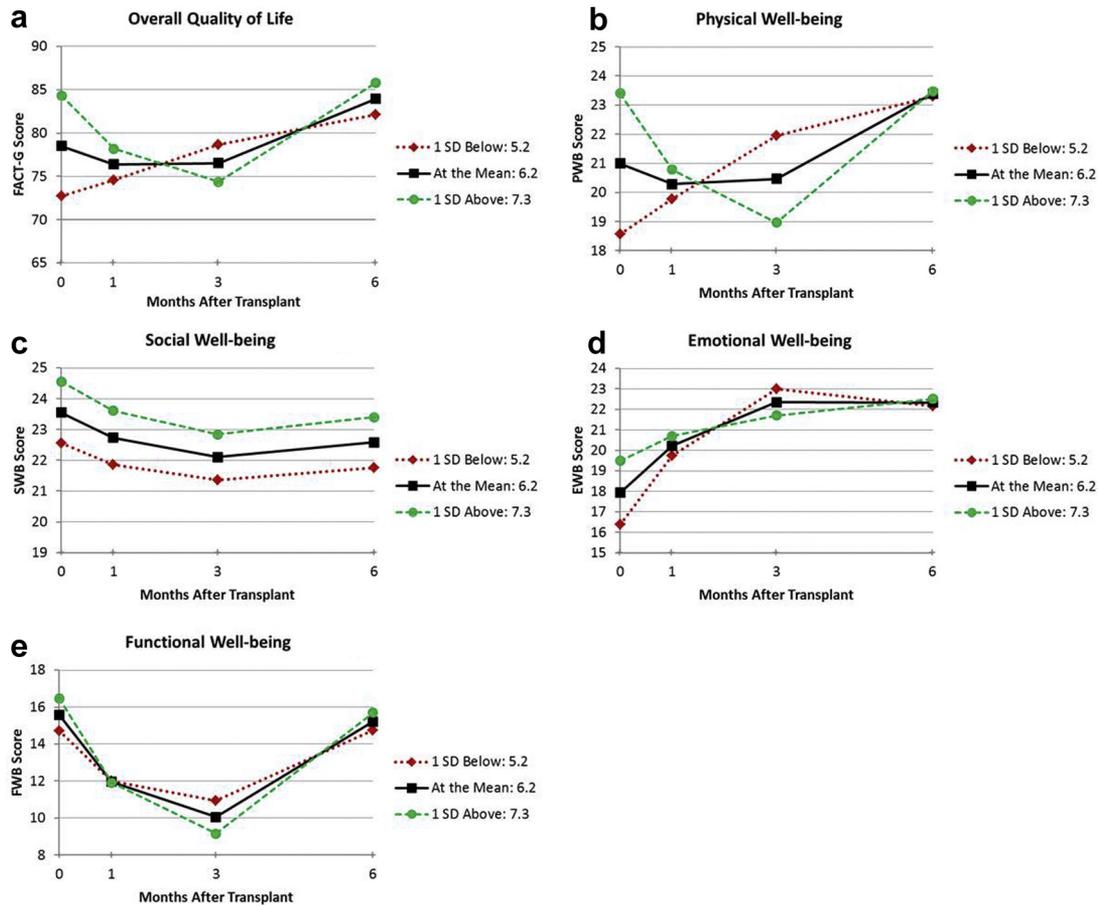[b]$P < .01$.
[c]$P < .05$.

Fig. 1. Unadjusted estimated means for duration of high activity compared with low activity (width ratio) (≤1 SD below mean, mean, and ≥1 SD above mean) by total QoL (FACT-G; a), PWB (b), SWB (c), EWB (d), and FWB (e). EWB = emotional well-being; FACT-G = Functional Assessment of Cancer Therapy-General; FWB = functional well-being; PWB = physical well-being; QoL = quality of life; SD = standard deviation; SWB = social well-being.

probing of subscales was conducted if the omnibus tests of total FACT-G were significant. Higher scores indicated better QoL.

Data Analysis

Data from participants who wore the actigraph for at least 72 hours were included in final analyses.[23] Means and standard deviations (continuous variables) and frequencies and percentages (categorical variables) were used to describe participant characteristics. Mixed models (i.e., PROC MIXED) were used to evaluate cross-sectional and longitudinal relationships between baseline circadian rhythmicity and the total FACT-G score over time, which allows for the use of all available data without having to impute missing data[30] and controls for outcomes at baseline (pre-transplant). To aid interpretation, circadian predictors were mean-centered, and width ratio was rescaled from 0–1 to 0–10 and f-statistic was divided by 100. Circadian rhythmicity was evaluated by including the interactions between circadian rhythmicity and time after controlling for potential

covariates (age, comorbidities), main effects, and other two-way interactions. Covariates were chosen a priori and included factors that have been shown by previous literature[4] to be associated with physical QoL. Consistent with previous literature suggesting a nonlinear relationship between time and QoL,[4] mixed models included the quadratic effect of time. To reduce the potential for Type 1 error, further probing of QoL was conducted if the omnibus tests of total FACT-G were significant. The effect size of the predictors was computed using pseudo-R^2.[30] All analyses were conducted in SAS, version 9.4 (Cary, NC). All tests were two sided, and alpha was set at $P < 0.05$.

Results

Fifty patients signed consent, but three did not receive HCT and were excluded from analyses. Of the remaining 47 patients, two had less than 72 hours of continuous accelerometer data and were excluded from analyses. The final sample consisted of 45
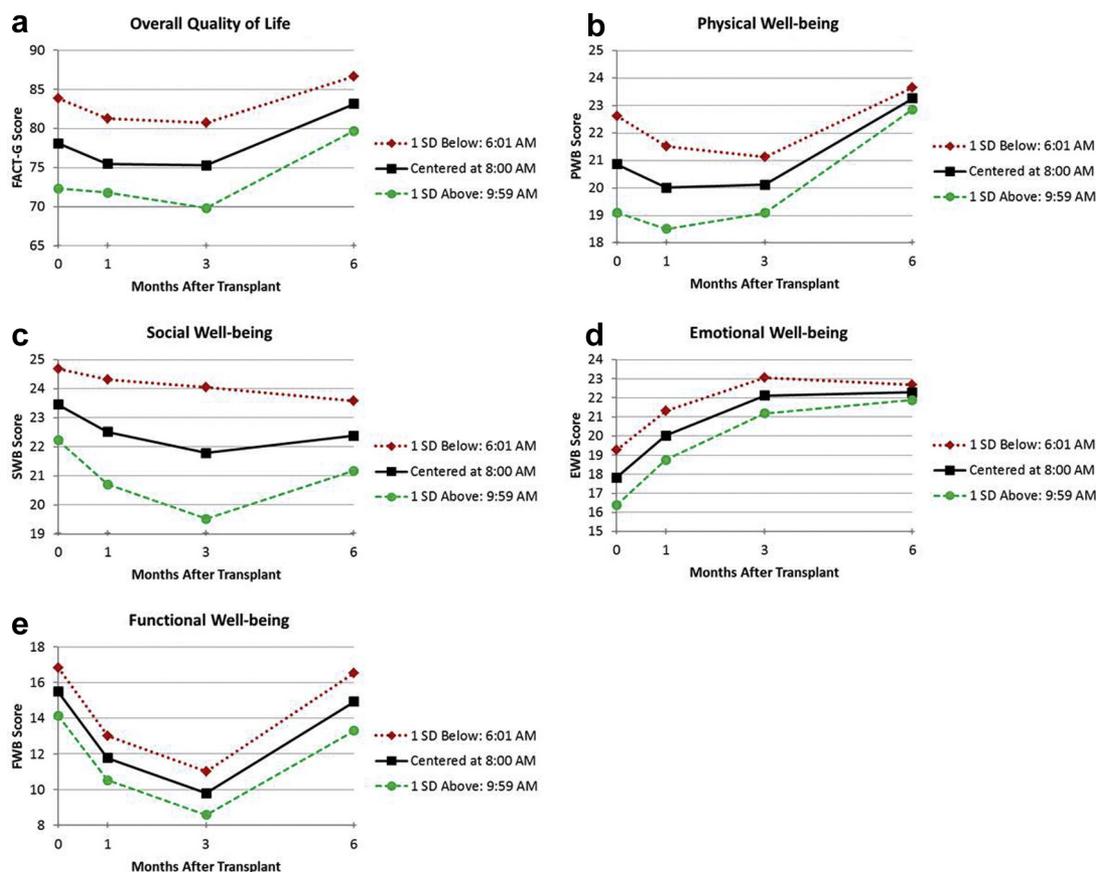
Fig. 2. Unadjusted estimated means for the time of day at which participants became active (up-mesor) (≤1 SD below mean, mean, and ≥1 SD above mean) by total QoL (a), PWB (b), SWB (c), EWB (d), and FWB (e). EWB = emotional well-being; FACT-G = Functional Assessment of Cancer Therapy-General; FWB = functional well-being; PWB = physical well-being; QoL = quality of life; SD = standard deviation; SWB = social well-being.

patients. Participant characteristics are shown in Table 1. Sociodemographic factors (age, comorbidities, gender) were not associated with total FACT-G before transplant (P's > .18). Consistent with previous literature, age and comorbidity were included as covariates.[3]

Before HCT, total FACT-G averaged 80.96 (SD = 16.05). Participants' scores dropped to 70.90 (SD = 14.70) by one month after transplant. At three months after transplant, total FACT-G rebounded to 79.77 (SD = 13.82), and by six months after transplant, scores were stable at 82.08 (SD = 13.63). On average, participants became active (up-mesor) at 7:55 AM (95% CI: 7:19 to 8:31 AM, range: 5:00 AM to 4:56 PM). Activity peaked (mean acrophase) at 3:25 PM (95% CI: 2:57 to 3:52 PM, range: 12:31 to 8:00 PM). On average, participants' activity declined for the evening (down-mesor) at 10:55 PM (95% CI: 10:19 to 11:30 PM, range: 6:12 PM to 4:29 AM).

The results of the mixed models adjusted for age and comorbidities are shown in Table 2. Figures depicting unadjusted QoL over time by a circadian predictor are presented for duration of high

activity (width ratio; Fig. 1A-E), the time at which participants became active (up-mesor; Fig. 2A-E), the time at which participants' activity declined in the evening (down-mesor; Fig. 3A-E), and overall circadian rhythmicity (f-statistic; Fig. 4A-E). Overall, circadian rhythmicity parameters accounted for 3%−22% of the variance in the intercept of total FACT-G. Before receiving HCT, patients with longer durations of high activity (width ratio) reported better concurrent total FACT-G (P = 0.02) (Fig. 1A), PWB (P = 0.005) (Fig. 1B), and EWB (P = 0.01) (Fig. 1D). Patients who became active earlier in the day (up-mesor) reported better concurrent total FACT-G (P = 0.05) (Fig. 2A) and EWB (P = 0.02) (Fig. 2D). Patients with more rhythmic daily patterns of activity (f-statistic) reported better concurrent total FACT-G (P = 0.01) (Fig. 4A) and FWB (P < 0.01) (Fig. 4E). There were no significant associations between the time at which patients' activity declined in the evening and concurrent total FACT-G (P's > 0.06). Thus, patients who were more active before HCT, started their day earlier, and had typical, consistent patterns of sleep and activity, had better concurrent QoL.
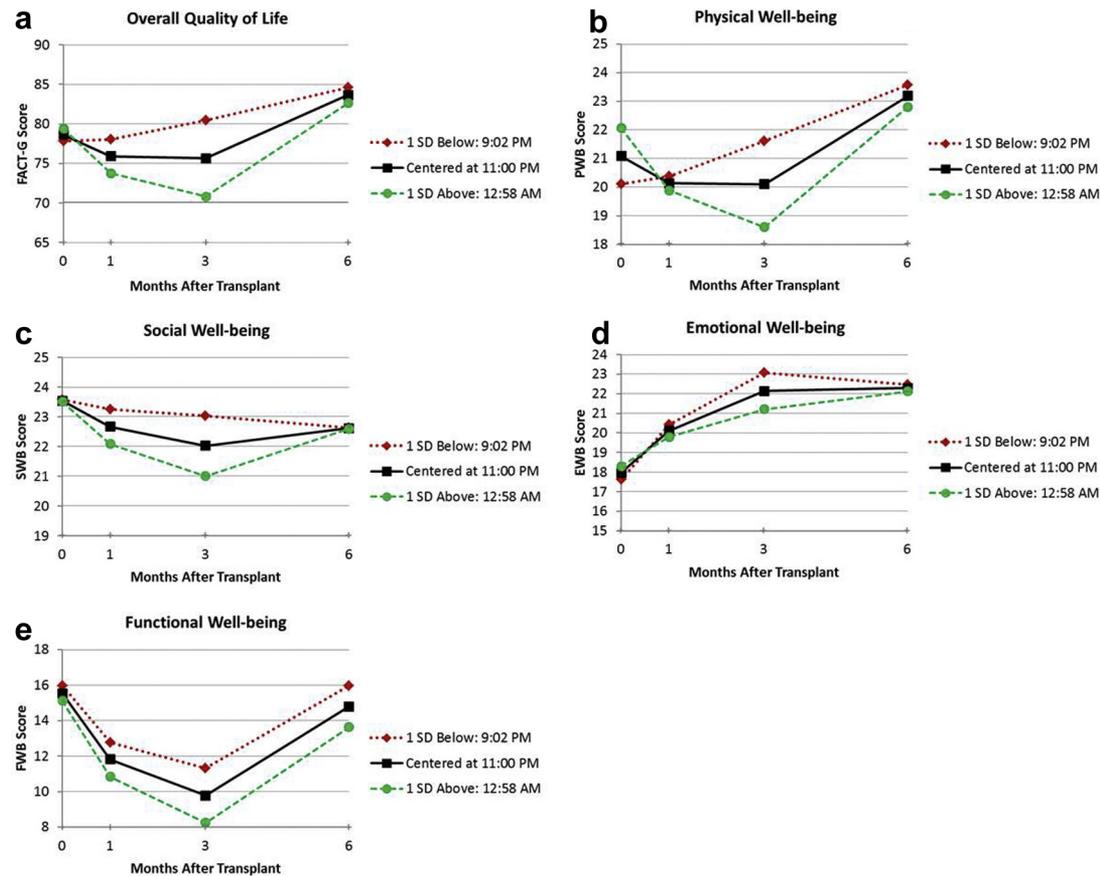
Fig. 3. Unadjusted estimated means for the time of day at which participants retired for the evening (down-mesor) (≤1 SD below mean, mean, and ≥1 SD above mean) by total QoL (a), PWB (b), SWB (c), EWB (d), and FWB (e). EWB = emotional well-being; FACT-G = Functional Assessment of Cancer Therapy-General; FWB = functional well-being; PWB = physical well-being; QoL = quality of life; SD = standard deviation; SWB = social well-being.

Throughout the transplant course, patients with longer durations of high physical activity (width ratio) before HCT had greater recovery of total FACT-G ($P = 0.02$) (Fig. 1A), PWB (linear $P = 0.02$, quadratic $P = 0.05$) (Fig. 1B), and EWB (linear $P = 0.02$, quadratic $P = 0.04$) (Fig. 1D). Patients whose activity declined earlier in the evening (down-mesor) before HCT had greater recovery of total FACT-G (linear $P=0.03$, quadratic $P=0.05$) (Fig. 3A) and PWB (linear $P=0.01$, quadratic $P=0.03$) (Fig. 3B). There were no significant associations between the time at which patients became active in the morning and recovery of total FACT-G (P's > 0.11). Thus, patients who were more active and whose activity declined earlier in the evening before HCT had better QoL throughout the transplant course.

Discussion

To our knowledge, this pilot study is the first to examine the relationship between circadian rhythmicity and QoL in patients receiving allogeneic HCT. Results indicate that circadian rhythmicity data from wearable sensors can predict recovery of QoL after HCT. There was a robust pattern of cross-sectional associations such that before transplantation, better QoL was associated with being active earlier in the morning, increased daily activity, and greater overall circadian rhythmicity. These findings extend previous research identifying associations between QoL and circadian patterns of rest and activity in other cancer populations, including patients with breast cancer,[15] metastatic colorectal cancer,[16,17,19] and advanced lung cancer.[18]

Previously examined sociodemographic and clinical predictors of post-transplant recovery of QoL have evidenced only moderate effectiveness.[31] Our data show that recovery of QoL after allogeneic HCT was predicted by longer durations of high activity and earlier declines in evening activity before transplantation. It is unclear why "early birds" might have better QoL throughout the transplant course, but these findings are consistent with cross-sectional findings in women with breast cancer before receiving chemotherapy.[15] Furthermore, our results suggest that the timing of
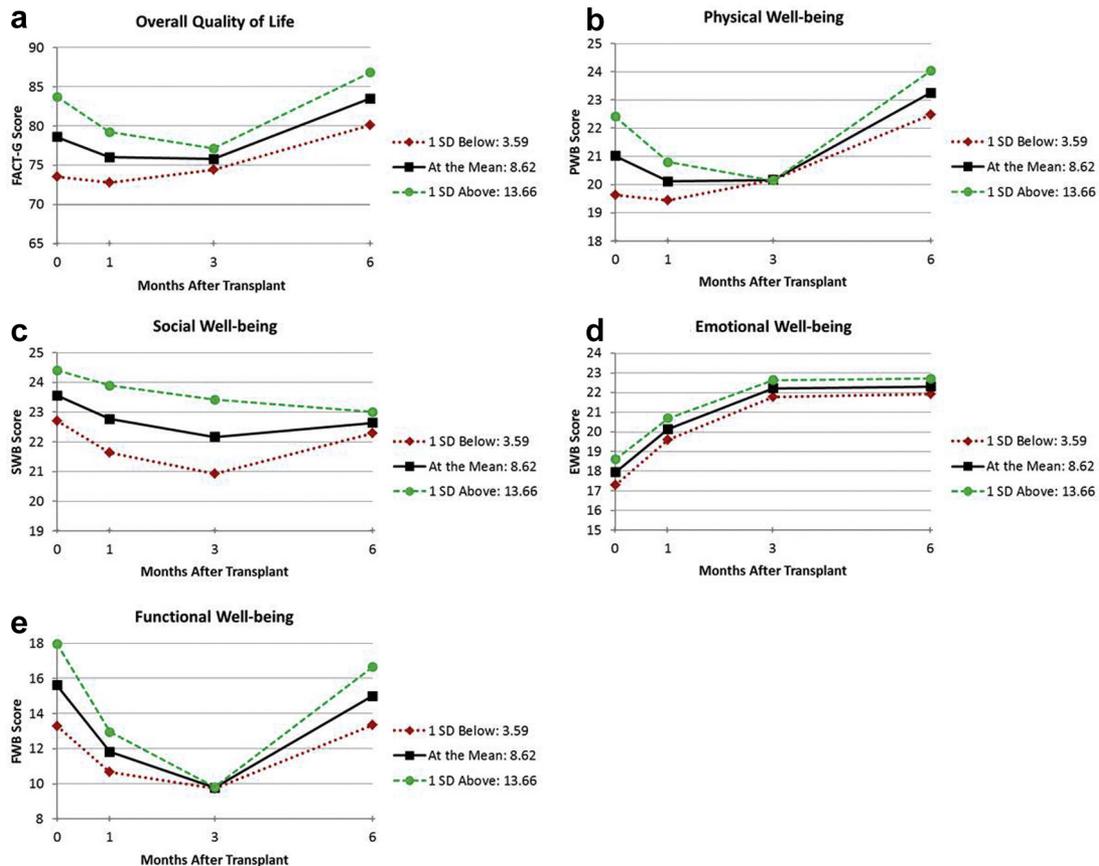
Fig. 4. Unadjusted estimated means for overall circadian rhythmicity (f-statistic) (≤1 SD below mean, mean, and ≥1 SD above mean) by total QoL (a), PWB (b), SWB (c), EWB (d), and FWB (e). EWB = emotional well-being; FACT-G = Functional Assessment of Cancer Therapy-General; FWB = functional well-being; PWB = physical well-being; QoL = quality of life; SD = standard deviation; SWB = social well-being.

daily activity—not just the quantity—is important for post-transplant outcomes. Before receiving HCT, patients had similar levels of QoL but different concurrent and longitudinal patterns of circadian activity. Thus, circadian rhythmicity may not be a proxy for QoL, but rather a useful predictor of QoL, particularly for patients receiving allogeneic HCT who may be especially likely to experience impairments in QoL.[3,32]

There are several approaches for modifying sleep and wake patterns to improve regulation of circadian rhythmicity. Suggested interventions for future evaluation might include cognitive-behavioral approaches tailored to sleep, wake, and activity patterns. For example, cognitive-behavioral therapy for insomnia involves "sleep restriction," a practice in which a patient anchors her wake time at a certain hour each morning and adjusts her bedtime accordingly to encourage efficient sleep. This therapy could be combined with gradual, consistent exercise (as acceptable medically), activity pacing, and daily scheduling to better manage sleep-wake patterns. Other interventions, such as bright light therapy[33] or melatonin administration,[34] may also improve QoL recovery patterns after HCT

in at-risk patients. In addition, preventive rehabilitation, or "prehab," may be effective at modifying patients' circadian patterns of activity before receiving HCT. From a mechanistic perspective, Costanzo et al.[35] suggest that behavioral factors (e.g., circadian patterns of rest and activity) in patients receiving HCT may directly influence immune recovery and subsequent QoL. Thus, modifying circadian patterns of activity may be especially efficacious in transplant recipients.

This longitudinal report is the first to our knowledge that includes a focused evaluation of circadian rhythmicity as a predictor of post-HCT QoL utilizing an innovative data collection method. Although our study demonstrates the predictive value of circadian rhythmicity on transplant recovery, limitations include a single assessment of circadian rhythmicity before HCT in a small sample that received heterogeneous HCT treatment protocols and no corrections for multiple comparisons. In addition, these transplant patients had very disordered circadian rhythms (e.g., wide ranges for the circadian parameters of interest). Nevertheless, this study's findings advance our

understanding of circadian patterns of activity as a correlate and predictor of QoL in patients receiving HCT.

In summary, research on predictors of QoL recovery is needed. Passive data collection strategies, which limit patient burden, offer objective measurements of circadian rhythmicity that may predict recovery of QoL. These approaches are particularly important for patients receiving HCT due to high rates of morbidity. In this study, predictive patterns of circadian rhythmicity were identified in under 72 hours before HCT. Clinically, replication of our results would suggest that use of passively collected data from wearable sensors to establish circadian patterns before treatment is feasible and clinically meaningful for predicting QoL recovery. With the increasing availability of commercial wearable fitness trackers (e.g., Fitbit), additional examination of the clinical efficacy of wearable sensors is warranted. Future research would benefit from confirming these results utilizing a larger cohort with circadian rhythmicity assessments before and after treatment.

Disclosures and Acknowledgments

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Appendix

Supplemental Table 1
Circadian Rhythmicity Parameter Definitions

Term	Description	Definition
Width ratio	Duration of high activity	Fraction of the day that activity is above the mesor. Bigger values = longer durations of high activity.
Up-mesor	Time of day when participants became active	Time when participants switched from low to high activity (from below the mesor to above the mesor). Bigger values = later time of day.
Down-mesor	Time of day when participants' activity declined for the evening	Time when participants switched from high to low activity (from above the mesor to below the mesor). Bigger values = later time of day.
f-statistic	Overall circadian rhythmicity	An adjustment to R-squared accounting for the number of observations and the number of parameters in the model. Bigger values = more rhythmic patterns of sleep and activity.