Long-term Neurocognitive Outcomes in Adult Survivors of Hematopoietic Cell Transplant

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Abstract

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Survivors of hematopoietic cell transplant (HCT) are at risk for neurocognitive impairments, which can impact quality of life. Given limited long-term studies, we aimed to characterize the late neurocognitive outcomes in a cohort of adult HCT survivors. Eligible survivors (age ≥21y at time of HCT and alive ≥2y followed HCT) completed a 60-question survey of neurocognitive function and quality of life, which included validated self-reported measures such as the Neuro-Quality of Life Cognitive Function Short Form (Neuro-QoL) and the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ). Analyses of risk factors included univariate comparisons and multivariable logistic regression. Participants (n=1861, 47.7% female, 65.6% allogeneic HCT) were surveyed at a median age of 64.2 years (interquartile range [IQR] 56.8-70.5) at survey and a median 12.0 years (IQR 6.0-21.0) from HCT. Participants reported average

Neuro-QoL scores (50.0 in allogeneic HCT survivors and 49.2 in autologous HCT survivors) compared with an expected mean score of 50 in the general population. On the CCSS-NCQ, 17.4-31.2% of participants reported impairments (Z-score >1.28) in task efficiency, memory, emotional regulation, or organization, compared with an expected 10% in the general population (all $p<0.01$). In multivariable regression analyses adjusted for sex and time since transplant, impaired Neuro-QoL (T-score <40) was independently associated with hearing issues (OR 2.13, 95% CI 1.46-3.10), and sleep impairment (OR 4.41, 95% CI 2.80-6.94) among allogeneic HCT survivors, with comparable values in autologous HCT survivors. In contrast, older age at time of survey was generally associated with a protective effect on cognitive quality of life. In conclusion, long-term adult survivors of HCT reported average cognitive quality of life compared with the general population at a median of 12.0 years following HCT. However, survivors reported persistent impairments in specific neurocognitive domains. Subsets of HCT survivors with certain co-morbid conditions were more likely to report lower quality of life and impaired neurocognitive function. These findings may help providers identify individuals at risk for impairments and facilitate targeted monitoring or potential interventions following HCT.

Introduction

Hematopoietic cell transplant (HCT) is increasingly performed as a potentially curative treatment for both malignant and non-malignant conditions. Patients who survive at least two years after HCT now have long-term survival proportions exceeding 70%.[1] Despite improving survival rates, HCT survivors remain at high-risk for chronic health conditions which contribute to increased morbidity and mortality compared with non-HCT cancer survivors and the general population.[1-3] Neurocognitive function is a broad category encompassing memory, attention, concentration, planning, organization, and problem solving, among other abilities.[4,5] Neurocognitive impairments can complicate the post-HCT course with substantial effects on both specific cognitive abilities as well as overall quality of life.[4,6] Despite this fact, few studies have described the late neurocognitive outcomes in HCT survivors.

Neurocognitive dysfunction in HCT survivors has been associated with risk factors such as sex, age, education, receipt of total body irradiation (TBI), and chronic graft-versus-host disease (cGVHD).[4,7,8] Additionally, multiple clinical risk factors may have a cumulative effect on cognitive function.[6] Studies of HCT survivors can be complicated by baseline cognitive impairments prior to transplant due to chemotherapy or other neurotoxic therapies,[9] as well as older age of patients now undergoing HCT.[10] Time from HCT may also impact study results, with some prospective studies finding that neurocognitive function declines initially following HCT with recovery in the majority of patients by the end of the first year.[9,11] Although a previous meta-analysis of several small cohort studies found no significant changes in cognitive function following HCT,[7] other studies have shown that neurocognitive dysfunction may persist long-term in some HCT survivors.[12]

Overall, the limited understanding of the incidence and characterization of neurocognitive dysfunction following HCT has been recognized as an important area deserving of further research.[1,4,5] In this study, we aim to address this gap in knowledge by characterizing late neurocognitive outcomes in a cohort of long-term adult HCT survivors. We also examine the association between treatment variables and medical co-morbidities and neurocognitive dysfunction in this patient population.

Methods

Participants

This study was approved by the Fred Hutchinson Cancer Research Center (FHCRC) Institutional Review Board. FHCRC maintains continuous follow-up of HCT survivors who consent to long-term follow-up via an annual patient-reported health survey, with the earliest transplant performed in 1971.[13,14] Patients included in this analysis underwent HCT for both malignant and non-malignant conditions, including immunodeficiencies and benign hematologic disorders. The following HCT survivors were eligible for this study: alive ≥2 years after HCT at FHCRC, age ≥21 years at time of transplant, and available current mailing address. Baseline demographic characteristics (including age, sex, race/ethnicity, underlying diagnosis) and HCT details (including conditioning regimen, donor type, cGVHD status) were retrieved from the FHCRC research database.

Survey Instruments

All FHCRC HCT survivors consenting to long-term follow-up receive an annual survey consisting of 236 questions mailed on their transplant anniversary. The annual survey includes standardized questions on interval changes in health and presence of cGVHD or other health conditions. For this study, a 60-question supplementary module was added to the annual survey to collect information on neurocognitive function and perceived cognitive quality of life. This supplementary module included questions taken from several validated self-reported survey measures. The Neuro-Quality of Life Cognitive Function Short Form (Neuro-QoL) Version 2.0 is an eight-question self-reported measure addressing perceived difficulties in cognitive abilities, as well as application of these abilities to daily tasks reflecting cognitive quality of life.[15] The Neuro-QoL was developed by the National Institute of Neurological Disorders and Stroke and validated in the adult general population.[15,16] The Childhood Cancer Survivor Study Neurocognitive Questionnaire (NCQ) is validated for use in adult survivors of childhood cancer and consists of 33 questions divided into four domains of emotional regulation, task efficiency, memory, and organization.[17] The factors of emotional regulation and organization are primarily measures of executive function, while task efficiency and memory address attention, processing speed, and both working and long-term memory.[18]

For medical co-morbidities, we selected *a priori* sleep problems, hearing issues, and neurologic conditions (e.g. previous strokes or seizures) to include in the survey, as we hypothesized that these would be the most relevant co-morbid conditions that would influence neurocognitive function. The Patient-Reported Outcomes Measure Information System (PROMIS) Sleep Disturbance Short Form 4a is a four-question survey to assess perception of sleep quality and restfulness and validated in the adult general population.[19] An additional three questions were

taken from the National Health and Nutrition Examination Survey (NHANES) 2011 Audiometry Questionnaire to screen for hearing issues (six-point Likert scale), need for hearing aid, or presence of tinnitus (five-point Likert scale).[20] Six questions were included to assess for neurologic conditions predicted to impact neurocognitive function, including previous stroke or transient ischemic attack and epilepsy or seizures. These questions were adapted from the relevant questions from the CCSS questionnaires (Yes/No/Don't Know).[21] Copies of the questionnaire are available on request. For this analysis, we used responses from surveys distributed from July 2018 to June 2019 with all results collected by November 2019. During this time, initial non-responders were sent two follow-up survey requests for a total of three mailings.

Statistical Analysis

Patient-reported surveys were scored and normalized to the general population (i.e. T or Z-scores) according to the instructions provided by the individual test developers, including methods for handling any missing data. Responses for the Neuro-QoL were summed as total raw scores and converted to standardized T-scores with a mean score of 50 and a standard deviation of 10, with lower T-scores suggesting lower cognitive quality of life.[15] The NCQ was scored by calculating a total raw score for each of the four domains, then converted to a Z-score, with higher Z-scores corresponding to worse neurocognitive scores.[17] The PROMIS Sleep Short Form 4a was summed as a total raw score and then translated into a T-score with a mean of 50 and a standard deviation of 10, with higher T-scores signifying worse sleep quality.[19] Hearing issues were defined as self-reported moderate/severe hearing trouble or deafness, current use of hearing aid, or moderate/severe tinnitus.

Descriptive statistics, including frequency distributions, medians, and interquartile ranges (IQR), were calculated for demographic and treatment variables. Primary outcome variables, including Neuro-QoL and individual NCQ domain scores, were further dichotomized into impaired vs. not impaired. Consistent with previous studies,[22] impairment was defined as T-score <40 for the Neuro-QoL (corresponding to 1 SD below the standardized mean)[23] and Z-score >1.28 for the NCQ (corresponding to the worst 10th percentile of scores based on healthy control age-adjusted norms).[17] Scores were compared using chi-squared test for categorical variables and analysis of variance or t-tests as appropriate for continuous variables. Statistical significance was considered at the level of $p < 0.01$ (two tailed), given multiple analyses. These results were not adjusted for multiple comparisons but were used to help identify the variables to be included in the multivariable analyses. Finally, the strength of the associations between certain clinical features and impairment on the CCSS-NCQ or Neuro-QoL were examined using multivariable logistic regression and reported as odds ratios (OR) with 95% confidence intervals (95% CI). Based on our univariate analyses, variables examined in the logistic regression were sex, time since transplant (continuous), current age (<50y, 50-59y, 60-70y, ≥70y), hearing issues, history of stroke or seizures, and sleep impairment. All analyses were completed using Stata (Version 16, StataCorp, College Station, TX).

Results

Of 3522 eligible adults who had survived ≥2 years from HCT, 1861 participated (52.8%) at a median age of 64.2 years (IQR 56.8-70.5) at time of survey and a median 12.0 years (IQR 6.0-21.0) from transplant (Table 1). Non-participants were more likely to be male and younger in age at time of survey. The majority of patients received an allogeneic HCT (65.6%) with 10.4% of

patients receiving more than one transplant. Most patients underwent transplantation for malignant conditions, including acute leukemia (22.5%), chronic leukemia (19.5%), and lymphoma (22.0%). Across all transplants, 47.9% of patients underwent conditioning with total body irradiation (TBI) with 29.5% receiving ≥1000cGy. The majority of patients (66.6%) who received allogeneic HCT reported a diagnosis of chronic graft-versus-host disease (cGVHD). The prevalence of moderate/severe hearing loss/tinnitus and history of stroke or seizures was 30.4% and 9.7%, respectively.

Participants reported average Neuro-QoL scores (50.0 in allogeneic HCT survivors and 49.2 in autologous HCT survivors) compared with an expected mean score of 50 in the general population (Table 2). For both allogeneic and autologous HCT survivors, characteristics associated with lower Neuro-QoL scores included female sex, lower educational achievement, hearing issues, and sleep disturbances ($p<0.01$). History of stroke/seizure was generally associated with lower Neuro-QoL scores, although this association was statistically significant among allogeneic HCT survivors only. Older participants appeared to report relatively higher NeuroQoL scores compared with younger participants, while time since transplant appeared to have little impact on scores. For both groups of survivors, no significant differences in Neuro-QoL scores were seen based on race/ethnicity, number of transplants, or cumulative TBI exposure (results not shown).

On the NCQ, 31.2% of allogeneic HCT survivors reported problems with task efficiency, 26.0% with memory, 20.9% with organization and 17.4% with emotional regulation, compared with an expected 10% in the general population (all $p <0.01$; Table 3a). In unweighted analyses, female

allogeneic survivors reported more issues in all domains relative to males, although only memory impairments rose to the level of statistical significance. Characteristics associated with impairments in most or all NCQ domains included hearing issues, history of stroke/seizure, and self-reported sleep disturbances. Allogeneic survivors with less educational achievement also reported significantly worse scores in emotional regulation and memory, while survivors with history of stroke/seizures reported worse scores in task efficiency and memory. Similar to our Neuro-QoL findings, older age appeared to have a general protective effect on neurocognitive function, with fewer impairments reported by older participants, particularly in emotional regulation and memory.

Autologous HCT survivors similarly reported impairments in all NCQ domains at higher rates compared with the general population (34.7% with task efficiency, 31.1% with memory, 24.3% with organization, 17.4% with emotional regulation; all $p<0.01$; Table 3b). Lower educational achievement, hearing issues, and self-reported sleep disturbances were consistently associated with lower NCQ scores. Autologous HCT survivors with a history of stroke/seizures reported more impairments in memory, but not in other domains.

In multivariable regression analysis adjusted for sex and time since transplant, older age at time of survey was independently associated with improved cognitive quality of life (OR 0.73 [95% CI 0.60-0.88] for every decade increase in age for allogeneic HCT survivors, with similar values in autologous HCT survivors; Table 4). In contrast, impaired Neuro-QoL was associated with hearing issues (OR 2.13, 95% CI 1.46-3.10) and sleep impairment (OR 4.41, 95% CI 2.80-6.94) among allogeneic HCT survivors, with comparable values in autologous HCT survivors.

For NCQ outcomes, sleep impairment was independently associated with impairments in almost all domains among both allogeneic and autologous HCT survivors. Among allogeneic HCT survivors, older age was associated with a protective effect on emotional regulation and memory. Hearing issues were associated with impaired emotional regulation, task efficiency, and memory, while a history of stroke or seizures was associated with impaired task efficiency and memory. For autologous HCT survivors, older age was associated with improved memory, while hearing issues were associated with worse task efficiency, organization, and memory.

Discussion

Our study found that adult HCT survivors reported average cognitive quality of life compared with general population norms at a median of 12.0 years post-HCT. Despite reported problems with specific cognitive abilities reflected as impairments on the NCQ, these cognitive problems were not perceived to interfere with daily functioning nor impact quality of life, as reflected on the Neuro-QoL. This may reflect compensatory strategies or a degree of resiliency to maintain well-being and quality of life despite treatment-related complications and ongoing cognitive deficits. Our study correlated with several other studies showing that long-term survivors of HCT report an overall quality of life comparable with age and sex-matched healthy controls.[8,24]

Survivors reported persistent impairments in specific NCQ domains of emotional regulation, task efficiency, memory, and organization. This was consistent with several studies demonstrating pervasive cognitive deficits in patients post-HCT.[6,8,12] In a small study of long-term HCT survivors (range 2-7 years post HCT), survivors were more likely to have objective impairments in attention, processing speed, and memory on cognitive testing, while 27.5% and 17.5% of

patients reported subjective moderate-severe problems in memory and attention, respectively.[8] We did not find any differences in neurocognitive outcomes based on time since transplant. Similarly, in a meta-analysis based on 11 studies comparing pre- and post-HCT neurocognitive assessments, time since transplant (ranging from mean 35 days to almost 9 years) was not associated with changes in cognitive function.[7] In contrast, several smaller studies found that cognitive function improves after the immediate post-HCT period.[11,25] In a previous longitudinal study at our institution, Syjrala et al. found that cognitive impairments were at the highest in the immediate post-transplantation period, with partial recovery by 1-year[11] and continued improvement by 5-years post-HCT.[12] This suggests some degree of cognitive recovery following transplant, however 41.5% of survivors at 5-years post-HCT demonstrated overall cognitive impairment compared with only 19.7% of case-matched non-HCT controls.[12]

Older age was consistently associated with improved cognitive quality of life and fewer impairments in specific neurocognitive domains in our study despite adjusting for time from transplant. In contrast, a small study of allogeneic HCT survivors found that older age (age ≥65 years) was associated with worse verbal memory and verbal fluency compared with younger patients in the first year post-transplantation.[10] As our study focused on long-term survivors, this suggests that older patients may be more susceptible to acute neurocognitive toxicities, but this effect may be mitigated with more time from transplant. Interestingly, a small study in adult HCT survivors at 6 months post-HCT found that older age was associated with more impairments in objective cognition tests, however younger patients made more subjective cognitive complaints (most commonly in the domains of remote memory, attention/concentration, and language).[26]

In our study, subsets of HCT survivors were more likely to report lower quality of life and impaired neurocognitive function, including those with hearing conditions (moderate to severe hearing loss or more bothersome tinnitus), history of stroke or seizures, or sleep disturbances. While studies have been limited in the adult HCT population, previous studies in adult survivors of pediatric cancers demonstrated the association of hearing and visual deficits with impaired emotional regulation and organization,[27] while history of stroke was associated with worse health-related quality of life and neurocognitive function, particularly task efficiency and memory.[28] Similarly, both hearing issues and history of stroke or seizures have been associated with neurocognitive dysfunction and worse quality of life in adult survivors of pediatric HCT.[22] While we explored other treatment-related factors or complications, similar to other studies we did not find that TBI[7,9] or cGVHD[9] were associated with neurocognitive outcomes. While we were unable to examine the additive effect of multiple co-morbidities, patients with more clinical risk factors in the acute setting (including transplant-related factors and HCT-related complications) have been reported to exhibit worse neuropsychological performance at 6-months post-HCT and less evidence of recovery at 12-months post-HCT.[6] Identification of vulnerable sub-groups of patients at higher risk for post-HCT complications is critical to improve preventative care measures and screening.[14]

Lastly, we found that self-reported sleep disturbances were significantly associated with worse cognitive quality of life and greater impairments in all CCSS-NCQ domains. Given the cross-sectional nature of our study, we were unable to determine if sleep issues had a causal effect on neurocognitive function, although sleep disturbances are generally associated with worse quality

of life and frequently identified as significant concerns following HCT.[29,30] Sleep impairment is common in the post-transplant period but generally improves/stabilizes by 1-year post-HCT.[29,31] In a previous short-term study, adult HCT survivors with sleep problems at 1-year post-HCT reported greater cognitive dysfunction, even after controlling for depressive symptoms, fatigue, and pain.[32] Our study corroborates with other long-term studies that sleep continues to be an ongoing issue for a subset of HCT survivors,[30] with considerable impact on neurocognitive function. Using similar neurocognitive measures as our study, long-term adult survivors of pediatric cancer and HCT who reported sleep disturbances exhibited greater impairments in all CCSS-NCQ domains.[22,33] Routine assessment of sleep by providers and additional research to better characterize specific sleep disorders may help determine targets for improvement in this patient population, although interventional studies have not yet been successful.[29]

Our study benefited from a long average follow-up duration and one of the largest samples examining neurocognitive outcomes in long-term HCT survivors. However, there were several limitations to this study. Our study was conducted at a single center and limited by lower response rate as well as limited racial/ethnic diversity; thus, our results may not be fully representative of the overall population of adult HCT survivors. We were also unable to account for pre-HCT exposures that may also increase neuropsychological risk factors, such as history of cranial irradiation or receipt of intrathecal chemotherapy. Additionally, among allogeneic transplant recipients, we did not separate myeloablative transplants from non-myeloablative transplants, which may have had an impact on late complications. Given the cross-sectional nature of this study, limited conclusions about the causality of the findings could be made. We

also lacked a control group, although we used self-reported measures that had been validated in and normalized to the general population.

Conclusions

Long-term adult survivors of HCT reported average cognitive quality of life compared with the general population at a median of 12.0 years following HCT. However, survivors had persistent impairments in specific neurocognitive domains of emotional regulation, task efficiency, memory, and organization. Subsets of HCT survivors with certain co-morbid conditions were more likely to report lower quality of life and neurocognitive dysfunction. Early identification of high-risk survivors, including those reporting sleep disturbances, may help mitigate the risk of long-term neurocognitive impairments.

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Table 1: Patient characteristics for eligible HCT survivors with participants sub-divided by allogeneic vs autologous transplant

	All participants N=1861	Allogeneic HCT (any) N=1220	Autologous HCT (only) N=641	Non-participants N=1661*
Female sex, n (%)	888 (47.7%)	584 (47.9%)	304 (47.4%)	696 (41.9%)
Race/ethnicity, n (%)				
White	1660 (89.2%)	1103 (90.4%)	557 (86.9%)	1347 (81.1%)
Non-white	116 (6.2%)	79 (6.5%)	37 (5.8%)	189 (11.4%)
Unknown or unreported	85 (4.6%)	38 (3.1%)	47 (7.3%)	125 (7.5%)
Current age, years, median (IQR)	64.2 (56.8, 70.5)	63.1 (55.3, 69.2)	66.4 (59.8, 72.0)	59.5 (50.9, 67.0)
Age <50y, n (%)	221 (11.9%)	170 (13.9%)	51 (8.0%)	390 (23.5%)
Age 50-59y, n (%)	408 (21.9%)	298 (24.4%)	110 (17.2%)	464 (27.9%)
Age 60-69y, n (%)	736 (39.6%)	479 (39.3%)	257 (40.1%)	523 (31.5%)
Age ≥70y, n (%)	496 (26.6%)	273 (22.4%)	223 (34.8%)	284 (17.1%)
Diagnosis, n (%)				
Acute leukemia	418 (22.5%)	407 (33.5%)	11 (1.7%)	403 (24.3%)
Chronic leukemia	363 (19.5%)	361 (29.7%)	2 (0.3%)	291 (17.5%)
Lymphoma	409 (22.0%)	104 (8.6%)	305 (48.0%)	422 (25.4%)
Multiple myeloma	320 (17.2%)	63 (5.2%)	257 (40.5%)	262 (15.8%)
Myelodysplastic syndrome	80 (4.3%)	80 (6.6%)	0	60 (3.6%)
Solid tumor	31 (1.7%)	3 (0.3%)	28 (4.4%)	34 (2.1%)
Aplastic anemia	45 (2.4%)	45 (3.7%)	0	49 (3.0%)
Other diagnosis	195 (10.5%)	153 (12.5%)	32 (5.0%)	140 (8.4%)
>1 transplant, n (%)	193 (10.4%)	168 (13.8%)	25 (3.9%)	174 (10.5%)
Time since transplant, yrs, median (IQR)	12.0 (6.0, 21.0)	15.0 (7.0, 22.7)	8.1 (4.3, 15.0)	11.5 (6.1, 20.2)
<5 years	378 (20.3%)	187 (15.3%)	191 (29.8%)	327 (19.7%)
5-9 years	439 (23.6%)	253 (20.7%)	186 (29.0%)	421 (25.4%)
10-14 years	270 (14.5%)	169 (13.9%)	101 (15.8%)	279 (16.8%)
15-19 years	260 (14.0%)	189 (15.5%)	71 (11.1%)	206 (12.4%)
20-25 years	224 (12.0%)	170 (13.9%)	54 (8.4%)	184 (11.1%)
25+ years	290 (15.6%)	252 (20.7%)	38 (5.9%)	244 (14.7%)
Era of initial transplant, n (%)				
Prior to 1980	138 (7.4%)	126 (10.3%)	12 (1.9%)	113 (6.8%)
1990-1999	423 (22.7%)	334 (27.4%)	89 (13.9%)	337 (20.3%)
2000-2009	538 (28.9%)	352 (28.9%)	186 (29.0%)	498 (30.0%)
2010-current	762 (41.0%)	408 (33.4%)	354 (55.2%)	713 (42.9%)
Received TBI (any), n (%)	891 (47.9%)	781 (64.0%)	110 (17.2%)	756 (45.5%)
Diagnosed with chronic GVHD, n (%)	812 (43.6%)	812 (66.6%)	0	686 (41.3%)
Education level if age >25, n (%)				
Less than 4-year college	800 (43.5%)	505 (41.9%)	295 (46.6%)	
Completed college	1039 (56.5%)	701 (58.1%)	338 (53.4%)	
Hearing loss, n (%)	434 (23.5%)	253 (21.0%)	181 (28.4%)	
Tinnitus, n (%)	251 (13.6%)	150 (12.4%)	101 (15.8%)	
Previous stroke/TIA, n (%)	126 (7.0%)	88 (7.4%)	38 (6.2%)	
Previous seizures/convulsions, n (%)	59 (3.4%)	40 (3.5%)	19 (3.2%)	

GVHD: graft-versus-host disease; TBI: total body irradiation; TIA: transient ischemic attack

*Non-participants consisted of 1045 allogeneic transplant recipients (62.9%) and 616 autologous transplant recipients (37.1%)

Table 2: Characteristics associated with differences in cognitive quality of life, assessed by the Neuro-Quality of Life Cognitive Function Short Form (Neuro-QoL Version 2.0)

	Allogeneic HCT (any)			Autologous HCT (only)		
	N	T-score, mean (95% CI)	% impaired*	N	T-score, mean (95% CI)	% impaired*
Total	1219	50.0 (49.5-50.5)	13.9%	641	49.2 (48.5-49.9)	17.2%
Sex						
Female	583	49.3 (48.6-50.0)	13.9%	304	48.2 (47.2-49.2)	18.1%
Male	636	50.6 (49.9-51.3)^	13.8%	337	50.2 (49.2-51.1)^	16.3%
Current age (by decade)						
Age <50y	170	48.4 (47.0-49.8)	18.8%	51	46.6 (43.7-49.5)	29.4%
Age 50-59y	298	49.5 (48.4-50.5)	14.4%	110	49.7 (47.8-51.6)	17.3%
Age 60-69y	479	50.6 (49.8-51.4)	14.8%	257	48.6 (47.4-49.7)	19.8%
Age ≥70y	272	50.5 (49.5-51.5)	8.5%	223	50.4 (49.3-51.4)	11.2%
Time since initial transplant						
<5 years	187	49.7 (48.3-51.0)	16.6%	191	50.6 (49.2-51.9)	14.1%
5-10 years	253	48.9 (47.9-50.0)	14.2%	186	48.2 (46.8-49.6)	24.2%
10-15 years	168	50.0 (48.7-51.3)	11.9%	101	49.0 (47.4-50.6)	10.9%
15-20 years	189	49.8 (48.6-51.0)	13.2%	71	49.8 (47.6-52.0)	15.5%
20-25 years	170	51.6 (50.1-53.0)	11.8%	54	47.8 (45.7-50.0)	18.5%
25+ years	252	50.3 (49.2-51.5)	14.7%	38	49.1 (46.1-52.1)	15.8%
Education level if age >25						
Less than 4-yr college	504	49.0 (48.2-49.7)	15.5%	295	47.7 (46.6-48.7)	21.7%
Completed college	701	50.7 (50.0-51.4)^	12.6%	338	50.6 (49.7-51.6)^	12.7%^
Hearing issues						
No	877	50.7 (50.1-51.3)	11.6%	411	50.5 (49.6-51.3)	13.4%
Yes	332	48.2 (47.2-49.2)^	19.9%^	229	47.0 (45.8-48.2)^	24.0%^
Stroke/seizures						
No	1074	50.3 (49.8-50.9)	13.2%	572	49.5 (48.7-50.2)	16.8%
Yes	122	47.4 (45.7-49.0)^	19.7%	55	47.0 (44.6-49.5)	23.6%
Sleep disturbance						
No (T-score <60)	1112	50.6 (50.1-51.1)	11.4%	593	49.7 (49.0-50.5)	15.7%
Yes (T-score ≥60)	104	43.6 (41.9-45.3)^	38.5%^	47	43.0 (40.6-45.4)^	36.2%^

*Impaired defined as T-score <40, with lower scores indicating greater impairment;
^Significantly different vs. value above ($p<0.01$)

Table 3a: Characteristics associated with differences in neurocognitive domains in allogeneic transplant survivors, assessed by the Childhood Cancer Survivor Study Neurocognitive Questionnaire (NCQ)

	N	Emotional Regulation		Task Efficiency		Organization		Memory	
		Mean (95% CI)	% Impaired*	Mean (95% CI)	% Impaired*	Mean (95% CI)	% Impaired*	Mean (95% CI)	% Impaired*
Total	1210	0.22 (0.16-0.29)^	17.4%^	0.69 (0.61-0.77)^	31.2%^	0.21 (0.15-0.28)^	20.9%^	0.61 (0.54-0.69)^	26.0%^
Sex									
Female	578	0.27 (0.17-0.36)	18.2%	0.79 (0.67-0.90)	32.5%	0.29 (0.19-0.39)	23.5%	0.78 (0.68-0.88)	29.4%
Male	633	0.18 (0.09-0.27)	16.6%	0.60 (0.50-0.71)	30.0%	0.14 (0.06-0.23)	18.5%	0.46 (0.37-0.56)^	22.9%^
Current age (by decade)									
Age <50y	169	0.44 (0.24-0.64)	23.7%	0.78 (0.59-0.98)	37.1%	0.24 (0.06-0.42)	21.9%	0.89 (0.67-1.10)	35.5%
Age 50-59y	297	0.33 (0.19-0.46)	19.2%	0.75 (0.58-0.92)	32.2%	0.32 (0.18-0.45)	23.8%	0.66 (0.51-0.82)	25.8%
Age 60-69y	474	0.16 (0.06-0.25)	16.9%	0.61 (0.49-0.73)	28.3%	0.13 (0.03-0.24)	18.8%	0.55 (0.43-0.66)	27.0%
Age ≥70y	270	0.10 (-0.02-0.21)	12.2%	0.71 (0.56-0.86)	31.4%	0.22 (0.10-0.35)	20.7%	0.51 (0.39-0.64)	18.6%
Time since initial transplant									
<5 years	184	0.28 (0.10-0.46)	19.6%	0.80 (0.60-1.00)	31.9%	0.28 (0.10-0.46)	21.5%	0.63 (0.43-0.83)	26.1%
5-10 years	253	0.29 (0.14-0.43)	19.0%	0.79 (0.62-0.95)	37.2%	0.25 (0.10-0.41)	21.4%	0.64 (0.48-0.79)	25.4%
10-15 years	168	0.12 (-0.05-0.28)	11.3%	0.59 (0.39-0.79)	27.4%	0.18 (0.00-0.36)	20.8%	0.62 (0.42-0.82)	26.2%
15-20 years	188	0.25 (0.09-0.41)	21.3%	0.71 (0.54-0.89)	30.7%	0.22 (0.07-0.37)	19.7%	0.66 (0.49-0.83)	27.7%
20-25 years	170	0.10 (-0.07-0.26)	12.4%	0.55 (0.34-0.76)	25.9%	0.13 (-0.03-0.30)	22.4%	0.49 (0.30-0.68)	22.9%
25+ years	247	0.26 (0.12-0.40)	18.6%	0.66 (0.48-0.84)	31.1%	0.19 (0.06-0.32)	19.8%	0.63 (0.47-0.79)	27.4%
Education level if age >25									
Less than 4-year college	503	0.34 (0.24-0.44)	20.5%	0.76 (0.65-0.88)	32.8%	0.19 (0.09-0.29)	19.5%	0.77 (0.66-0.89)	31.1%
Completed college	695	0.14 (0.06-0.22)^	15.0%	0.64 (0.54-0.74)	30.0%	0.23 (0.14-0.32)	21.8%	0.49 (0.40-0.58)^	22.0%^
Hearing issues									
No	870	0.14 (0.07-0.22)	15.2%	0.59 (0.51-0.68)	28.2%	0.14 (0.07-0.22)	20.2%	0.52 (0.44-0.60)	23.9%
Yes	333	0.44 (0.32-0.57)^	23.4%^	0.94 (0.78-1.09)^	38.6%^	0.37 (0.25-0.50)^	22.3%	0.84 (0.70-0.98)^	31.1%
Stroke/seizures									
No	1069	0.20 (0.13-0.27)	16.7%	0.63 (0.55-0.71)	29.3%	0.19 (0.12-0.25)	20.2%	0.56 (0.49-0.64)	24.6%
Yes	122	0.41 (0.19-0.63)	23.0%	1.19 (0.93-1.45)^	45.1%^	0.37 (0.16-0.57)	24.6%	0.97 (0.73-1.21)^	36.1%^
Sleep disturbance									
No (T-score <60)	1106	0.14 (0.08-0.21)	15.3%	0.59 (0.51-0.66)	29.0%	0.14 (0.08-0.21)	19.0%	0.53 (0.45-0.60)	23.9%
Yes (T-score ≥60	102	1.07 (0.81-1.33)^	39.2%^	1.73 (1.42-2.04)^	52.9%^	0.94 (0.68-1.20)^	40.8%^	1.53 (1.25-1.82)^	48.0%^

*Impaired defined as Z-score >1.28, with higher scores indicating greater impairment;
^Significantly different ($p<0.01$) vs. value of 0 (for mean total Z-score), 10% (for % impaired), or value above (for all 2-level categorical variables)

Table 3b: Characteristics associated with differences in neurocognitive domains in autologous transplant survivors, assessed by the Childhood Cancer Survivor Study Neurocognitive Questionnaire (NCQ)

	N	Emotional Regulation		Task Efficiency		Organization		Memory	
		Mean (95% CI)	% Impaired*	Mean (95% CI)	% Impaired*	Mean (95% CI)	% Impaired*	Mean (95% CI)	% Impaired*
Total	633	0.26 (0.17-0.35)^	17.4%^	0.84 (0.73-0.95)^	34.7%^	0.33 (0.23-0.42)^	24.3%^	0.74 (0.64-0.85)^	31.1%^
Sex									
Female	301	0.32 (0.19-0.45)	17.9%	0.98 (0.82-1.14)	38.6%	0.40 (0.26-0.54)	25.9%	0.95 (0.80-1.10)	35.0%
Male	332	0.21 (0.09-0.33)	16.9%	0.71 (0.56-0.86)	31.0%	0.26 (0.13-0.39)	22.9%	0.56 (0.42-0.70)^	27.6%
Current age (by decade)									
Age <50y	51	0.43 (0.09-0.78)	21.6%	1.10 (0.66-1.53)	47.1%	0.41 (0.05-0.78)	29.4%	1.23 (0.79-1.67)	45.1%
Age 50-59y	107	0.28 (0.04-0.52)	16.8%	0.70 (0.42-0.99)	26.9%	0.26 0.00-0.51)	24.3%	0.72 (0.44-0.99)	27.8%
Age 60-69y	253	0.30 (0.16-0.44)	17.8%	0.95 (0.78-1.13)	38.2%	0.45 (0.29-0.61)	25.7%	0.83 (0.66-099)	34.5%
Age ≥70y	222	0.16 (0.02-0.30)	16.2%	0.71 (0.55-0.87)	31.5%	0.20 (0.06-0.34)	21.6%	0.55 (0.40-0.71)	25.7%
Time since initial transplant									
<5 years	188	0.26 (0.10-0.41)	17.0%	0.75 (0.56-0.95)	33.0%	0.22 (0.06-0.38)	23.9%	0.63 (0.44-0.82)	28.0%
5-10 years	185	0.41 (0.23-0.60)	21.1%	1.03 (0.81-1.25)	39.5%	0.44 (0.25-0.63)	28.7%	0.90 (0.70-1.10)	35.1%
10-15 years	99	0.27 (0.07-0.46)	16.2%	0.77 (0.53-1.02)	31.0%	0.31 (0.08-0.53)	20.2%	0.80 (0.57-1.03)	35.0%
15-20 years	70	0.13 (-0.14-0.41)	14.3%	0.74 (0.41-1.07)	32.9%	0.28 (-0.02-0.58)	24.3%	0.65 (0.34-0.97)	27.1%
20-25 years	53	-0.03 (-0.29-0.24)	11.3%	0.80 (0.44-1.17)	31.5%	0.36 (0.02-0.70)	20.8%	0.67 (0.32-1.02)	25.9%
25+ years	38	0.16 (-0.19-0.51)	18.4%	0.71 (0.26-1.15)	36.8%	0.36 (-0.05-0.78)	21.1%	0.71 (0.31-1.10)	31.6%
Education level if age >25									
Less than 4-year college	291	0.50 (0.36-0.64)	24.4%	1.06 (0.89-1.23)	40.8%	0.48 (0.33-0.63)	29.2%	0.98 (0.82-1.14)	37.5%
Completed college	335	0.06 (-0.05-0.16)^	11.6%^	0.63 (0.49-0.78)^	28.9%^	0.20 (0.08-0.32)^	20.3%	0.53 (0.40-0.67)^	25.0%^
Hearing issues									
No	406	0.20 (0.09-0.31)	16.0%	0.67 (0.54-0.80)	30.4%	0.17 (0.06-0.28)	19.7%	0.62 (0.49-0.74)	26.2%
Yes	227	0.37 (0.22-0.52)	19.8%	1.14 (0.95-1.33)^	42.3%^	0.61 (0.44-0.78)^	32.6%^	0.98 (0.80-1.15)^	40.1%^
Stroke/seizures									
No	565	0.24 (0.15-0.34)	17.0%	0.82 (0.70-0.93)	34.7%	0.29 (0.19-0.39)	23.0%	0.70 (0.59-0.81)	29.8%
Yes	55	0.35 (0.02-0.68)	20.0%	1.02 (0.66-1.37)	34.6%	0.59 (0.25-0.92)	32.7%	1.14 (0.76-1.52)	41.8%
Sleep disturbance									
No (T-score <60)	587	0.22 (0.12-0.31)	16.9%	0.75 (0.64-0.86)	32.1%	0.27 (0.18-0.37)	23.0%	0.68 (0.58-0.79)	29.5%
Yes (T-score ≥60	46	0.85 (0.52-1.17)^	23.9%	1.95 (1.56-2.33)^	67.4%^	1.01 (0.61-1.41)^	41.3%^	1.54 (1.16-1.91)^	52.2%^

*Impaired defined as Z-score >1.28, with higher scores indicating greater impairment;
^Significantly different ($p<0.01$) vs. value of 0 (for mean total Z-score), 10% (for % impaired), or value above (for all 2-level categorical variables)

Table 4: Risk of neurocognitive impairment associated with selected exposures and co-morbidities using multivariable logistic regression*

Co-variate	Neuro-QoL†		Emotional Regulation‡		Task Efficiency‡		Organization‡		Memory‡	
	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
Current age (by decade)										
Allogeneic HCT	0.73 (0.60-0.88)	0.001	0.73 (0.62-0.87)	<0.001	0.87 (0.76-1.00)	0.05	0.94 (0.81-1.10)	0.45	0.74 (0.64-0.86)	<0.001
Autologous HCT	0.70 (0.55-0.88)	0.003	0.92 (0.73-1.16)	0.50	0.93 (0.77-1.13)	0.52	0.86 (0.70-1.06)	0.16	0.78 (0.64-0.95)	0.01
Hearing issues (vs none)										
Allogeneic HCT	2.13 (1.46-3.10)	<0.001	2.00 (1.42-2.82)	<0.001	1.72 (1.29-2.30)	<0.001	1.13 (0.81-1.58)	0.46	1.73 (1.28-2.35)	<0.001
Autologous HCT	2.54 (1.62-3.98)	<0.001	1.33 (0.86-2.08)	0.21	1.94 (1.35-2.79)	<0.001	2.18 (1.47-3.25)	<0.001	2.18 (1.50-3.17)	<0.001
Stroke/seizures (vs none)										
Allogeneic HCT	1.58 (0.94-2.65)	0.08	1.46 (0.91-2.35)	0.12	2.01 (1.36-2.97)	<0.001	1.27 (0.81-1.99)	0.29	1.77 (1.17-2.68)	0.007
Autologous HCT	1.56 (0.78-3.09)	0.21	1.22 (0.60-2.46)	0.58	0.92 (0.50-1.68)	0.79	1.61 (0.87-2.97)	0.13	1.66 (0.93-2.99)	0.09
Sleep impairment (vs none)										
Allogeneic HCT	4.41 (2.80-6.94)	<0.001	3.11 (2.00-4.85)	<0.001	2.42 (1.59-3.69)	<0.001	2.87 (1.86-4.41)	<0.001	2.59 (1.69-3.96)	<0.001
Autologous HCT	2.52 (1.29-4.93)	0.007	1.52 (0.73-3.16)	0.26	3.93 (2.03-7.62)	<0.001	2.07 (1.08-3.98)	0.03	2.13 (1.13-4.03)	0.02

*Model includes all variables listed (current age by decade, hearing issues, stroke/seizures, sleep impairment) and additionally adjusted for sex and time since transplant (continuous)
†Impairment defined as lower T-score <40
‡Impairment defined as higher Z-score >1.28