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Association of geriatric measures and global frailty with cognitive decline after allogeneic hematopoietic cell transplantation in older adults

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Abstract

Introduction: Allogeneic hematopoietic cell transplantation (alloHCT) is increasingly offered to older adults, and its potential impact on cognition in this population is understudied. This work aims to evaluate the ability of cancer-specific geriatric assessments (cGA) and a global frailty index based on accumulation of deficits identified in the cGA to predict the risk of cognitive decline after alloHCT in older adults.

Materials and Methods: AlloHCT recipients aged 50 years or older completed a cGA, including a cognitive evaluation by the Blessed Orientation Memory Concentration (BOMC) test, at baseline prior to alloHCT and then at 3, 6, and 12 months after transplant. Baseline frailty was assessed using a deficit accumulation frailty index (DAFI) calculated from the cGA.

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Manuscript Writing: Huang, Steinman, Olin.

Approval of Final Article: all authors.

Ethics Approval and Informed Consent

The study was approved by the University of California San Francisco's Institutional Review Board, and all patients consented to participate.

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Declaration of Competing Interest

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A multinomial logit model was used to examine the association between predictors (individual cGA measures, DAFI) and the following three outcomes: alive with stable or improved cognition, alive with cognitive decline, and deceased. In post-hoc analyses, analysis of variance was used to compare BOMC scores at baseline, 3, 6, and 12 months across frailty categories.

Results: In total, 148 participants were included, with a median age of 62 (range 50–76). At baseline, 12% had cognitive impairment; at one year, 29% of survivors had improved BOMC scores, 33% had stable BOMC, and 37% had worse BOMC. Prior to transplant, 25% were pre-frail and 11% were frail. Individual baseline cGA measures were not associated with cognitive change at one year as assessed by BOMC. Adjusting for age, sex, and education, those who were frail at baseline were 7.4 times as likely to develop cognitive decline at one year than those who were non-frail, although this finding did not reach statistical significance (95% confidence interval [CI] 0.74–73.8, $p = 0.09$). The probability of being alive with stable/improved cognition at 12 months for the non-frail, pre-frail, and frail groups was 43%, 34%, and 8%, respectively.

Discussion: Baseline geriatric measures and frailty were not significantly associated with cognitive change as assessed by BOMC in adults aged 50 or older after alloHCT. However, the study was underpowered to detect clinically meaningful differences, and future work to elucidate potential associations between frailty and cognitive outcomes is warranted.

Keywords

Cognition; Frailty; Geriatric assessment; Allogeneic hematopoietic cell transplantation

1. Introduction

Allogeneic hematopoietic cell transplantation (alloHCT), a potentially curative therapy for many hematologic malignancies, is increasingly offered to older adults due to improvements in supportive care and the development of reduced-intensity conditioning [1]. In 2020, 27% of alloHCT recipients in the US were aged 65 or older, compared to 10% in 2010 [2]. With the expansion of this therapy in the aging population, the need to understand its potential impact on cognition is paramount. Cognitive impairment is frequently detected at baseline prior to alloHCT [3–11], and cognitive status worsens acutely in the period immediately following alloHCT [3,4,6,7,10,12]. On average, cognitive function subsequently recovers to near baseline levels, though the time it takes to recover varies, ranging from months to years [4,7–9,12–14]. However, cognitive deficits persist or worsen long-term in a subset of patients, with 38–40% of survivors exhibiting cognitive impairment at three to six years after alloHCT [12,15,16]. Cognitive decline is important to study because it can interfere with medication adherence and symptom reporting in alloHCT recipients specifically, and in older adults more generally it can lead to poor quality of life, functional decline, and loss of independence. Cognitive impairment also predicts inferior survival in older patients with hematologic malignancies [17–20]. Thus, there is a need to identify older adults at highest risk of long-term cognitive decline after alloHCT to improve treatment decision-making and implement targeted screening and interventions.

Previous studies identified certain baseline factors such as older age [7,14,15], male sex [15], lower education [7,9,15], lower cognitive reserve [7,15], lower income [15], worse

functional status [9], intensity of conditioning chemotherapy [11,15], and certain genetic variants [21] as risk factors for post-alloHCT cognitive decline. Events following alloHCT may also impact cognitive outcomes, such as increased inflammation [22], post-alloHCT medication side effects, greater cumulative cognitive risk factors, and greater hospital length-of-stay [23]. However, the existing literature usually encompasses patients of all ages and does not focus on older adults, who are at higher risk for poor cognitive outcomes. Risk assessment tools from geriatric oncology, such as cancer-specific geriatric assessments (cGA) and frailty indices, provide a valuable opportunity to improve our ability to predict which older adults may suffer cognitive decline after alloHCT. A cGA uses validated instruments to assess an array of different domains (functional status, comorbidity, cognition, nutrition, mental health, social support) [24,25] and has been shown to predict adverse outcomes in older adults with hematologic malignancies [17,20,26,27]. A cGA can be useful in two ways. First, individual geriatric measures contained within a cGA such as functional status may help predict outcomes of interest. Second, a key tenet of geriatrics is that the accumulation of multiple deficits can strongly predict outcomes that result from multifactorial causes, such as cognitive decline. Thus, an index based on this deficit accumulation model of frailty may be more clinically valuable than evaluating each risk factor in isolation [28].

This study leverages an existing database of a longitudinal prospective study of 148 adults aged 50 or older who underwent alloHCT. This database includes demographics, clinical characteristics, and cGA performed at baseline and at 3, 6, and 12 months after alloHCT. In this study, we evaluated the hypotheses that deficits in individual geriatric measures and global frailty (based on a deficit accumulation frailty index) can predict increased risk for cognitive decline post-alloHCT.

2. Materials and Methods

2.1. Study Design and Population

In this prospective cohort study, patients planned to undergo alloHCT at the University of California San Francisco (UCSF) were screened for the following inclusion criteria: age ≥ 50 years, ability to read and write in English (cGA validated only in English at time of study design), and ability to provide informed consent and complete the protocol requirements. Participants completed a cGA including a cognitive measure within 3 months prior to alloHCT and at 3, 6, and 12 months after alloHCT. The cGA results were not provided to the treating physician unless severe cognitive impairment was detected, which triggered additional evaluation. Patients also reported sociodemographic information including race/ethnicity, marital status, and education. Study staff extracted the following information from electronic medical records: diagnosis, remission status, donor type, American Society for Blood and Marrow Transplantation (ASBMT) disease risk classification [29], and Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) score [30]. The age threshold of 50 years was chosen based on prior literature in similar populations showing a high prevalence of cGA impairments [31,32]. The research protocol was approved by the UCSF Institutional Review Board.

2.2. Data Collection and Measurement: Predictors

The cGA used in this study included minor modifications from the original developed by Hurria et al. [24,33,34] and has been described in prior publications [27,32]. The cGA includes validated instruments assessing the individual domains of functional status, comorbidities, cognition, nutrition, mental health, and social support. Individual cGA measures evaluated as predictors included: Medical Outcomes Study (MOS) Physical Functioning (continuous, per 10 point increase), instrumental activities of daily living (IADL; dichotomous, any deficits), Karnofsky Performance Status (KPS)-physician reported (continuous, per 10 point increase), KPS-patient reported (continuous, per 10 point increase), Timed-up-and-go (TUG; continuous, per second increase), number of falls in last six months (continuous), Mental Health Inventory (MHI; continuous, per 10 point increase), body mass index (BMI; continuous, per 5 unit increase), percent weight loss in six months (continuous, per 1 unit increase), Older Adults Resources & Services (OARS) comorbidity subscale (continuous, per 1 unit increase), number of medications (continuous per 1 unit increase), Social Support Survey (continuous, per 10 point increase). The only physician-reported predictors are physician-reported KPS, TUG, BMI, and weight loss.

The deficit accumulation frailty index (DAFI) was developed by Cohen et al. to summarize the components of the cGA into a global frailty score relevant to cancer treatment, which has been correlated with outcomes such as toxicity, treatment discontinuation, and hospitalization [28]. Our DAFI index consisted of the following items: marital status, IADL (phone, travel, shopping, meal preparation, housework, medications, money), MOS Physical Functioning (lifting groceries, climbing stairs, bending/kneeling, walking >1 block, walking 1 block, bathing/dressing), KPS (both patient- and provider-rated), TUG, number of falls, MHI, nutrition (BMI, weight loss), OARS comorbidities (other cancer, arthritis, glaucoma, emphysema, hypertension, heart disease, circulation, diabetes, gastrointestinal, osteoporosis, liver/kidney, stroke, depression, eyesight, hearing), number of medications, and social support (help when confined to bed, help take to physician, help prepare meals, help with daily chores). To construct the DAFI, the individual assessment items from the cGA are first assigned frailty risk points of 0 (absent), 1 (intermediate), or 2 (most adverse). Then for each subject, points for all non-missing items are summed and divided by the sum of the total possible points across all non-missing items. The DAFI is thus the ratio of the actual deficit score over the potential deficit score, ranging from 0.0 to 1.0. The DAFI cut-offs are 0.0 to <0.2 for non-frail, 0.2 to <0.35 for pre-frail, and ≥ 0.35 for frail. Baseline cognition was not included as an item within the DAFI calculation since it was also incorporated into the outcome measure of cognitive change.

2.3. Data Collection and Measurement: Outcome

The outcome measure of cognition was evaluated by the Blessed Orientation-Memory-Concentration (BOMC) test. The BOMC is a 6-item provider-administered test of orientation, memory, and concentration/attention with a maximum of 28 points, with higher scores indicating greater cognitive impairment. The BOMC has been validated as a screening tool for cognitive impairment with cutoff scores of ≥7 for cognitive impairment and ≥ 11 for severe cognitive impairment [35]. The BOMC has good test-retest reliability when repeated after one month [36,37], with no significant practice effect, and serial

administration every 2 to 3 months over 6 to 21 months of follow-up found scores to be stable over time [36]. While there is no widely accepted clinically meaningful difference for the BOMC, a study in patients with neurological diseases found that deterioration by >2 points over time is unlikely to be attributed to test-retest variation and thus likely represents a real decline in cognitive function [38].

2.4. Statistical Analysis

Descriptive statistics were used to summarize the baseline participant characteristics. Predictors were the scores on individual cGA measures and the DAFI. We included in our multivariate model a set of pre-specified key predictors (age, sex, education) as well as any other demographic/clinical predictors significant in bivariate analyses with $p < 0.05$.

Because of potential bias introduced by the high attrition due to death in alloHCT studies, we accounted for the competing risk of death by using a multinomial logit model to examine the association between predictors and outcomes. The cognitive outcome was dichotomized at the study sample's median BOMC change score (defined as BOMC at one year minus BOMC at baseline), with positive values indicating a decline in cognition. Additionally, death was included as a third outcome. Thus, the multinomial model had three possible outcomes: alive with cognitive change equal to or better than the median (reference), alive with cognitive change worse than the median, and deceased. We calculated the relative risk ratios of the risk of being alive with cognitive change worse than the median compared to being alive with cognitive change equal to or better than the median. We did not present the risk ratios for the third outcome (deceased) since the risk of being deceased compared to being alive with cognitive change equal to or better than the median is not clinically relevant. Multinomial logit regressions are used frequently in other settings where the investigators wish to account for the competing risk of death, including in studies looking at risk factors for cognitive decline [39–41].

We performed exploratory analyses to further characterize the relationship between frailty category and cognitive change. We visualized the mean BOMC score trajectories from baseline to 3, 6, and 12 months by baseline frailty status. Based on initial findings, post-hoc analysis of variance was used to compare the mean BOMC scores of the three frailty categories at each time point.

For all analyses, *p*-values were two-sided and not adjusted for multiple comparisons. Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc) and STATA 16.1 (Stata Corp).

3. Results

3.1. Baseline Clinical, Geriatric, and Frailty Measures

Participant demographics and clinical characteristics are described in Table 1. The median age was 62 (age 50–76), with 62% of participants aged 60 or older. The most common diagnoses were acute myeloid leukemia (43%) and myelodysplastic syndrome (26%). Only 13% of participants had a Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) score of 0, while 55% had scores of 1–2 and 32% had scores of 3 or higher. Sixty-eight

percent of participants received reduced-intensity conditioning. At one year, 50 participants were lost to follow-up due to death, and another 23 were alive but missing the outcome measure of BOMC scores (18 missing entire cGA, 5 with partial cGA but missing BOMC). Those alive but missing BOMC scores at 12 months were not significantly different from those with non-missing data on key factors that may influence cognition (age, baseline BOMC, baseline DAFI score, education, progression, overall survival) (analyses not shown).

Geriatric impairments were prevalent (Table 2), with functional impairments found in 57% based on the Medical Outcomes Study Physical Health Subscale and 39% based on instrumental activities of daily living. In addition, 44% showed impairments in mental health. At baseline, 12% ($n = 18$) had cognitive impairment defined as a BOMC score ≥ 7. The median BOMC score was 2 (range 0–14). Impairments were seen both in those aged 50–59 and those aged 60 or older.

Prior to transplant, 25% were considered pre-frail by DAFI score, and 11% were considered frail. The most common frailty indicators for the DAFI were low or elevated BMI (66%), polypharmacy (64%), patientrated KPS ≤80 (45%), Mental Health Inventory-5 score ≤ 76 (44%), limitations in bending or kneeling (40%), limitations in lifting groceries (36%), limitations in walking >1 block (33%), and needing help with housework (32%).

3.2. Post-Transplant Survival and Cognitive Outcomes

The median overall survival was 46.5 months. By one year, 50 patients died. For the non-frail, pre-frail, and frail groups, three-month survival was 95%, 84%, and 88%; six-month survival was 89%, 76%, and 63%; and one-year survival was 71%, 59%, and 56%, respectively. The loss-to-follow-up rate by one year was 15%, 14%, and 25% for the non-frail, pre-frail, and frail groups, respectively.

Of those surviving with non-missing BOMC data ($n = 75$), the median BOMC change score was 0 after one year, and the mean BOMC change score was 0.15 (standard deviation 3.42). Of these, 29% had improvement in their BOMC scores, 33% had stable BOMC scores, and 37% had worsening BOMC scores. In total, 5% ($n = 4$) had scores meeting criteria for cognitive impairment (BOMC≥7), all representing a decline in cognitive performance from their baseline (BOMC score change from 0 to 8, 2 to 12, 2 to 8, 9 to 13). Among the 50 participants who died by one year, the mean age was 63 years, and 8 had cognitive impairment at baseline defined as BOMC score ≥ 7.

3.3. Predictors of Cognitive Outcomes at One Year Post-alloHCT

Because the median BOMC change score was 0, the three outcomes in our multinomial model can be simplified to: alive with stable/improved cognitive scores (reference), alive with worsened cognitive scores, and deceased. Baseline clinical characteristics (age, sex, marital status, race, ethnicity, education, diagnosis, remission status, ASBMT risk classification, HCT-CI, transplant intensity) were not significantly associated with BOMC change at one year after alloHCT in univariate analysis (Table 3). Cognitive decline and cognitive impairment defined as BOMC≥7 were seen in both those aged 50–59 years and those aged 60 years or older.

The association between baseline geriatric assessment and frailty measures and BOMC change at one year post-transplant is presented in Table 4. Individual baseline cGA measures were not significantly associated with cognitive change at one year as assessed by BOMC in univariate or multivariate analysis adjusting for age, sex, and education. In univariate analysis, those who were frail at baseline were 7.8 times as likely to develop worsening BOMC scores at one year than those who are non-frail; however, the 95% confidence interval (CI) was wide at 0.81–74.8, and this association did not reach statistical significance ($p = 0.08$). In multivariate analysis adjusting for age, sex, and education, those who were frail were 7.4 times as likely to develop worsening BOMC scores at one year though, again, this finding did not reach statistical significance (95% CI 0.74–73.8, $p = 0.09$).

3.4. Cognitive Trajectories by Frailty Status

In exploratory analyses, visual examination of BOMC trajectories post-alloHCT suggested different patterns of cognitive recovery depending on the baseline frailty category (Fig. 1). On average, those who were non-frail at baseline exhibited an increase (worsening) in BOMC score at three months but decreased by six months (mean BOMC score improvement by 0.5 from baseline). Those who were pre-frail at baseline had an increase in BOMC score at three months and six months but decreased by 12 months (mean BOMC score improvement by 0.6 from baseline). Those who were frail at baseline exhibited an increase in BOMC score at three months that never recovered, worsening even further by 12 months (mean BOMC score worsening by 1.7 from baseline). No group exhibited a deterioration in BOMC score by more than 2 points, which has been suggested as reflective of real cognitive decline not attributable to simple test-retest variation [38].

To evaluate the differences visualized between frailty categories at different time points, post-hoc analyses were performed evaluating the association between baseline frailty category and raw BOMC scores at each time point, without adjusting for other variables. At baseline and three months, frailty status was not associated with BOMC scores. At six months, baseline frailty status was significantly associated with BOMC scores, with those who were pre-frail and frail exhibiting worse BOMC scores (mean ± standard error: 3.35 ± 0.63 and 3.5 ± 1.13, respectively) than those who were non-frail (1.99 ± 0.28, $p = 0.04$). At 12 months, despite a greater than 2-point difference in mean BOMC scores between those who were non-frail (2.19 ± 0.36) and pre-frail (2.47 ± 0.61) compared to frail (4.6 ± 2.04), baseline frailty status was not significantly associated with raw BOMC scores ($p = 0.18$). Notably, the standard error ranges are wide for the frail category at 12 months, likely reflecting the high attrition due to death and loss-to-follow-up (only five surviving and not missing of the initial 16 frail participants) and limiting power for this analysis. A flow diagram of cognitive status and mortality at 12 months by baseline frailty category is shown in Fig. 2. The probability of being alive with stable/improved cognition at 12 months for the non-frail, pre-frail, and frail groups was 43%, 34%, and 8%, respectively.

4. Discussion

In this single-center prospective cohort study, we did not find a statistically significant association between individual baseline geriatric measures or baseline global frailty and the

risk of cognitive decline as assessed by BOMC at one year post-alloHCT. The probability of being alive with stable/improved BOMC scores at 12 months for the non-frail, pre-frail, and frail groups was 43%, 34%, and 8%, respectively.

While previous studies have found specific baseline factors such as older age [7,14,15], male sex [15], lower education [7,9,15], worse functional status [9], intensity of conditioning chemotherapy [11,15], to be risk factors for post-alloHCT cognitive decline in adults of all ages, our study in older adults did not find associations between age, sex, education, functional status, or conditioning intensity with cognitive decline as assessed by BOMC at one year after alloHCT. One potential reason for this discrepancy is the low sensitivity of the BOMC to detect subtle cognitive change compared to formal neuropsychological testing. While the BOMC may be adequate for detecting severe cognitive impairment, it is not designed to differentiate milder cognitive changes, and the floor effect is evident in our study sample with a median baseline score of 2 out of a possible range of 0 to 28. Additionally, our focus on adults aged 50 or older may contribute to the discrepancy as well. If age is correlated with certain risk factors such as functional status or conditioning intensity, restricting the study population only to those who are older may decrease the strength of association between these factors and cognitive outcome.

Post-hoc analysis found baseline frailty was significantly associated with cognitive scores at six months. While baseline frailty was not significantly associated with cognitive scores at 12 months, those who were frail had BOMC scores that were worse by over 2 points compared to those who were pre-frail or non-frail. However, within the frail group, the mean BOMC score worsened by 1.7 points from baseline to one year, not meeting the criteria of greater than 2 points deterioration to suggest real decline [38]. The high attrition rate of those who were frail at baseline (only five surviving and not lost to follow-up of original 16) resulted in limited power and low analytical precision for the frail group at 12 months, as evidenced by the wide error bars. The non-significant ($p = 0.09$) but large effect size of 7-fold higher risk of cognitive decline as assessed by BOMC in those who are frail at baseline is thought-provoking, as it raises the question of whether this finding would reach statistical significance in a larger sample or in a study with a more sensitive cognitive measure. Future studies in a larger sample or with a more sensitive cognitive measure are needed to better test our hypothesis that geriatric measures and global frailty can predict post-alloHCT cognitive decline.

While the results were not significant, we note the larger effect size with frailty as a predictor compared to individual cGA measures. While this could be due to chance and the magnitude of effect is highly uncertain due to small sample sizes, it suggests the possibility that frailty based on a deficit accumulation model may be a more robust way to identify those at risk of cognitive decline, compared to individual geriatric measures. Frailty, a measure of increased vulnerability due to diminished biologic reserve and decreased resilience caused by cumulative deficits across various systems, has been proposed as a useful concept in studying cancer-related cognitive impairment [42,43]. Because the etiology of cancer-related cognitive impairment is likely multifactorial involving complex interactions between patient factors, treatment factors, cancer biology, and the biology of aging, evaluating cumulative risk factors, rather than individual risk factors, may be a more

useful approach to studying cognition in this setting. However, further studies are needed to confirm this.

To our knowledge, our study is the first to examine global frailty as a predictor of post-alloHCT cognitive decline. One prior study sought to evaluate if frailty is associated with worse cognition at baseline in the alloHCT population. Smith et al. used the Short Physical Performance Battery (SPPB) as a surrogate of frailty and found an association between worse baseline SPPB scores and worse baseline Montreal Cognitive Assessment scores [44]. However, the SPPB is more accurately classified as an assessment of physical function rather than global frailty, and this study did not assess cognition post-alloHCT. Thus, our study adds to the literature on cognitive decline in alloHCT by (1) using a measure of global frailty and (2) examining longitudinal change in cognition after alloHCT.

Several other studies have examined frailty in the alloHCT population in different contexts, such as reporting baseline prevalence of frailty in transplant recipients [31,45], evaluating the association between baseline frailty and standard transplant outcomes such as toxicity and mortality [46–48], or evaluating the association of frailty with mortality in long-term HCT survivors [49,50]. It is worth underscoring some differences in the frailty rates and measures used in our study and in the literature. Our study found 11% baseline frailty. This is lower than reported baseline frailty rates in other studies, which range from 18.9% to 37.6%. These differences are likely related to the specific frailty criteria used, as well as differences in patient populations and institutional transplant eligibility criteria. Our frailty rate of 11% is defined by a DAFI calculated from a cGA, which is based on Rockwood's multi-domain model of frailty [51]. Several studies used Fried's criteria for frailty, which is based on the phenotype of unintentional weight loss, selfreported exhaustion, weakness, slow walking speed, and low physical activity [52], and reported a fairly consistent frailty prevalence of 18.9% to 25%. Lastly, Salas et al. used a Clinical Frailty Score that considers the primary hematologic malignancy, comorbidities, function, and associated features in alloHCT recipients aged 18 or older and reported a baseline frailty prevalence of 37.6%.

Studies of frailty in the alloHCT population have also noted mixed results in outcomes. Ombres et al. found that baseline frailty was not significantly associated with death at three or six months after alloHCT [47]. However, Salas et al. found that frailty was associated with worse non-relapse mortality but not overall survival, and Pamukcuoglu et al. and Arora et al. found that frailty was associated with a higher risk of toxicity and overall mortality [46,48,49]. Differences in study populations, frailty measure used, analytical approach, and outcomes measured may account for some of these differences in findings. More research is needed to determine which frailty measures may be most useful in the alloHCT population and what outcomes these measures can help predict. While most other studies have used Fried's criteria for frailty, the DAFI is flexible to missing data and can be calculated if one has a basic set of GA measures. We suggest future studies collecting cGA information in older adults with cancer also calculate a DAFI based on the cGA data, as a global assessment of frailty will add to our overall understanding of risk factors and outcomes in older adults with cancer.

We acknowledge several limitations to our study. First, as discussed previously, the BOMC is not as sensitive to mild cognitive changes as other cognitive assessments such as neuropsychological testing, and our sample exhibited a strong floor effect. This may have limited our ability to detect a difference, as cancer-related cognitive impairment can often manifest as more subtle cognitive changes. Second, a sample size of 75 patients may have insufficient power to evaluate the predictive value of cGA and frailty measures, particularly given the limitations of the BOMC, low rates of frailty, and high attrition. Third, some participants had baseline cognitive impairments, and we cannot assess if subsequent impairment is due to pre-existing neurocognitive processes versus the effects of alloHCT. Due to concerns for collinearity, we did not include cognition in our DAFI calculation, and separate analysis of baseline BOMC scores as a predictor of subsequent BOMC change resulted in findings consistent with regression to the mean (data not shown). Fourth, cGA data was collected even after relapse, but our study was not designed or adequately powered to be able to describe the possible impact of post-relapse treatment on cognition. Fifth, using age 50 and older may be considered too young for the use of “geriatric” assessments. However, the high prevalence of both baseline GA impairments and frailty as well as the prognostic value of such deficits shown in prior studies with similar age cutoffs support the utility of cGA in this population. Sixth, given the selective nature of transplant evaluations, few participants were categorized as frail at baseline (11%), and thus our population may be skewed towards fitness on the frailty spectrum. In addition, while we were able to account for attrition due to death in the multinomial analysis, we cannot know the outcomes of people who remained alive but did not complete follow-up assessments, nor how their status might have impacted the results. Lastly, generalizability is limited by the single-center nature of the study, limitation to English speakers, as well as the homogeneous sample of mostly White, non-Hispanic, highly educated (84% college level or higher education) participants.

To our knowledge, this study is the first to examine a global frailty index as a risk factor for long-term cognitive decline after alloHCT. We did not find any significant associations between baseline geriatric measures or frailty and the risk of cognitive decline as measured by BOMC at one year after alloHCT. However, our low sample size and use of an insensitive measure of cognitive change likely limited our ability to detect clinically significant effects, and future studies in larger samples using more sensitive cognitive measures would be of value to further investigate this question.

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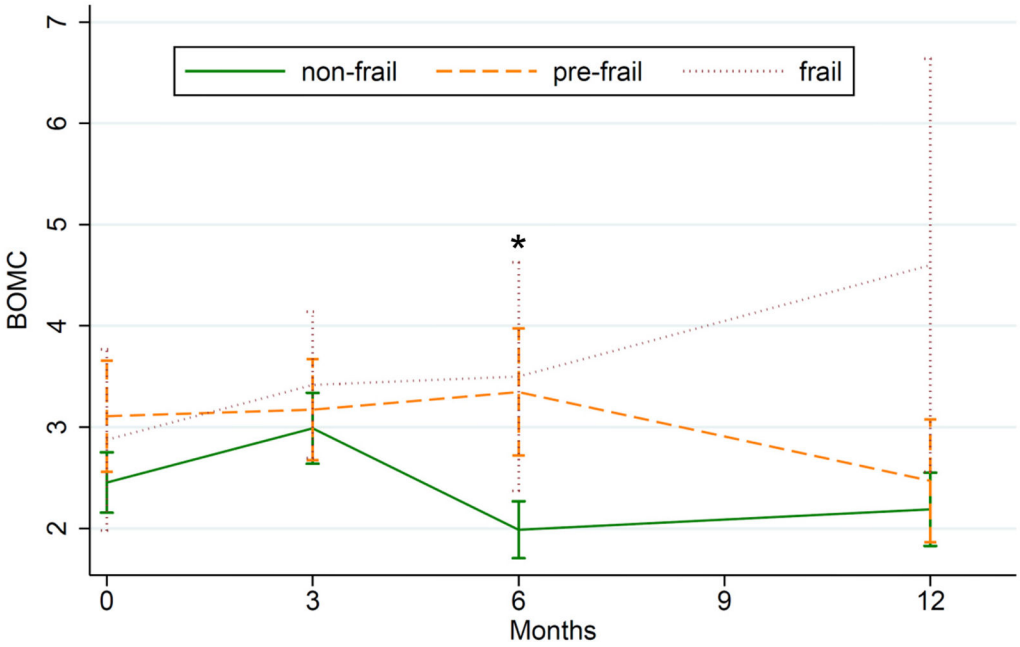

	Baseline		*3 months*		*6 months*		*12 months*	
	N	BOMC mean±SE	N	BOMC mean±SE	N	BOMC mean±SE	N	BOMC mean±SE
Non-frail	95	2.45±0.30	86	2.99±0.35	75	1.99±0.28	53	2.19±0.36
Pre-frail	37	3.11±0.55	29	3.17±0.50	26	3.35±0.63	17	2.47±0.61
Frail	16	2.88±0.89	12	3.42±0.72	10	3.5±1.13	5	4.6±2.04
p-value		0.53		0.88		0.04		0.18

Fig. 1.

Trajectories of mean Blessed Orientation-Memory-Concentration (BOMC) scores by baseline frailty status: non-frail (solid), pre-frail (dashed), frail (dotted). Higher BOMC scores reflect worse cognitive function. Vertical lines indicate the standard error of the measures at a given time point. P-values correspond to comparisons between mean scores between frailty categories at each timepoint; * = p-value <0.05. SE = standard error.

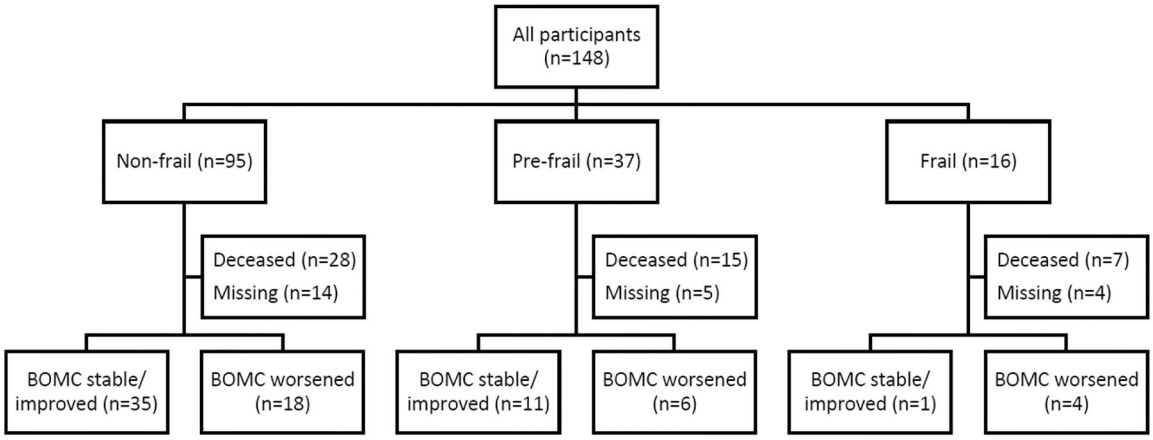

Fig. 2.

Flow diagram of BOMC change and mortality at 12 months after allogeneic transplant by baseline frailty category.

Table 1

Baseline patient demographics and clinical characteristics.

Clinical characteristic	*N* = 148
Age, median (range)	62 (50–76)
Age categories, n (%)	
50–59	56 (38%)
60–69	78 (53%)
70+	14 (9%)
Female, n (%)	58 (39%)
Married, n (%)	115 (78%)
Race, White, n (%)	113 (76%)
Ethnicity, non-Hispanic, n (%)	125 (84%)
Education, n (%)	
Through high school	25 (17%)
Through college	72 (49%)
Post-college	51 (35%)
Diagnoses	
Acute myeloid leukemia	63 (43%)
Myelodysplastic syndrome	38 (26%)
Acute lymphoblastic leukemia	14 (9%)
Non-Hodgkin Lymphoma	8 (5%)
Myelofibrosis/Myeloproliferative Disorder	4 (3%)
Other	21 (14%)
Remission status, CR1 or PR1, n (%)	78 (53%)
ASBMT disease risk	
Low	78 (52%)
Intermediate	26 (18%)
High	38 (26%)
Other/unknown	6 (4%)
KPS, provider-rated, median (range)	90 (30–100)
HCT-CI score	
0	19 (13%)
1–2	81 (55%)
3+	48 (32%)
Stem cell source, n (%)	
Peripheral blood	136 (92%)
Bone marrow	7 (5%)
Umbilical cord	5 (3%)
Donor type, n (%)	
Matched sibling	46 (31%)
10/10 MUD	64 (43%)
9/10 MUD	25 (17%)

Clinical characteristic	*N* = 148
Other	13 (9%)
Reduced-intensity conditioning, n (%)	101 (68%)

CR = complete remission. PR = partial remission. ASBMT = American Society of Blood and Marrow Transplantation. KPS = Karnofsky performance status. HCT-CI = Hematopoietic Cell Transplantation-Comorbidity Index. MUD = matched unrelated donor.

Table 2

Baseline cancer-specific comprehensive geriatric assessment measures.

Domain	Measure	Sample median (observed range)	Impairment threshold (possible range)	Sample % impaired	% impaired age 50–59	% impaired age 60+
Functional status	MOS Physical Health subscale	80 (0–100)	<85 (0–100)	57%	60%	55%
	Instrumental Activities of Daily Living (OARS subscale)	0 (0–10)	≥1 (0–14)	39%	37%	40%
	KPS, physician-reported	90 (30–100)	<80 (0–100)	3%	2%	4%
	KPS, patient-reported	90 (30–100)	<80 (0–100)	28%	36%	24%
	Timed-up-and-go	9 (4–50)	>13.5 s	8%	5%	9%
	Number of falls in last 6 months	0 (0–7)	≥1 fall	21%	18%	23%
Cognition	Blessed Orientation-Memory-Concentration Test	2 (0–14)	≥7 (0–28)	12%	16%	10%
Mental health	Mental Health Inventory	80 (40–100)	≤76 (0–100)	44%	46%	42%
Nutrition	Body mass index	26 (17–45)	<18.5	1%	0%	1%
	% unintentional weight loss in 6 months	−1% (−32–47%)	–	–	–	–
Comorbidities	OARS comorbidity subscale	1 (0–8)	– (0–13)	–	–	–
Polypharmacy	Number of medications (OARS Physical Health section)	5 (0–24)	–	–	–	–
Social support	MOS Social Support Survey	98 (0–100)	– (0–100)	–	–	–
Global frailty	Deficit accumulation frailty index	0.15 (0–0.77)	Prefrail: 0.2 < 0.35 Frail: ≥0.35 (0–1)	25% 11%	32% 9%	21% 12%

MOS = Medical Outcomes Study. OARS = Older Americans Resources & Services. KPS = Karnofsky performance status.

Table 3

Univariate analysis of the association between baseline clinical variables and risk of cognitive decline as assessed by BOMC at one year post-transplant using multinomial logistic regression.

Predictors	Relative risk ratio (95% CI)	p-value
Clinical variables		
Age *(continuous, per decade increase)*	0.95 (0.88, 1.03)	0.19
Male sex *(dichotomous, reference = female)*	0.69 (0.25, 1.88)	0.47
Married *(dichotomous, reference = not married)*	0.53 (0.16, 1.70)	0.28
Race *(categorical, reference = White, n = 113)*		
Non-White (*n* = 13)	1.41 (0.22, 9.18)	0.72
Unknown (*n* = 22)	2.81 (0.85, 9.33)	0.09
Ethnicity *(categorical, reference = non-Hispanic, n = 125)*		
Hispanic (*n* = 8)	8.42 (0.88, 80.56)	0.06
Unknown (*n* = 15)	1.75 (0.48, 6.48)	0.4
Education *(categorical, reference = through high school, n = 25)*		
Through college (*n* = 72)	0.64 (0.16, 2.57)	0.53
Post-college (*n* = 51)	0.41 (0.09, 1.88)	0.25
Diagnosis *(categorical, reference = acute myeloid leukemia, n = 63)*		
Acute lymphoblastic leukemia (n = 14)	0.77 (0.11, 5.34)	0.79
Myelodysplastic syndrome (*n* = 38)	0.58 (0.19, 1.78)	0.34
Non-Hodgkin Lymphoma (n = 8)	1.15 (0.14, 9.38)	0.89
Myelofibrosis/Myeloproliferative Disorder (n = 4)	1.15 (0.07, 20.34)	0.92
Other (*n* = 21)	0.23 (0.04, 1.25)	0.09
Remission status *(dichotomous, reference = CR1 or PR1, n = 78)*	1.14 (0.44, 2.94)	0.78
ASBMT risk category *(categorical, reference = low risk,* n = 78*)*		
Intermediate risk (*n* = 26)	0.94 (0.26, 3.39)	0.92
High risk (n = 38)	0.64 (0.20, 2.02)	0.45
Other/unknown (n = 6)	1.50 (0.09, 25.75)	0.78
HCT-CI score *(categorical, reference = 0, n = 19)*		
1–2 (*n* = 81)	1.08 (0.27, 4.27)	0.92
3+(*n* =48)	1.00 (0.22, 4.50)	1
Reduced-intensity conditioning *(dichotomous, reference = myeloablative conditioning, n = 47)*	1.05 (0.40, 2.73)	0.92

CI = confidence interval. CR = complete remission. PR = partial remission. ASBMT = American Society of Blood and Marrow Transplantation. HCT-CI = Hematopoietic Cell Transplantation-Comorbidity Index.

Table 4

Univariate and multivariate analyses of the association between baseline geriatric assessment and frailty measures and risk of cognitive decline as assessed by BOMC at one year post-transplant using multinomial logistic regression.

	Univariate		Multivariate*	
	Relative risk ratio (95% CI)	**p-value**	**Relative risk ratio (95% CI)**	**p-value**
Cancer-specific geriatric assessment measures				
MOS Physical Functioning *(continuous, per 10 point increase)*	0.99 (0.97–1.01)	0.43	0.99 (0.97–1.01)	0.55
IADL *(dichotomous, any deficits, n = 56)*	1.46 (0.52–4.16)	0.47	1.46 (0.50–4.26)	0.48
KPS-physician reported *(continuous, per 10 point increase)*	0.97 (0.91–1.02)	0.26	0.97 (0.91–1.03)	0.29
KPS-patient-reported *(continuous, per 10 point increase)*	0.98 (0.95–1.01)	0.23	0.98 (0.95–1.02)	0.28
Timed-up-and-go *(continuous, per second increase)*	1.06 (0.95–1.19)	0.27	1.07 (0.95–1.20)	0.29
Number of falls in last 6 months *(continuous)*	1.30 (0.78–2.16)	0.31	1.30 (0.76–2.21)	0.34
Mental Health Inventory *(continuous, per 10 point increase)*	0.99 (0.96–1.03)	0.69	0.99 (0.96–1.03)	0.62
Body mass index *(continuous, per 5 unit increase)*	0.99 (0.89–1.09)	0.83	0.99 (0.89–1.10)	0.82
Percent weight loss in 6 months *(continuous, per 1 unit increase)*	0.98 (0.93–1.04)	0.56	0.98 (0.93–1.04)	0.56
OARS comorbidity subscale *(continuous, per 1 unit increase)*	1.34 (0.91–1.97)	0.13	1.36 (0.92–2.00)	0.12
Number of medications *(continuous, per 1 unit increase)*	1.06 (0.93–1.20)	0.40	1.08 (0.95–1.22)	0.26
Social support survey *(continuous, per 10 point increase)*	1.00 (0.97–1.03)	0.91	0.99 (0.96–1.02)	0.61
Frailty measures				
DAFI continuous (range 0–1)	23.8 (0.68, 829.3)	0.08	16.7 (0.43, 653.6)	0.13
DAFI category *(categorical, reference = non-frail, n = 95)*				
Pre-frail (*n* = 37)	1.06 (0.34, 3.34)	0.92	0.78 (0.23, 2.62)	0.68
Frail (*n* = 16)	7.78 (0.81, 74.8)	0.08	7.38 (0.74, 73.8)	0.09

*In multivariate analyses, multinomial logistic models were adjusted for age, sex, and education.

CI = confidence interval. MOS = Medical Outcomes Study. IADL = Instrumental Activities of Daily Living. KPS = Karnofsky performance status. OARS = Older Americans Resources & Services. DAFI = deficit accumulation frailty index.