Published in final edited form as:

Cancer. 2020 January 01; 126(9): 2003–2012. doi:10.1002/cncr.32736.

Pain in Older Survivors of Hematologic Malignancies after Blood or Marrow Transplantation – a BMTSS report

Naveed Farrukh¹, Lindsey Hageman, MPH¹, Yanjun Chen, MS¹, Jessica Wu, MPH¹, Emily Ness, MPH¹, Michelle Kung, MA¹, Liton Francisco¹, Mariel Parman, MPH¹, Wendy Landier, PhD¹, Mukta Arora, MD MS², Saro Armenian, DO MPH³, Smita Bhatia, MD MPH¹, Grant R. Williams, MD^{1,*}

¹Institute for Cancer Outcomes & Survivorship, University of Alabama at Birmingham, Birmingham, AL

²University of Minnesota, Minneapolis, MN

³City of Hope, Duarte, CA

Abstract

Background—Blood or marrow transplantation (BMT) is increasingly offered to older adults with hematologic malignancies; however, their risk for severe pain is poorly understood. Using the BMTSS study, we investigated the prevalence and predictors of pain after BMT (allogeneic or autologous), as well as its association with physical performance impairments and frailty.

Methods—The cohort included 736 patients with hematologic malignancies who received BMT at age ≥60y at one of 3 transplant centers between 1974 and 2014 and survived ≥2y after BMT; 183 unaffected siblings also participated. Study participants reported on 4 pain domains (non-minor everyday pain, moderate-to-severe bodily pain, prolonged pain, and moderate-to-extreme pain interference) wherein presence of ≥1 domain was indicative of a composite variable severe pain.

Results—Overall, 39.4% of the BMT survivors reported severe pain with a 2.6-fold greater odds of reporting pain when compared with sibling control. Among BMT recipients, those with lower education, lower income, and active chronic graft versus host disease had higher odds of reporting pain. In multivariable analyses, BMT survivors with pain were more likely to have impaired physical performance and more likely to meet the frailty criteria. BMT survivors reported higher use of pain medications (17.8 vs 9.3%) and opioid pain medications (6.5 vs 2.2%) when compared to sibling control.

*Corresponding Author: Grant R. Williams, MD, Assistant Professor, Divisions of Hematology/Oncology & Gerontology, Geriatrics, and Palliative Care, Institute of Cancer Outcomes and Survivorship, O'Neal Comprehensive Cancer Center at UAB, University of Alabama at Birmingham, 1600 7th Avenue South, Lowder 500, Birmingham, AL 35233, gwillia@uab.edu, Phone: 001-205-638-7000, Fax: 001-205-638-2121 USA.

Author Contributions: NF, LH, SB, and GW were responsible for the concept of the study. NF, GW, and SB drafted the manuscript. All authors were involved in the analysis, interpretation, revising, and have approved of the final manuscript version.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Conclusion—Nearly 40% of older BMT survivors followed for a median of 5y after BMT report pain, and BMT survivors are at a 2.6-fold higher odds of reporting severe, non-minor or life-interfering pain as compared with siblings.

Keywords

pain; opioids; blood or marrow transplantation; geriatric oncology; aging

INTRODUCTION

The Institute of Medicine has identified pain as an unmet need in cancer survivors.^{1,2} Previous work has shown that ~10% of cancer survivors report chronic/severe pain, and a substantial proportion take prescription pain medications, including opioids.^{3–6} However, absence of a non-cancer comparison group has precluded an understanding of the contribution of cancer or its treatment to long-term chronic/severe pain.

Over the past decade, blood or marrow transplantation (BMT) has been increasingly offered to older patients with hematologic malignancies.^{7–9} Pain is a common factor affecting quality of life in the older BMT recipients.¹⁰ Previous studies have evaluated pain after BMT in the context of specific complications (primarily those with ocular, oral, or joint manifestations of graft-versus-host-disease [GvHD]) and in the immediate post-BMT period, but, few studies have comprehensively evaluated pain several years after BMT in older survivors.^{11,12} The older cancer population is exquisitely vulnerable to the downstream effects of pain and the attendant polypharmacy, potentially resulting in increased functional decline, delirium, falls, and frailty.^{11,13,14} Therefore, there is a need to examine the nature and severity of pain reported by older BMT survivors when compared with the general population, and its potential downstream effects.

This study aimed to address these gaps in knowledge by investigating the prevalence and predictors of pain in older adult survivors after BMT (allogeneic or autologous), compared to a sibling comparison group, examining the association of pain with physical performance and frailty, and assessing the use of prescription pain medications, including opioids.

METHODS

Study Participants

Study participants were drawn from the BMT Survivor Study (BMTSS), a retrospective cohort study of patients who received a BMT at City of Hope, University of Minnesota, or University of Alabama at Birmingham between 1974 and 2014 for hematologic malignancies. Eligibility criteria for the cohort under consideration in this study included patients who had a BMT at age ≥60y, survived at least 2y after transplantation, and were alive at study participation.^{15,16} The comparison group consisted of 183 similarly-aged siblings without cancer. The Institutional Review Board at each participating site approved the study; informed consent was provided according to the Declaration of Helsinki.

Of the eligible 1172 BMT patients, 887 (75.7%) were contacted. Of those contacted, a total of 736 (83%) completed the questionnaire; 601 (67.8%) completed the full version and 135

(15.2%) completed an abbreviated version. Data from the 601 BMT survivors who completed the full questionnaire were used in analyses involving bodily pain, pain interference, chronic/severe pain (a composite variable), frailty, and prescription pain medication use; the entire cohort of 736 participants were included in all other analyses.

BMTSS Questionnaire

Participants (BMT survivors and siblings) completed a 255-item survey, of which the following domains were included in this analysis: sociodemographic characteristics (age, sex, race/ethnicity, education, annual household income, insurance), health-risk behaviors (smoking, alcohol use, and physical activity), physical performance, pain, and prescription medication use. BMT survivors also reported whether they had ever been diagnosed with chronic GvHD, as well as presence of active chronic GvHD. Additionally, participants reported depression (using SF-36), a single item anxiety measure, and the use of any depression medications. Reliability and validity of the BMTSS questionnaire has been previously tested, indicating that survivors are able to report the occurrence of medical conditions with accuracy.¹⁷ BMT survivors completed the questionnaire between May 2013 and September 2017. Siblings completed the questionnaire between July 2014 and June 2017.

Clinical Characteristics

Clinical information regarding primary cancer diagnosis, donor source (allogeneic, autologous), source of stem cells (bone marrow, peripheral blood stem cells, cord blood), and conditioning regimen (chemotherapeutic agents, total body irradiation [TBI]) were obtained from corresponding institutional databases.

Outcome Measures

Pain—A composite measure of pain was developed using responses from four individual pain questions that exhibited distinct characteristics of the pain experience: (1) general pain (adapted from the Nordic Musculoskeletal Questionnaire)¹⁸; (2) prolonged pain (adapted from the Childhood Cancer Survivor Study)¹⁹; (3) bodily pain (adapted from the Medical Outcomes Study Short Form-12 [MOS SF-12])²⁰; (4) pain interference (adapted from the MOS SF-12)²⁰. The purpose of the composite measure was to create a broad and multifaceted pain measure that included the various pain aspects. The presence of at least one of the four types of reported pain was considered positive for our composite pain outcome variable. Details of the question items, scoring, and construction of the composite measure of pain are presented in table 1.

Prescription Pain Medication—Prescription pain medication utilization was coded from free text responses that asked about prescribed drugs. Responses were evaluated for both generic and brand name drugs. Opioids as well as medications for neuropathic pain (e.g., gabapentin) and anti-inflammatory medications used for analgesic relief (e.g., diclofenac) were included.

Physical Performance Impairment—Impaired physical performance was defined as a response indicating limitations in common activities such as “vigorous activities”, “moderate

activities”, “lifting or carrying groceries”, “climbing several flights of stairs”, “climbing one flight of stairs”, “bending, kneeling, or stooping”, “walking more than a mile”, “walking several blocks”, “walking one block”, and “bathing or dressing yourself” (as utilized by the RAND 36-Item Short Form Health Survey [SF-36]).^{21,22}

Frailty Phenotype—We used the frailty phenotype as previously reported based on responses to the following domains of the BMTSS questionnaire: (1) clinically underweight; (2) exhaustion; (3) low energy expenditure; (4) slowness; (5) weakness.^{23,24} Participants who met at least three of the above five criteria were classified as having the frail phenotype.

Statistical Analyses

The primary purpose of this analysis was to (1) describe the prevalence and predictors of pain in older BMT survivors compared to a sibling comparison group as well as within the BMT cohort; (2) evaluate the association of pain with physical performance and frailty; (3) assess the relation between pain and use of prescription pain medications, including opioids.

Survivors vs. Siblings—Presence of chronic/severe pain and pain medication use were compared between BMT survivors and the siblings, using logistic regression analysis. The magnitude of association was reported as odds ratios (OR) with 95% confidence intervals (95% CI). Multivariable models were adjusted for age at study participation, sex, race/ethnicity (non-Hispanic whites [reference], Hispanics, Blacks, other), depression (as assessed by SF-36 or the use of depression medications), anxiety, education (college graduate [reference], some college, high school), annual household income (\$100,000 [reference], \$50,000-\$99,999, <\$50,000), and health insurance (private [reference], public, other, none). Variables with *p*-values <0.05 in univariable analysis were retained in the final multivariable model.

Predictors of Pain and Pain Medication Use in BMT Survivors—Predictors of the four domains of pain and prescription pain medication use among BMT survivors, stratified by transplant type (allogeneic, autologous), were identified using logistic regression analyses. Univariable analyses were conducted to examine associations between pain as well as prescription pain medication use and the following variables: age at study, sex, race/ethnicity, depression, anxiety, education, annual household income, health insurance, years post-transplant (2–5y [reference], 6–10y, 11y). For the allogeneic BMT cohort, the following variables were also examined: primary hematologic disease (acute myeloid leukemia [AML]/myelodysplasia [MDS] [reference], other), cGvHD (no/resolved cGvHD [reference], active cGvHD), conditioning regimen (Fludarabine/Melphalan +/- cyclophosphamide +/- ATG [reference], Fludarabine/TBI only, Fludarabine/TBI +/- cyclophosphamide +/- ATG, other). For the autologous BMT cohort, the following variables were also examined: primary hematologic disease (non-Hodgkin lymphoma [NHL] [reference], plasma cell dyscrasias [PCD], other), conditioning regimens (melphalan alone, cytarabine/carmustine/etoposide +/- melphalan +/- Rituxan, other). Variables with *p*-values <0.05 in univariable analysis were entered into the multivariable model, and ORs and 95% CIs were calculated.

Impact of Pain on Physical Performance and Frailty Phenotype—Logistic regression was used to evaluate the association between physical performance impairment, frailty phenotype, and pain in BMT survivors stratified by type of BMT, adjusting for the following variables: age at study, sex, race/ethnicity, education, annual household income, health insurance, primary hematologic disease, time since BMT, cGvHD, BMI (<30 [reference], 30), physical activity (sedentary [reference], active), smoking (never [reference], former smoker, current smoker), alcohol (never [reference], formerly used, current drinker). Variables with p -values <0.05 in univariable analysis were retained in the final model and used to calculate OR with corresponding 95% CI to establish the association between pain with physical performance impairment and frailty phenotype.

Data were analyzed using SAS statistical software version 9.4 (SAS Institute, Cary, NC). All statistical tests were 2-sided and p values <0.05 were considered statistically significant.

RESULTS

Demographic and Clinical Characteristics of BMT Survivors and Siblings

Demographic and clinical characteristics of the BMT survivors and siblings are presented in Table 2. In total, 736 BMT survivors (240 [32.6%] autologous and 496 [67.4%] allogeneic) and 183 siblings were included in this analysis. Participation rate for the BMT survivors was 63% and that for the siblings was 60%. Compared to the siblings, BMT survivors were more likely to be older (median age at enrollment 70.7 vs. 68.9 years, $p<0.0001$), male (60.3% vs. 37.8%, $p<0.0001$), and less likely to be non-Hispanic white (82.6% vs. 92.9%, $p=0.004$). No significant differences were seen in education, household income, or health insurance between BMT survivors and siblings.

The median length of follow-up was 5y (range, 2–18 years) since BMT. While AML/MDS was the most prevalent diagnosis among allogeneic BMT recipients (72.5%), PCD (57.1%) and NHL (36.7%) were the most prevalent diagnoses among autologous BMT recipients. Among allogeneic BMT survivors, 52.7% received conditioning with Fludarabine/Melphalan-based regimens and 22.6% received TBI-based regimens. Among autologous BMT survivors, 52.5% received conditioning with Melphalan alone. Of the 149 (76.5%) allogeneic BMT recipients reporting a history of cGvHD, 83 (55.7%) reported active cGvHD at time of survey.

Prevalence and Predictors of Pain

Compared with siblings, a significantly larger proportion of BMT survivors reported general pain (31.3% vs. 25.1%, $p=0.05$), bodily pain (23.4% vs. 15.9%, $p=0.007$), pain interference (19.4% vs. 12.0%, $p=0.002$), prolonged pain (18.6% vs. 8.7%, $p=0.002$), and composite pain measure (39.4% vs. 20.8%, $p<0.001$) (Figure 1). Patients with PCDs had the highest proportion of pain at 47.6%, followed by NHL (15.6%), AML/MDS (35.0%), and other (31.4%). Multivariable analysis (adjusting for age at enrollment, sex, race/ethnicity, education, depression, anxiety, annual household income, and health insurance) revealed that when compared to the siblings, the odds were significantly higher for BMT survivors to report pain (OR=2.6, 95%CI, 1.7–4.1; $p<0.001$), general pain (OR=1.5; 95%CI, 1.0–2.2;

$p=0.05$), bodily pain (OR=2.3; 95% CI, 1.4–3.6; $p=0.007$), pain interference (OR=2.3; 95% CI, 1.4–3.9; $p=0.002$), and prolonged pain (OR=2.5; 95% CI, 1.4–4.4; $p=0.002$) (Figure 1).

Autologous BMT recipients were more likely to report overall pain than allogeneic BMT recipients (43.0% vs. 32.5%, $p=0.01$), but no significant differences were seen in the individual pain categories. Among autologous BMT survivors, low annual household income (<\$50,000: OR=2.29, 95% CI, 1.1–4.4, $p=0.02$; referent group: \$100,000) was associated with greater odds of reporting pain, whereas male sex (OR=0.4, 95% CI, 0.2–0.7, $p=0.0004$; referent group: female) was associated with lower odds of reporting prolonged pain (Table 3). Among allogeneic BMT survivors, low education (high school diploma: OR=4.75, 95% CI, 1.4–16.2, $p=0.013$; referent group: college graduate), low annual household income (\$50,000–\$99,999: OR=3.81, 95% CI, 1.3–11.3, $p=0.02$; \$100,000–\$149,999: OR=4.77, 95% CI, 1.4–15.8; referent group: \$150,000), and active cGvHD (OR=4.24, 95% CI, 1.8–9.8, $p<0.001$; referent no/resolved cGvHD) were associated with greater odds of reporting pain (Table 3).

Association of Pain with Physical Performance and Frailty

Overall, physical performance was impaired in 51.1% and frailty criteria was met by 11.1% of the older BMT survivors. There were no significant differences in the prevalence of frailty (12.9% vs. 10.3%, $p=0.5$) and physical performance limitations (46.2% vs. 53.4%, $p=0.09$) between allogeneic and autologous BMT survivors. In multivariable analyses, BMT survivors with pain were more likely to have impaired physical performance (allogeneic BMT: OR=2.7, 95% CI, 1.2–6.0, $p=0.02$; autologous BMT: OR=3.0, 95% CI, 1.9–4.9, $p<0.0001$) and more likely to meet the frailty criteria (allogeneic: OR=8.2, 95% CI, 2.4–27.6, $p=0.0007$; autologous: OR=7.5, 95% CI, 3.3–16.8, $p<0.0001$) (Table 4).

Prescription Pain Medication and Opioid Use

Overall, 17.8% of the BMT survivors reported using prescription pain medication compared to 9.3% of the siblings ($p=0.006$) and 6.5% reported using opioids compared to 2.2% of the siblings ($p=0.03$) (Figure 2a). Among BMT survivors reporting pain, the risk of prescription pain medication use was 2.5 times higher (95% CI, 1.6–4.0, $p<0.0001$) and the risk of opioid use was 5.2 times higher (95% CI, 2.4–11.3; $p<0.0001$) when compared with those without pain (see Supplemental Table 1). After adjusting for pain, neither the use of prescription pain medication (OR 1.7, 95% CI, 1.0–3.0; $p=0.06$) nor the use of opioid pain medications (OR 2.5 95% CI, 0.9–7.2, $p=0.09$) were significantly higher in BMT survivors compared to siblings (Figure 2b).

DISCUSSION

In our cohort of older BMT survivors followed for a median of 5 years, nearly 40% reported pain. Compared to a sibling cohort without a history of cancer/BMT, BMT survivors were 2.5-times more likely to report pain. Among BMT survivors, those with lower education, lower income, and the presence of active cGvHD were more likely to report pain. Furthermore, survivors with pain had greater odds of impaired physical performance and

frailty. Finally, while older BMT survivors reporting pain were significantly more likely to use prescription pain medication and opioids, the use of these medications was not significantly higher than that reported by the siblings, after accounting for the underlying pain.

Prior work on pain in long-term adult survivors of childhood cancer has demonstrated a 3.9-times increased risk in comparison to a sibling cohort.³ Our cohort of older BMT survivors was at a 2.5-fold higher risk of reporting chronic/severe pain in comparison to a sibling cohort. Current efforts are underway to increase the understanding of the underlying etiology of chronic/severe pain in cancer survivors, such as neuropathies (chemotherapy-induced, post-operative pain syndrome), rheumatologic (arthralgias), skeletal (osteonecrosis secondary to chronic steroid use), gastrointestinal (gastritis), and genitourinary (cystitis) – related pain.^{25,26} Specifically in BMT patients, pain persisting after BMT has been shown to be attributable to chronic GvHD, chemotherapy-induced peripheral neuropathies, chronic steroid-induced osteopenia, and opportunistic infections (e.g., herpes zoster).¹² Interestingly, although we found chronic GvHD to increase the risk of pain, autologous transplant recipients reported higher overall pain, potentially related to different underlying disease processes and different thresholds for transplantation. Results from our study have demonstrated the burden of pain in older, long-term BMT survivors; however further efforts to characterize this pain could help inform more effective and targeted treatment strategies.

Obtaining insights into patient factors associated with a greater risk of experiencing pain may help identify which populations that may benefit most from targeted future interventions. Among older BMT survivors who underwent allogeneic BMT, we found that lower education, lower income, and the presence of cGvHD increased the risk for pain, whereas male sex was associated with decreased risk. We also found similar findings amongst those undergoing autologous BMT regarding lower income and sex. Previous studies have also demonstrated that low income contributed to reports of greater pain among patients with cancer.^{27,28} In prior reports, women are more likely to report chronic pain in general, and this may help to explain the lower risk of pain among male BMT survivors.^{29,30}

Presence of pain in older BMT survivors has potential significant collateral implications, as older BMT survivors with pain were more likely to report impaired physical performance and frailty when compared to those without pain. Similar studies have also shown the impact of pain on decreased physical abilities in long term cancer survivors.^{5,31–33} The higher proportion of frailty found in those reporting chronic/severe pain is also of particular concern, given the increased mortality associated with frailty in older adults.^{34–36}

Nearly 40% of BMT survivors reported pain, while only approximately 18% reported using prescription pain medication. Compared to siblings, a higher proportion of BMT survivors reported using both prescription pain medications and opioid pain medications. Although the individual risk/benefit decision regarding pain medications in older BMT survivors should be made on a case-by-case basis, physicians should consider more closely assessing pain in older BMT survivors. Current recommendations suggest that chronic pain in cancer survivors should be targeted through a comprehensive, multidisciplinary approach involving psychosocial and behavioral interventions, physical therapy, and local therapies (massage,

heat application, patches).³⁷ Prior work has shown that a high prevalence of cancer survivors report using complementary and alternative treatments as well.³⁸ Further research should investigate the potential efficacy and risk of adverse outcomes related to prescription pain medication in the older BMT survivor population with chronic/severe pain, and aim to better understand the long-term impact of chronic opioid use in cancer survivors, as some groups have shown that chronic opioid therapy has marginal therapeutic benefit and can potentially delay functional recovery.²⁶

Our study is not without its limitations. Our population of interest centered on older survivors who have been shown to have multiple morbidities; however, comorbidities were not captured in our present models.^{39,40} Over 90% of older adults with cancer report one or more comorbid conditions and nearly one-third of all older cancer survivors report at least two or more chronic conditions, thus making it more difficult to isolate the contribution of BMT and cancer history to pain.^{40,41} Our retrospective study design was based on self-reported information. We have conducted prior validation studies demonstrating the reliability of self-report patient data;¹⁷ however, it is possible that an element of recall bias could still exist. Recall of physical limitations – especially in the older population – could fluctuate depending on survivors' recent health status and recent procedures; thus, some physical performance limitations may be due to other reasons than pain. Given pain is a subjective experience, we had to rely on self-reported pain measurements and were unable to directly measure pain symptoms. Although the BMTSS questionnaire relies on many previously validated measures, some items lack psychometric data regarding internal consistency and reliability. As opioids were captured under "other prescribed drugs" and not specifically addressed in the BMTSS questionnaire and given the associated stigma in their use, the use of opioids may have been underreported. Nevertheless, despite these limitations, our study comprehensively examined pain in older BMT survivors, and its association with physical performance impairments, frailty, and the use of prescription pain medication. Furthermore, we utilized an all-encompassing definition of pain to create a composite pain outcome, to allow for a broad and multifaceted identification of chronic pain.

CONCLUSION

Years after resolution of a hematologic malignancy and treatment with BMT, older BMT survivors still experience a significant burden of pain, especially in comparison to a similar older, non-cancer sibling control population. We found that pain experienced by older BMT survivors is associated with impaired physical performance, frailty, and greater use of prescription pain medication and opioid pain medication, compared with siblings. Providers treating older survivors of BMT should be aware of these results, and routinely query their patients regarding their pain symptoms. In the future, we aim to develop a better understanding of the underlying etiology of this newly-identified pain in older BMT survivors, which could allow for the development of more appropriate strategies to target pain in this population. Although many questions remain unanswered regarding pain in cancer survivors, this study draws attention to the increased morbidity older BMT survivors face, and provides evidence for the need to develop effective strategies to identify and address the underlying causes of pain in older long-term BMT survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by grants from the National Institutes of Health (R01 CA078938, U01 CA213140, S.B, K08CA234225, G.W.) and the Leukemia & Lymphoma Society (2191-02; 6256-13; R6502-16, S.B.). The content is solely the responsibility of the authors and does not necessarily represent the official view of the National Institutes of Health.

REFERENCES

1. Medicine Io. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press; 2011.
2. Medicine Io, Council NR. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: The National Academies Press; 2006.
3. Lu Q, Krull KR, Leisenring W, et al. Pain in Long-Term Adult Survivors of Childhood Cancers and Their Siblings: A Report from the Childhood Cancer Survivor Study. *Pain*. 2011;152(11):2616–2624. [PubMed: 21907493]
4. Glare PA, Davies PS, Finlay E, et al. Pain in Cancer Survivors. *Journal of Clinical Oncology*. 2014;32(16):1739–1747.
5. Brown MRD, Ramirez JD, Farquhar-Smith P. Pain in cancer survivors. *British Journal of Pain*. 2014;8(4):139–153. [PubMed: 26516548]
6. Moryl N, Coyle N, Essandoh S, Glare P. Chronic pain management in cancer survivors. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2010;8(9):1104–1110. [PubMed: 20876547]
7. Atallah E, Horowitz MM, Logan B, et al. Outcome of Patients 65 Years and Older with Myelodysplastic Syndrome (MDS) Receiving Allogeneic Hematopoietic Stem Cell Transplantation Compared to Patients 55–64 Years of Age. *Blood*. 2015;126(23):193.
8. Ustun C, Lazarus HM, Weisdorf D. To transplant or not: a dilemma for treatment of elderly AML patients in the twenty-first century. *Bone marrow transplantation*. 2013;48(12):1497–1505. [PubMed: 23645167]
9. Atallah E, Bylow K, Troy J, Saber W. Treatment of Older Patients with High-Risk Myelodysplastic Syndromes (MDS): The Emerging Role of Allogeneic Hematopoietic Stem Cell Transplantation (Allo HSCT). *Current hematologic malignancy reports*. 2014;9(1):57–65. [PubMed: 24398726]
10. Deschler B, Binek K, Ihorst G, et al. Prognostic factor and quality of life analysis in 160 patients aged > or =60 years with hematologic neoplasias treated with allogeneic hematopoietic cell transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2010;16(7):967–975.
11. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended Screening and Preventive Practices for Long-term Survivors after Hematopoietic Cell Transplantation. *Bone marrow transplantation*. 2012;47(3):337–341. [PubMed: 22395764]
12. Niscola P, Romani C, Scaramucci L, et al. Pain syndromes in the setting of haematopoietic stem cell transplantation for haematological malignancies. *Bone marrow transplantation*. 2008;41(9):757–764. [PubMed: 18246112]
13. Deimling GT, Stern S, Fau - Bowman KF, Bowman Kf, Fau - Kahana B, Kahana B. The health of older-adult, long-term cancer survivors. *Cancer Nursing*. 2005;26(6):415–424.
14. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA : the journal of the American Medical Association*. 2011;306(17):1874–1883. [PubMed: 22045765]

15. Sun C-L, Francisco L, Kawashima T, et al. Prevalence and predictors of chronic health conditions after hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study. *Blood*. 2010;116(17):3129–3139. [PubMed: 20656930]
16. Sun CL, Francisco L, Baker KS, Weisdorf DJ, Forman SJ, Bhatia S. Adverse psychological outcomes in long-term survivors of hematopoietic cell transplantation: a report from the Bone Marrow Transplant Survivor Study (BMTSS). *Blood*. 2011;118(17):4723–4731. [PubMed: 21821714]
17. Louie AD, Robison LL, Bogue M, Hyde S, Forman SJ, Bhatia S. Validation of self-reported complications by bone marrow transplantation survivors. *Bone marrow transplantation*. 2000;25(11):1191–1196. [PubMed: 10849532]
18. Dickinson CE, Campion K, Foster AF, Newman SJ, O'Rourke AM, Thomas PG. Questionnaire development: an examination of the Nordic Musculoskeletal questionnaire. *Applied ergonomics*. 1992;23(3):197–201. [PubMed: 15676868]
19. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol*. 2002;38(4):229–239. [PubMed: 11920786]
20. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220–233. [PubMed: 8628042]
21. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473–483. [PubMed: 1593914]
22. Jolly TA, Deal AM, Nyrop KA, et al. Geriatric assessment-identified deficits in older cancer patients with normal performance status. *The oncologist*. 2015;20(4):379–385. [PubMed: 25765876]
23. Bouillon K, Kivimaki M, Hamer M, et al. Measures of frailty in population-based studies: an overview. *BMC geriatrics*. 2013;13:64. [PubMed: 23786540]
24. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *The journals of gerontology. Series A, Biological sciences and medical sciences*. 2001;56(3):M146–156.
25. Brown M, Farquhar-Smith P. Pain in cancer survivors; filling in the gaps. *Br J Anaesth*. 2017;119(4):723–736. [PubMed: 29121290]
26. Carmona-Bayonas A, Jimenez-Fonseca P, Castanon E, et al. Chronic opioid therapy in long-term cancer survivors. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*. 2017;19(2):236–250.
27. Ramsey SD, Andersen MR, Etzioni R, et al. Quality of life in survivors of colorectal carcinoma. *Cancer*. 2000;88(6):1294–1303. [PubMed: 10717609]
28. Kenzik K, Pisu M, Johns SA, et al. Unresolved Pain Interference among Colorectal Cancer Survivors: Implications for Patient Care and Outcomes. *Pain Med*. 2015;16(7):1410–1425. [PubMed: 25799885]
29. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. *British journal of anaesthesia*. 2013;111(1):52–58. [PubMed: 23794645]
30. Rosseland LA, Stubhaug A. Gender is a confounding factor in pain trials: women report more pain than men after arthroscopic surgery. *Pain*. 2004;112(3):248–253. [PubMed: 15561379]
31. Green CR, Hart-Johnson T, Loeffler DR. Cancer-related chronic pain. *Cancer*. 2011;117(9):1994–2003. [PubMed: 21509777]
32. Ness KK, Hudson MM, Ginsberg JP, et al. Physical Performance Limitations in the Childhood Cancer Survivor Study Cohort. *Journal of Clinical Oncology*. 2009;27(14):2382–2389. [PubMed: 19332713]
33. Pisu M, Azuero A, Halilova KI, et al. Most impactful factors on the health-related quality of life of a geriatric population with cancer. *Cancer*. 2018;124(3):596–605. [PubMed: 29250775]
34. Arora M, Sun CL, Ness KK, et al. Physiologic Frailty in Nonelderly Hematopoietic Cell Transplantation Patients: Results From the Bone Marrow Transplant Survivor Study. *JAMA Oncol*. 2016;2(10):1277–1286. [PubMed: 27254472]

35. Brown JC, Harhay MO, Harhay MN. The Prognostic Importance of Frailty in Cancer Survivors. *Journal of the American Geriatrics Society*. 2015;63(12):2538–2543. [PubMed: 26566767]
36. Guerard EJ, Deal AM, Chang Y, et al. Frailty Index Developed From a Cancer-Specific Geriatric Assessment and the Association With Mortality Among Older Adults With Cancer. *Journal of the National Comprehensive Cancer Network: JNCCN*. 2017;15(7):894–902. [PubMed: 28687577]
37. Denlinger CS, Ligibel JA, Are M, et al. Survivorship: pain version 1.2014. *Journal of the National Comprehensive Cancer Network : JNCCN* 2014;12(4):488–500. [PubMed: 24717568]
38. Yates JS, Mustian KM, Morrow GR, et al. Prevalence of complementary and alternative medicine use in cancer patients during treatment. *Support Care Cancer*. 2005;13(10):806–811. [PubMed: 15711946]
39. Deimling GT, Bowman KF, Wagner LJ. The effects of cancer-related pain and fatigue on functioning of older adult, long-term cancer survivors. *Cancer Nurs*. 2007;30(6):421–433. [PubMed: 18025913]
40. Williams GR, Mackenzie A, Magnuson A, et al. Comorbidity in older adults with cancer. *Journal of geriatric oncology*. 2016;7(4):249–257. [PubMed: 26725537]
41. Williams GR, Deal AM, Lund JL, et al. Patient-Reported Comorbidity and Survival in Older Adults with Cancer. *The oncologist*. 2018;23(4):433–439. [PubMed: 29242282]

Key Points (Precis for use in the Table of Contents)

- Nearly 40% of older BMT survivors reported non-minor, life-interfering pain, with 2.6-fold greater odds of pain compared with controls.
- Non-minor, life-interfering pain was associated with impaired physical function, frailty, and increased prescription pain and opioid medication use.

Figure 1:
Prevalence of pain in BMT survivors compared to sibling non-cancer control, and multivariable results of the report of pain in BMT survivors compared with sibling non-cancer controls, after adjusting for age at enrollment, sex, race/ethnicity, education, annual household income, and health insurance.

Figure 2:

Proportion of BMT survivors and sibling non-cancer controls who report use of prescription pain medications and opioids (2a), and multivariable results of the odds of prescription pain medication and opioid use after adjusting for age at enrollment, sex, race/ethnicity, education, annual household income, health insurance, and the presence of chronic/severe pain, in BMT survivors compared with sibling non-cancer controls (2b).

Table 1 -

Pain questions and scoring of the composite pain measure

Question	Responses	Scoring and Composite Variable
Have you had any pain in the past 4 weeks?	1= "no pain", 2= "some minor everyday pain, such as pain from minor headaches, bumps, bruises or toothaches", 3= "pain other than minor everyday pain"	Report of "pain other than minor everyday pain" contributed to the composite variable
Prolonged pain in arms, legs, or back	"no, never", "yes, but no longer present", "yes, still present"	Report of prolonged pain reported as "yes, still present" contributed to the composite variable
How much bodily pain have you had during the past 4 weeks?	1= "none" to 6= "severe"	Reported bodily pain as "moderate", "severe", or "very severe" contributed to the composite variable
During the past 4 weeks, how much did the pain interfere with your normal work (including both work outside the home and housework)?	1= "not at all" to 5= "extremely"	Reported pain interference as "moderately", "quite a lot", and "extremely" contributed to the composite variable

Table 2 -

Demographic and Clinical Characteristics of Older Blood or Marrow Transplant Survivors and Siblings

Age at study participation in years						
Median (range)	69.7 (63–89)	71.2 (61–84)	<0.0001	70.7 (61–89)	68.9 (65–80)	<0.0001
Sex (n, %)						
Males	135 (56.3)	309 (62.3)	0.1	444 (60.3)	69 (37.8)	<0.0001
Race/Ethnicity (n, %)						
Non-Hispanic white	208 (86.7)	400 (80.7)	0.007	608 (82.6)	170 (92.9)	0.004
Hispanic	19 (7.9)	37 (7.5)		56 (7.6)	3 (1.6)	
Black	3 (1.3)	37 (7.5)		40 (5.4)	7 (3.8)	
Other	10 (4.2)	21 (4.2)		31 (4.2)	3 (1.6)	
Education (n, %)						
College graduate	117 (48.8)	235 (47.4)	0.1	352 (47.8)	92 (50.3)	0.7
Some college or other training	89 (37.1)	163 (32.9)		252 (34.2)	63 (34.4)	
High school diploma	32 (13.3)	97 (19.6)		129 (17.5)	28 (15.3)	
Missing	2(0.8)	1(0.2)		3 (0.4)	0 (0.0)	
Household Income, \$/year						
100,000	72 (30.0)	108 (21.8)	0.09	180 (24.5)	55 (30.1)	0.2
50,000 – 99,999	71(29.6)	169 (34.1)		240 (32.6)	64 (35.0)	
50,000	57 (23.4)	137 (27.6)		194 (26.4)	38 (20.8)	
Missing	40 (16.7)	82 (16.5)		122 (16.6)	26 (14.2)	
Health Insurance (n, %)						
Private	130 (54.2)	262 (52.8)	0.8	392 (53.3)	96 (52.5)	0.1
Public	102 (42.5)	208 (41.9)		310 (42.1)	83 (45.4)	
Other/None	3 (1.3)	8 (1.6)		11 (1.5)	4 (2.2)	
Missing	5 (2.1)	18 (3.6)		23 (3.1)	0 (0.0)	
Mental Health, (n,%)						
Depression	70 (34.2)	121 (30.6)	0.38	191 (31.8)	57 (26.0)	<0.0001

	Allogeneic BMT (n = 240)	Autologous BMT (n = 496)	p-value*	All BMT (n = 736)	Siblings (n = 183)	p-value†
Anxiety	3 (1.5)	9 (2.3)	0.49	12 (1.6)	7 (3.8)	0.16
Years Post-BMT (n, %)						
2–5	138 (57.5)	255 (51.4)	0.2	393 (53.4)	-	
6–10	86 (35.8)	192 (38.7)		278 (37.8)	-	
11	16 (6.7)	49 (9.9)		65 (8.8)	-	
Primary Diagnosis (n, %)						
AML/MDS	174 (72.5)	13 (2.6)	<0.0001	187 (25.4)	-	
NHL	33 (13.8)	182 (36.7)		215 (29.2)	-	
PCD	8 (3.3)	283 (57.1)		291 (39.5)	-	
Missing	25 (10.4)	18 (3.6)		43 (5.8)	-	
Chronic GvHD (n, %)						
None	40 (20.5)	-		412 (71.7)	-	
Resolved	66 (33.9)	-		68 (11.8)	-	
Active	83 (42.6)	-		83 (14.4)	-	
Missing	6 (3.1)	-		12 (2.1)	-	
Conditioning Regimen (Allogeneic BMT recipients) (n, %)						
Fludarabine/Melphalan +/- cyclophosphamide +/- ATG	117 (52.7)	-		-	-	
Fludarabine/TBI	25 (11.3)	-		-	-	
Fludarabine/TBI +/- cyclophosphamide +/- ATG	25 (11.3)	-		-	-	
Other	55 (24.8)	-		-	-	
Conditioning Regimens (Autologous BMT recipients) (n, %)						
Melphalan alone	-	240 (52.5)		-	-	
Cytarabine/carmustine/etoposide +/- melphalan +/- Rituximab	-	148 (32.4)		-	-	
Other	-	69 (15.1)		-	-	

* p-value – demonstrates comparison of autologous BMT recipients with allogeneic BMT recipients

[†] p-value – demonstrates comparison of all BMT recipients with siblings

Table 3.

Risk Factors for Pain in Allogeneic and Autologous BMT Survivors

Characteristic	General Pain		Bodily Pain*		Pain Interference*		Prolonged Pain		Chronic/Severe Pain*	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Allogeneic[†]										
Race/Ethnicity										
Non-Hispanic white	REF		REF		REF		REF		REF	
Other	1.97 (0.74,5.23)	0.2	4.66 (1.37,15.89)	0.01	5.26 (1.49,18.5)	0.010	4.91 (1.69,14.26)	0.003	4.63 (1.34,16.0)	0.016
Education										
College Graduate	REF		REF		REF		REF		REF	
Some college/training	1.74 (0.81,3.74)	0.2	1.21 (0.47,3.13)	0.7	1.07 (0.40,2.88)	0.9	1.17 (0.41,3.39)	0.8	1.41 (0.59,3.33)	0.4
High school diploma	2.10 (0.71,6.19)	0.1	5.25 (1.46,18.83)	0.011	3.43 (0.95,12.46)	0.06	2.39 (0.65,8.85)	0.2	4.75 (1.40,16.17)	0.013
Annual Household Income, \$/year										
100,000	REF		REF		REF		REF		REF	
50,000 – 99,999	1.13 (0.46,2.76)	0.8	3.32 (1.03,10.72)	0.045	3.14 (0.91,10.81)	0.07	1.36 (0.34,5.44)	0.7	3.81 (1.28,11.29)	0.02
50,000	1.14 (0.43,3.01)	0.8	2.44 (0.65,9.13)	0.2	3.59 (0.94,13.69)	0.06	2.56 (0.67,9.74)	0.2	4.77 (1.43,15.85)	0.011
Missing	0.40 (0.13,1.26)	0.1	1.68 (0.41,6.87)	0.5	2.38 (0.56,10.09)	0.2	2.17 (0.49,9.65)	0.3	2.34 (0.65,8.36)	0.2
Chronic GVHD										
No/resolved chronic GVHD	REF		REF		REF		REF		REF	
Active chronic GVHD	0.91 (0.44,1.92)	0.8	4.22 (1.70-10.48)	0.002	5.53 (2.16,14.21)	<0.001	1.26 (0.45,3.57)	0.7	4.24 (1.83,9.80)	<0.001
Autologous^{††}										
Sex										
Female	REF		REF		REF		REF		REF	
Male	0.91 (0.59,1.42)	0.7	0.92 (0.55,1.53)	0.7	0.76 (0.44,1.3)	0.3	0.39 (0.23,0.66)	0.0004	0.68 (0.42,1.11)	0.1
Annual Household Income, \$/year										
100,000	REF		REF		REF		REF		REF	
50,000 – 99,999	0.71 (0.40,1.27)	0.2	1.02 (0.52,2.01)	0.9	1.04 (0.46,2.22)	0.9	1.13 (0.55,2.34)	0.7	1.29 (0.68,2.46)	0.4
50,000	0.74 (0.39,1.42)	0.4	1.30 (0.62,2.73)	0.5	1.79 (0.80,3.97)	0.2	2.04 (0.94,4.40)	0.07	2.29 (1.12,4.67)	0.02
Missing	1.12 (0.56,2.22)	0.7	0.72 (0.31,1.70)	0.5	1.36 (0.55,3.35)	0.5	1.76 (0.76,4.04)	0.2	1.51 (0.69,3.30)	0.3

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

* Modified sample size of n=601

[†]For allogeneic stratified patients, each type of pain was an individual model additionally adjusted for age at enrollment, sex (female, male), health insurance (private, public, other), primary disease (AML/MDS, other), depression (yes/no), anxiety (yes/no), years post-BMT (2–5, 6–10, 11), cGVHD (none, active, resolved), conditioning regimen (fludarabine/melphalan +/- cyclophosphamide +/- ATG, fludarabine/TBI only, fludarabine/ TBI +/- cyclophosphamide +/- ATG, other)

^{††}For autologous stratified patients, each type of pain was an individual model additionally adjusted for age at enrollment, race/ethnicity (non-Hispanic white, others), education (college graduate, some college or other training, high school diploma), health insurance (private, public/other), primary disease (NHL, PCD, other), depression (yes/no), anxiety (yes/no), years post-BMT (2–5, 6–10, 11), cGVHD (none, active, resolved), conditioning regimen (melphalan only, cytarabine/carmustine/etoposide +/- melphalan +/- rituximab, other)

Table 4.
Impact of Pain on Physical Performance & Frailty Among Allogeneic and Autologous BMT Survivors

Type of Pain	Physical Performance Impairment				Frailty [‡]			
	Allogeneic		Autologous		Allogeneic		Autologous	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
General Pain in the past 4 weeks								
No pain or some minor everyday pain	REF		REF		REF		REF	
Pain other than minor everyday pain	3.16 (1.48,6.74)	0.003	1.33 (0.82,2.16)	0.3	2.89 (1.01,8.25)	0.05	3.09 (1.54,6.20)	0.002
Bodily Pain during past 4 weeks								
None to mild	REF		REF		REF		REF	
Moderate to Very Severe	2.57 (1.07,6.17)	0.03	2.86 (1.68,4.87)	0.0001	23.84 (5.74,98.89)	<0.0001	8.41 (3.97,17.81)	<0.0001
Pain Interference during past 4 weeks								
Not at all or a little bit	REF		REF		REF		REF	
Moderately to Extremely	4.08 (1.50,11.11)	0.006	4.62 (2.46,8.70)	<0.0001	7.07 (2.26,22.09)	0.0008	12.15 (5.61,26.27)	<0.0001
Prolonged pain in arms, legs, or back								
No Never/Not present	REF		REF		REF		REF	
Yes , present	2.20 (0.75,6.50)	0.2	2.01 (1.08,3.71)	0.03	3.74 (1.03,13.54)	0.04	3.02 (1.44,6.33)	0.003
Chronic/Severe Pain								
No	REF		REF		REF		REF	
Yes	2.66 (1.17,6.03)	0.02	3.03 (1.90,4.85)	<0.0001	8.15 (2.41,27.58)	0.0007	7.47 (3.32,16.81)	<0.0001

[‡] Modified sample size of n=601

Each type of pain was an individual model adjusted for age at enrollment, sex (female, male), race/ethnicity (non-Hispanic white, others), education (college graduate, some college or other training, high school diploma), annual household income in \$/year (100,000, 50,000 – 99,999, 50,000, missing), and health insurance (private, public/other), primary disease (for allo only [AML/MDS, other], for auto only [NHL, PCD, other]), years post-BMT (2–5, 6–10, 11), cGVHD (none, active, resolved), BMI (<30, 30), exercise status (sedentary, active), smoking status (never, yes), alcohol status (never, yes but not presently, yes currently drink)