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Research Article

Sleep-wake Disturbance following Allogeneic Hematopoietic Stem Cell Transplantation: Trajectory and Correlates

Muthu Veeraputhiran[1], Jennifer Gernat[2], Naveen Yarlagadda[1], Milan Bimali[3] and Ellyn E. Matthews[4*]

[1]Department of Internal Medicine, University of Arkansas for Medical Sciences, Arkansas, USA
[2]College of Nursing, University of Arkansas for Medical Sciences, Arkansas, USA
[3]College of Medicine, Biostatistics, University of Arkansas for Medical Sciences, Arkansas, USA
[4]Loretta Heights School of Nursing, Regis University, Denver, Colorado, USA

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ABSTRACT

Adults undergoing allogeneic hematopoietic stem-cell transplant (HSCT) experience progressive physical and psychosocial distress in early stages post-HSCT, including sleep-wake disturbance (SWD), psychological distress, and fatigue. We conducted a longitudinal feasibility study to determine severity/trajectory of SWDs and investigated relationships among actigraphic sleep parameters, sleepiness, insomnia severity, fear of cancer recurrence (FCR), anxiety, depression, and fatigue at 100 (T1), 150 (T2), and 180 days (T3) post-HSCT. Eight adults enrolled. Median total sleep time (TST) at T1–T3 days was adequate (7.24, 7.17, and 7.09 hours), but sleep efficiency (SE) was suboptimal (78.9%, 78.5%, 83.67%). Median Epworth Sleepiness Scale (ESS) and Insomnia Severity Index (ISI) scores indicated minimal drowsiness and subclinical insomnia at T1–T3. Median FCR Inventory (FCRI) scores indicate diminishing FCR over time. Median scores across time for anxiety (48.05, 50.2, and 44.1) and depression (44.9, 41, and 41) suggest moderate–mild distress with slight fluctuations. Surprisingly, fatigue scores increased from T1–T3 (46, 50.9, and 52.1). Increases in ISI and FCRI scores were associated with modest increases in anxiety. Findings suggest the need to evaluate and address sleep, psychological distress, and fatigue in HSCT recipients. Larger studies to confirm prevalence of SWD and association with psychological factors are warranted.

Introduction

Hematopoietic stem-cell transplant (HSCT) includes radiotherapy and/or high-dose chemotherapy to achieve immunosuppression and permit engraftment of healthy hematopoietic stem cells from a donor (allogeneic) or patient's own cells (autologous). Although allogeneic HSCT is curative for many adults with hematological malignancies, treatment can be associated with progressive physical and psychosocial distress [1-6]. Sleep-wake disturbance (SWD), psychological distress, and fatigue are frequent but commonly overlooked adverse effects of HSCT [2, 7, 8]. SWD can include difficulty falling asleep and staying asleep, awakening earlier than intended, and non-restorative sleep [9].

During the first 180 days after transplant, SWD, psychological distress, and fatigue can lessen performance status and increase healthcare utilization [6, 10]. There is growing evidence that SWD greatly diminishes quality of life (QOL), psychological status, and functioning, and can lead patients to abandon cancer treatments [1, 3, 4, 11-13]. Research suggests HSCT recipients with SWD experience fatigue, psychological distress including fear of cancer recurrence (FCR;, depression, and anxiety [3, 14-17]. SWD and FCR are leading concerns in cancer survivorship. In one study of 67 cancer survivors, more than half reported poor sleep quality, and those with higher levels of FCR were at greater risk for sleep problems [17].

Correspondence to: Ellyn E. Matthews, PhD, RN, AOCNS, CBSM, FAAN, Loretta Heights School of Nursing, Regis University, 3333 Regis Boulevard G-8, Denver Colorado 80221, USA; Tel: 3034584355; E-mail: ematthews001@regis.edu

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HSCT recipients frequently suffer high levels of non-restorative sleep at one month post-HSCT [1]. Moderate to severe levels of SWD (39%) and fatigue (55%) have been reported in autologous HSCT patients at the time of white blood cell nadir [14]. A recent review indicates 50% of HSCT recipients experience SWD pre-transplant, up to 82% during hospitalization, and up to 43% after transplant, which can lead to impaired functional status, poor QOL (particularly in the first month after transplantation), and decreased survival time [6, 7, 14, 18]. Some individuals have moderate improvement at 100 days and more stable sleep up to one year after HSCT [1, 3]. Conversely, in a study of over 200 HSCT recipients, half continued to report moderate or severe SWD at 6–12 months post-HSCT, indicating the need to examine persistent HSCT-related SWD [3]. Limitations of recent HSCT studies include reliance on self-reported sleep measures and cross-sectional design.

Existing literature is characterized by reliance upon self-reporting to measure sleep problems with little use of actigraph technology. Actigraphy involves the objective measurement of movement by means of an accelerometer [19]. It has been successfully used to measure sleep-wake patterns in cancer patients and it correlates at a rate of about 90% agreement with polysomnography [20, 21]. Actigraphy provides a more complete picture of sleep disruption among HSCT recipients. Although sleep has been linked to behavioural and biological factors in other cancer populations, there is little research using objective sleep measures to address the complexity of factors in the context of HSCT [22-24].

Although SWD, psychological distress, and fatigue have implications for therapeutic approaches, these conditions are often inadequately evaluated and poorly managed, especially in allogeneic HSCT patients [7]. Therefore, the aims of this longitudinal pilot study are to 1) determine the severity/trajectory of SWDs during the first 100–180 days post-HSCT and 2) investigate the relationships among sleepiness, insomnia, FCR, psychological distress, and fatigue.

Methods

I Participants and Procedures

Participants were recruited from the University of Arkansas for Medical Sciences (UAMS) Cancer Center. Approximately 30 allogeneic transplants were performed annually at UAMS during the recruitment period. Edibility included a) hematologic malignancy diagnosis, b) allogeneic HSCT 100 days ± 14 prior to study enrollment, c) ≥18 years of age, d) written and verbal English comprehension, and e) capacity for informed consent. The timeframe was based on previous literature, suggesting sleep disturbance occurs during this post-transplant period [7]. Data were collected from July 2016-September 2018.

The UAMS Institutional Review Board approved the study. Eligibility was determined via medical record review. Participants were recruited during a scheduled outpatient appointment during which they completed informed-consent, demographic, cancer-specific-factors, and self-report questionnaires. Participants wore an actigraph watch and completed a sleep log for one week. Participants received $25 gift cards after completing the requirements for each T1–T3 study visit.

II Measures

Participants completed a standardized demographic form and provided information on recent use of sleep medications. Relevant clinical information was collected via medical records. To assess objective SWD, participants wore an Actiwatch-2 (Philips Respironics, Andover, MA) continuously for seven days on their non-dominant wrist. Consistent with published recommendations, sleep parameters included total sleep time (TST: hours of actual sleep time in a sleep episode), sleep efficiency (SE: percentage of time spent sleeping relative to time spent in bed), sleep latency (SL: number of minutes it takes to fall asleep after lights out), and wake after sleep onset (WASO: minutes of wakefulness occurring after sleep onset) [25]. TST and SE are the primary variables of interest in this study. Data were downloaded into a password-protected computer; sleep parameters were calculated with a standard scoring algorithm. Data for each participant was analysed across seven days; participants with < 3 days of actigraphy data were not included.

Epworth Sleepiness Scale (ESS) is an established measure of subjective sleep propensity using eight daytime situations on a four-point scale [26]. Total scores range from 0–24; scores ≥10 indicate substantial sleepiness. Insomnia Severity Index (ISI), a seven-item instrument assessing the nature, severity, and impact of insomnia during the past week, is an established measure of insomnia in adult and cancer populations [27, 28]. ISI scores are interpreted as: < 7 = no clinically significant insomnia, 8–14 = subthreshold insomnia, 15–21 = clinical insomnia (moderate severity), and 22–28 = clinical insomnia (severe). Fear of Cancer Recurrence Inventory-Short Form (FCRI) is a nine-item self-report rapid screening for fear/worry that cancer will return or progress [29]. A score of 13 or greater indicates clinical levels of FCR. The FCRI short form is strongly correlated with the previous longer 42-item version and has high internal consistency ($\alpha = 0.89$) and validity in cancer survivors [29, 30]. Brief Patient-Reported Outcomes Measurement System (PROMIS®) evaluates psychological distress (anxiety, depression) and cancer-related fatigue. Patient-reported outcomes (PRO) measure patients' symptoms, functioning, and health-related QOL [31]. PROMIS® uses a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD). Higher scores indicated more of the concept being measured [32].

III Statistical Analysis

Descriptive statistics are reported as mean (standard deviation) and median (inter-quartile range) for continuous variables, and as frequency (percentage) for categorical variables. The association between sleep parameters and psychosocial parameters were examined using multivariable linear regression. Generalized estimation equation was employed to account for correlation between measurements within same patients. Multivariable adjustments were incorporated as follows: psychological parameters were regressed on anxiety (and separately on fatigue) scores to obtain unadjusted estimates; then age at transplant, gender, and race were included in the model to obtain adjusted estimates. Difference in TST (hours) and SE (%) across the three time points was assessed using the Kruskal-Wallis test. The parameter estimates, together with two-sided 95% confidence interval, were reported. A two-sided *P* value of 0.05 was used to assess statistical significance. The analysis was done using SAS 9.4.

Results

Of the approximately 30 allogeneic HSCT performed annually at the study institution, 12 eligible patients were invited to participate in the study over 27 months and 10 (83%) agreed to participate. Of the 10 participants who enrolled in the study, two left the study due to their feeling they could not keep up with daily documentation (80% retention rate). Eight participants completed all the measures at T1–T3.

I Demographic, Sleep, and Psychosocial Characteristics

The baseline demographic characteristics of the patients are summarized in (Table 1). The median age at transplant was 66 years. There were six (75%) females and six (75%) Caucasians. Three participants were prescribed sleep medications prior to HSCT. Table 2 provides summary statistics for sleep and psychosocial parameters. The TST, SE, SL, and WASO were based on Actiwatch data. The median TST at T1 (100 days), T2 (150 days), and T3 (180 days) were 7.25, 7.17, and 7.09 hours respectively. Median SE percentages at T1–3 were 78.89, 78.46, and 83.67. SL remained relatively stable and WASO decreased slightly. The median ESS T1–3 scores were 7.5, 8, and 8.5, and ISI scores were 7, 7.5, and 7.5. The median FCRI and anxiety scores fluctuated across three time points (12 / 14 / 8.5 and 48.05 / 50.2 / 44.1, respectively). The median fatigue scores showed a slight increase across the time points (46, 50.9, and 52.1). The TST and SE for each of the eight patients is provided in (Figure 1).

Table 1: Demographic variables.

Variable	**Mean (SD)**	**Median (IQR)**
Age at Transplant	63.38 (5.53)	65.5 (4)
Variable	**Level**	**Count (%)**
Gender	Female	6 (75)
	Male	2 (25)
Race	Black	2 (25)
	White	6 (75)
Year of Transplant	2016	2 (25)
	2017	5 (62.5)
	2018	1 (12.5)

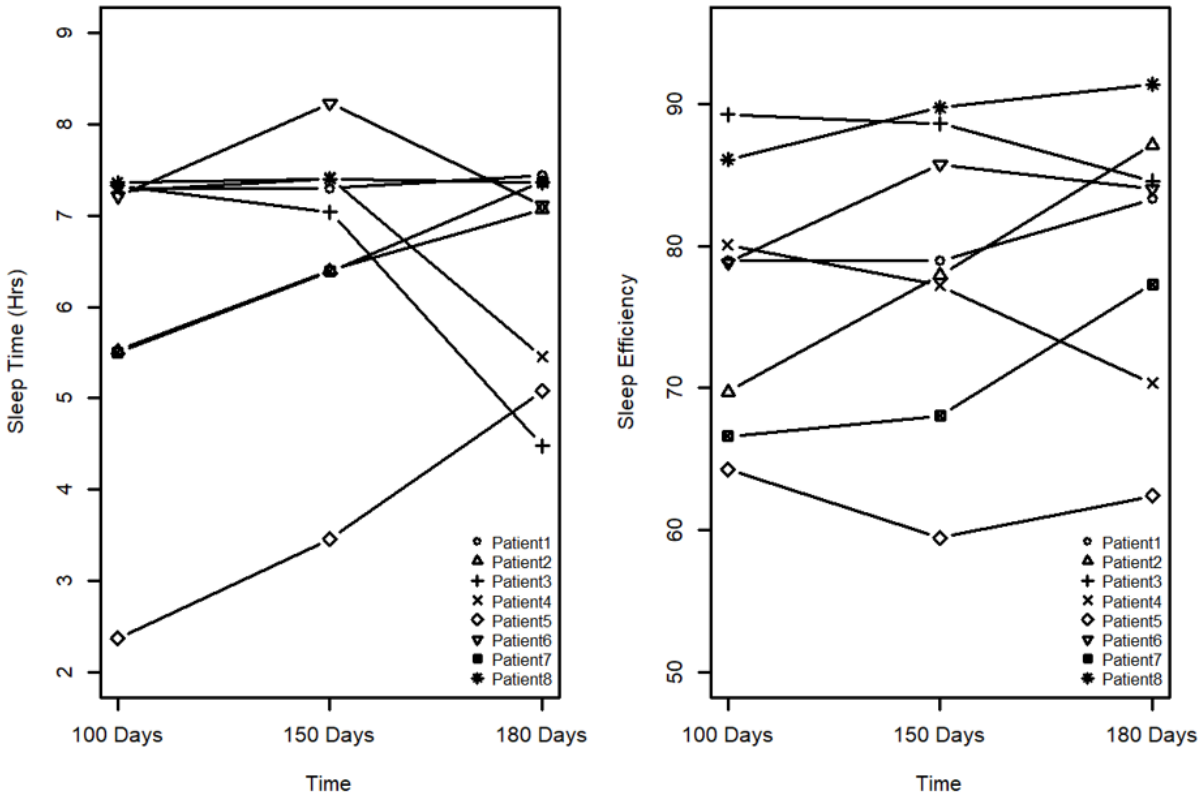

Figure 1: Plot of Sleep Time and Sleep Efficiency vs Time.

Table 2: Summary statistics for Psychosocial Score and Sleep Parameters.

Variable	Visit 1	Visit 2	Visit 3
ESS Score	8.5 (4.14) 7.5 (5)	7.63 (2.62) 8 (4)	9.25 (4.4) 8.5 (7.5)
ISI Score	6.63 (4.53)7 (8)	8.13 (5.54) 7.5 (10)	6.75 (5.04) 7.5 (7)
FCRI Score	12.75 (6.78) 12 (10.5)	13 (4.81) 14 (6.5)	9.88 (6.33) 8.5 (6.5)
Sleep (Hours)	6.23 (1.76) 7.24 (1.81)	6.70 (1.44) 7.17 (1.01)	6.42 (1.21) 7.09 (2.1)
Sleep Efficiency (%)	76.72 (9.03) 78.89 (14.9)	78.22 (10.38) 78.46 (14.55)	80.06 (9.54) 83.67 (12.02)
Anxiety Scores	48.33 (8.26) 48.05 (12.9)	47.98 (6.8) 50.2 (12.2)	45.05 (5.25) 44.1 (9.5)
Fatigue Scores	48.34 (9.72) 46 (11.75)	51.55 (7.58) 50.9 (8.55)	50.9 (8.43) 52.1 (13.05)

The values in cells are mean (standard deviation) and median (inter-quartile range).
The scores for Anxiety and fatigue are t-scores computed based on transformation of raw scores.

II Sleep Trajectory

The change in TST did not attain statistical significance (P = .77), nor did the change in SE (78.89% vs 78.46% vs 83.67%; P = .44). Similarly, SL and WASO did not change over time.

III Association between Sleep Parameters and Psychological Outcomes

Increases in ISI and FCRI scores were associated with modest increase in anxiety (Table 3). A unit increase in ISI score was associated with an average increment in ISI score of 0.38 (95% CI: 0.05–0.72, P = .02) after adjusting for the effects of age at transplant, race, and gender. Similarly, a unit increase in FCRI score was associated with an average increment in ISI score of 0.62 (95% CI: 0.19–1.05, P = .01) after adjusting for these effects. A unit increase in FCRI score was associated with an average increment in fatigue of 0.39 (95% CI: 0.25–0.52, P < .01) after adjusting for these effects (Table 3).

Table 3: Associations between ESS, ISI, FCRI and Anxiety and Fatigue.

	Estimate (95% CI)	Estimate (95% CI)[1]
Association with Anxiety Score		
ESS Score	0.37 (−0.83,0.08) P = 0.11	−0.30 (−0.86,0.26) P = 0.30
ISI Score	0.37 (¯0.05,0.79) P = 0.08	0.38 (0.05,0.72) P = 0.02
FCRI Score	0.39 (−0.20,0.98) P = 0.20	0.62 (0.19,1.05) P = 0.01
Association with Fatigue Score		
ESS Score	0.25 (−0.20,0.70) P = 0.27	0.22 (−0.19,0.63) P = 0.30
ISI Score	0.31 (−0.20,0.83) P = 0.24	0.47 (-0.14,1.08) P = 0.13
FCRI Score	0.32 (0.14,0.50) P < 0.01	0.39 (0.25,0.52) P < 0.01
1: Adjusted for age at transplant, race, and gender.		

ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; FCRI: Fear of Cancer Recurrence Inventory.

Discussion

In this study, the actigraphy revealed important findings about SWD in HSCT recipients. TST and SL remained relatively stable over time, and medians were close to or within normal ranges seen in healthy adults. Experts recommend seven to eight hours of sleep, and normative values for SL in healthy adults is usually < 30 minutes; TST is likely to decrease and SL to increase with age [33, 34]. SE showed a small improvement for five participants at 180 days. Of these five participants, only one was prescribed a sleep aid prior to transplant, suggesting participants were

beginning to increase actual sleep even without sleep-aid use. Our finding that the median and mean SE was suboptimal at each time point is consistent with Nelson *et al*. (2018), who reported an average SE of 78% in autologous HCT recipients at 6–18 months after transplant [35]. SE ≥ 85% is considered an indicator of good sleep quality; SE below 84% is poor, and ratings below 75% can be indicative of sleeping disorders like insomnia [34, 36]. SE decreases with age, which could partially explain poor levels in this sample [34]. SE also reflects the duration of WASO, which remained twice the desired ≤ 30 minutes per night in this study, in line with WASO estimates in the survivorship period following HSCT [35]. Overall, the findings are consistent with the literature describing sleep-maintenance problems among HSCT recipients [3, 7, 35]. Such SWD may be improved by decreasing fragmented sleep stemming from wake time in bed, perhaps with behavioural interventions to reduce the number and duration of nighttime arousals.

The plot illustrating individual trajectories of TST and SE suggests there are distinct phenotypes for TST: i) consistently adequate TST, ii) adequate TST that worsens, and iii) inadequate TST that improves. Likewise, SE also demonstrates individual phenotypes: i) consistently good SE, ii) moderate SE with some improvement or worsening at T3, and iii) poor SE with variable improvement. These phenotypes are comparable to classifications based on sleep disruption in HSCT recipients developed by Jim and colleagues [37]. Overall, our findings suggest that SWD can be very individual and treatment factors may influence sleep adequacy, efficiency, and quality in this population [37].

Median ESS levels < 10 indicate that participants experienced minimal sleepiness; however, over time there was a trend toward heightened sleepiness, which did not reach significance. Median ISI scores indicate most participants experienced minimal or subthreshold (transient) insomnia symptoms, which is generally consistent with estimates in the survivorship period following HSCT [3, 35, 38, 39]. Investigations of SWD in HSCT recipients, however, often include autologous transplant recipients with different rates of SWD than allogeneic recipients, who receive steroids that can interfere with sleep [35, 40]. In one study, for example, investigators found SWD was more pronounced in allogeneic transplant patients than in autologous [41]. One would expect that the ISI score incrementally improves after transplant; however, ISI scores remained stable across time similar to TST and SL, suggesting that SWD was relatively unchanged between day 100–180 post-HSCT. Lack of improvement may reflect a mild degree of insomnia with limited room to improve, recall bias, or small sample size.

FCRI scores were at clinically significant levels at T1 and T2, then decreased to a subclinical level at T3. Consistent with our findings, Nelson and colleagues reported moderate FCRI scores (M = 15.67, SD = 8.04) in 84 autologous HSCT recipients at 6–18 months post-transplant [35]. In contrast, other investigators used the short version of the FoP-Q-SF to assess FCR and reported high levels of FCR at 100 days and one year or more after allogeneic HSCT [42-44]. A systematic review of 130 studies of mixed cancer survivors corroborated low–moderate levels of FCR that remained stable over the survivorship trajectory [45].

Median anxiety scores indicate mild–moderate levels with slight increase at T2 and then a decrease at T3. Evidence suggests anxiety is highest in anticipation of the transplant but reaches stability post-HSCT [46]. As our findings suggest, a subset of HSCT patients continue to experience significant levels of anxiety after HSCT, which may impact recovery, function, and health outcomes [47].

For depression, median scores indicate mild fluctuating levels of distress during the early post-HSCT period. Other researchers have reported that depression is prevalent (35%) during all stages of HSCT treatment up to five years after the transplant [46, 48]. In a prospective study of autologous and allogeneic transplant recipients, El-Jawahri *et al*. found that depressed patients had a three-fold greater risk of dying than non-depressed patients between 6 and 23 months after HSCT [48]. This highlights the need for timely assessment and treatment of depression using diagnostic tools developed specifically for HSCT patients [47].

Median fatigue levels remained in the mild range. Cancer-related fatigue may be due to SWD, cytotoxic therapy-induced cellular damage and repair efforts, cytokine activation, anemia, poor nutritional status, and/or the demands of coping with treatment [49, 50]. The increase in fatigue from T1–T3 in the present study raises the question of whether participants become more physically and mentally active at home as the distance from transplant increases, resulting in higher perceived fatigue.

There were significant associations between ISI and anxiety, FCRI and anxiety, and FCRI and fatigue. In previous studies of women with breast cancer, distress and FCR have been associated with SWD [51, 52]. Other studies have reported an association between FCR and anxiety and depression in cancer survivors [45, 53]. Few studies, however, have examined the relationship between psychosocial factors and FCR or SWD in HSCT survivors [35]. One recent study of patients with hematological cancer reported a strong relationship between FCR and anxiety, but not depression [54].

Regarding the association between FCR and fatigue, a possible explanation is that ongoing stress from the threat of treatment failure may contribute to tiredness and fatigue. SWD, fatigue, and psychological distress may also share common mechanisms and have synergistic effects. SWD and resulting fatigue may arise from alterations in sleep-regulating hormones, effects of adjuvant medications, and/or psychological disturbances due to worries about health, family, and financial impact of illness [55].

The enrollment and retention of willing participants indicate study procedures were acceptable and associated measures were not overly burdensome. Other factors contributing to the study's success included support from nursing leadership and staff, a dedicated study coordinator, ample time to explain study processes, monetary incentives, and willingness to enroll. Barriers included scheduling participant appointments, varying levels of enthusiasm for repeated measures, and questions about how many days to wear the Actiwatch. Participant responses demonstrate that retaining HSCT participants in a study examining sleep and psychosocial factors is possible on a larger scale.

The current study has several strengths including a clinically meaningful question, prospective longitudinal design, and subjective and objective measures of sleep. There are several limitations that should also be noted. The purpose of this study was exploratory; findings from such a

small sample and recruitment at a single center limit generalizability. Moreover, patients' sleep patterns before transplant were not measured, which would have been helpful to compare with SWD post-transplant. Finally, the ESS, ISI, and PROMIS® anxiety, depression, and fatigue instruments ask participants to evaluate their status retrospectively during the past one to two weeks. Although this approach is valuable, it requires participants not only to remember their subjective sleep, anxiety, depression, and fatigue but also to average and evaluate these perceptions.

Despite study limitations, our findings call attention to SWD issues HSCT recipients experience, underscoring the limited understanding of underlying factors and consequences of SWD, psychological distress, and fatigue that accompany HSCT. Larger sample size and extending the study beyond 180 days may help determine at what point SWD consistently improves. Although pharmacological and behavioural interventions have been successful in managing fatigue and psychosocial challenges after HSCT, additional research will determine the most optimal assessment tools, intervention strategies, and long-term care to address psychiatric comorbidity in this understudied patient population [47]. Our results highlight the need for more research to prevent or mitigate long-term morbidity after HSCT, since late effects are associated with poor health, diminished functional status, and higher healthcare costs. Possible sleep/fatigue and psychosocial interventions could be tested at the time of transplantation or during early post-transplantation, including comprehensive supportive care, patient education, and closer monitoring in high-risk patients as a part of long-term survivorship. Close coordination with the transplantation center and encouraging self-management support for patients and families have the potential to improve survival and quality of life.

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Conflicts of Interest

None.

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the IRB # 206182 on 8/8/2019 of University of Arkansas for Medical Sciences.

Informed Consent

Informed consent to participate in the study was obtained from all the study participants.

Author Contributions

Authors 1 and 3 enrolled patients and conducted the study. Author 2 helped in data collecting and data management.

Author 4 helped in statistics. Author 5 designed and conducted the study. All authors contributed to the study conception and design. Material preparation and data collection were performed by Jennifer Gernat and analysis were performed by Milan Bimali. The first draft of the manuscript was written by Jennifer Gernat and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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