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# Prevalence of self-reported sleep dysfunction before allogeneic hematopoietic cell transplantation

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## To the Editor

Allogeneic hematopoietic cell transplantation (alloHCT) is an increasingly utilized high-risk therapy used to treat various malignant and non-malignant diseases.[1] The numbers of alloHCT performed each year continue to increase for all age groups, particularly those aged 60 and older,[1] and it remains a physically and psychologically arduous treatment approach.[2, 3] Nearly 75–80% of hospitalized HCT patients experience sleep disruption in the early post-transplant setting;[4, 5] this can exacerbate impaired quality of life, depression, and fatigue in HCT recipients.[6] Sleep is a restorative biologic process essential for maintaining health.[7] There is epidemiologic evidence that sleep disturbance independently contributes to inflammation and that improving sleep quality in older adults with insomnia can reduce biomarkers of multisystem biological risk including C-reactive protein, hemoglobin A1C, insulin, lipoproteins and triglycerides among others, in a randomized clinical trial setting.[8, 9] Sleep dysfunction may adversely impact alloHCT outcomes through increased pro-inflammatory pathways as shown in HCT and other populations and may lead to adverse post-alloHCT outcomes.[5, 10] Based on this intriguing background, we hypothesized that patient-reported sleep disturbance before alloHCT would correlate with early post-alloHCT outcomes. We used the Center for International Blood and Marrow Transplant Research (CIBMTR) database to conduct this research.

From 2011–2013, the CIBMTR prospectively enrolled 390 patients from 7 transplant centers to assess the feasibility of collecting patient-reported outcomes.[11] Of these, 340 patients completed the baseline survey including 84 pediatric patients. Adult patients completed the 36-item short form health survey (SF-36) and Functional Assessment of Cancer Therapy-

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Bone Marrow Transplantation subscale (FACT-BMT) questionnaires before HCT and at day 100, 6 months, and 1 year after HCT. Herein, we focus on responses to the sleep-specific question from FACT-BMT in all adult patients included in this pilot who underwent alloHCT for acute and chronic leukemias, myelodysplastic syndromes, and myeloproliferative neoplasms (N=198). We excluded small numbers of patients with non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma and variety of non-malignant diseases owing to a wide heterogeneity in pre-transplant treatments as well as duration of disease. The sleep question in FACT-BMT is a single question applied to the past 7 days, "I am sleeping well," with 5 response options: (0-not at all, 1-a little bit, 2-somewhat, 3-quite a bit, 4-very much). We analyzed 0/1/2 as 'poor sleep' and 3/4 as 'good sleep' groups as reported on the before HCT questionnaire. Descriptive statistics were used to summarize the characteristics of the groups and the Kaplan-Meier estimator was used to evaluate survival. The primary outcome of interest was overall survival (OS). Other outcomes included transplant-related mortality, relapse, and graft-versus-host disease, acute (aGVHD) and chronic (cGVHD); GVHD was analyzed as a time-dependent variable. Multivariate analysis was conducted using a Cox proportional hazards model. Factors assessed in multivariate analysis included baseline sleep group (main effect), age at transplant, gender, Karnofsky Performance Score (KPS), disease, disease risk, conditioning intensity, total body irradiation (TBI) dose, stem cell source, donor and anti-thymocyte globulin/alemtuzumab use. The analysis was performed in SAS v9.4 (SAS Institute Inc., Cary, NC).

Table 1 shows the baseline characteristics of the study population. There were 90 patients in the poor sleep group and 108 patients in the good sleep group. Baseline characteristics were similar in the two groups except for the following: patients with poor sleep before HCT were more likely to be <55 years (57% vs 43%, p=0.04), and have a KPS <90% (50% versus 34%, p=0.03) compared to the good sleep group. Although nearly half of the annual income data was missing, when available, there was a significant association between annual household income <$60,000 and poor sleep compared to good sleep (50% vs 25%, p-value 0.03). The median follow up of survivors was comparable in both groups.

On univariate survival analysis, baseline poor sleep was associated with lower OS at 100–days, 6 months, and 1 year with the greatest difference seen in patients aged 18–54 years but not in those aged 55 and older (table 2). In multivariate analysis, no difference was seen between outcomes in the poor sleep compared to good sleep group: transplant related mortality; hazard ratio (HR) 1.59, 95% confidence interval (95% CI) 0.82–12.56, p=0.21, relapse; HR 1.02, 95% CI, 0.63–1.66, p=0.92, aGVHD; HR 1.30, 95% CI, 0.71–2.48, p=0.39, cGVHD; HR 1.38, 95% CI, 0.91–2.08, p=0.13 and OS; HR 1.27, 95% CI, 0.86–1.87, p=0.22.

One-year sleep score was available in 93 patients; of these, 66% of patients who reported poor sleep before HCT reported poor sleep again at 1-year and 65% of patients who reported pre-transplant good sleep maintained that rating at 1-year. No significant differences were seen in baseline characteristics or in post-transplant GVHD or relapse rates among patients whose quality of sleep changed from baseline to 1-year after HCT.

AlloHCT is a 'high-stakes' procedure with a substantial risk of transplant-related morbidity and mortality, GVHD, and late complications including cardiovascular disease, diabetes, chronic fatigue, secondary malignancies in addition to relapse of the primary disease.[12] Sleep impairment is frequently overlooked as a side-effect of transplant and may include a spectrum of symptoms including difficulty falling asleep, staying asleep, awakening earlier than intended, and/or nonrestorative sleep.[5] In a comprehensive review by Jim, et al. it was noted that sleep disturbance and disorders prior to transplant may be associated with several treatment-related factors such as intensive chemotherapy, side-effects of treatment (e.g. peripheral neuropathy), restless leg syndrome, anxiety, and depression.[5] Pre-alloHCT sleep disturbances have not been well studied, although reports in the autoHCT setting suggest a wide range of prevalence estimates, ranging from similar to population norms to as high as 43%.[5] One study of 74 participants reported insomnia in over 50% of alloHCT patients at baseline by self-report.[13] Our study extends these observations and shows that in a representative population of patients with myeloid disorders undergoing alloHCT at multiple centers, the prevalence of poor sleep prior to transplant was 46%. Further, we found self-reported poor sleep was more common in younger patients, those with worse physician-rated functional status, and those with lower annual household income (though limited by significant missing data), demonstrating an interplay between sleep with sociodemographic variables, and overall health. While our data did not show a relationship between baseline sleep and post-alloHCT outcomes, our sample size only had 23% power to show a 27% difference in hazard of mortality.

In this analysis, we note that a proportion of patients move from one sleep group to the other between baseline and 1 year suggesting that patients are not restricted to the same sleep group throughout. Sleep interventions include cognitive behavioral therapy, mindfulness, pharmacotherapy, correction of conditions such as obstructive sleep apnea, restless leg syndrome, etc. and could be considered to help ameliorate sleep dysfunction.[5, 14] In-hospital sleep disturbance may be exacerbated by frequent sleep interruptions for care and may be another opportunity for improvement. The health care team may also play a positive role by counseling patients during clinic visits on sleep hygiene, role of daytime exercise, and avoidance of electronic devices in bed.

Although limited by the sample size and dependence on a single item sleep question, we made the following clinically important observations: 1) 46% of adults undergoing alloHCT for leukemias and chronic myeloid diseases have self-reported poor sleep at pre-transplant baseline, 2) univariate analysis showed an association between baseline sleep with 1-year survival in patients under 55 years but not in those 55 and older; however, on multivariate analysis we were underpowered to show a difference, 3) stage migration between the good sleep and poor sleep groups is seen in one-third of patients between pre-transplant and 1-year post-transplant. We believe further research is needed in larger numbers to study the impact of sleep disturbance on alloHCT outcomes. Given the prevalence of sleep dysfunction, we propose that interventions to improve sleep including mindfulness-based and/or pharmaceutical interventions should be tested.

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## References

1. D'Souza A, Lee S, Zhu X, Pasquini M. Current Use and Trends in Hematopoietic Cell Transplantation in the United States. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2017; 23(9):1417–1421. DOI: 10.1016/j.bbmt.2017.05.035
2. Mosher CE, Redd WH, Rini CM, Burkhalter JE, DuHamel KN. Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. Psycho-oncology. 2009; 18(2):113–127. DOI: 10.1002/pon.1399 [PubMed: 18677717]
3. Grulke N, Albani C, Bailer H. Quality of life in patients before and after haematopoietic stem cell transplantation measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire QLQ-C30. Bone marrow transplantation. 2012; 47(4): 473–482. DOI: 10.1038/bmt.2011.107 [PubMed: 21602898]
4. Boonstra L, Harden K, Jarvis S, Palmer S, Kavanaugh-Carveth P, Barnett J, et al. Sleep disturbance in hospitalized recipients of stem cell transplantation. Clin J Oncol Nurs. 2011; 15(3):271–276. DOI: 10.1188/11.CJON.271-276 [PubMed: 21624862]
5. Jim HS, Evans B, Jeong JM, Gonzalez BD, Johnston L, Nelson AM, et al. Sleep disruption in hematopoietic cell transplantation recipients: prevalence, severity, and clinical management. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2014; 20(10):1465–1484. DOI: 10.1016/j.bbmt.2014.04.010
6. Ghazikhanian SE, Dorfman CS, Somers TJ, O'Sullivan ML, Fisher HM, Edmond SN, et al. Cognitive problems following hematopoietic stem cell transplant: relationships with sleep, depression and fatigue. Bone marrow transplantation. 2017; 52(2):279–284. DOI: 10.1038/bmt.2016.248 [PubMed: 27941775]
7. Irwin MR, Opp MR. Sleep Health: Reciprocal Regulation of Sleep and Innate Immunity. Neuropsychopharmacology. 2017; 42(1):129–155. DOI: 10.1038/npp.2016.148 [PubMed: 27510422]
8. Irwin MR, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. Biological psychiatry. 2016; 80(1):40–52. DOI: 10.1016/j.biopsych.2015.05.014 [PubMed: 26140821]
9. Carroll JE, Seeman TE, Olmstead R, Melendez G, Sadakane R, Bootzin R, et al. Improved sleep quality in older adults with insomnia reduces biomarkers of disease risk: pilot results from a randomized controlled comparative efficacy trial. Psychoneuroendocrinology. 2015; 55:184–192. DOI: 10.1016/j.psyneuen.2015.02.010 [PubMed: 25770704]
10. Nelson AM, Coe CL, Juckett MB, Rumble ME, Rathouz PJ, Hematti P, et al. Sleep quality following hematopoietic stem cell transplantation: longitudinal trajectories and biobehavioral correlates. Bone marrow transplantation. 2014; 49(11):1405–1411. DOI: 10.1038/bmt.2014.179 [PubMed: 25133898]
11. Shaw BE, Brazauskas R, Millard HR, Fonstad R, Flynn KE, Abernethy A, et al. Centralized patient-reported outcome data collection in transplantation is feasible and clinically meaningful. Cancer. 2017; doi: 10.1002/cncr.30936
12. D'Souza A, Pasquini M, Spellecy R. Is 'informed consent' an 'understood consent' in hematopoietic cell transplantation? Bone marrow transplantation. 2014; doi: 10.1038/bmt.2014.207

13. Bevans MF, Mitchell SA, Marden S. The symptom experience in the first 100 days following allogeneic hematopoietic stem cell transplantation (HSCT). Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2008; 16(11):1243–1254. DOI: 10.1007/s00520-008-0420-6 [PubMed: 18322708]

14. Berger AM, Kuhn BR, Farr LA, Von Essen SG, Chamberlain J, Lynch JC, et al. One-year outcomes of a behavioral therapy intervention trial on sleep quality and cancer-related fatigue. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009; 27(35):6033–6040. DOI: 10.1200/JCO.2008.20.8306 [PubMed: 19884558]

## Table 1

Baseline characteristics

| Variable | Baseline Poor Sleep (N=90) | Baseline Good Sleep (N=108) | P-value |
|---|---|---|---|
| Median age at transplant (range), years | 54 (19–71) | 57 (21–75) | 0.06 |
| Age | | | 0.04 |
| 18–54 | 51 (57) | 45 (42) | |
| 55+ | 39 (43) | 63 (58) | |
| Gender, Male | 50 (56) | 67 (62) | 0.36 |
| Pre-transplant KPS < 90% | 45 (50) | 37 (34) | 0.03 |
| Race | | | 0.66 |
| White | 83 (92) | 99 (92) | |
| Other | 7 (8) | 8 (7) | |
| Unknown/declined | 0 | 1 (<1) | |
| Marital status | | | 0.28 |
| Married or living with partner | 62 (69) | 85 (79) | |
| Single/separated/divorced/widowed | 19 (21) | 15 (14) | |
| Missing | 9 (10) | 8 (7) | |
| Education | | | 0.06 |
| Secondary education or less | 22 (24) | 23 (21) | |
| Vocational school or associates degree | 31 (34) | 21 (19) | |
| Bachelors or graduate degree | 34 (38) | 59 (55) | |
| Missing | 3 (3) | 5 (5) | |
| Household annual income | | | 0.03 |
| < $60,000 | 20 (22) | 14 (13) | |
| ≥ $60,000 | 20 (22) | 42 (39) | |
| Missing | 50 (56) | 52 (48) | |
| Disease | | | 0.91 |
| Acute leukemia | 60 (67) | 69 (64) | |
| MDS/MPN | 21 (23) | 28 (26) | |
| Other leukemia * | 9 (10) | 11 (10) | |
| Disease risk # | | | 0.23 |
| Low risk | 45 (50) | 56 (52) | |
| Intermediate risk | 22 (24) | 15 (14) | |
| High risk | 19 (21) | 32 (30) | |
| Not classified | 4 (4) | 5 (5) | |
| Conditioning regimen | | | 0.16 |
| Myeloablative – non-TBI | 27 (30) | 27 (25) | |
| Myeloablative – TBI containing | 18 (20) | 35 (32) | |
| Reduced intensity/non-myeloablative– non-TBI | 26 (29) | 32 (30) | |

| Variable | Baseline Poor Sleep (N=90) | Baseline Good Sleep (N=108) | P-value |
|---|---|---|---|
| Reduced intensity/non-myeloablative – TBI | 19 (21) | 14 (13) | |
| Stem cell source | | | 0.51 |
| Bone marrow | 11 (12) | 15 (14) | |
| Peripheral blood | 67 (74) | 84 (78) | |
| Umbilical cord blood | 12 (13) | 9 (8) | |
| Donor | | | 0.77 |
| Unrelated | 51 (57) | 59 (55) | |
| Related | 39 (43) | 49 (45) | |
| Antithymocyte globulin/Alemtuzumab use | 18 (20) | 23 (21) | 0.82 |
| GVHD prophylaxis regimen | | | 0.35 |
| CNI+ MMF ± other(s) | 29 (32) | 32 (30) | |
| CNI + MTX ± other(s) | 49 (54) | 59 (55) | |
| CNI ± other(s) (not MMF/MTX) | 2 (2) | 1 (<1) | |
| Ex-vivo T-cell depletion/CD34 selection | 8 (9) | 16 (15) | |
| Missing | 2 (2) | 0 | |
| Median follow-up of survivors (range), months | 49 (13–62) | 52 (13–64) | |

*Other leukemias: CLL, N=18, PLL, N=2; KPS- Karnofsky Performance Score; MDS/MPN- myelodysplastic syndrome/myeloproliferative neoplasm; CNI- Calcineurin Inhibitor, MMF- Mycophenolate mofetil, MTX- Methotrexate

#Based on the ASBMT RFI Classification

**Table 2**

Univariate survival outcomes by age and sleep group. Survival is shown as probability with 95% confidence interval.

| Overall survival | Young-Good Sleep (N = 45) | Young-Poor Sleep (N = 51) | Old-Good Sleep (N= 63) | Old-Poor Sleep (N = 39) | P-value |
|---|---|---|---|---|---|
| | | | | | <0.001 |
| 100-day | 98 (92–100)% | 82 (71–91)% | 86 (76–93)% | 85 (72–94)% | |
| 6 months | 93 (84–99)% | 76 (64–87)% | 78 (67–87)% | 74 (60–87)% | |
| 1-year | 82 (70–92)% | 69 (55–81)% | 60 (48–72)% | 54 (38–69)% | |

Young- 18–54 years, Old- ≥55 years

Good Sleep: Answered 3 (quite a bit) or 4 (very much) on FACT-BMT sleep question: "I sleep well"

Poor Sleep: Answered 0 (not at all) or 1 (a little bit) or 2 (somewhat) on FACT-BMT sleep question: "I sleep well"

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